LBA1 **Plenary Session**

Perioperative (neoadjuvant and adjuvant) apalutamide (APA) + androgen deprivation therapy (ADT) vs placebo (PBO) + ADT with radical prostatectomy (RP) in high-risk localized or locally advanced prostate cancer (HR LPC/LAPC): Final analysis of the PROTEUS phase 3 study.

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Background: RP is potentially curative for patients (pts) with HR LPC/LAPC, yet ≈50% of pts relapse. PROTEUS evaluated whether APA + ADT vs PBO + ADT before and after RP with pelvic lymph node dissection (henceforth, RP) improves pathologic complete response/minimal residual disease (pCR/MRD) and metastasis-free survival (MFS) in HR LPC/LAPC. **Methods:** Pts with newly diagnosed HR LPC/LAPC (histology, prostate-specific antigen [PSA], and cN0/cN1 on conventional imaging) were randomized 1:1 to blinded APA (240 mg/d) or PBO as neoadjuvant treatment (tx) for 6 mo + ADT, with a 2-wk break prior to and a 4-wk break post RP, followed by 6 mo of assigned tx. Dual primary end points, pCR/MRD (≤ypT2, ≤5 mm tumor diameter) and MFS based on conventional or prostate-specific membrane antigen positron emission tomography (PSMA PET) imaging, were assessed by blinded independent central review (BICR). Secondary end points included event-free survival (EFS), time to first subsequent tx (TTST1), time to distant metastasis (TTDM), and safety. Exploratory end points included residual cancer burden (RCB/MRD; ≤ypT2, ≤0.25 cm^3) and investigator-assessed MFS. **Results:** Of 2109 pts randomized (APA + ADT [1057] or PBO + ADT [1052]), median (range) age was 66.0 (41-89) years (y); PSA, 14.8 (0.0-2798.0) ng/mL; GS ≥8, 95.8%. Median follow-up was 61.7 mo. Both primary end points were met with APA + ADT vs PBO + ADT: pCR/MRD rate was significantly higher, 8.9% vs 1.0% (odds ratio [OR] 10.17; 95% CI 5.27-19.64; p<0.0001); MFS by BICR was significantly improved with HR 0.80; 95% CI 0.67-0.96; p=0.0169 and 5-y MFS rate of 78.2% vs 73.5%; median not reached [NR]. Investigator-assessed MFS favored APA + ADT, with HR 0.74; 95% CI 0.62-0.87; nominal p=0.0004. EFS, TTST1, TTDM were all significantly improved with APA + ADT (Table), as was RCB/MRD: MRD 30.6% vs 11.7%; OR 3.36; 95% CI 2.67-4.23; nominal p<0.0001. Grade 3/4 tx-emergent adverse events (TEAEs) for APA + ADT vs PBO + ADT were 39.6% vs 31.0%, with discontinuation due to TEAEs 7.4% vs 2.7%, respectively. **Conclusions:** APA + ADT significantly increased the curative success of RP in pts with HR LPC/LAPC, with a 10-fold higher odds of pCR/MRD and a clinically meaningful 20% reduction in risk of distant metastasis or death. Secondary end points all favored APA + ADT. These results support combined APA + ADT and RP as a new standard of care for pts with HR LPC/LAPC. Clinical trial information: NCT03767244. Research Sponsor: Johnson & Johnson.

	HR (95% CI)	p Value[a]	APA + ADT n=1057 Median (mo)	PBO + ADT n=1052 Median (mo)
EFS	0.71 (0.63-0.80)	<0.0001	57.1	38.4
TTST1 (local, regional, or systemic, including ADT reinitiation)	0.65 (0.57-0.73)	<0.0001	74.2	41.5
TTDM (conventional or PSMA PET imaging)	0.68 (0.55-0.83)	0.0002	NR	NR

[a]Stratified by GS (7, ≥8), nodal status, and geographic region (North America, European Union, rest of world).

LBA2 Plenary Session

SARC041: A phase 3 randomized double-blind study of abemaciclib versus placebo in patients with advanced dedifferentiated liposarcoma.

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Background: Dedifferentiated liposarcoma (DDLS) remains a difficult disease to treat with limited systemic therapy options. Approved drugs offer modest benefit such as trabectedin (median progression-free survival [mPFS] 2.2 months [m]) or eribulin (mPFS 2.0m). The Cyclin-dependent kinase 4 (CDK4) oncogene is ubiquitously amplified in DDLS and is a rational therapeutic target. In single-arm phase 2 studies, treatment with selective CDK4 inhibitors resulted in mPFS 4.2m with palbociclib and mPFS 7.7m with abemaciclib. We hypothesized that treatment with abemaciclib would improve PFS compared to placebo in patients with recurrent or metastatic DDLS. **Methods:** SARC041 was a phase 3 randomized double-blind study of abemaciclib versus placebo. The study was open at 9 academic medical centers in the USA. Eligible patients (pts) had recurrent or metastatic DDLS (purely well-differentiated liposarcoma excluded), progression of disease by RECIST 1.1 in the 6 months prior to study entry, any number of prior systemic therapies, and adequate organ function and performance status. Pts were stratified by prior lines of therapy (0 vs 1 or more) and randomized 1:1 between abemaciclib 200 mg PO twice a day or matching placebo. Scans were every 6 weeks (every 12 weeks after week 36) and pts with progression of disease on placebo could cross over to open label abemaciclib. The primary endpoint was PFS. The design provided 80% power with two-sided 10% significance level to detect a hazard ratio of 0.6 by log-rank test. Secondary endpoints were overall response rate (ORR), PFS and response rate after crossover, and overall survival (OS). Data cutoff was March 1, 2026. **Results:** In total, 108 pts were randomized to receive abemaciclib (n = 54) or placebo (n = 54). Demographic/baseline characteristics were generally similar across treatment arms. Abemaciclib demonstrated a statistically significant improvement in PFS at 9.67m vs placebo at 1.52m (hazard ratio [HR] 0.39; 95% confidence interval [CI], 0.25–0.59; $p < 0.001$). ORR was 9.3% for abemaciclib vs 0% for placebo ($p = 0.057$). mOS was not reached with abemaciclib vs 25.45m with placebo (HR 0.55; 95% CI, 0.28–1.07; $p = 0.077$). mPFS after crossover from placebo to abemaciclib was 3.44m (95% CI 2.66, 6.84). ORR after crossover was 4.3% (95% CI 0.53%, 15%). mOS after crossover was 24.03m (95% CI: 11.7, NA). Grade 3 or higher adverse event rates were similar in both arms ($p > 0.99$). No new safety signals were observed. **Conclusions:** Abemaciclib demonstrated a statistically significant improvement in PFS vs placebo in pts with dedifferentiated liposarcoma, with an encouraging OS trend. These results support abemaciclib as a new treatment option for dedifferentiated liposarcoma. Clinical trial information: NCT04967521. Research Sponsor: Eli-Lilly.

LBA3 **Plenary Session**

Event-free survival with adjuvant selpercatinib in stage IB-IIIA *RET* fusion-positive NSCLC: Primary results of the phase 3 LIBRETTO-432 trial.

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Background: Selpercatinib, a highly selective, potent and brain-penetrant *RET* inhibitor, is approved for *RET* fusion-positive (*RET+*) advanced/metastatic non-small cell lung cancer (NSCLC). RET-directed therapy has yet to be examined in patients (pts) with stage IB-IIIA *RET+* NSCLC, where recurrence rates after definitive therapy remain high, and no adjuvant targeted therapy is approved. Here, we report the efficacy and safety of selpercatinib vs placebo in this population. **Methods:** LIBRETTO-432 (NCT04819100) is a placebo-controlled, double-blind, phase 3 randomized (1:1) trial of selpercatinib 160mg BID vs placebo for up to 3 years in pts with stage IB-IIIA *RET+* NSCLC after definitive locoregional treatment. Primary endpoint was investigator-assessed event-free survival (EFS) in stage II-IIIA pts. Secondary endpoints were investigator-assessed EFS in all randomized pts (overall population, stage IB-IIIA), EFS by blinded independent central review (BICR), overall survival and safety. Crossover from placebo to selpercatinib was allowed upon disease recurrence. **Results:** In total, 151 pts were randomized (selpercatinib n=75; placebo n=76) and baseline characteristics were balanced across treatment arms. Median follow-up was 24 months for selpercatinib and 27 months for placebo. At the preplanned efficacy analysis, selpercatinib demonstrated significantly improved EFS in pts with stage II-IIIA disease (n=109), HR 0.172 (95% CI: 0.058, 0.509; p=0.0003). The median EFS was not reached for selpercatinib vs 31.8 months for placebo (4 vs 19 EFS events, respectively). EFS by BICR, HR=0.125 (95% CI: 0.028, 0.552; p=0.0011), was consistent with investigator-assessed EFS. The 2-year EFS rate was 91.5% for selpercatinib vs 61.1% for placebo. In the overall population (n=151), error-controlled EFS HR was 0.165 (95% CI: 0.056, 0.485; p=0.0002), and median EFS was not reached on either treatment arm. Adverse events (AEs) with selpercatinib were comparable to those reported in metastatic *RET* + NSCLC. The most common AEs were increased ALT/AST. Only 3 deaths were observed, all occurred in the placebo arm due to the study disease. No pts died during assigned study treatment. **Conclusions:** Selpercatinib achieved a statistically significant and clinically meaningful improvement in event-free survival compared to placebo in patients with early-stage *RET+* NSCLC. These data add to the body of evidence for targeted therapy, including EGFR and ALK inhibitors, in the adjuvant NSCLC setting and underscore the importance of comprehensive genomic testing at diagnosis of NSCLC across disease stages to inform optimal therapeutic decision-making. Clinical trial information: NCT04819100. Research Sponsor: Eli Lilly and Company.

LBA4 Plenary Session

Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy in previously untreated advanced squamous non–small cell lung cancer: Overall survival results of the phase 3 HARMONi-6 trial.

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Background: In the prespecified interim analysis of progression-free survival (PFS) from the HARMONi-6 study, ivonescimab combined with chemotherapy significantly improved PFS compared with tislelizumab plus chemotherapy in patients with previously untreated advanced squamous NSCLC(sq-NSCLC). Here we report the results of the prespecified overall survival (OS) analysis. **Methods:** Patients with previously untreated stage III-IV sq-NSCLC were randomly assigned (1:1) to receive ivonescimab 20 mg/kg every 3 weeks (Q3W) or tislelizumab 200 mg Q3W, each in combination with paclitaxel (175 mg/m^2) and carboplatin (AUC 5) for 4 cycles, followed by maintenance ivonescimab or tislelizumab monotherapy. Randomization was stratified by disease stage (IIIB/IIIC versus IV) and PD-L1 tumor proportion score (TPS; ≥1% versus <1%). The primary endpoint was PFS assessed by independent radiographic review committee per RECIST v1.1. OS was a key secondary endpoint and was hierarchically tested using a closed sequential testing procedure. PFS was tested first at one-sided α level of 0.025, OS was tested at the same α only after statistical significance for PFS was established. This analysis represents the first planned OS analysis with an efficacy boundary of one-sided P=0.0049. **Results:** A total of 532 patients were randomly assigned (n=266 per arm). As of February 27, 2026, at a median follow-up of 21.4 months, ivonescimab plus chemotherapy significantly improved OS compared with tislelizumab plus chemotherapy. Median OS was 27.9 months (95% CI, 27.89 to NE) with ivonescimab plus chemotherapy versus 23.7 months (95% CI, 20.11 to NE) with tislelizumab plus chemotherapy (hazard ratio [HR], 0.66; 95% CI, 0.50 to 0.87; one-sided P =0.0017), meeting the prespecified boundary (P<0.0049) for statistical significance.The OS benefit was consistent across prespecified subgroups. Among patients with PD-L1 TPS <1%, median OS was NE versus 18.6 months (HR, 0.64; 95% CI, 0.43 to 0.96). Among patients with PD-L1 TPS≥1%, median OS was NE versus 27.3 months (HR, 0.68; 95% CI, 0.46 to 0.99). The safety profile of ivonescimab plus chemotherapy was manageable and consistent with prior reports, with no new safety signals observed. **Conclusion:** Ivonescimab plus chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS compared with tislelizumab plus chemotherapy in previously untreated patients with advanced sq-NSCLC. Notably, ivonescimab plus chemotherapy is the first regimen to show clinical superiority over an active PD-1 inhibitor control arm in the first-line setting. The dual-targeted approach of ivonescimab delivers improved survival outcomes with a favorable risk-benefit profile, establishing a compelling new standard of care in the management of advanced sq-NSCLC. Clinical trial information: NCT05840016. Research Sponsor: Akeso Biopharma, Inc., Zhongshan, China.

LBA5 **Plenary Session**

Daraxonrasib, a RAS(ON) multi-selective inhibitor vs chemotherapy in previously treated metastatic pancreatic adenocarcinoma (mPDAC): Primary and final analysis from the phase 3 RASolute 302 study.

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Background: Available 2L therapies offer limited clinical benefit in mPDAC with reported mPFS of 3–4 mo and mOS of 6–7 mo. Aberrant RAS pathway activation is the key driver of PDAC, with oncogenic RAS mutations (mut) identified in >90% of cases, most commonly at codon G12. Daraxonrasib is an oral, RAS(ON) multi-selective, tri-complex inhibitor of the active, GTP-bound state of mutant and wild type RAS. **Methods:** RASolute 302 (NCT06625320) is a global, randomized, open-label, Ph 3 study in pts with 2L mPDAC and ECOG PS 0-1. Pts were randomized 1:1 to receive daraxonrasib 300 mg PO QD or investigator's choice of SOC cytotoxic chemo. Dual primary endpoints were OS and PFS by BICR in the RAS G12 mutant (RAS G12) population. Key secondary endpoints included OS and PFS by BICR in the overall population, ORR by BICR in RAS G12 and overall populations. **Results:** 248 pts were randomized to daraxonrasib and 252 to chemo. Baseline characteristics were balanced between arms. At data cutoff (Feb 10, 2026; mFU: 8.5 mo), all primary and key secondary endpoints were met. Statistically significant, clinically meaningful improvements in OS and PFS were observed with daraxonrasib vs chemo in the RAS G12 and overall populations (Table). Gr ≥3 TRAEs occurred in 43.6% of pts receiving daraxonrasib vs 57.5% receiving chemo. The most common (≥10%) Gr ≥3 TRAEs were rash (13.7%) and stomatitis (12.0%) for daraxonrasib; neutrophil decrease (18.2%) and anemia (16.4%) for chemo. TRSAEs occurred in 10.8% of pts receiving daraxonrasib vs 18.7% receiving chemo. Discontinuation due to TRAEs occurred in 1.2% of pts for daraxonrasib vs 11.2% for chemo. Median/mean daraxonrasib dose intensity was 93.1%/84.7%. **Conclusions:** Daraxonrasib demonstrated unprecedented improvements in OS and PFS vs chemo in pts with 2L mPDAC with or without an identified tumor RAS mut. Daraxonrasib was generally well tolerated, with a manageable safety profile and with no new safety signals. Results support daraxonrasib as the new SOC for 2L mPDAC. Clinical trial information: NCT06625320. Research Sponsor: The study was sponsored by Revolution Medicines. Medical writing support was provided by Marcia Gamboa, PhD, of Nucleus Global, an Inizio Company, and was funded by Revolution Medicines.

		RAS G12		Overall[b]	
		Daraxonrasib n=228	Chemo n=231	Daraxonrasib n=248	Chemo n=252
OS	Median; mos	13.2	6.6	13.2	6.7
	(95% CI)	(10.0–NE)	(5.4–8.2)	(10.0–NE)	(5.8–8.0)
	HR	0.40		0.40	
	(95% CI)	(0.30-0.54)		(0.30-0.53)	
	P-value	<0.0001		<0.0001	
PFS[a]	Median; mos	7.3	3.5	7.2	3.6
	(95% CI)	(6.3–8.1)	(2.9–3.8)	(5.7–7.5)	(2.9–4.2)
	HR	0.45		0.49	
	(95% CI)	(0.34-0.59)		(0.38-0.64)	
	P-value	<0.0001		<0.0001	
ORR[a]	%	33.2	11.8	31.6	11.2
	(95% CI)	(27.0–39.9)	(7.8–16.8)	(25.8–38.0)	(7.5–15.9)

[a]By BICR.
[b]RAS G12, G13 or Q61 mut or no RAS mut identified.

LBA100 **Clinical Science Symposium**

NHS-Galleri: Primary results from a randomised controlled trial to assess the clinical utility of a multi-cancer early detection (MCED) test in population screening.

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Background: MCED blood tests can detect a shared cancer signal from circulating cell-free DNA. NHS-Galleri (NCT05611632) is a randomised controlled trial in England of 142,924 enrolled participants evaluating the clinical utility of an MCED test (Galleri) for annual screening of asymptomatic individuals aged 50–79 yrs. **Methods:** Peripheral blood samples were taken at up to 3 annual visits (Y0, Y1, Y2). After the Y0 blood draw, participants were randomised 1:1 to the intervention (I; blood tested by MCED test) or control (C; blood not tested) arms. I arm participants with a cancer signal detected MCED test result were referred into the NHS for diagnostic workup via appropriate urgent suspected cancer pathways. As agreed with NHS England, clinical utility was assessed by reduction in late stage (Stage III/IV [primary objective] and Stage IV [key secondary objective]) cancer incidence in I vs C arm ~3 yrs after the last participant's randomisation. **Results:** Trial arms were well balanced. The primary endpoint of statistically significant Stage III/IV reduction in 12 prespecified cancers was not met (706 vs 688; incidence rate ratio [IRR] 1.03; Table). In these 12 cancers, Stage III/IV decreased from the prevalence screening round (IRR 1.19) to incidence rounds (0.95; 0.88). A 14% reduction in Stage IV cancers (342 vs 397) was observed after 3 yrs of screening (Y0: 9%; Y1: 22%; Y2: 26%). Stage I/II cancers increased by 16% (647 vs 559; relative risk [RR] 1.16 [1.03, 1.30]) after 3 yrs of screening. Similarly, Stage I-III cancers increased by 19% (1007 vs 846; RR 1.19 [1.09, 1.30]). Across all cancer types, 3637 and 3400 were diagnosed in I and C arms, respectively, over 3 yrs of screening. MCED quadrupled the number of screen-detected cancers (1173 vs 290). MCED reduced clinically-detected cancers by 21% (2464 vs 3110) and emergency presentations by 21% (225 vs 286). Aggregate test performance (99.55% specificity, 52.0% positive predictive value, 92.5% top-two and 87.0% top-one cancer signal origin accuracy) was consistent with prior studies and real-world evidence. There were 381 and 333 related adverse events (AEs) in I and C arms, respectively, and no related serious AEs. **Conclusions:** Although the primary endpoint was not met, adding annual MCED testing to standard-of-care cancer screening substantially increased screen-detected cancers and reduced Stage IV cancers and emergency presentations. This evidence combined with the favourable safety profile and robust performance suggests that integrating MCED into population screening programs may help reduce late stage cancer burden. Clinical trial information: NCT05611632. Research Sponsor: GRAIL, Inc.

Late-stage IRR (I/C) of 12 prespecified cancers.

	Stage III/IV	Stage IV
Y0	1.19 (95% CI: 0.98, 1.43)	0.91 (0.71, 1.18)
Y1	0.95 (0.77, 1.17)	0.78 (0.57, 1.06)
Y2	0.88 (0.73, 1.07)	0.74 (0.57, 0.95)
Overall	1.03 (0.92, 1.14) p=0.6324	0.86 (0.744, 0.998)

LBA101 **Clinical Science Symposium**

Osimertinib with/without chemotherapy in patients with persistent ctDNA EGFR mutant (EGFRm) NSCLC at 3 weeks after 1L osimertinib: A randomized phase II study (FLAME study).

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Background: Persistent plasma ctDNA EGFR mutations (EGFRm) at 3 weeks after first-line osimertinib predict poor outcomes in advanced EGFR-mutated NSCLC. Though osimertinib plus chemotherapy outperformed osimertinib alone in the FLAURA2 trial, it remains unclear whether patients(pts) with persistent ctDNA EGFR mutations can benefit from this combination therapy. This study aims to evaluate the efficacy and safety of osimertinib plus chemotherapy versus osimertinib monotherapy in locally advanced or metastatic EGFRm NSCLC pts with persistence plasma ctDNA EGFRm at 3weeks of 1L osimertinib monotherapy. **Methods:** FLAME study is a multicenter, randomized controlled, phase II study in advanced NSCLC with EGFR Ex19del/L858R mutation who retain detectable plasma ctDNA EGFRm after 3 weeks of osimertinib. Plasma ctDNA EGFRm were analyzed by Super ARMS-PCR. Pts were randomized 1:1 to osimertinib plus carboplatin-pemetrexed or osimertinib monotherapy until progression or discontinuation criterion. The clinical data of screen failures patients were collected as part of real-world study. Randomization was stratified by CNS metastases (yes/no) and EGFRm subtype. The primary endpoint is investigator-assessed PFS per RECIST 1.1. Secondary endpoints include OS rate at 18 months, ORR, DCR, DoR, depth of response, safety and resistance profile. Exploratory endpoints: dynamic multi-omics biomarkers and quality of life. Data cutoff: 26 Jan 2026. **Results:** Of 448 screened pts with EGFRm, 134 had persistent plasma ctDNA EGFRm after 3 weeks of osimertinib. 80 pts were randomized to osimertinib plus chemotherapy (n=40) or continued osimertinib monotherapy (n=40). Baseline characteristics were generally balanced across arms (osimertinib plus chemotherapy/osimertinib): median age, 58/61 years; 60/55% female; 53/50% Ex19del; 48/50% L858R; 35/35% CNS metastases. Osimertinib plus chemotherapy significantly improved PFS versus osimertinib monotherapy (HR 0.53; 95% CI 0.31, 0.92; p=0.024; 67.5% maturity). Median PFS was 23.1 vs.12.7 months. ORR per investigator assessment was 50% vs. 35%, and median DoR was 15.6 months and 10.5 months, respectively. Grade≥3 treatment related adverse events (TRAEs) were higher in the combination group (65% vs. 10%) but manageable; no new safety signals were identified. **Conclusions:** This is the first perspective randomized controlled trial showing osimertinib plus chemotherapy significantly prolongs PFS versus osimertinib in pts who exhibit persistent ctDNA EGFR mutation at 3 weeks after 1L osimertinib monotherapy. This study provides prospective evidence for individualized escalation combination therapy based on dynamic molecular detection. Funded by AstraZeneca; ClinicalTrials.gov number, NCT04769388. Clinical trial information: NCT04769388. Research Sponsor: AstraZeneca.

LBA503 Oral Abstract Session

Omission of completion axillary dissection in patients with breast cancer and sentinel lymph node macrometastases: Overall survival and patient-reported arm morbidity from the randomized SENOMAC trial.

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Background: Axillary lymph node dissection (ALND) causes arm-related morbidity. The SENOMAC trial evaluates whether the omission of completion ALND in patients with 1-2 sentinel lymph node (SLN) macrometastases is oncologically safe. It differs from previous trials in size and the inclusion of larger tumors and patients receiving mastectomy. **Methods:** SENOMAC (NCT02240472) is an international non-inferiority trial. Adult patients with primary invasive, clinically node-negative T1-3 breast cancer and up to two SLN macrometastases were randomized 1:1 to completion ALND (standard) or its omission (intervention). Adjuvant treatment followed standards of care. The primary endpoint was overall survival (OS), requiring 190 deaths to conclude non-inferiority (upper one-sided 90% CI for the hazard ratio < 1.44) with ALND as the reference group. The secondary endpoint breast cancer-specific survival (BCSS) required 66 breast cancer deaths. Patient-reported outcomes were recorded 1, 3, and 5 years after randomization by the questionnaires Lymph-ICF (arm morbidity), EORTC QLQ-C30 and BR23 (health-related quality of life). **Results:** From 1/2015 to 12/2021, 2766 patients were randomized in 5 countries. The per-protocol population comprised 2540 patients (1205 randomized to ALND and 1335 to its omission). The median follow-up was 60.1 months (1.5-122.7 months). Questionnaire response rates were 81.3% and 74.6% at 3 and 5 years, respectively. Overall, 196 patients died, 75 of whom due to breast cancer. Five-year OS was 93.4% (95% CI 91.9%-94.9%) in the ALND and 94.4% (95% CI 93.1%-95.7%) in the omission group, with a country-adjusted hazard ratio of 0.84 (95% CI 0.64-1.12). Five-year BCSS was 97.3% (95% CI 96.4%-98.3%) in the ALND and 97.8% (95% CI 97.0%-98.6%) in the omission group, with a country-adjusted hazard ratio of 0.86 (95% CI 0.55-1.34). Both endpoints fell significantly ($p = 0.238$ for OS and $p = 0.504$ for BCSS) below the pre-specified non-inferiority margin. Arm physical function according to the Lymph-ICF questionnaire was significantly better in the omission than the ALND group with a clinically relevant mean score difference of 6.14 at 3 years (95% CI 5.00-7.43, $p < 0.001$) and 5.71 at 5 years (95% CI 4.46-7.25, $p < 0.001$). Similarly, arm symptoms according to EORTC QLQ-BR23 were significantly more pronounced in the ALND than the omission group both after 3 (mean score 20.80+/-21.24 versus mean score 10.83+/-15.48, $p < 0.001$) and after 5 years (mean score 19.40+/-21.07 versus mean score 9.31+/-15.58, $p < 0.001$). Global health-related quality of life did not show any statistically significant differences after 3 and 5 years. **Conclusions:** Omission of completion ALND after a positive SLN biopsy is oncologically safe and mitigates postoperative patient-reported arm morbidity. Clinical trial information: NCT02240472. Research Sponsor: Swedish Cancer Society; Swedish Scientific Council; Nordic Cancer Union; Swedish Breast Cancer Association.

LBA510 **Rapid Oral Abstract Session**

Primary results of the BETTER-CARE trial: Implementation of a needs-adapted and individualized follow-up care after primary breast cancer.

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Background: Follow-up care after primary breast cancer is a central component of oncological care and is gaining importance in light of increasing survival rates. In addition, an increasing variety of adjuvant treatment concepts with differing toxicities exists and individual physical, psychological, and social consequences of the disease and its treatment are receiving greater attention. However, internationally standardized follow-up care only partially meets these heterogeneous and dynamic needs. The aim of this study was to evaluate a needs-adapted follow-up care concept within the framework of a cluster intervention study. **Methods:** BETTER-CARE is a parallel-arm controlled trial with 30 clusters (certified Breast Cancer Centers) across Germany randomized 1:1, that was funded by the Federal Joint Committee (G-BA, grant 01NVF20015). Breast cancer patients of all genders aged 18 years or older no later than 10 weeks after completion of curative primary treatment with informed consent were included. The needs- and risk-adapted complex intervention comprised a multidisciplinary care network, digital platforms and just-in-time adaptive interventions. The control group received usual care defined by clinical guidelines. The primary endpoint was health-related quality of life (HRQoL, EORTC QLQ-C30 global health) at 12-month. Secondary endpoints included treatment adherence, late effects and psychiatric comorbidities, among others. To detect an effect with a power of 90% and a significance level of 5%, a sample size of 570 patients per arm was planned. Linear univariable and multivariable mixed-effects models were applied adjusting for respective baseline values, age, molecular subtype, BRCA detection and Charlson-Comorbidity-Index. **Results:** Between 2023 and 2025, 30 clusters were randomly assigned to the intervention (n=15) or control group (n=15), no cluster dropped out. 338 of 410 patients in the intervention and 445 of 523 in the control group were included in the modified ITT analysis (data on primary endpoint available). At follow-up there was no significant difference in HRQoL (adjusted Odds Ratio (aOR): 1.61 (95%-CI: -1.4-4.62)). The intervention group showed significantly lower proportions of fatigue (18.3% vs 24.4%, aOR: 0.57 (95%-CI: 0.37-0.86)), depression (11.3% vs 19.3%, aOR 0.46 (95%-CI: 0.28-0.75)), cognitive impairment (35.5% vs 47.5%, aOR: 0.52 (95%-CI: 0.38-0.71)), neurotoxicity (40.8% vs 50.3%, aOR: 0.68 (95%-CI: 0.5-0.93)) and restrictions in daily activities (42.3% vs 50.1%, aOR: 0.65 (95%-CI: 0.48-0.88)). No differences were identified for the remaining secondary endpoints. **Conclusion:** No differences were identified between the intervention and control group regarding the primary endpoint HRQoL. Positive effects regarding psychiatric comorbidities, late side effects and activities in daily living were found in the intervention group. Implementing this complex intervention can be particularly useful for improving neuropsychiatric outcomes. Clinical trial information: DRKS00028840. Research Sponsor: Federal Joint Committee (G-BA); 01NVF20015.

LBA514 Rapid Oral Abstract Session

Neoadjuvant rilvegostomig (R) + trastuzumab deruxtecan (T-DXd) in high-risk HER2-negative breast cancer: Results from the I-SPY 2.2 trial.

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Background: Preclinical and clinical data show that antibody-drug conjugates (ADCs) such as T-DXd may synergize with immunotherapy. Rilvegostomig (R) is a monovalent, Fc-reduced, dual checkpoint bispecific IgG1 monoclonal antibody against PD-1 and TIGIT receptors. R + T-DXd was evaluated as neoadjuvant therapy for up to 4 cycles. **Methods:** I-SPY2.2 is a phase II neoadjuvant trial with three neoadjuvant sequences (Blocks A/B/C). All HER2-negative subtypes were eligible for R + T-DXd in Block A. Predicted responders at the end of Block A or B could undergo surgery; otherwise, they continued to Block B +/- C. Block B pts received paclitaxel +/- carboplatin +/- pembrolizumab and Block C pts doxorubicin + cyclophosphamide (AC) +/- pembrolizumab, HR+ immune+ received IO in Blocks B/C. Results are analyzed by receptor and response predictive subtypes (RPS), that include expression-based immune, and luminal signatures with hormone receptor (HR) and HER2 status. Some pts were randomized to a control regimen (skipping R + T-DXd in block A and starting in block B). To minimize risk of interstitial lung disease (ILD) that could lead to treatment discontinuation, pts underwent pulmonary function tests and high-resolution chest CTs every 6 weeks. Abnormalities were reviewed in real time. The primary endpoint was pathologic complete response (pCR), within each RPS and HR/HER2 signature, with estimated pCR (EpCR) rates compared to subtype-specific block A goal rates and control pts in those groups. Other endpoints included safety and treatment discontinuation. **Results:** 105 pts were treated with R + T-DXd in block A, while 31 pts were randomized to the control regimen. Block A EpCR rate was 57% in the 12 HR+Immune+ pts vs a pre-specified goal of 15% (posterior probability, PP $>$ .99). In 35 HR-Immune+ pts EpCR was 52% vs a pre-specified goal of 40% (PP = .87). No other groups (Immune-) had a PP $>$ .85 for their respective pCR goal rate. HER2-IHC was 0 (27.6%), 1+ (49.5%) and 2+ (22.9%) in the treatment arm vs. 37.7%, 37.7%, and 24.7% in the control arm, with no difference in distribution between arms in immune subtypes. The most common adverse events in Block A were fatigue (84.8%), nausea (81.0%) and alopecia (58.1%). ILD was the most common adverse event of special interest in Block A and overall, occurring in 12 pts (11.4%; 7G1, 4G2, 1G3) during Block A and in 3 pts (G1, 2.9%) in other Blocks. 8 pts discontinued T-DXd + R due to ILD and proceeded to the next Block. **Conclusions:** When considering the full treatment strategy including block B and C regimens, experimental strategies had similar EpCR rates vs. controls in immune+ subtypes but block A rates exceeded pre-defined goal thresholds. This infers that treatment beginning with R + T-DXd has equivalent efficacy to standard of care for immune+ pts, but 64% pts with pCR skip chemotherapy (Block B) and 97% avoid AC (Block C). R + T-DXd participants avoided persistent ILD. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; P01CA210961; Quantum Leap Healthcare Collaborative; Safeway Foundation; William K. Bowes Jr. Foundation; Breast Cancer Research Foundation.

LBA515 Rapid Oral Abstract Session

Role of neoadjuvant versus adjuvant chemotherapy, dose density, and treatment schedule in biologically high-risk HR+/HER2- breast cancer: A pooled analysis of the WSG ADAPT-HR+/HER2- and PlanB trials.

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Background: Dose-dense anthracycline-taxane chemotherapy (CTx) is standard for high-risk early breast cancer (eBC) and is often given in the neoadjuvant setting if CTx is clearly indicated (e.g., recurrence score, RS > 25 and/or > 4 positive lymph nodes by imaging) or if downstaging is needed. While dose-dense CTx improves outcomes irrespective of hormone receptor (HR) status in meta-analyses, its benefit in node-negative HR+ eBC appears limited. Further meta-analyses on neoadjuvant vs adjuvant use, and on mono- vs combined therapy, showed mixed results. These findings highlight an unmet need for a refined treatment selection, informed by the assessment of relative survival benefit. We therefore pooled the WSG ADAPT-HR+/HER2- and PlanB trials to estimate the impact of dose density, anthracycline use, and treatment setting on survival. **Methods:** Invasive (iDFS), distant disease-free survival (dDFS), and overall survival (OS) were analyzed retrospectively in a pooled analysis of HR+/HER2- patients (pts) in ADAPT-HR+/HER2- (n = 2331) and PlanB (n = 2220) who received chemotherapy and had follow-up data (data cut: Jan 26, 2026). In ADAPT-HR+/HER2-, pts at high-risk received 8× weekly nab-paclitaxel vs. 4× biweekly sb-paclitaxel, followed by epirubicin + cyclophosphamide (EC) in either the neoadjuvant or adjuvant setting. PlanB randomized pts at intermediate- to high-risk to adjuvant 4× EC followed by 4× docetaxel (EC-T) vs. 6× TC. To minimize bias, predefined uniform cross-trial subgroups (RS > 25 any pN; pN2–3 any RS) were considered here, and propensity scoring for non-random allocations (neoadjuvant vs adjuvant CTx in ADAPT-HR+/HER2-, physician choice). **Results:** This pooled analysis included 1467 pts with RS > 25 and 551 with clinically (neoadjuvant cohort in ADAPT-HR+/HER2-) or pathologically N2-3 eBC. Dose-dense anthracycline or paclitaxel yielded inferior iDFS and dDFS than q3w docetaxel, even after adjustment for cT, age, and grade. This effect, favoring a (longer) docetaxel-based CTx, was present among N2-3 pts with RS ≤25, who showed better iDFS, dDFS, and OS, and among RS > 25 pts (in particular, in N0-1), who showed better dDFS. Informed by these results, we assessed the impact of anthracyclines in PlanB pts with RS > 25 and/or N2-3 and observed no significant survival differences. There was no significant survival difference between neoadjuvant vs adjuvant CTx in the corresponding subset of ADAPT-HR+/HER2- pts, even in propensity-scored analysis. **Conclusions:** Our exploratory retrospective analysis does not show a significant survival difference by anthracycline use or treatment setting (neoadjuvant vs adjuvant) in high-risk HR+/HER2- eBC pts who are candidates for CTx. Optimal use of dose-dense CTx in the context of docetaxel-based treatment requires further investigation. Clinical trial information: NCT01779206; NCT01049425. Research Sponsor: Exact Sciences; Celgene; Amgen; AOK Rheinland/Hamburg; Genomic Health Inc; Sanofi Aventis.

LBA538 **Poster Session**

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

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Background: This phase III trial is a prospective, randomized, double-blinded, multi-center study (NCT05232916) in HLA-A*02 patients at approximately 140 sites in the US and Europe. A third non-randomized arm of approximately 250 non-HLA-A*02 patients is now fully enrolled and preliminary immune response data is presented below. GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. **Methods:** After standard of care neoadjuvant and adjuvant therapy, 6 intradermal injections of GLSI-100 will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up. Immune responses to GP2 were measured over time using delayed-type-hypersensitivity (DTH) skin tests and injection site reactions (ISRs). The patient population is defined by these key eligibility criteria: 1) HER2/neu positive and HLA, 2) Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy, 3) Exclude Stage IV, and 4) Completed at least 90% of planned adjuvant trastuzumab-based therapy. **Results:** All patients (n=247) were vaccinated with GLSI-100. Injection site reactions and erythema (redness) were assessed at various time points and represent an in vivo immune response in patients. The ISR orthogonal mean was measured 48-72 hours following vaccination with GLSI-100. For GP2 treated patients, there was a significant increase in the percentage of patients experiencing ISRs in the 4th, 5th or 6th vaccination compared to the ISRs from the 1st vaccination. In this preliminary analysis, the frequency of ISRs increased significantly from 20.2% of the patients experiencing an ISR after the first vaccination to 55.3% of the patients experiencing an ISR after the 4th, 5th or 6th vaccination (McNemar $p < 0.001$). The study is ongoing and data collection and cleaning continue, so final results may vary. **Conclusions:** Preliminary injection site reaction data comparing vaccination over time in GLSI-100 treated non-HLA-A*02 patients showed a significant increase in immune response. Future studies may explore the use of immune responses to assess correlation of DTH to ISRs, immunogenicity of GLSI-100 by specific HLA type, timing of boosters to sustain immunity, clinical site performance, and the discontinuation of treatment for non-responders. Funding: This trial is supported by Greenwich LifeSciences. Clinical trial information: NCT05232916. Research Sponsor: Greenwich LifeSciences.

LBA660 Oral Abstract Session

Anbenitamab plus albumin-bound docetaxel (nab-docetaxel) ± carboplatin (Cb) versus trastuzumab and pertuzumab plus docetaxel (THP) ± Cb as neoadjuvant therapy for HER2-positive early or locally advanced breast cancer: A randomized, open-label, multicenter, phase 3 trial.

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Background: THP ± Cb represent the standard neoadjuvant treatment for HER2-positive breast cancer. Despite achieving total pathological complete response (tpCR) rates between 39.3% and 56.0%, there remains a clinical need to further improve outcomes, as tpCR is strongly correlated with long-term survival. Anbenitamab (KN026) is a novel biparatopic antibody targeting HER2 domains II and IV. This phase 3 study (NCT06747338) compared the efficacy and safety of an Anbenitamab-based regimen to the standard-of-care THP± Cb regimen in the neoadjuvant setting. **Methods:** Patients with HER2-positive early or locally advanced breast cancer were randomized 1:1 to receive 6 cycles of either Anbenitamab plus nab-docetaxel ± Cb [Anbenitamab arm] or trastuzumab, pertuzumab, and docetaxel ± Cb [THP ± Cb arm]. Randomization was stratified by clinical stage, hormone receptor status, and planned carboplatin use. The primary endpoint was tpCR (ypT0/is, ypN0) as assessed by a Blinded Independent Review Committee (BIRC). **Results:** A total of 521 patients were randomized. The study met its primary endpoint, with a significantly higher tpCR rate in Anbenitamab arm compared to THP ± Cb arm (62.4% [95% CI: 56.2–68.2] vs. 51.2% [95% CI: 44.9–57.4]). The stratified difference in tpCR was 11.4% (95% CI: 3.2–19.6); one-sided P = 0.0036). Consistent results were observed for investigator assessed tpCR (63.9% [95% CI: 57.8–69.7] vs. 51.2% [95% CI: 44.9–57.4], one-sided P = 0.0011). Similar improvements in BIRC-tpCR were observed across all prespecified subgroups, including those defined by hormone receptor status, clinical stage, and planned carboplatin use. BIRC-assessed breast pCR was also significantly higher in Anbenitamab arm (64.6% vs 55.0%, one-sided P = 0.0099). The overall incidence of treatment emergent adverse events (TEAEs) was 98.5% in Anbenitamab arm versus 98.8% in THP ± Cb arm. Grade ≥3 TEAE rates were similar (29.3% vs 28.3%). Most common Grade ≥3 TEAEs were neutropenia (11.4 % vs 10.9%) and leukopenia (7.6% vs 8.5%). TEAEs leading to interruption of any study drug occurred in 5.7% vs 7.4% of patients. Permanent discontinuations due to TEAEs occurred in 4.9% vs 3.5% of patients. Safety profiles were primarily hematologic and gastrointestinal toxicities， consistent with known safety profiles of respective single agents, and no new safety signal was observed. **Conclusions:** Anbenitamab plus nab-docetaxel ± Cb significantly improved tpCR rate compared with standard of care as neoadjuvant therapy in patients with early or locally advanced HER2-positive breast cancer, with a manageable safety profile. These results support Anbenitamab-based regimen as a potential new standard of care. Clinical trial information: NCT06747338. Research Sponsor: Shanghai JMT-BIO Technology Co., Ltd.

LBA1000 Oral Abstract Session

Progression-free survival after next line of treatment (PFS2) and subsequent therapies (subs tx) in the ASCENT-04 study of participants (pts) with previously untreated PD-L1+ metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG) plus pembrolizumab (pembro) vs chemotherapy (chemo) plus pembro.

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Background: In ASCENT-04, first-line (1L) SG + pembro led to a statistically significant and clinically meaningful improvement in PFS vs chemo + pembro (median, 11.2 vs 7.8 mo; hazard ratio [HR], 0.65; 95% CI, 0.51-0.84; $P < .001$) in pts with previously untreated PD-L1+ mTNBC. Overall survival (OS) data are immature. PFS2 is more strongly associated with OS than PFS and can be used to measure long-term clinical benefit in the absence of mature OS data or when OS may be impacted by crossover. We report PFS2 and subs tx from ASCENT-04. **Methods:** Pts (N = 443) were randomized 1:1 to SG (10 mg/kg IV, days 1 & 8) + pembro (200 mg, day 1, max 35 cycles) in 21-day cycles or chemo (gemcitabine + carboplatin, paclitaxel, or nab-paclitaxel) + pembro; the primary end point was PFS by blinded independent central review (BICR). Eligible pts in the chemo + pembro group could receive 2L SG provided on study via crossover following BICR-verified progressive disease (PD) or in any subs line commercially; other subs txs per local practice were also permitted. PFS2 was defined as the time from randomization to first documented PD on next-line therapy per investigator assessment or death due to any cause, whichever occurred first. **Results:** Median follow-up for OS was 14.0 mo; 95 (43%) pts remained on study tx in the SG + pembro group (n = 221) and 52 (23%) in the chemo + pembro group (n = 222). Of the 125 pts in the SG + pembro group who discontinued tx, 69 received any subs tx, the most frequent of which were taxanes (42%), platinum chemo (33%), and capecitabine (33%). Of the 170 pts in the chemo + pembro group who discontinued tx, 119 received any subs tx, the most frequent of which were SG (81%), taxanes (9%), and capecitabine (9%). Median PFS2 and PFS2 rates are in the Table. Median (95% CI) time to first subs tx was 17.3 mo (12.7-not reached [NR]) for SG + pembro and 9.8 mo (8.7-10.9) for chemo + pembro; median (95% CI) time to second subs tx was NR (22.9 mo-NR) and 21.0 mo (16.6-NR). **Conclusions:** PFS2 was improved in the SG + pembro group vs chemo + pembro group despite crossover tx, with most pts who initiated subs tx in the chemo + pembro group receiving SG. In pts with previously untreated PD-L1+ mTNBC, SG + pembro provided clinically relevant continued benefit beyond first progression, further supporting SG + pembro as a potential new standard of care. Clinical trial information: NCT05382286. Research Sponsor: Gilead Sciences, Inc.

	SG + pembro	Chemo + pembro
Pts with PFS2 events, n/N (%)	55/221 (25)	83/222 (37)
Median PFS2 (95% CI), mo	NR (NR-NR)	21.0 (16.0-NR)
Stratified HR[a] (95% CI)	0.67 (0.48-0.95)	
Stratified log-rank nominal *P*-value[a]	.0224	
PFS2 rate (95% CI), %		
12 mo	80.0 (73.8-84.9)	75.7 (69.1-81.1)
18 mo	71.9 (64.5-78.0)	53.0 (44.5-60.8)
24 mo	63.7 (51.1-73.9)	45.6 (35.6-55.1)

[a]SG + pembro vs chemo + pembro.

LBA1003 Oral Abstract Session

Izalontamab brengitecan (iza-bren) versus physician's choice of chemotherapy in patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC): A randomized phase III study.

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Background: Triple-negative breast cancer (TNBC) remains a therapeutic challenge due to its aggressive biology and limited treatment options beyond first-line immunotherapy plus chemotherapy. Patients who progress after taxane-containing regimens face poor outcomes and have a high unmet need. Izalontamab brengitecan (iza-bren) is a first-in-class bispecific antibody–drug conjugate (ADC) targeting EGFRxHER3 with a potent topoisomerase I inhibitor payload. Here we report the results of a pre-planned interim analysis from a phase III study of iza-bren in patients with TNBC. **Methods:** This randomized, multicenter, open-label, phase III study enrolled patients with unresectable locally advanced or metastatic TNBC who had disease progression after 1–2 prior lines of systemic therapy for advanced disease—including prior taxanes. Patients were randomized 1:1 to receive iza-bren (2.5 mg/kg D1D8 Q3W) or treatment of physician's choice (TPC) (eribulin, capecitabine, gemcitabine, or vinorelbine). Randomization was stratified by prior lines of therapy (1 vs. 2), prior anti-PD-(L)1 (yes vs. no), and HER2 IHC (0 vs. 1+/2+ ISH-). The dual-primary endpoints were progression-free survival (PFS) by blinded independent central review (BICR) and overall survival (OS). **Results:** A total of 418 patients were randomized (iza-bren/TPC: 207/211) and 412 were treated (iza-bren/TPC: 207/205). As of the data cutoff (Jan 13, 2026), median follow-up was 11.0 months. The median PFS by BICR was 8.5 months with iza-bren and 3.1 months with TPC (HR, 0.29 [95% CI, 0.22-0.38]; stratified log-rank $P<0.0001$). The median OS was 15.9 months with iza-bren and 12.5 months with TPC (HR, 0.60 [95% CI, 0.42-0.85]; stratified log-rank P=0.0019). The confirmed objective response rate (cORR) assessed by BICR was 51.7% with iza-bren and 20.5% with TPC (odds ratio, 4.28 [95% CI, 2.75-6.66]). Most common grade ≥3 TEAEs (iza-bren vs TPC) were neutrophil count decreased (58.0% vs 46.8%), white blood cell count decreased (56.0% vs 33.2%), platelet count decreased (52.7% vs 2.4%), and anemia (46.9% vs 3.9%). All-grade ILD was reported in 3 (1.4%) and 0 patients in the iza-bren and TPC arms, respectively. Treatment discontinuation due to TEAEs occurred in 4 (1.9%) patients in the iza-bren arm and 1 (0.5%) patient in the TPC arm. No new safety signals were observed. **Conclusions:** This pre-planned interim analysis met both dual-primary endpoints of PFS by BICR and OS. Iza-bren demonstrated a statistically significant and clinically meaningful improvement in both PFS and OS compared with chemotherapy, with a manageable safety profile in heavily pre-treated TNBC patients, supporting iza-bren as a new standard of care in this population. Clinical trial information: NCT06382142. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

LBA1006 Oral Abstract Session

Giredestrant (GIRE) + palbociclib (PALBO) vs letrozole (LET) + PALBO as first-line (1L) therapy in patients (pts) with estrogen receptor–positive, HER2-negative locally advanced or metastatic breast cancer (ER+, HER2– LA/mBC): Primary analysis of the phase III persevERA BC trial.

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Background: The combination of endocrine therapy (ET) with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is the current standard of care (SOC) for 1L treatment of pts with ER+, HER2– LA/mBC. GIRE, a next-generation oral selective full ER antagonist and degrader, has shown superior efficacy vs SOC ET in the adjuvant setting (lidERA BC; Bardia SABCS 2025) and in combination with everolimus vs SOC ET + everolimus in the post-CDK4/6i LA/mBC setting (evERA BC; Mayer ESMO 2025). Primary analysis results of persevERA BC (NCT04546009) are presented. **Methods:** Pts with *de novo* mBC or recurrent LA/mBC, measurable disease/evaluable bone disease, and no prior systemic LA/mBC therapy were randomized 1:1 to GIRE (30 mg daily [QD]) + LET placebo (QD) + PALBO (125 mg QD on Days 1–21) or LET (2.5 mg QD) + GIRE placebo (QD) + PALBO on each 28-day cycle (with a luteinizing hormone-releasing hormone agonist in pre-/peri-menopausal women, and men). The primary endpoint was investigator-assessed progression-free survival (INV-PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), and safety. **Results:** 992 pts were randomized (495 to GIRE; 497 to LET). Median age was 63.0 years; 80.1% were post-menopausal; 19.1% had *de novo* mBC; 69.3% had recurrent disease with treatment-free interval (TFI) >12 months (mo); 60.4% had visceral disease. At data cutoff (01/30/26), median follow-up was 52.2 mo and 623 INV-PFS events were observed. The hazard ratio (HR) for INV-PFS was 0.89 (95% confidence interval [CI] = 0.76, 1.05; p = 0.1553); median INV-PFS was 33.1 mo with GIRE + PALBO vs 28.2 mo with LET + PALBO (Δ 4.9 mo) (Table). The most common grade 3–4 adverse events (AEs) in the GIRE arm were hematologic abnormalities associated with PALBO. ET discontinuations due to AEs were similar (6.5% with GIRE vs 5.5% with LET). **Conclusion:** 1L GIRE + PALBO resulted in a numerical improvement in INV-PFS vs LET + PALBO in ER+, HER2– LA/mBC, though it did not meet pre-defined statistical significance. The safety profile was tolerable, consistent with individual agents, with no unexpected findings. The ongoing 1L pionERA BC study (NCT06065748) is exploring GIRE vs fulvestrant, in combination with physician's choice of CDK4/6i in pts who have relapsed on adjuvant ET or with <12 mo TFI. Clinical trial information: NCT04546009. Research Sponsor: F. Hoffmann-La Roche Ltd.

	GIRE + PALBO (n = 495)	LET + PALBO (n = 497)
Median PFS, mo (95% CI)	33.1 (30.2, 38.3)	28.2 (25.0, 33.1)
HR* (95% CI); p-value†	0.89 (0.76, 1.05); 0.1553	
Median OS, mo (95% CI)	NE (NE)	NE (61.3, NE)
HR* (95% CI); p-value†	1.03 (0.83, 1.28); 0.777	
ORR, %	60.2	58.8
Median DoR, mo (95% CI)	38.5 (30.4, 48.7)	30.4 (25.3, 36.1)
HR* (95% CI); p-value†	0.80 (0.63, 1.01); 0.056	
CBR, %	82.6	82.1

*Stratified.
†Stratified log-rank.
NE, not evaluable.

LBA1007 **Oral Abstract Session**

First-line (1L) camizestrant (CAMI) for emergent *ESR1* mutations (*ESR1*m) in advanced breast cancer (ABC): Final progression-free survival 2 (PFS2) from the phase III SERENA-6 trial.

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Background: CAMI is a next-generation SERD and complete ER antagonist. SERENA-6 enrolled patients (pts) with HR+/HER2− ABC receiving 1L aromatase inhibitor (AI) + CDK4/6i and without disease progression. Switching to CAMI, with continued CDK4/6i, at *ESR1*m emergence during 1L AI + CDK4/6i significantly improved PFS (HR: 0.44 [95% CI: 0.31–0.60]; p<0.0001; median follow-up: 12.6 mo). Here, we report the final PFS2 results. **Methods:** SERENA-6 was powered for PFS (primary endpoint) and the key secondary endpoint of investigator-assessed PFS2 (time from randomization to the earliest of disease progression after first subsequent therapy or death). Pts had scans to assess PFS2 every 8–12 weeks after first progression. PFS2 analysis was planned after ~158 PFS2 events (77% power to detect HR of 0.65) and analyzed using an adjusted log-rank test and a 2-sided significance level of ~5%. Chemotherapy/ADC-free survival was a secondary endpoint. **Results:** 157 pts were randomized to CAMI + CDK4/6i and 158 pts to AI + CDK4/6i. After 23.5 mo median follow-up (data cutoff: Jan 3, 2026), median PFS2 was 25.7 mo with CAMI + CDK4/6i vs 19.1 mo with AI + CDK4/6i; statistically significant improvement, HR: 0.63 (95% CI: 0.46–0.86); p=0.00373 (Table). Endocrine-based therapy was the most common first subsequent treatment (CAMI + CDK4/6i arm, 55.2%; AI + CDK4/6i arm, 66.7%). CAMI + CDK4/6i prolonged chemotherapy/ADC-free survival (HR: 0.64 [95% CI: 0.47–0.87]; nominal p=0.00375; Table) and TTD in GHS/QoL (0.48 [0.31–0.76]); nominal p<0.001). PFS benefit with CAMI + CDK4/6i was maintained with longer follow-up (Table); 30-mo PFS rate was 30.4% vs 2.7% with continued AI + CDK4/6i. PFS benefit was not impacted by common co-mutations (*PIK3CA* in 41.3% of pts, HR: 0.44 [95% CI: 0.28–0.68]; *TP53* in 25.4% of pts, 0.49 [0.30–0.82]). At 30% maturity, OS HR was 0.87 (0.57–1.30). Safety was consistent with previous results. **Conclusions:** Switching to CAMI + CDK4/6i at *ESR1*m emergence continued to result in PFS benefit, with approximately a third of pts still progression-free at 30 mo. PFS benefit was maintained beyond first progression; PFS2 was significantly improved and the clinically meaningful endpoint of chemotherapy/ADC-free survival was prolonged vs continuing AI + CDK4/6i. These results continue to support a switch to CAMI + CDK4/6i for pts with *ESR1*m during 1L therapy to delay disease progression and deteriorations in QoL. Clinical trial information: NCT04964934. Research Sponsor: AstraZeneca.

DCO3		CAMI + CDK4/6i (n=157)	AI + CDK4/6i (n=158)	HR (95% CI)
PFS	Events, n (%)	99 (63.1)	124 (78.5)	0.45 (0.34–0.59);
	Median, mo	16.8	9.2	p<0.00001
	24-mo rate, %	34.9	14.2	
	30-mo rate, %	30.4	2.7	
PFS2	Events, n (%)	80 (51.0)	90 (57.0)	0.63 (0.46–0.86);
	Median, mo	25.7	19.1	p=0.00373
	24-mo rate, %	50.8	36.3	
	30-mo rate, %	41.5	29.7	
Chemotherapy/ADC-free survival	Events, n (%)	85 (54.1)	98 (62.0)	0.64 (0.47–0.87); nominal
	Median, mo	22.6	18.7	p=0.00375

LBA1008 Oral Abstract Session

A randomized, open-label, phase 3 study of gedatolisib + fulvestrant ± palbociclib vs standard of care in HR+/HER2−/*PIK3CA*-mutant (MT) advanced breast cancer (VIKTORIA-1 Study 2).

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Background: Current standard treatment (tx) for patients (pts) with HR+/HER2-/*PIK3CA*-MT advanced breast cancer (ABC) includes selective inhibitors of the PI3K/AKT/mTOR (PAM) pathway, which induce class-effect toxicities (e.g., hyperglycemia, diarrhea). Gedatolisib (geda) is a highly potent, IV-administered, comprehensive inhibitor of the PAM pathway that targets all class I *PI3K* isoforms, mTORC1, and mTORC2. Geda has superior preclinical potency and cytotoxicity compared to alpelisib, capivasertib, and everolimus and demonstrated activity in *PIK3CA*-MT and wild-type (WT) breast cancer cell lines. The randomized, open-label phase 3 VIKTORIA-1 clinical trial evaluated, in 2 cohorts by *PIK3CA* status, geda regimens in HR+/HER2- ABC that progressed during/after CDK4/6i + aromatase inhibitor (AI). In the *PIK3CA*-WT cohort, geda/fulv +/- palbo significantly improved PFS (HR vs. fulv, 0.24; 95% CI, 0.17-0.35; P<0.001, and 0.33; 95% CI, 0.24-0.48; P<0.001, respectively). We now present primary findings of the *PIK3CA*-MT cohort. **Methods:** Eligible pts had HR+/HER2- ABC with prior CDK4/6i + AI, no chemotherapy for advanced disease, no prior PAMi, measurable disease (RECIST v1.1), and HbA1c <6.5%. Pts with *PIK3CA*-MT disease were randomized 3:3:1 to geda/palbo/fulvestrant, alpelisib/fulv or geda/fulv in 28-day cycles of geda 180 mg IV weekly for 3 weeks on/1 week off; palbo 125 mg daily for 21 days with 7 days off; fulv 500 mg IM every 2 weeks in cycle 1 then every 4 weeks; alpelisib 300 mg per day. Response was assessed per RECIST v1.1 by blinded independent central review. The primary endpoint was PFS for the geda triplet vs. alpelisib/fulv. Secondary endpoints include PFS for the geda doublet vs. alpelisib/fulv, OS, safety, ORR, DOR, TTR, CBR, QOL, and geda PK. Statistical comparisons were performed by stratified log-rank test. **Results:** At data cut-off (3/09/2026; N=362), median follow-up for PFS was 11.0 mos. The trial met its primary endpoint. Median PFS for geda triplet (n=155) vs alpelisib/fulv (n=155) was 11.1 vs. 5.6 mos (HR, 0.50; 95% CI, 0.37-0.68; P<0.0001). Median PFS for the geda doublet (n=52) vs alpelisib/fulv was 11.3 vs. 5.6 mos (HR, 0.51; 95% CI, 0.33-0.79; P<0.0013). Safety was generally consistent with the individual agents, with low rates of D/C of assigned therapy due to tx-related adverse events (2.6% for geda triplet; 3.8% for geda doublet; 7.1% for alpelisib/fulv). All-grade tx-related hyperglycemia was 15.0%, 11.5%, 57.9% (grade 3: 2.6%, 0%, 13.8%), and all-grade tx-related stomatitis was 61.4%, 61.5%, and 34.2% (grade 3: 16.3%, 5.8%, and 5.3%), respectively, for geda triplet, geda doublet, and alpelisib/fulv. **Conclusion:** These data demonstrate that gedatolisib combination therapies offer a potential new standard of care as 2L treatment of HR+/HER2- ABC, irrespective of *PIK3CA* mutation status. Clinical trial information: NCT05501886. Research Sponsor: Celcuity.

LBA1018 Rapid Oral Abstract Session

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

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Background: In Asia, BC incidence is increasing and peaks before menopause; tamoxifen is commonly used for pre/perimenopausal BC. However, tamoxifen was not approved for use in combination with CDK4/6 inhibitors in many countries. PATHWAY previously showed significantly improved progression-free survival (PFS) for palbociclib plus tamoxifen (± goserelin) at the primary analysis (data cut-off 15 Sep 2022) with immature OS. Here, we report updated PFS and final OS. **Methods:** This phase 3 trial was conducted in Japan, Korea, Taiwan, and Singapore (NCT03423199). Eligible patients were women with locally advanced or metastatic HR-positive, HER2-negative BC who were candidates for 1st- or 2nd-line tamoxifen-based endocrine therapy and had not received a prior CDK4/6 inhibitor. Patients were randomized 1:1 to receive palbociclib (125 mg daily, days 1–21 of a 28-day cycle) or placebo, each with tamoxifen 20 mg daily. Pre/perimenopausal patients also received goserelin. Randomization was stratified by line of therapy and menopausal status. Investigator-assessed PFS (primary endpoint) and OS were analyzed using Kaplan–Meier methods and compared using a stratified log-rank test with 1-sided p values; hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a stratified Cox proportional hazards model. **Results:** 184 patients were randomized (Feb 2018–Jul 2019) at 22 sites. Overall, 28.3% were pre/perimenopausal and 71.7% postmenopausal; 60.9% received study treatment as 1st-line and 39.1% as 2nd-line endocrine therapy. At the end of study in October 2025, 154 PFS events and 105 deaths occurred. Updated PFS remained significantly improved with palbociclib plus tamoxifen vs placebo plus tamoxifen (HR 0.594; 95% CI, 0.427–0.825; $P < 0.001$), with median PFS 24.4 months (95% CI, 13.1–32.4) vs 11.1 months (95% CI, 7.4–14.6), respectively. PFS benefit was observed regardless of menopausal status (pre/perimenopausal: HR 0.343; 95% CI, 0.175–0.675; postmenopausal: HR 0.697; 95% CI, 0.479–1.012). Final OS also favored palbociclib plus tamoxifen (HR 0.772; 95% CI, 0.525–1.134; $P = 0.093$), with median OS 71.7 months (95% CI, 57.1–not estimable) vs 62.0 months (95% CI, 49.9–73.1); OS results were consistent across menopausal subgroups (pre/perimenopausal: HR 0.747; 95% CI, 0.339–1.647; postmenopausal: HR 0.772; 95% CI, 0.497–1.198). Palbociclib plus tamoxifen was generally well tolerated; adverse events were manageable with dosing interruptions/dose reductions, and no new safety findings. **Conclusions:** With longer follow-up, palbociclib plus tamoxifen (± goserelin) provided durable PFS benefit and a favorable OS trend with manageable safety, supporting this regimen as an effective option regardless of menopausal status. Clinical trial information: NCT03423199. Research Sponsor: Pfizer Inc; Conquer Cancer, the ASCO Foundation; 16lk1203001j0001; Conquer Cancer, the ASCO Foundation; 17lk1503003j0001; Conquer Cancer, the ASCO Foundation; 18lk1503003j0002; Conquer Cancer, the ASCO Foundation; 19lk1503003j0003; Conquer Cancer, the ASCO Foundation; 24lk1503003j0008; Conquer Cancer, the ASCO Foundation; 25lk1503003j0009; Conquer Cancer, the ASCO Foundation; 20lk0201002j0001; Conquer Cancer, the ASCO Foundation; 21lk0201005j0001; Conquer Cancer, the ASCO Foundation; 22lk0201007j0001; Conquer Cancer, the ASCO Foundation; 23lk0201009j0001; Conquer Cancer, the ASCO Foundation; 24lk0201009j0002; Conquer Cancer, the ASCO Foundation; 25lk0201009j0003; Conquer Cancer, the ASCO Foundation; 20lk1503003j0004; Conquer Cancer, the ASCO Foundation; 21lk1503003j0005; Conquer Cancer, the ASCO Foundation; 22lk1503003j0006; Conquer Cancer, the ASCO Foundation; 23lk1503003j0007.

LBA1510 Clinical Science Symposium

Low-dose pembrolizumab with chemotherapy in advanced NSCLC: A phase 3 randomized trial.

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Background: Pembrolizumab plus Platinum doublet chemotherapy is the standard of care for advanced non-small cell lung cancer (NSCLC) without actionable genomic alterations (AGAs). Access to Pembrolizumab & other immune checkpoint inhibitors (ICIs) is limited due to their cost. There is evidence to suggest that ICIs are efficacious at lower doses. The efficacy of low-dose Pembrolizumab & Nivolumab has been demonstrated in phase 3 trials in other settings. There is no randomised data for low-dose Pembrolizumab in advanced NSCLC. We conducted this study to evaluate the efficacy of low-dose Pembrolizumab in this setting. **Methods:** This is a phase 3 open-label randomised trial with a superiority design that included patients with advanced NSCLC without AGAs. Participants aged ≥18 years & ECOG PS ≤2 were randomised 1:1 to receive Platinum-doublet chemotherapy (Arm A) or Platinum-doublet chemotherapy with low-dose Pembrolizumab (Arm B). Chemotherapy included Pemetrexed/Paclitaxel plus Carboplatin/Cisplatin for 4-6 cycles. Pembrolizumab 50 mg was administered every 3 weeks for the first 4 doses & then every 6-weeks. Treatment was continued until disease progression or intolerable side effects. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), safety, & QoL. The Kaplan-Meier method & the Cox proportional hazards model were used for analysis. **Results:** 380 participants were randomised,187 to Arm A &193 to Arm B. Participants were predominantly male (76.1%), with a median age of 57 yrs; 61.1% had ECOG PS 0-1, 38.9% had ECOG PS 2, 54.5% were former/current smokers. The most common histological subtype was adenocarcinoma (68.4%). Brain metastases were present in 27.1%. The median follow-up was 13 mos (95% CI 12.2-14.1). The median OS was 10.47 mos (95% CI 8.38-12.56) in Arm A and 13.46 mos (95% CI 11.71-15.22) in Arm B; HR 0.72 (95% CI 0.54-0.95) (p=0.020). The 1-year OS was 44.4% (95% CI 37.2-53) in Arm A and 57.32% (95% CI 44.93-65.79) in Arm B. The median PFS was 4.70 mos (95% CI 4.06-5.34) in Arm A and 6.73 mos (95% CI 5.51-7.96) in Arm B, HR 0.70 (95% CI 0.56-0.89), p=0.003. The 1-year PFS was 18.79% (95% CI 13.59 - 25.99) in Arm A and 26.72% (95% CI 20.23 - 35.29) in Arm B. Grade 3 or higher neutropenia was significantly higher in Arm B (28%) compared to Arm A (17.6%), p=0.02. There was no difference in the incidence of grade 3 or higher anemia or thrombocytopenia. Grade 3 or higher immune-related pneumonitis was seen in 3.1% in Arm B. **Conclusion:** The addition of low-dose Pembrolizumab to chemotherapy significantly improved overall survival and progression-free survival in patients with advanced NSCLC. There were no new safety signals. This regimen will improve access to ICIs in resource-limited settings. Clinical trial information: CTRI/2023/08/056715. Research Sponsor: Tata Memorial Centre Research Administration Council; KamalUdwaadia Foundation (KUF); RJ Manudhane Foundation; Mankind Pharma; Nuclear Power Corporation of India Limited (NPCIL).

LBA2000 **Oral Abstract Session**

Final results of a randomized, controlled, phase 3 trial comparing resection and post-operative stereotactic radiation versus resection and cesium-131 tile-based radiation for treatment of newly diagnosed brain metastases.

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Background: Post-operative stereotactic radiation (SRT) is the standard to reduce recurrence of resected brain metastases (BM). Cesium-131 tile-based radiation therapy (TBRT) (GT Medical Technologies) delivers focal radiation (RT) immediately upon resection and may offer logistical and therapeutic advantages. ROADS (NCT04365374) compared TBRT vs SRT in patients with newly diagnosed resectable BM. **Methods:** In this open label phase 3 trial across 32 US centers, patients requiring resection of one newly diagnosed BM were randomized 1:1 to surgery + SRT or surgery + TBRT. Up to 5 additional unresected BM were allowed and treated with SRT in both arms. Co-primary endpoints were time to surgical bed recurrence (SBR; independently centrally reviewed) and surgical bed recurrence free survival (SB-RFS), analyzed using Cox proportional hazards models with stratification factors as covariates. Multiplicity was controlled by hierarchical testing. Key secondary endpoints were overall survival (OS), leptomeningeal disease (LMD; independently centrally reviewed), radiation necrosis (RN) and treatment related adverse events (TRAEs). Exploratory endpoints were time to SBR or RN and time to total cranial management (TTCM, time from surgery to completion of all RT). Analyses used the modified intent to treat (mITT) population, defined as patients who underwent surgery and had follow up information. **Results:** 230 patients with balanced patient and tumor characteristics were randomized (115 per arm). 204 patients (101 SRT, 103 TBRT) comprised the mITT population. Median follow-up time was 12.9 mo (IQR:5.9-22.8 months). SBR occurred in 11.9% (SRT) vs 1.0% (TBRT). Median time to SBR was 17.4 mo in SRT and not reached in TBRT (HR: 0.06, 95% CI: 0.01-0.46, p=0.007). SB-RFS was significantly improved with TBRT: median SB-RFS was 10.9 mo in SRT vs not reached in TBRT (HR: 0.48, 95% CI: 0.30-0.76, p=0.002). OS was significantly improved with TBRT (HR: 0.59, 95% CI: 0.37-0.96; p=0.032); estimated 24-mo survival was 35.7% (SRT) vs 61.7% (TBRT). LMD occurred in 3.0% (SRT) vs 9.7% (TBRT) (p=0.146). The 24-mo probability of being alive without LMD was 35.9% (SRT) vs 57.7% (TBRT) (HR: 0.68, 95% CI: 0.43-1.08, p=0.102). RN occurred in 6.9% of patients (SRT) vs 7.8% (TBRT) (p=0.495). TBRT extended time to SBR or RN: median time was 18.3 mo in SRT vs not reached in TBRT (HR: 0.28, 95% CI: 0.12-0.66, p=0.004). Median TTCM was 30 days (SRT) vs 1 day (TBRT) ($p<0.001$). Grade ≥ 3 TRAEs were 19.3% (SRT) vs 18.1% (TBRT). **Conclusions:** TBRT improved surgical bed control and OS compared to SRT for patients with a newly diagnosed resectable BM. Safety was equivalent. Completing total cranial treatment faster with TBRT, coupled with fewer SBR occurrences may lead to fewer gaps in systemic therapy perhaps resulting in the observed OS benefit. Clinical trial information: NCT04365374. Research Sponsor: GT Medical Technologies, Inc.

LBA2007 Oral Abstract Session

Efficacy and safety of asandeutertinib versus osimertinib as first-line treatment in EGFR-mutated NSCLC patients with brain metastases: Interim analysis of an open-label, multicenter, randomized, pivotal phase II study (ESAONA).

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Background: Asandeutertinib (TY-9591), a novel EGFR-TKI candidate, demonstrated outstanding efficacy and manageable safety in its Phase I and Phase II studies. The ESAONA study was designed to compare the efficacy and safety between asandeutertinib and osimertinib in EGFR-mutated non-small cell lung cancer (NSCLC) with brain metastases (BM). **Methods:** In the ESAONA study, treatment-naïve NSCLC pts with EGFR-sensitizing mutations and stable BM have been enrolled and randomized 1:1 to receive either asandeutertinib (160 mg orally, QD) or osimertinib (80 mg orally, QD). Randomization was stratified according to the number of intracranial lesions (>3 or ≤3) and EGFR mutation type (L858R or 19Del). The primary endpoints were intracranial objective response rate (iORR) and intracranial progression-free survival (iPFS), assessed by the blinded independent central review (BICR) per RECIST version 1.1. **Results:** From August 14, 2023 to December 15, 2025, 224 eligible pts were enrolled and randomized to asandeutertinib (n=111) or osimertinib (n=113), with a median follow-up of 18.86 months (mo) and 19.12 mo, respectively. Baseline characteristics were well balanced. Results showed that asandeutertinib significantly improved the BICR-assessed iORR compared with osimertinib (95.5% [95%CI, 89.8%-98.5%] vs. 79.6% [95%CI, 71.0%-86.6%]; p=0.0004). INV-assessed iORR was 92.8% [95%CI, 86.3%–96.8%] in asandeutertinib and 77.9% [95%CI, 69.1%-85.1%] in osimertinib (p=0.0019). INV-assessed iORR per RANO-BM showed a consistent trend (91.9%, [95%CI, 85.2%-96.2%] vs. 77.9%, [95%CI, 69.1%-85.1%], p=0.0039). BICR-assessed Median iPFS (miPFS) was not reached [95%CI, 22.24–NA] in asandeutertinib and 17.51 mo [95%CI, 15.18–NA] in osimertinib (HR 0.46 [95%CI, 0.28-0.76]; p=0.0020). The trend in miPFS was consistent across subgroups. INV-assessed miPFS was not reached [95%CI, 21.45–NA] in asandeutertinib and 17.51 mo [95%CI, 15.38–21.36] in osimertinib (HR 0.56 [95%CI, 0.36-0.89]; p=0.0122). INV-assessed miPFS per RANO-BM also favored asandeutertinib (22.64 vs. 17.51 mo; HR 0.60 [95%CI, 0.39-0.94]; p=0.0232). BICR-assessed mPFS was not reached [95%CI, 17.22–NA] with asandeutertinib vs 17.22 mo [95%CI, 15.18–19.55] with osimertinib (HR 0.64 [95%CI, 0.41-1.00]; p=0.0473). Systemic efficacy was numerically favored asandeutertinib, and OS remained immature. Treatment-related adverse events (TRAEs) was 99.1% in asandeutertinib and 95.6% in osimertinib. Treatment-related serious adverse events was 10.8% in asandeutertinib and 7.1% in osimertinib. **Conclusions:** Asandeutertinib significantly improved iORR and iPFS compared to osimertinib, with manageable safety profile, supporting its potential as a new first-line treatment for EGFR-mutated NSCLC pts with BM. Clinical trial information: NCT05948813. Research Sponsor: TYK Medicines Inc.

LBA3500 Oral Abstract Session

Disease-free survival (DFS) and time to recurrence (TTR) with circulating tumor (ct) DNA–based decision for adjuvant treatment in colon cancer stage II (CIRCULATE): An AIO (KRK-0217)/ABCSG trial.

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Background: Adjuvant chemotherapy (ACT) provides limited benefit in unselected stage II colon cancer patients (pts). Postoperative ctDNA has higher prognostic value than classical clinical or molecular markers but has not been proven to predict benefit from ACT. **Methods:** Pts with UICC II, pMMR/MSS colon cancer were tested for ctDNA using an academic, tumor-informed, NGS based test (Stasik, Front Genet 2022). ctDNA positive (pos) pts were randomized (planned 2:1) to CHEMO (6 mo capecitabine [cape] or 3-6 mo cape+oxaliplatin) vs observation without ACT (OBS). ctDNA negative (neg) pts were randomized 1:4 to OBS vs OFF-STUDY. Patients in OBS and their investigators remained blinded to the ctDNA status. The primary endpoint was DFS in ctDNApos pts (CHEMO vs. OBS), the TTR was reported as 3-y recurrence rate. Differences were tested using one-sided log-rank tests. The planned sample size was 1,540 randomized pts assuming 10% ctDNApos. Because the funding period expired, the trial ended early and was finally analyzed. **Results:** From 06/2020 to 07/2025, 2,126 pts were screened at 138 sites in Germany/Austria. The ctDNApos rate was lower than expected among randomized pts (2.9%) and screened but not randomized pts (4.3%). Overall, 1,396 pts were randomized: 1,083 to OFF-STUDY, 287 to OBS (15 ctDNApos), and 26 pts to CHEMO (all ctDNApos). Median age was 64 y, 63% were male. Classical risk factors were present in 9.5% (4.8% pT4, 5.0% unplanned resection). In CHEMO, 21/26 pts (81%) started cape, 33% of them received oxaliplatin, median no of cycles was 6. There was one treatment-related death. DFS and OS were significantly higher in ctDNAneg vs ctDNApos pts (3-y-DFS 87% vs 52%, HR 0.23 [95%CI 0.13-0.43], $p < 0.001$; 3-y-OS 98% vs 88%, HR 0.18 [95%CI 0.05-0.61], $p = 0.001$). In the per-protocol (PP) analysis (excluding CHEMO pts not treated), CHEMO improved recurrence rates and DFS compared to ctDNApos/OBS (3-y recurrence rate19% vs 62%, HR 0.21 [95%CI 0.06-0.80], $p = 0.009$; 3-y-DFS 77% vs 38%, HR 0.28 [95%CI 0.09-0.94], $p = 0.022$). Cancer-specific survival (CSS) was numerically higher with CHEMO (3-y-CSS 100% vs 84%, HR 0.25 [95%CI 0.03-2.44]). In the ITT cohort (including the non-treated pts), the differences between arms were not significant (3-y recurrence rate 35% vs 62%, HR 0.48 [95%CI 0.17-1.33], $p = 0.08$; 3-y-DFS 61% vs 38%, HR 0.52 [95%CI 0.20-1.39], $p = 0.12$; 3-y-CSS 94% vs 84%, HR 0.40 [95%CI 0.07-2.38], $p = 0.15$). **Conclusion:** This is the first prospective randomized trial demonstrating that ctDNA guided ACT improves TTR and DFS in stage II colon cancer pts without clinical risk factors, supporting ctDNA testing for adjuvant decision making in the clinical practice. Limitations include the relatively low number of randomized ctDNApos pts, the sensitivity of the academic test developed 10 y ago and the reliance on PP analysis. Clinical trial information: NCT04089631. Research Sponsor: German Aerospace Center for the Federal Ministry of Research, Technology and Space; 01KG1817.

LBA3503 Oral Abstract Session

BREAKWATER: Progression-free and overall survival analyses of first-line (1L) encorafenib + cetuximab (EC) + FOLFIRI in BRAF V600E-mutant metastatic colorectal cancer (mCRC).

Scott Kopetz, Josep Tabernero, Sara Lonardi, Lin Shen, Harpreet Singh Wasan, Takayuki Yoshino, Eric Van Cutsem, Tae Won Kim, Cathy Eng, Fortunato Ciardiello, Jayesh Desai, Tim Maughan, Rona Yaeger, Tiziana Usari, Xiaoxi Zhang, Elena Beyzarov, Ave Mori, Elizabeth Whalley, Xiaosong Zhang, Elena Elez; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), University of Vic-Central University of Catalonia, Barcelona, Spain; Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Beijing Cancer Hospital, Beijing, China; Hammersmith Hospital, Division of Cancer, Imperial College, London, United Kingdom; National Cancer Center Hospital East, Kashiwa, Japan; University Hospitals Gasthuisberg and University of Leuven (KU Leuven), Leuven, Belgium; Oncology Department, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Vanderbilt Ingram Cancer Center, Nashville, TN; University of Campania Luigi Vanvitelli, Naples, Italy; Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, VIC, Australia; University of Liverpool, Liverpool, United Kingdom; Memorial Sloan Kettering Cancer Center, New York, NY; Pfizer Inc., Milan, Italy; Pfizer Inc., New York, NY; Pfizer, Inc., New York, NY; Pfizer S.R.L., Milan, Italy; Pfizer Inc., Seattle, WA; Pfizer, Inc., South San Francisco, CA; Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: Leucovorin/5-FU in combination with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are common chemotherapies (chemo) used in 1L treatment (tx) of mCRC. In patients (pts) with BRAF V600E-mutant mCRC, BREAKWATER Phase 3 demonstrated clinically meaningful and statistically significantly improved ORR by blinded independent central review (BICR), PFS by BICR, and OS with 1L EC+mFOLFOX6 vs chemo ± bevacizumab (bev) (Kopetz *Nat Med* 2025; Elez *N Engl J Med* 2025). The BREAKWATER safety lead-in previously showed that EC+FOLFIRI was tolerable with promising antitumor activity. BREAKWATER Cohort 3 was therefore conducted to study EC+FOLFIRI. The primary endpoint (EP) of BREAKWATER Cohort 3 was met, demonstrating clinically meaningful and statistically significant improvement in confirmed ORR by BICR with EC+FOLFIRI (64.4%) vs FOLFIRI±bev (39.2%; control) (odds ratio 2.76 [95% CI 1.42, 5.35; one-sided *P*=0.001]) (Kopetz ASCO GI 2026). Reported here are PFS by BICR (key secondary EP), and updated OS and safety data from BREAKWATER Cohort 3. **Methods:** Eligible pts in Cohort 3 had untreated BRAF V600E-mutant mCRC, measurable disease (RECIST 1.1), and ECOG PS 0-1. Pts were randomized 1:1 to receive EC+FOLFIRI or control. The primary EP was ORR by BICR. The key secondary EP was PFS by BICR; other secondary EPs included OS and safety. **Results:** 147 pts were randomized to EC+FOLFIRI or control; the median follow-up for PFS was 18.0 and 14.4 mo, respectively, for OS it was 20.6 and 20.7 mo, respectively (data cutoff: Jan 6, 2026). Baseline demographics and disease characteristics were generally balanced between arms. EC+FOLFIRI demonstrated a clinically meaningful and statistically significant PFS improvement vs control, meeting the key secondary EP (Table). Prolonged OS was observed (Table). The median duration of study tx was 67.9 wk for EC+FOLFIRI and 32.1 wk for control. Discontinuation of chemo (± bev as appropriate for the respective tx arms) due to AEs was similar between arms (14% [EC+FOLFIRI] vs 10% [control]). **Conclusions:** BREAKWATER Cohort 3 demonstrated clinically meaningful and statistically significant ORR and PFS improvements and prolonged OS with EC+FOLFIRI vs control. The safety profile was consistent with that known for each agent with no new safety signals. EC+FOLFIRI expands practice-changing standard-of-care options to deliver pt-centered care for pts with BRAF V600E-mutant mCRC. Clinical trial information: NCT04607421. Research Sponsor: Pfizer Inc.

	EC+FOLFIRI (n=73)	Control (n=74)
mPFS (95% CI), mo	15.2 (13.6, NE)	8.3 (6.9, 9.8)
PFS HR[a] (95% CI)	0.44 (0.27, 0.70)	
	One-sided *P*=0.0002	
mOS (95% CI), mo	NE (21.0, NE)	20.3 (13.2, NE)
OS HR[a] (95% CI)	0.56 (0.34, 0.94)	
18-mo OS rate (95% CI), %	72.0 (60.0, 80.9)	54.5 (42.0, 65.4)
	n=71	**n=68**
Serious TEAEs, %	49	44
Maximum Grade 3/4 TEAEs, %	70	81

NE, not estimable; TEAE, tx-emergent adverse event.
[a]Stratified by ECOG PS (0 vs 1) at randomization.

LBA3506 Oral Abstract Session

Adjuvant hepatic arterial infusion pump chemotherapy with floxuridine for patients with resectable colorectal liver metastases and a low clinical risk score: A randomized controlled trial—The PUMP trial.

Loubna Outmani, Florian Buisman, Wills Floris Filipe, Karen Bolhuis, Leni Van Doorn, Pascal G. Doornebosch, Jan Willem de Groot, Paul D. Gobardhan, Jeroen Hagendoorn, Joost van der Hoeven, Niels F. Kok, J. Sven D. Mieog, Karolina Sikorska, Rutger-Jan Swijnenburg, Maarten Vermaas, Cornelis Verhoef, Marjolein Y.V. Homs, Koert Kuhlmann, Dirk J. Grunhagen, Bas Groot Koerkamp; Erasmus MC, Rotterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Surgical Oncology IJsselland Hospital, Capelle Aan Den Ijssel, Zuid-Holland, Netherlands; Isala Oncology Center, Zwolle, Overijssel, Netherlands; Department of Surgery, Amphia Hospital, Breda, Noord-Brabant, Netherlands; Department of Surgery, University Medical Center Utrecht, Utrecht, Utrecht, Netherlands; Albert Schweitzer ziekenhuis, Dordrecht, Zuid-Holland, Netherlands; Netherlands Cancer Institute, Amsterdam, Noord Holland, Netherlands; Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands; Department of Biostatistics, Erasmus Medical Center, Amsterdam, Netherlands; Amsterdam UMC, location Vrije Universiteit, Amsterdam, Noord-Holland, Netherlands; Department of Surgery, IJsselland Hospital, Capelle Aan Den Ijssel, Zuid-Holland, Netherlands; Department of Surgical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Erasmus MC, Department of Surgical Oncology, Rotterdam, Netherlands; Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: Recurrence after local treatment for colorectal liver metastases (CLM) occurs in up to 70% of patients, frequently confined to the liver. Dutch guidelines do not recommend adjuvant chemotherapy, because three randomized controlled trials (RCTs) have shown no overall survival (OS) benefit of perioperative systemic chemotherapy in resectable CLM. Hepatic arterial infusion pump (HAIP) chemotherapy delivers high doses of floxuridine directly to the liver. This trial evaluated the effectiveness of adjuvant HAIP chemotherapy with floxuridine compared to resection alone in patients with resectable CLM and a low clinical risk score (CRS). **Methods:** This is an open-label, investigator-initiated, multicenter, randomized phase III trial. Adult patients with resectable CLM, no extrahepatic disease, and CRS 0–2 were randomized 1:1 to resection plus adjuvant HAIP chemotherapy with floxuridine versus resection alone, both without adjuvant systemic chemotherapy. Preoperative systemic chemotherapy prior to randomization was allowed. Patients in both groups who signed informed consent but did not fulfill inclusion criteria at the time of surgery were excluded and replaced. Patients were scheduled for 6 cycles of HAIP chemotherapy with floxuridine (0.12 mg/kg/day) that was initiated 4–12 weeks after placement of a Tricumed constant flow pump. The primary endpoint was progression-free survival (PFS) calculated from the date of surgery to the date of a recurrence or death. Secondary endpoints included hepatic PFS (hPFS) and ninety-day mortality. Survival was estimated using Kaplan-Meier method and compared using a log-rank test. **Results:** Between August 2018 and March 2026, 243 patients were randomized to resection followed by adjuvant HAIP (n=120) or resection alone (n=123). At time of surgery, 25 patients were excluded due to presence of extrahepatic disease, unresectable CLM or histopathological confirmation of benign disease. In this analyses, 110 patients were included in the resection and adjuvant HAIP group and 108 patients in the resection alone group. In the HAIP group, 100 patients (91%) initiated HAIP chemotherapy, and the median number of administered cycles was 5 [IQR 3-6]. Treatment was discontinued in 8 patients (8%) due to recurrence and in 32 patients (32%) due to toxicity. The median PFS was 15.0 months in HAIP group vs 16.0 months in resection alone group (HR 0.88; 95% CI 0.62–1.25; p=0.48). The median hPFS was 37.6 months in HAIP group vs 21.8 months in resection alone group (HR 0.80; 95% CI 0.54–1.17; p=0.25). Ninety-day postoperative mortality was observed in 4 patients (3.3%) in the HAIP group and in 1 patient (0.8%) after resection alone. No mortality was attributed to pump placement or HAIP chemotherapy. **Conclusion:** In patients with resectable CLM and a low CRS, no improvement in PFS after adjuvant HAIP chemotherapy with floxuridine compared to resection alone could be demonstrated. Mature results for overall survival are expected in 2029. EudraCT number: 2018-001696-21. Clinical trial information: 2018-001696-21. Research Sponsor: Dutch Cancer Society (KWF); KWF10516; Tricumed Medizintechnik GmbH; Boston Scientific.

LBA3508 Oral Abstract Session

Adjuvant aspirin for stage III colorectal cancer after curative resection: Primary analysis of the randomized double-blind placebo-controlled phase III trial (EPISODE-III: JCOG1503C).

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Background: Observational studies suggest aspirin benefits in colorectal cancer (CRC), but adjuvant evidence remains limited. In unselected populations, phase III trials have not shown a clear benefit, while biomarker-selected studies suggest a benefit in PI3K-altered tumors. EPISODE-III evaluates whether low-dose aspirin improves disease-free survival (DFS) in unselected stage III CRC receiving standard adjuvant chemotherapy. **Methods:** EPISODE-III is a multi-institutional, two-arm, randomized, double-blind, placebo-controlled phase III trial at 36 institutions in Japan. Eligible patients (20–80 years; ECOG PS 0–1) with histologically confirmed, R0-resected stage III adenocarcinoma from the cecum to upper rectum (lower rectum excluded) after D2/D3 lymph node dissection were randomized 1:1 to low-dose aspirin (100 mg once daily) or matched placebo for 3 years, in addition to standard adjuvant chemotherapy (capecitabine, mFOLFOX6, or CAPOX). Randomization was balanced by institution, sex, stage (IIIA/IIIB/IIIC), and planned oxaliplatin use. The primary endpoint was DFS (event: relapse, second cancer, or death). Secondary endpoints included overall survival (OS), relapse-free survival (RFS), relative dose intensity (RDI) of aspirin and placebo, and safety. The planned sample size was 880 (279 DFS events), providing 80% power with a one-sided α = 0.05 to detect hazard ratio (HR) of 0.741 (assumed 3-year DFS 74% vs. 80%). **Results:** Between Mar 2018 and Oct 2022, 882 patients (placebo 442; aspirin 440) were enrolled. At the data cutoff (Oct 2025), the median follow-up for all randomized patients was 4.0 years, with 231 DFS events (placebo 124; aspirin 107). Baseline characteristics were balanced (median age 65 vs. 64 years; pIIIA/IIIB/IIIC 19/63/18% vs. 19/62/19%; planned oxaliplatin-containing regimen 70% vs. 71%). Three-year DFS was 75.4% with placebo and 78.8% with aspirin (+3.4%); the primary endpoint was not met (HR 0.84, 95% CI 0.65–1.09; one-sided p=0.0987). DFS, RFS, and OS are shown in the Table. Grade ≥3 adverse events were similar between arms, and grade ≥3 aspirin-related adverse events were <1% (lower GI bleeding n=4). One treatment-related death was observed in the aspirin arm during chemotherapy (ischemic heart disease). RDI was high and comparable (median 98.6% in both arms). **Conclusion:** Low-dose aspirin added to standard adjuvant chemotherapy did not significantly improve DFS in unselected stage III CRC. However, a numerical DFS improvement with good tolerability was observed. Exploratory biomarker analyses including PI3K/PIK3CA are ongoing and will inform a planned collaborative meta-analysis of randomized trials. Clinical trial information: jRCTs031180009. Research Sponsor: Japan Agency for Medical Research and Development.

	3-year (%) placebo vs. aspirin	HR (95% CI)	P (one-sided)
DFS	75.4 vs. 78.8	0.84 (0.65–1.09)	0.0987
RFS	77.2 vs. 79.5	0.87 (0.66–1.14)	-
OS	96.6 vs. 95.2	1.02 (0.65–1.60)	-

LBA3509 Rapid Oral Abstract Session

A phase III, randomized, open-label study of tunlametinib plus vemurafenib versus investigator's choice of therapy in patients with previously treated *BRAF*^{V600E}-mutant metastatic colorectal cancer.

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Background: The BRAF V600E mutation present in approximately 10% of metastatic colorectal cancer (mCRC) cases, confers a poor prognosis with limited response to chemotherapy. Tunlametinib is a novel, oral, high-potent MEK1/2 inhibitor. Synergistic effect of tunlametinib with vemurafenib was seen in BRAF mutant non-small cell lung cancer and mCRC in the previously published phase I trial (NCT03781219.). Based on promising Phase I/II data, we have this BRAF/MEK inhibitor dual-target regimen to advance to a Phase III randomized controlled trial in this population, addressing a significant unmet need. **Methods:** This randomized, open-label, phase III trial (NCT06008119) enrolled patients. with BRAF V600E–mutant mCRC after ≥1 prior line of systemic therapy. Patients were randomized 2:1 to tunlametinib (12 mg BID) + vemurafenib (720 mg BID) (T+V) or investigator's choice of therapy (control). A prespecified crossover from the control to the experimental arm is allowed upon IRC-confirmed disease progression. The primary endpoint is progression-free survival (PFS) assessed by a blinded Independent Review Committee per RECIST v1.1. Secondary endpoints include overall survival (OS), objective response rate (ORR), and safety. The primary endpoint PFS analysis will use a stratified log-rank test, with the hazard ratio (HR) and its 95% confidence interval estimated using a Cox proportional hazards model. **Results:** As of the data cutoff date for this analysis (March 5, 2026), the full analysis set included 157 patients (105 T+V, 52 control). Based on investigator assessment (IRC assessment ongoing), median PFS was significantly prolonged with T+V versus control (4.2 months vs. 1.5 months; HR 0.374; 95% CI 0.252–0.555; $P < 0.001$). The ORR was 37.1% (95% CI 27.9–47.1) in the T+V group versus 7.7% (95% CI 2.1–18.5) in the control group. $P < 0.0001$. DCR was 81.9% versus 38.5% ($P < 0.0001$), respectively. OS data was immature. Treatment-related grade≥3 adverse events (TRAEs) occurred in 62.0% vs 44.2% of patients, Permanent treatment discontinuation due to TRAEs occurred in 0.9% and 3.8%, respectively. Safety was consistent with that known for each agent. **Conclusions:** This is the first phase III randomized controlled trial to demonstrate that a BRAF/MEK inhibitor combination (tunlametinib plus vemurafenib) significantly improves PFS and ORR compared with conventional chemotherapy-based regimens in previously treated BRAF V600E–mutant mCRC, with a manageable safety profile and the added benefit of a convenient all-oral regimen. Clinical trial information: NCT06008119. Research Sponsor: Shanghai Kechow Pharma, Inc.

LBA3515 Rapid Oral Abstract Session

Node-sparing modified short-course radiotherapy combined with CAPOX and tislelizumab versus conventional short-course preoperative chemoradiotherapy for proficient mismatch repair or microsatellite stable locally advanced rectal cancer (mRCAT-III): A multicenter, randomized, open-label, phase 3 trial.

Zhangfa Song, Bingjun Bai, Min Chen, Weifeng Lao; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; Sir Run Run Shaw Hospital, School of Medicine, Hangzhou, China

Background: Total neoadjuvant chemoradiotherapy is the standard of care for locally advanced rectal cancer (LARC) to control local recurrence and achieve organ preservation. However, for proficient mismatch repair (pMMR) or microsatellite stable (MSS) LARC, which accounts for nearly 90% of rectal cancers, conventional chemoradiotherapy has limited efficacy and is associated with significant side effects. Recent studies have shown that combining radiotherapy with immunochemotherapy can improve pathological complete response (pCR) rates, but the inclusion of tumor-draining lymph nodes (TDLNs) in the conventional irradiation field may impair T-cell immunity and reduce response to immunotherapy. Our previous single-arm phase II trial demonstrated that node-sparing modified short-course radiotherapy combined with chemotherapy and PD-1 blockade could achieve a high pCR rate of 78.8% in pMMR LARC.[1] Building on these findings, we initiated this phase III trial to compare this new treatment regime with conventional short-course chemoradiotherapy in improving pCR rates.[2] **Methods:** This is a phase III, open-label, multicenter, randomized trial conducted across 17 hospitals in China. A total of 154 eligible MSS/pMMR middle or low rectal cancer patients (cT3-4N0/+M0) will be recruited and randomly assigned (1:1) to two groups: control group (conventional short-course chemoradiotherapy), experimental group (node-sparing modified short-course chemoradiotherapy plus PD-1 blockade). The innovative node-sparing modified short-course radiotherapy targets only the primary tumor bed, excluding TDLNs. Following randomization, patients will receive short-course radiotherapy (conventional or node-sparing) followed by four cycles of CAPOX ± tislelizumab: tislelizumab 200 mg IV on day 1, oxaliplatin 130 mg/m^2 IV on day 1, and capecitabine 1000 mg/m^2 orally on days 1-14, and Total mesorectal excision (TME) will be performed at weeks 14-15. The primary endpoint is pCR rate, while secondary endpoints include organ preservation rate, disease-free survival, overall survival, adverse effects, and quality of life. The primary and secondary endpoints will be analyzed in the intent-to-treat (ITT) population. Safety analyses will be performed in the safety population, defined as patients who received at least one dose of study treatment. **Results:** 247 patients were assessed for eligibility, a total of 154 patients were enrolled in the ITT population (77 per group). Baseline characteristics were well balanced between the two groups. In the ITT population, the experimental group demonstrated a significantly superior pCR rate compared to the Control group: 61.4% (47/77) vs 28.6% (22/77) ($P < 0.001$). The MPR rate was also significantly higher in the experimental group (80.5% vs 50.6%). All patients in both groups received sphincter-sparing surgery. Regarding safety, the incidence of grade 3-4 treatment-related adverse events (TRAEs) was comparable between the experimental and control groups (23.4% vs 22.1%). Immune-related adverse events (irAEs) occurred in 7.8% (6/77) of patients in the experimental group, primarily grade 1-2. **Conclusions:** Compared with conventional short-course preoperative chemoradiotherapy, node-sparing modified radiotherapy combined with CAPOX and PD-1 blockade significantly improved pCR rates in patients with pMMR/MSS LARC, with a manageable safety profile. This regimen represents a promising and highly effective neoadjuvant strategy for MSS rectal cancer. Clinical trial information: NCT06507371. Reference : 1. Annals of Oncology (2024) 24 (suppl_1): 1-20. 10.1016/iotech/iotech100744; 2. 2025;43 16_suppl. https://doi.org/10.1200/jco.2025.43.16_suppl.tps3641. Clinical trial information: NCT06507371. Research Sponsor: None.

LBA3563 Poster Session

Efficacy and safety of fruquintinib combined with chemotherapy versus bevacizumab combined with chemotherapy as second-line treatment for metastatic colorectal cancer: A prospective, multicenter, randomized controlled trial.

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Background: The optimal second-line treatment for metastatic colorectal cancer (mCRC) after failure of oxaliplatin-based chemotherapy therapy remains an area of active research, while bevacizumab combined with chemotherapy is a standard option. Fruquintinib (Fru) is a highly selective and potent oral tyrosine kinase inhibitor of VEGFR 1, 2, and 3. This study aimed to compare the efficacy and safety of fruquintinib combined with chemotherapy versus bevacizumab combined with chemotherapy as second-line treatment for mCRC. **Methods:** This was a non-inferiority trial conducted across 12 hospitals and cancer centers in China. Patients with mCRC who had progressed on fluoropyrimidine and oxaliplatin-based first-line chemotherapy therapy were randomly assigned (1:1) to receive either Fru (4 mg orally, once daily for 3 weeks on/1 week off) plus FOLFIRI, or bevacizumab (Bev) (5 mg/kg intravenous, every 2 weeks) plus FOLFIRI. Randomization was stratified by primary tumor location and RAS/BRAF status. During combination therapy, pts who achieve disease control after 4-6 months of treatment proceeded to maintenance therapy, receiving either fruquintinib combined with capecitabine or bevacizumab combined with capecitabine. The primary endpoint was progression-free survival (PFS). Final analysis occurred after either 97 PFS events or after the last patient had completed 12 months of follow-up, whichever occurred first. The non-inferiority upper margin of HR was 1.33. **Results:** Between Jul 13, 2023, and Mar 4, 2025, 122 pts were enrolled and randomly assigned to the Fru group (n=60) or the Bev group (n=62). The median age was 59.0 (IQR 54-69) and 60.0 (IQR 51-70) years, 45 (75%) and 48 (77%) had left-sided tumors, 36 (60%) and 36 (58%) were RAS/BRAF mutant, respectively. At data cut-off (Feb 28, 2026), the median PFS of the Fru group was non-inferior to the Bev group, whether in the Intention to Treat Population (ITT) (9.40 vs 7.39 months, hazard ratio [HR]=0.806 [95% CI 0.522–1.244, 80% CI 0.607-1.07]; p=0.33) or the per-protocol set (PPS) (9.49 vs 7.85 months, HR=0.848 [95% CI 0.542–1.326, 80% CI 0.633-1.136]; p=0.469). In the subgroup analysis , the Fru group showed longer PFS in prior never used VEGF inhibitor pts (10.6 vs 8.5 months, HR=0.94, 95% CI 0.54-1.62), and pts without liver metastasis (14.5 vs 9.9 months, HR=0.97, 95% CI 0.43-2.22) compared to the Bev group. The objective response rate was 35.0% with Fru vs 22.6% with Bev group. Any-grade treatment-emergent adverse events (TEAEs) occurred in 100.0% (Grade ≥3, 28.1%) of the Fru group and 93.2% (Grade ≥3, 28.8%) of the Bev group. **Conclusions:** Fruquintinib combined with FOLFIRI demonstrated non-inferiority in PFS compared with bevacizumab combined with FOLFIRI as a second-line treatment for mCRC, with a manageable safety profile. Clinical trial information: NCT05555901. Research Sponsor: None.

LBA4000 **Oral Abstract Session**

Efficacy and safety results from EMERALD-3: A phase 3, randomized study of tremelimumab plus durvalumab with or without lenvatinib combined with trans-arterial chemoembolization (TACE) in participants (pts) with unresectable embolization-eligible hepatocellular carcinoma (eeHCC).

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Background: TACE, a global standard of care (SoC) for unresectable eeHCC, induces a tumor immune response. STRIDE (Single Tremelimumab [T] Regular Interval Durvalumab [D]) has shown OS benefit at 6-year follow-up and is a SoC for unresectable advanced HCC. We report preplanned analyses from EMERALD-3 (NCT05301842), which combined STRIDE ± lenvatinib (L) with TACE. **Methods:** Eligible pts (≥18 yr) with confirmed eeHCC were randomized 1:1:1 to STRIDE (T 300 mg + D 1500 mg on Day 1 then D 1500 mg Q4W) + L (8 or 12 mg QD) + TACE; STRIDE + TACE; or TACE until reaching 175 pts/arm. Randomization continued 1:1 until STRIDE + L + TACE and TACE reached 275 pts/arm. D and L continued for ≤36 months (mo), until disease progression, unacceptable toxicity, or withdrawn consent. Pts were stratified by region, any prior palliative embolization, and baseline tumor burden by the Up-To-Seven criteria. The primary endpoint was PFS for STRIDE + L + TACE vs TACE by a stratified Cox proportional hazards model and stratified log-rank test. Key secondary endpoints were OS (STRIDE + L + TACE vs TACE), and PFS plus OS (STRIDE + TACE vs TACE). **Results:** As of Feb 23, 2026, 293 pts were randomized to STRIDE + L + TACE, 175 to STRIDE + TACE, and 292 to TACE. Baseline characteristics were broadly balanced across arms. STRIDE + L + TACE showed a statistically significant improvement in PFS vs TACE (HR, 0.70; 95% CI, 0.57–0.86; p=0.0007), and a positive OS trend (HR, 0.84; 95% CI, 0.65–1.09; p=0.1814). STRIDE + TACE also improved PFS (HR, 0.71; 95% CI, 0.56–0.91) and OS (HR, 0.70; 95% CI, 0.51–0.95) vs TACE. STRIDE ± L + TACE showed higher 24-mo OS rate vs TACE (Table). The incidence of treatment-related AEs of maximum grade 3/4 was 62.7% for STRIDE + L + TACE, 48.6% for STRIDE + TACE, and 18.6% for TACE. **Conclusions:** STRIDE + L + TACE significantly improved PFS vs TACE. At interim analysis, with ≤45% maturity, a positive trend for OS with STRIDE ± L + TACE vs TACE was observed. STRIDE + TACE also improved PFS vs TACE. AEs were aligned with known safety profiles of individual therapies. The EMERALD-3 results support STRIDE ± L + TACE as potential new treatment option in unresectable eeHCC. Clinical trial information: NCT05301842. Research Sponsor: AstraZeneca.

	STRIDE + L + TACE (n=293)	TACE (n=292)	STRIDE + L + TACE (n=first 175)	STRIDE + TACE (n=175)	TACE (n=first 175)
PFS (95% CI)					
HR	0.70 (0.57–0.86) p=0.0007*			0.71 (0.56–0.91)†	
Maturity	64%*			75%†	
Median, mo	13.0 (12.2–16.7)*	9.8 (8.0–11.4)*	13.1 (11.0–17.7)†	12.9 (10.2–15.9)†	8.1 (6.5–10.2)†
OS (95% CI)					
HR	0.84 (0.65–1.09) p=0.1814†			0.70 (0.51–0.95)†	
Maturity	40%†			45%†	
Median, mo	39.5 (34.1–NC)†	34.7 (28.8–NC)†	39.5 (32.6–NC)†	NC (37.7–NC)†	32.9 (24.1–43.2)†
24-mo rate, %	66.9 (61.0–72.2)†	61.5 (55.4–67.0)†	67.8 (60.3–74.2)†	68.0 (60.4–74.5)†	57.8 (50.1–64.9)†

NC, not calculable.
Based on Data cutoff 1: *Sep 2, 2025; 2: †Feb 23, 2026.

LBA4026 **Poster Session**

Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (Chemo)/ trastuzumab (Tra) for first-line (1L) HER2-expressing locally advanced or metastatic (la/m) gastric cancer (GC): Updated results from the RC48-C027 trial.

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Background: For patients (pts) with HER2-high (defined as IHC 3+, or IHC 2+/FISH+ based on Chinese CSCO GC guidelines) GC, current 1L therapy consisting of trastuzumab combined with pembrolizumab and chemotherapy offers limited efficacy. For pts with HER2-intermediate/low (defined as IHC 1+, or IHC 2+/FISH- as per Chinese guidelines) GC, no HER2-targeted precision treatment is available. Previous analysis of the RC48-C027 randomized phase 2 part showed notable objective response rates (ORRs): 82.4% with DV + Tor + Tra in HER2-high GC; 72.0% with DV + Tor + CAPOX (oxaliplatin and capecitabine) in HER2-intermediate/low GC, and lowering the CAPOX dose showed improved safety while maintaining efficacy (ORR: 71.4%) (Shen et al. J Clin Oncol. 2025). We report updated results with extended follow-up, including tumor response, mature progression-free survival (PFS), and overall survival (OS) data. **Methods:** Pts with HER2-high, untreated, la/m gastric/gastroesophageal junction (G/GEJ) cancer were randomized at a ratio of 1:1:1 to receive DV + Tor + CAPOX (DTC), or DV + Tor +Tra (DTT), or Tor + Tra + CAPOX (TTC). For HER2-intermediate/low, untreated, la/m G/GEJ cancer, pts were randomized at 1:1 to receive DV + Tor + CAPOX (DTC), or Tor + CAPOX (TC) in Stage 1; to enhance the overall tolerability, Stage 2 was initiated and randomized pts at 1:1:1 to receive DV + Tor + dose-reduced CAPOX (DTCr), or dose-reduced DV + Tor + dose-reduced CAPOX (DrTCr), or Tor + CAPOX (TC). The primary endpoint was ORR; secondary endpoints included PFS, duration of response (DoR), OS, and safety. **Results:** By the data cutoff (Jan 16, 2026), durable responses, a clinically meaningful improvement in PFS, and a favorable trend in OS were observed with DTT and DTCr. No new safety signals emerged. More outcomes are detailed in the Table. **Conclusions:** With extended follow-up, DTT and DTCr demonstrated sustained and clinically meaningful efficacy as 1L treatments for HER2-high and HER2-intermediate/low G/GEJ cancer, respectively. These findings warrant further confirmation in phase 3 trials. Clinical trial information: NCT05980481. Research Sponsor: RemeGen Co., Ltd.

	HER2-high pts			HER2-intermediate/low pts				
	/			Stage 1		Stage 2		
	DTC (n=18)	DTT (n=17)	TTC* (n=16)	DTC (n=25)	TC* (n=23)	DTCr (n=14)	DrTCr (n=15)	TC* (n=16)
OS follow-up (m), median		23.3		21.3			16.6	
Confirmed ORR^, % (95% CI)	66.7 (41.0-86.7)	82.4 (56.6-96.2)	68.8 (41.3-89.0)	75.0 (53.3-90.2)	47.8 (26.8-69.4)	76.9 (46.2-95.0)	66.7 (38.4-88.2)	60.0 (32.3-83.7)
DoR (m), median	NR	NR	13.9	12.4	10.0	NR	12.9	10.6
PFS (m), median (95% CI)	NR (8.2-NR)	18.0 (8.5-NR)	13.8 (3.1-19.6)	9.9 (5.8- NR)	7.2 (5.4-11.3)	9.5 (4.8-NR)	12.7 (2.4-NR)	9.9 (2.8-13.4)
HR	0.39	0.58	/	0.58	/	0.59	0.70	/
OS (m), median	NR	NR	21.6	16.9	18.7	NR	NR	NR
HR	0.63	0.43	/	1.04	/	0.61	0.95	/

*Control arm. ^In pts with ≥1 post-baseline tumor assessment. m, months; NR, not reached; HR, hazard ratio.

LBA4075 Poster Session

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by D2 gastrectomy and adjuvant chemotherapy for locally advanced gastric cancer (Neo-CRAG): A randomized, multicenter, phase 3 trial.

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Background: Neoadjuvant chemoradiotherapy (CRT) has been proposed to improve tumor response over neoadjuvant chemotherapy (CT) in patients with locally advanced gastric cancer (LAGC). However, there are limited phase III clinical trials to confirm its survival benefit. **Methods:** The Neo-CRAG study is a multicenter phase III trial conducted in China. Patients with stage cT3N2/N3M0, cT4aN+M0, or cT4bNanyM0 gastric or esophagogastric junction (EGJ, Siewert type II/III) adenocarcinoma were randomly assigned (1:1) to the CRT or CT group. All patients received 3 cycles of preoperative XELOX, followed by D2 gastrectomy and adjuvant XELOX. In CRT group, radiotherapy (45Gy/25Fx) started after the first CT cycle, dose modifications were made with concurrent CRT (oxaliplatin: 130 to 100 mg/m^2; capecitabine: 1000 to 825 mg/m^2). The radiation target volume chiefly included moderate mucosal CTV expansion (3cm) beyond primary tumor (fasting state), and comprehensive elective regional lymph node irradiation (station 16a2 as the lower border). The primary endpoint was disease-free survival (DFS). The secondary endpoints were overall survival (OS), pathological complete response (pCR), R0 resection, and safety. **Results:** Between 2013-2022, 620 patients (310 per group) were enrolled from 13 referral hospitals, including 225 (36.3%) patients with EGJ primary. Median follow-up was 69.7 months (IQR, 49.6–97.4). The primary endpoint of DFS was met (HR 0.750, 95%CI 0.607-0.928; P=0.008). The 3-year DFS rate was 55.6% (95% CI, 50.1 - 61.1) in the CRT group and 42.4% (36.9 - 47.9) in the CT group, and median DFS was 52.7 months with CRT versus 24.4 months with CT. Meanwhile, the 5-year OS rate was 50.1% versus 44.2% (HR 0.781, 95% CI 0.628-0.970; P=0.025) and the median OS was 67.5 months with CRT compared to 37.6 months with CT. Subgroup analyses showed that the survival benefit of CRT over CT was consistent. 448 patients underwent D2 gastrectomy. pCR was achieved in 33/223 (14.8%) of patients in the CRT group and 14/225 (6.2%) in the CT group. ypN0 rates were 125/223 (56.1%) in the CRT group and 82/225 (36.4%) in the CT group. Tumor downstaging (ypT0-2) occurred in 95/223 (42.6%) of CRT group and 53/225 (23.6%) of CT group. In patients who underwent R0 resection, lower locoregional recurrence rate was observed in the CRT group (20/213, 9.4%), compared with the CT group (38/208, 18.3%). The safety population comprised 603 patients. Grade 3+ hematologic toxicity was relatively higher in the CRT group (44/302 [14.6%] vs 31/301 [10.3%]). Grade 3+ postoperative complication rates were comparable (20/223 [9.0%] vs 17/225 [7.6%]). **Conclusion:** For patients with LAGC, intensifying perioperative CT with preoperative radiotherapy improves survival and is an effective strategy for high-risk cases in need of enhanced locoregional control. Clinical trial information: NCT01815853. Research Sponsor: Sun Yet-Sen University Clinical Research 5010 Program; National Natural Science Foundation of China; Natural Science Foundation of Guangdong Province for Distinguished Young Scholars.

LBA4082 Poster Session

Pathological complete response and ctDNA analyses in SCIENCE: Results from a randomized, phase III trial of neoadjuvant chemotherapy plus sintilimab and chemoradiotherapy plus sintilimab versus chemoradiotherapy in resectable locally advanced esophageal squamous cell carcinoma.

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Background: The optimal neoadjuvant strategy for resectable locally advanced esophageal squamous cell carcinoma (RLA-ESCC) remains unclear. SCIENCE is a randomized phase III trial comparing neoadjuvant chemotherapy (nCT) plus sintilimab (S), neoadjuvant chemoradiotherapy (nCRT) plus S, and nCRT in RLA-ESCC, aiming to determine whether immunotherapy-based neoadjuvant therapy can improve efficacy without increasing toxicity or compromising surgical feasibility, and to explore ctDNA as an early molecular marker of treatment response. **Methods:** Pts with histologically confirmed, resectable thoracic ESCC (cT1N2–3M0 or cT2–4 aN0–3M0 per AJCC/UICC 8th) were randomized 1:1:1 to nCT + S (A), nCRT + S (B), or nCRT (C), followed by surgery 6–8 weeks after neoadjuvant therapy. Co-primary endpoints were pCR and EFS. Longitudinal ctDNA was assessed (tumor-informed, personalized assay) at baseline, on-treatment, and preoperatively. pCR and EFS were compared using chi-square and log-rank tests, respectively, with overall two-sided α=0.05 controlled by allocating 0.02 to pCR and 0.03 to EFS. Interim analysis for pCR was prespecified. **Results:** At the time of data cutoff (Jan 19, 2026), 307 pts had completed neoadjuvant therapy and undergone surgery and were evaluable for pCR (Group A/B/C: 100/103/104). Most pts were male (88.3%) and had clinical stage III disease (81.4%). R0 resection was achieved in 303 pts (99 (99.0%) Group A; 102 (99.0%) Group B; 102 (98.1%) Group C). pCR rates were 18.0% in Group A, 57.3% in Group B, and 49.0% in Group C. Compared with Group A, pCR was significantly higher in Group B (OR 6.1, 95% CI 3.3–11.9; p<0.0001) and Group C (OR 4.4, 95% CI 2.3–8.5; p<0.0001). The safety profile was tolerable across three arms. Among 92 ctDNA-evaluable pts, detectability decreased from 96.7% at baseline to 48.9% preoperatively. Preoperative ctDNA positivity was significantly higher in Group A (78.6%) than in Group B (40.0%) and Group C (32.4%) (p<0.001). Importantly, on-treatment ctDNA status after cycle 1 was already associated with pathological response (p=0.0043). Pts with ctDNA clearance had higher pCR rates than those with persistent ctDNA (62.2% vs 9.1%, p<0.001). ctDNA clearance rates increased stepwise across pathological response categories: pCR (84.8%), MPR (48.1%), and non-responders (12.5%). **Conclusion:** Neoadjuvant CRT + S significantly improved pCR versus CT + S in RLA-ESCC. Preoperative ctDNA clearance status closely tracked pathological response, supporting ctDNA as a promising early molecular marker of treatment effect. EFS will be reported with longer follow-up. Clinical trial information: NCT05244798. Research Sponsor: None.

	nCT + S	nCRT + S	nCRT
pCR (95% CI)	18% (11, 26.9)	57.3% (47.2, 67)	49% (39.1, 59)
P-value (vs. Group A)		<0.0001	<0.0001
P-value (vs. Group B)			0.2942

LBA4226 Poster Session

A multicenter randomized phase II trial of AHCC combined with multidisciplinary treatment for resectable/borderline resectable pancreatic ductal adenocarcinoma (jRCTs051200029).

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Background: Malnutrition, impaired immunity, and limited tolerance to intensive chemotherapy remain major challenges in the multidisciplinary treatment of pancreatic ductal adenocarcinoma (PDAC). AHCC, a standardized extract derived from cultured *Lentinula edodes* mycelia, has demonstrated immunomodulatory, anti-inflammatory, and antioxidant effects and may enhance tolerance to chemotherapy. This multicenter randomized phase II trial was designed to evaluate whether long-term administration of AHCC improves clinical outcomes in patients with resectable (R) or borderline resectable (BR) PDAC undergoing multimodal treatment. **Methods:** This investigator-initiated, double-blind, placebo-controlled, multicenter phase II trial enrolled 230 patients with histologically confirmed resectable or borderline resectable PDAC across eight high-volume centers in Japan. Patients were randomly assigned in a 1:1 ratio to receive oral AHCC (3.0 g/day) or matched placebo, starting from the initiation of neoadjuvant therapy and continuing for up to two years postoperatively. The primary endpoint was 2-year disease-free survival (DFS). Secondary endpoints included 2-year overall survival (OS), treatment compliance, chemotherapy-related adverse events, and longitudinal changes in nutritional and immune parameters across treatment phases, including neoadjuvant therapy, adjuvant therapy, and post-recurrence treatment. Survival analyses will be conducted according to the intention-to-treat principle. **Results:** A total of 230 patients (115 per arm) were analyzed with balanced baseline characteristics. The resection rate tended to be higher in the AHCC group than in the placebo group (86.1% vs 77.4%, P=0.088). For the entire cohort, median OS was 45.1 months and median DFS 22.6 months. The primary endpoint, 2-year DFS, did not differ between groups (22.6 vs 19.2 months, P=0.809). However, median OS was significantly longer in the AHCC group (NR) than in the placebo group (38.8 months, P=0.026). Among patients with recurrence (n=135), post-recurrence survival was significantly longer in the AHCC arm (20.8 vs 10.8 months, P=0.006), whereas no difference was observed among patients without recurrence (both NR, P=0.720). Completion of neoadjuvant and adjuvant therapy rates were similar between groups. At 24 months after treatment initiation, immune-nutritional indices were significantly better preserved in the AHCC group, including NLR, PNI, CAR, and PLR (all $P<0.001$). **Conclusions:** Although AHCC did not significantly improve DFS, it was associated with significantly prolonged overall survival, particularly among patients with recurrence. Preservation of immune-nutritional status may have contributed to the observed survival benefit. Clinical trial information: jRCTs051200029. Research Sponsor: Study material provided by AminoUp.

LBA4511 **Clinical Science Symposium**

Durvalumab monotherapy versus active monitoring for resected primary renal cell carcinoma in RAMPART: An international, phase 3, randomized controlled trial.

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Background: RAMPART is evaluating one year of immune checkpoint inhibitor therapy versus active monitoring in patients with renal cell carcinoma (RCC) at intermediate or high risk of recurrence following nephrectomy according to the Leibovich Score (LS) or following complete resection of limited metastatic disease (M1NED). The trial has already shown that durvalumab and tremelimumab improves disease free survival (DFS), largely driven by effect in the higher risk population (LS high and M1NED). **Methods:** We recruited participants (pts) from 80 sites and randomised them in a 3:2:2 ratio between: Arm A, active monitoring; Arm B, 1 year (13 cycles) of durvalumab (1500mg); or Arm C, 1 year (13 cycles) of durvalumab (1500mg) plus tremelimumab (75mg, cycles 1 and 2 only). Based on the results of the KEYNOTE-564 trial, pembrolizumab became a treatment option for many of the patients who would be eligible for RAMPART, and recruitment was stopped earlier than planned. We revised the RAMPART design without knowledge of the accumulating trial results. In the modified design there is 80% power to detect a hazard ratio (HR) for the primary outcome of DFS of 0.60 for arm B vs. A, and of 0.55 for arm C vs. A. The overall familywise type I error rate remains strongly controlled at 2.5% (1-sided) across all primary analyses. The analysis plan includes a pre-specified, pre-powered analysis by risk of relapse. **Results:** Between October 2018 and June 2023, we randomised 790 pts (340, 225, and 225 to arms A, B, and C) from the UK (70%), France (21%), Australia (5%) and Spain (4%). Baseline characteristics were balanced across arms. Median age (range) was 60 (22, 83) years, 72% were male, 84% clear cell histology. Treatment with durvalumab (Arm B) was associated with a 26% relative reduction in the hazard of disease recurrence or death; conventional statistical significance was not reached (DFS HR = 0.74; 95% CI 0.53–1.04; 1p=0.041). DFS at 3 years was 78% with Arm B vs 72% Arm A. In the pre-specified DFS analysis by risk of recurrence, no evidence of a treatment-by-subgroup interaction was observed. This contrasts with the results of Arm C vs Arm A. Table 1 summarises results of the two RAMPART primary analyses. Exposure to treatment, safety, quality of life, overall survival and efficacy in non-clear cell subtypes will be presented. **Conclusion:** In RAMPART, durvalumab plus tremelimumab was associated with a statistically significant improvement in DFS, which was not observed with durvalumab monotherapy. Clinical trial information: NCT03288532. Research Sponsor: Astra Zeneca; Kidney Cancer UK; Medical Research Council; Cancer Research UK; Conquer Cancer, the ASCO Foundation.

Primary analysis results.

	Arm C vs A	Arm B vs A
All pts	N=565; HR=0.65, 95%CI 0.45-0.93	N=565; HR=0.74, 95 CI 0.53–1.04
Higher Risk	N=311; HR=0.52, 95%CI 0.34-0.80	N=312, HR=0.77, 95%CI 0.53–1.12
Intermediate Risk	N=254, HR= 1.19, 95% CI 0.61-2.32	N=253, HR= 0.64, 95%CI 0.30–1.34
Test for Interaction	HR=0.43, 95%CI 0.19-0.95	HR=1.20, 95%CI 0.52-2.74

LBA5003 Oral Abstract Session

First interim analysis of SWOG S1823: Operating characteristics of circulating microRNA 371a-3p (miR371) in predicting active germ cell malignancy (aGCM) in patients (pts) with early-stage testicular cancer.

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Background: Circulating miR371 has been reported in retrospective studies as a biomarker with high accuracy for predicting aGCM. However, large prospective data of miR371 in identifying early stage disease are missing. S1823/GCC.1 (NCT04435756) is an international prospective cohort study designed to define the operating characteristics of plasma miR371 in detecting tumor relapse in pts with early stage aGCM managed with active surveillance (AS). **Methods:** Serial plasma samples for miR371 assessment were obtained within 56 days from new diagnosis of GCM (baseline) and every 6-12 months (according to risk of relapse) during AS, for maximum 3 years or until relapse. Samples most proximate to relapse were analyzed. Control pts were histology-matched 2:1 to cases. miR371 was measured by RT-PCR and expression was analyzed both qualitatively and quantitatively. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) were evaluated to define miR371 operating characteristics. **Results:** 948 eligible pts were enrolled from June 2020 to May 2024 (median f/u= 32.7 months). The CSI and IIA pts managed with AS (n=630) formed the cohort of interest. At the time of data cutoff, 103 pts (16.3% overall; 14.7% of seminoma; 19.3% of nonseminoma) had relapsed. Results are from the 224 pts selected for the pre-specified interim analysis. PPV/NPV for the whole cohort was 0.66 (95% CI: 0.51, 0.80)/0.90 (95% CI: 0.88, 0.92), for seminoma 0.58 (95% CI: 0.36, 0.80)/ 0.92 (95% CI: 0.90, 0.94), for nonseminoma 0.75 (95%CI: 0.58, 0.92)/0.86 (95% CI: 0.83, 0.89). Sensitivity increased with stage at relapse (IIA,IIB, IIC/III) (p = 0.07) (Table). **Conclusions:** S1823 achieved the primary objective of defining the operating characteristics of plasma miR371 during AS. In aggregate, S1823 results showed high specificity and NPV suggesting potential clinical utilities of miR371 in managing pts with germ cell tumors. Future miR371-informed interventional trials to integrate miR371 in clinical practice are either underway or planned. Clinical trial information: NCT04435756. Research Sponsor: U.S. National Institutes of Health; R37CA264798; U.S. National Institutes of Health; UG1CA189974; U.S. National Institutes of Health; U10CA180820; U.S. National Institutes of Health; U10CA180821; U.S. National Institutes of Health; U10CA180863; U.S. National Institutes of Health; U10CA180868; U.S. Department of Defense; W81XWH-22-1-0687; Michael Smith Health Research BC; HPI-2020-0725; The Hope Foundation; Canadian Cancer Society; 707213; U.S. National Institutes of Health; CA180863.

Operating characteristics of miR371.

Group	N (Cases; Controls)	Sensitivity (95% CI)	Specificity (95% CI)	Median time to relapse (mo)[1]	Median miR371 at relapse (log RQ)[2]
Overall	224 (69; 155)	0.54 (0.42, 0.65)	0.94 (0.90, 0.97)	5.8	17.17
Seminoma	108 (33; 75)	0.52 (0.35, 0.69)	0.93 (0.88, 0.99)	7.4	16.89
Nonseminoma	116 (36; 80)	0.56 (0.39, 0.72)	0.94 (0.88, 0.99)	5.3	17.50
Low-risk	184 (48; 136)	0.52 (0.38, 0.66)	0.93 (0.89, 0.98)	6.6	17.15
Moderate-risk	40 (21, 19)	0.57 (0.36, 0.78)	0.95 (0.85, 1.00)	4.1	17.27
Stage at Relapse[3]					
IIA	23	0.39 (0.19, 0.59)	—	6.8	16.89
IIB	28	0.57 (0.39, 0.76)	—	5.7	17.32
IIC/III	16	0.69 (0.46, 0.92)	—	5.3	17.37

[1]From orchiectomy; [2]Amongst miR371+ cases; RQ: relative expression; [3]Stage at relapse unavailable for 2 pts whose relapse was identified by STM only.

LBA5007 Oral Abstract Session

TALAPRO-3: Talazoparib (TALA) + enzalutamide (ENZA) compared with placebo (PBO) + ENZA for the treatment of patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) harboring homologous recombination repair (HRR) gene alterations.

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Background: In the Phase 3 TALAPRO-2 trial, adding the poly(ADP-ribose) polymerase inhibitor TALA to the androgen-receptor pathway inhibitor (ARPI) ENZA significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) in pts with metastatic castration-resistant prostate cancer (mCRPC), with the HRR-deficient cohort experiencing the greatest benefit. The TALAPRO-3 trial investigates the efficacy and safety of TALA + ENZA in men with mCSPC bearing HRR gene alterations. **Methods:** In the Phase 3, double-blind TALAPRO-3 trial, pts were randomized 1:1 to TALA 0.5 mg (0.35 mg if moderate renal impairment) or PBO plus ENZA 160 mg once daily, stratified by de novo vs relapsed mCSPC, high- vs low-volume disease, and *BRCA* vs non-*BRCA* mutational status. Key eligibility criteria are ECOG PS 0 or 1, presence of HRR gene alteration(s) (*ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*) confirmed by tumor tissue and/or circulating tumor DNA testing, ongoing androgen deprivation therapy (ADT), no prior treatment with docetaxel (protocol amendment in Sept 2021), and ≤3 mo of ADT with or without an approved ARPI for mCSPC. Primary endpoint is investigator-assessed rPFS; OS is the alpha-protected key secondary endpoint. **Results:** 599 pts were randomized (300 to TALA + ENZA; 299 to PBO + ENZA). At a median follow-up of 37.6 mo (TALA + ENZA) and 37.7 mo (PBO + ENZA) at data cutoff (Feb 18, 2026), TALA + ENZA significantly improved rPFS vs PBO + ENZA (HR, 0.481; 95% CI, 0.357–0.647; 2-sided $P<0.0001$; median rPFS not reached vs 45.8 mo). The HR for rPFS was 0.368 (95% CI, 0.222–0.609) in the *BRCA*-mutated subgroup (n=207; 34.6%) and 0.567 (95% CI, 0.392–0.819) in the non-*BRCA*-mutated subgroup (n=392; 65.4%). Interim analysis of OS favored TALA + ENZA but has not reached statistical significance (74 deaths TALA + ENZA, 91 deaths PBO + ENZA; HR, 0.767; 95% CI, 0.564–1.044). The most common all-grade TEAEs in the TALA + ENZA group were anemia (71.2%), fatigue (28.4%), neutrophil count decreased (27.1%), neutropenia (22.1%), asthenia (21.4%) and white blood cell count decreased (21.4%), with no new safety signals identified. TEAEs were generally manageable with dose modifications; 56 pts (18.7%) discontinued TALA due to TEAEs. **Conclusions:** Treatment with TALA+ENZA led to a statistically significant and clinically meaningful improvement in the primary endpoint of rPFS with a trend towards improved OS vs standard-of-care ENZA in pts with HRR-deficient mCSPC. The safety profile was generally manageable and consistent with those for TALA and ENZA. Clinical trial information: NCT04821622. Research Sponsor: This study was funded by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

LBA5009 Clinical Science Symposium

Safety and dosimetry of ^{177}Lu-rosopatamab tetraxetan plus SoC in patients with metastatic castration-resistant prostate cancer: Preliminary results from part 1 of phase 3 ProstACT Global study.

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Background: ProstACT Global is a Phase 3 study of ^{177}Lu-rosopatamab + standard of care (SoC) for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). We present preliminary safety, dosimetry, & pharmacokinetics results from Part 1 (Lead-In). **Methods:** Eligible pts had PSMA+ mCRPC (confirmed on ^{68}Ga-PSMA-11 PET/CT) with disease progression on ≥12w prior therapy on their 1st androgen receptor pathway inhibitor in metastatic castration-sensitive PCa, non-mCRPC, or mCRPC setting. Pts may have received docetaxel in mCSPC setting if ≥6 months prior. Pts received 2 single IV injections ^{177}Lu-rosopatamab (76 mCi each), 14d apart, with assigned SoC (Cohort 1, +abiraterone; Cohort 2, +enzalutamide; Cohort 3, followed by docetaxel; planned n=10 each). Pts were monitored for treatment-emergent adverse events (TEAEs; onset on or after initiation of study treatment). Pts underwent serial SPECT/CT imaging after ^{177}Lu-rosopatamab administration (4, 24, 96, 168, 360h) for dosimetry & blood sampling for pharmacokinetics (PK). Co-primary endpoints were safety & dosimetry of ^{177}Lu-rosopatamab + SoC. Analyses were preplanned, descriptive, & overseen by IDMC. No formal statistics were performed. Dosimetry & biodistribution were evaluated using observed values without formal hypothesis testing. **Results:** Data from 36 pts (baseline median PSA: 18.18 ng/mL) who received any study treatment was included (Cohorts 1, 2, 3: n=11, 11, 14, resp.). 55.6% pts had Gleason score 8-10, 72% pts were 2L mCRPC, & 25% pts had previous taxane exposure. No new safety signals were identified; TEAEs were predominantly transient & manageable hematologic events. Hematologic TEAEs (% pts any grade; Grade ≥3) included thrombocytopenia (77.8%; 44.4%), neutropenia (63.9%; 47.2%), & lymphopenia (55.6%; 41.7%). Non-hematologic TEAEs were all Grade ≤2, except for 1 Grade 3 dizziness. Fatigue (19 events) was most common. Only 9 xerostomia events reported (all Grade 1). No Grade 5 treatment-related TEAEs reported. Blood activity concentration over time demonstrated bi-exponential clearance kinetics. Liver received highest absorbed radiation (range, 1.62-5.08 mGy/MBq), with lower doses received by kidneys (0.336-0.961 mGy/MBq) & salivary glands (0.001-0.104 mGy/MBq). Lesion activity concentrations were higher than in normal tissues & detectable at last imaging timepoint (15d). **Conclusions:** ^{177}Lu-rosopatamab + SoC for pts with mCRPC demonstrates a manageable safety & tolerability profile; predictable PK profile with prolonged tumor residence; & organ radiation exposure below recommended thresholds. Radiation absorbed dose was highest for liver (clearance organ), which is comparatively radio-resistant. Data support continued investigation in Part 2. Disclosure: This study is sponsored by Telix Pharmaceuticals. Clinical trial information: NCT06520345. Research Sponsor: Telix Pharmaceuticals.

LBA5012 Rapid Oral Abstract Session

Early results of COMPPARE, a prospective comparison of outcomes with proton and photon radiation in prostate cancer.

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Background: There is a critical evidence gap on the relative benefits and harms of proton therapy (PT) compared with photon-based intensity-modulated radiation therapy (IMRT) in prostate cancer. Herein we report early results from COMPPARE, a non-randomized comparative study of outcomes with PT and IMRT in prostate cancer. **Methods:** Between 2018-2022, 2524 patients from 51 facilities (28 PT and 23 IMRT) enrolled in COMPPARE, including 1501 treated with PT and 1023 treated with IMRT, and were followed prospectively. Treatment naïve patients with localized prostate cancer except those with very high-risk disease were eligible. Treatment was pragmatic with daily standard fractionation (1.8-2.1 Gy) and moderate hypofractionation (2.4-3.1 Gy) permitted. Use of rectal spacers and androgen deprivation were at physician discretion. Patient-reported quality of life data and treatment team-reported toxicity and disease control outcomes were collected at baseline and pre-specified time intervals via VisionTreeOptimalCare; treatment planning and delivery data were collected via the Advanced Treatment Consortium. We analyzed 1404 PT patients and 939 IMRT patients. We report the early primary endpoint of the study, a comparison of patient reported bowel urgency and bowel frequency at 2-years using the EPIC tool, and the secondary endpoints of 2-year CTCAE v5 $\geq$ grade 2 gastrointestinal toxicity outcomes and 3-year freedom from biochemical progression (FFBP) results reported by the study teams. **Results:** Study sample size was targeted at 1,500 PT patients and 1,000 IMRT patients, and median follow-up time was 4.0 years. The primary endpoint and secondary toxicity 2-year endpoints focused on the alternative hypothesis of PT superiority. All results include inverse probability of treatment weighting. Using generalized linear mixed effects models, we found there to be no significant difference in EPIC bowel urgency scores ($p = 0.324$) or bowel frequency scores ($p = 0.514$) between PT and IMRT cohorts over time up to the 2-year endpoint. For grade 2 gastrointestinal toxicity, the 2-year cumulative incidence was 5.2% for PT and 5.6% for IMRT. Gray's Test for competing risks showed a hazard ratio (HR) of 0.91 [95% confidence interval (CI): 0.65-1.28, $p = 0.6$] for PT versus IMRT. The exploratory non-inferiority endpoint of 3-year FFBP was 98.0% for PT and 97.9% for IMRT, and Gray's Test showed a HR of 0.95 (95% CI: 0.52-1.71, $p = 0.90$). **Conclusions:** Analysis of early results of COMPPARE show no significant differences between PT and IMRT in patient reported bowel frequency and urgency, grade $\geq$2 gastrointestinal toxicity, or FFBP. Assessment of long-term disease control, late toxicity and secondary malignancy will require longer follow-up. Clinical trial information: NCT03561220. Research Sponsor: Patient-Center Outcomes Research Institute.

LBA5504 Oral Abstract Session

A phase III CHIPRO study of chiauranib plus weekly paclitaxel for platinum-resistant or refractory ovarian cancer.

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Background: Platinum-resistant or refractory ovarian cancer is associated with poor prognosis and has limited treatment options. Chiauranib (Ibcasertib) is an oral, novel small-molecule multi- kinase inhibitor that targets tumor cell proliferation, neoangiogenesis, and immunosuppressive tumor microenvironment through inhibition of Aurora B, VEGFR1/2, PDGFRα/β, and CSF-1R. Prior studies suggested clinical activity with chiauranib in combination with etoposide or weekly paclitaxel in this setting. **Methods:** We conducted a randomized, double-blind, placebo-controlled, multicenter phase III trial (CHIPRO) to evaluate the efficacy and safety of chiauranib plus weekly paclitaxel in patients with platinum-resistant or refractory ovarian cancer. Patients were randomized 1:1 to receive weekly paclitaxel plus either chiauranib (CP group) or placebo (PP group). Randomization was stratified by prior lines of chemotherapy (1-2 vs $\geq$3) and platinum-free interval ($\geq$6 months vs $<$6 months). Patients received up to six cycles of combination therapy followed by maintenance chiauranib or placebo in those without progression. Dual primary endpoints were progression-free survival (PFS) per blinded independent review committee according to RECIST v1.1 and overall survival (OS). The study was designed to demonstrate superiority of the experimental regimen in either endpoint. **Results:** Between December 20, 2021, and July 29, 2025, 459 patients were enrolled; 70% had received prior anti-angiogenic therapy. At the data cutoff (July 29, 2025), the median follow-up was 16.0 months (95% CI, 14.3–17.7). Median PFS was 4.57 months (95% CI, 4.14–5.52) in the CP group versus 2.69 months (95% CI, 1.58–2.76) in the PP group (HR, 0.427; 95% CI, 0.34–0.54; $P < 0.001$), representing a 57% reduction in progression risk. PFS benefit was observed with CP regardless of prior anti-angiogenic exposure. Median OS was 12.09 months (95% CI, 10.51–15.18) in the CP group and 12.12 months (95% CI, 10.25–13.31) in the PP group (HR, 0.932; 95% CI, 0.73–1.20; P=0.583). A statistically significant OS benefit was observed in patients who did not receive subsequent anticancer therapy (HR, 0.599; 95% CI, 0.39–0.91; $P = 0.016$). Favorable OS trends were also noted in subgroups previously treated with PARP inhibitors and in those received subsequent platinum-based chemotherapy. The most common grade $\geq$3 treatment-emergent adverse events in the CP group were leukopenia, neutropenia and anemia. Safety was consistent with prior experience, and no new safety signals were identified. **Conclusion:** Chiauranib plus weekly paclitaxel significantly prolonged PFS in patients with platinum-resistant or refractory ovarian cancer, with a manageable and predictable safety profile. Significant benefit was also observed in the subgroup previously treated with anti-angiogenic agents, supporting this regimen as a promising new treatment option. Clinical trial information: NCT04921527. Research Sponsor: Chipscreen Biosciences Ltd., Shenzhen, China.

LBA6005 Oral Abstract Session

Adjuvant sintilimab-capecitabine versus capecitabine alone in locoregionally advanced nasopharyngeal carcinoma with suboptimal response to induction chemotherapy: An open-label, randomized, controlled, phase 2 trial.

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Background: Induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) is the current standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC); however, patients with a suboptimal response to IC remain at high risk of disease progression. Although adjuvant capecitabine has demonstrated efficacy in high-risk LA-NPC, whether intensifying adjuvant therapy by adding sintilimab, a highly selective, fully humanized monoclonal PD-1 inhibitor to capecitabine, can further improve survival outcomes remains unclear. **Methods:** This open-label, randomized, phase 2 trial enrolled patients aged 18–70 years with untreated, non-keratinising, stage II–IVA LA-NPC according to the eighth edition of the American Joint Committee on Cancer classification system with suboptimal response to IC, defined as detectable EBV DNA and/or stable or progressive disease after platinum-based IC. After CCRT, all patients were randomly assigned (1:1) to receive either adjuvant sintilimab plus capecitabine or capecitabine alone. Sintilimab (200 mg intravenously) was administered on days 1 and 14 after randomization as a lead-in phase, and then every 3 weeks starting 28 days after CCRT, combined with capecitabine (1000 mg/m^2 twice daily, days 1–14) for eight cycles; the control group received capecitabine alone on the same schedule starting 28 days after CCRT for eight cycles. The primary endpoint was 2-year progression-free survival (PFS) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of the assigned treatment. The study was registered at ClinicalTrials.gov (NCT05201859), and patients are under follow-up. **Results:** One hundred fifty patients were randomised (76 to sintilimab–capecitabine group; 74 to capecitabine group). At a median follow-up of 41 (IQR 35-44) months, the 2-year PFS was 88.2 % in the sintilimab–capecitabine group and 87.8% in the capecitabine group (stratified HR 0.85; 90% CI 0.43–1.70; p=0.77). Grade 3-4 adverse events were reported in 25 (34%) patients in the sintilimab–capecitabine group and in 22 (31%) patients in the capecitabine group; hand-foot syndrome was the most common adverse event in both groups (8% vs. 10%). Immune-related grade 3 myocarditis were occurred in 2 (3%) patients in the sintilimab–capecitabine group. No treatment-related deaths occurred. **Conclusion:** In patients with LA-NPC who had a suboptimal response to IC, intensification of adjuvant therapy with the addition of sintilimab to capecitabine did not result in a significant improvement in progression-free survival. Future studies are warranted to focus on biomarker-driven patient selection and optimization of immunotherapy sequencing with conventional treatments. Clinical trial information: NCT05201859. Research Sponsor: None.

LBA6007 Oral Abstract Session

Ultra-low-dose immunotherapy plus oral metronomic chemotherapy versus paclitaxel-carboplatin in platinum-sensitive recurrent or metastatic head and neck squamous cell carcinoma: A randomized phase III trial.

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Background: Standard first-line therapy for recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) includes platinum-based chemotherapy (PBC) combined with pembrolizumab or cetuximab; however, these regimens remain inaccessible for many patients globally, particularly in resource-limited settings. Triple oral metronomic chemotherapy combined with ultra-low-dose immunotherapy (TMC-I) has demonstrated promising activity and tolerability in earlier studies. We conducted a randomized phase III trial comparing TMC-I with PBC (paclitaxel and carboplatin) in patients with R/M-HNSCC receiving first-line palliative therapy. **Methods:** In this open-label, multicenter, phase III trial conducted at two centers, 422 patients with R/M-HNSCC were randomized (1:1) to receive paclitaxel 175 mg/m^2 plus carboplatin AUC 6 every 3 weeks (Arm-A) or TMC-I (oral methotrexate 9 mg/m^2 weekly, celecoxib 200 mg twice daily, erlotinib 150 mg daily, and nivolumab 20 mg IV every 3 weeks) (Arm-B). Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), safety, and quality of life (QoL). The planned sample size of 422 patients (211 per arm) provided 80% power with a two-sided α of 0.05. The trial was registered with the Clinical Trials Registry–India (CTRI/2024/01/061661). **Results:** The median age was 49.5 years (IQR 42–58), 85.5% were male, 78.9% had oral tobacco use, 76.3% had oral cavity primaries, 25.6% had metastatic disease, and 30.6% had ECOG performance status 2. After a median follow-up of 10.8 months (95% CI 8.1–13.6) in Arm-A and 11.9 months (95% CI 10.3–13.4) in Arm-B, the primary endpoint of OS was significantly improved with TMC-I compared with PBC. Twelve-month OS was 46% versus 23%, and six-month OS was 69% versus 52% ($p < 0.001$). Median OS was 10.3 versus 6.2 months (HR 0.565, 95% CI 0.439–0.728; $p < 0.001$). Median PFS was 5.5 versus 2.7 months (HR 0.465, 95% CI 0.371–0.582; $p < 0.001$). ORR was higher with TMC-I than with PBC (53.4% vs 24.1%; $p < 0.001$), with fewer grade $\geq$3 adverse events (34.1% vs 46.4%; $p = 0.010$). No treatment-related deaths were observed, and patient-reported QoL was preserved with TMC-I. **Conclusion:** TMC-I significantly improved survival outcomes and response rates while reducing severe toxicity and preserving QoL compared with PBC. At approximately USD 230 per month, TMC-I represents a promising and cost-effective first-line treatment option for patients with R/M-HNSCC. Clinical trial information: CTRI/2024/01/061661. Research Sponsor: Tata Memorial Centre Research Administration Council (TRAC); Mankind Pharmaceutical; Nuclear Power Corporation of India Limited (NPCIL).

LBA6500 Oral Abstract Session

Selinexor plus ruxolitinib in JAK inhibitor–naïve myelofibrosis: Phase 3 SENTRY trial.

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Background: Myelofibrosis (MF) is a debilitating myeloproliferative neoplasm marked by splenomegaly, constitutional symptoms, and reduced life expectancy. JAK inhibitors (JAKi), such as ruxolitinib (R), are standard frontline therapy; however, only ~1/3 of R-treated patients (pts) achieve spleen volume reduction ≥35% (SVR35). Despite observed symptom improvements, durable modification of underlying disease biology, including reductions in variant allele frequency (VAF), is limited. Importantly, gains in overall survival remain modest, highlighting a critical unmet need. Selinexor (S), an inhibitor of XPO1-mediated nuclear export, has biologic activity in MF and synergy with R in MPN models. SENTRY evaluated S+R in pts with JAKi–naïve MF. **Methods:** Pts with JAKi-naïve MF were randomized 2:1 to S 60 mg weekly plus R (per label) or placebo plus R, stratified by DIPSS risk, spleen volume, and baseline platelet count. Eligibility included spleen volume ≥450 cm^3, active symptoms, DIPSS Int-1 or higher and platelets ≥100×10^9/L. Co-primary endpoints were SVR35 and absolute mean change in TSS (AbsTSS; excluding fatigue) at Week 24. SVR35 used a stratified Cochran–Mantel–Haenszel test; TSS used a mixed-effects model for repeated measures. Hierarchical testing (one-sided α=0.025) evaluated SVR35 then AbsTSS. Secondary endpoints included safety and overall survival (OS). Changes in VAF were exploratory. **Results:** 353 pts were randomized (S+R n=235; R n=118). Baseline characteristics were balanced. At Week 24 SVR35 was achieved in 49.8% of pts in S+R vs 28.0% in R (difference, 21.8%; OR 2.58; 95% CI 1.60 to 4.17; $P < .0001$). Responses occurred early and were sustained, with SVR35 rates of 49.4% vs 20.3% at Week 12 and 46.9% vs 23.0% at Week 36. SVR35 was achieved at any time in 67.7% vs 44.9%. Mean percent change in spleen volume at Week 24 was −40.0% vs −26.7%. Mean (95% CI) AbsTSS change at Week 24 was −9.9 (−11.2 to −8.6) vs −10.9 (−12.6 to −9.1); adjusted mean difference 0.97 (95% CI -1.07 to 3.02; P = .825). As of Feb 20, 2026, 224 (95.3%) pts in S+R and 106 (89.8%) in R were alive. With median follow-up of 11.6 and 12.6 months, OS favored S+R (HR 0.43; 95% CI 0.19 to 1.00; nominal P = .022) with early separation of Kaplan–Meier curves emerging around Month 9. VAF reduction ≥20% at Week 24 occurred in 32.0% vs 23.9% and correlated with SVR35 response. TEAEs occurred in 99.1% in S+R and 97.4% in R (grade ≥3 in 70.1% vs 50.0%); however, TEAEs leading to treatment discontinuation were low (14.5% and 8.6%). TEAEs leading to death occurred in 0.9% vs 2.6%. Confirmed leukemic transformation was 1.7% in each arm. **Conclusions:** S+R significantly improved spleen response vs R alone with earlier, deeper, and sustained response rates, comparable symptom improvement from baseline, and a manageable safety profile. The improved spleen response, early OS signal, and VAF reductions observed in SENTRY position S+R as a novel combination approach for frontline treatment of MF. Clinical trial information: NCT04562389. Research Sponsor: Karyopharm Therapeutics.

LBA7000 Oral Abstract Session

frontMIND: Phase 3 study of tafasitamab (Tafa) plus lenalidomide (Len) and R-CHOP for patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL).

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Background: ~40% of DLBCL pts are not cured with first-line (1L) R-CHOP, underscoring a significant unmet need for more effective 1L regimens. Tafa (anti-CD19 mAb) + Len-R-CHOP in the phase 1b First-MIND study demonstrated safety and efficacy in pts with newly diagnosed disease. frontMIND, a phase 3, double-blind, placebo-controlled study, compared Tafa-Len-R-CHOP vs R-CHOP in pts with high-risk aggressive BCLs. **Methods:** Pts aged 18–80 y with newly diagnosed, high-intermediate/high-risk DLBCL or HGBL (IPI 3–5, aaIPI 2–3 if ≤60 y) and ECOG PS 0–2 were randomized 1:1 to Tafa-Len-R-CHOP or R-CHOP. Primary endpoint was investigator-assessed PFS; secondary endpoints included: EFS, OS, CR, ORR, safety. **Results:** At primary analysis (data cutoff Oct 20, 2025), 899 pts were randomized to Tafa-Len-R-CHOP (n=448) or R-CHOP (n=451); baseline characteristics were similar between arms. With a median follow-up of 35.2 mo, Tafa-Len-R-CHOP achieved a statistically significant improvement in PFS vs R-CHOP (HR 0.75 [95% CI: 0.59, 0.96]; *P*=0.019) in the overall population; in pts with centrally confirmed lymphoma subtypes (n=773), PFS HR was 0.68 (95% CI: 0.52, 0.88) and 24-mo PFS was 72.7% vs 62.2%. PFS benefit was observed with Tafa-Len-R-CHOP in both molecular COO subtypes, ABC and GCB (data will be presented). Tafa-Len-R-CHOP significantly improved EFS vs R-CHOP; CR and ORR were similar between arms and HR for OS was 0.85 (final OS planned at 5y) (Table). Any-grade TEAEs were similar in treatment arms (98.6% vs 97.1%); more grade ≥3 TEAEs occurred with Tafa-Len-R-CHOP vs R-CHOP (86.7% vs 76.1%). Discontinuations due to TEAEs occurred in 25.7% vs 17.9% and deaths due to TEAEs in 5.9% vs 3.8% of pts for Tafa-Len-R-CHOP vs R-CHOP. Overall, there were fewer deaths with Tafa-Len-R-CHOP vs R-CHOP (18.5% vs 21.7%). **Conclusions:** The primary endpoint of frontMIND was met; Tafa-Len-R-CHOP resulted in a significant 25% reduction in risk of disease progression or death compared with R-CHOP, with an 8.2% difference in 24-month PFS rate in the overall population and 10.5% difference in pts with centrally confirmed lymphoma subtypes. TEAEs were manageable and consistent with the expected safety profile. Tafa-Len-R-CHOP represents a potential new 1L standard of care for pts with both COO subtypes of high-risk DLBCL or HGBL. Clinical trial information: NCT04824092. Research Sponsor: Incyte Corporation, Wilmington, DE. The study was conducted with scientific support of the Fondazione Italiana Linfomi and the German Lymphoma Alliance.

Efficacy outcomes by treatment arm.*

Variable	Tafa-Len-R-CHOP (n=448)	R-CHOP (n=451)	HR or OR (95% CI)	*P* value
PFS, # events (%)†	121 (27.0)	155 (34.4)	0.75 (0.59, 0.96)	0.019
PFS rate at 24 mo, %	71.1	62.9	–	–
PFS rate at 36 mo, %	67.3	60.7	–	–
EFS, # events (%)	154 (34.4)	191 (42.4)	0.79 (0.64, 0.97)	0.026
OS, # events (%)	82 (18.3)	95 (21.1)	0.85 (0.63, 1.14)	0.270
CR at EOT, n (%)	292 (65.2)	294 (65.2)	0.998 (0.76, 1.31)	0.987‡
ORR at EOT, n (%)	360 (80.4)	343 (76.1)	1.290 (0.94, 1.78)	0.120‡

*Investigator-assessed. †Progressive disease or death from any cause. ‡Nominal *P* value.

LBA7506 Oral Abstract Session

Mezigdomide, carfilzomib, and dexamethasone (MeziKd) vs carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): Results from the phase 3 SUCCESSOR-2 trial.

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Background: A growing number of patients (pts) entering second-line treatment (tx) are anti-CD38 monoclonal antibody (mAb)- and lenalidomide (LEN)-exposed, limiting tx options. Mezigdomide (Mezi), a potent oral CELMoD, induces maximal, rapid Ikaros/Aiolos degradation leading to enhanced MM cell death and immune stimulation vs IMiDs. We report initial results from SUCCESSOR-2 (NCT05552976), the first randomized phase 3 study of Mezi in RRMM, evaluating MeziKd vs Kd. **Methods:** In this phase 3, 2-stage, inferentially seamless trial, eligible adult pts had ≥1 prior line of therapy (LOT) including an anti-CD38 mAb and LEN. Pts were randomized 3:3:3:2 (Mezi 0.3, 0.6, 1.0 mg + Kd, or Kd) to identify the optimal Mezi dose in stage 1, and 3:2 to compare efficacy and safety of MeziKd vs Kd in stage 2. MeziKd was given in 28-day (D) cycles of Mezi (D1–21), 56 mg/m^2 carfilzomib (CFZ) weekly (QW), and 40 mg dexamethasone (DEX) QW. The Kd arm received CFZ 56 mg/m^2 twice weekly or 70 mg/m^2 QW + DEX. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, selected Mezi dose (stage 1), overall response rate (ORR), and safety. **Results:** The Mezi dose selected for stage 2 was 1.0 mg. In total, 479 pts (288 MeziKd at 1.0 mg Mezi; 191 Kd) were included in the analysis. Median (range) age was 68 (30–85) y with 25.1% of pts ≥75 y; median (range) number of prior LOTs was 2 (1–9); 92.1% of pts were triple-class-exposed, with 85.8% refractory to an anti-CD38 mAb and 75.8% to LEN; 37.2% were exposed to pomalidomide and 7.3% to anti-BCMA tx. At data cutoff, median follow-up was 10.6 mo with 52.4% (MeziKd) and 31.4% (Kd) of pts still on tx. Median tx duration was 8.9 (up to 32.1) mo for MeziKd vs 6.2 (up to 25.0) for Kd. MeziKd significantly improved PFS vs Kd (median [95% CI], 18.0 [14.5–22.1] vs 8.3 [5.6–10.7] mo; HR, 0.48 [95% CI, 0.36–0.63]; $P<0.0001$), which was consistent across subgroups, including pts with >2 prior LOTs, prior tx exposure/refractoriness, high-risk cytogenetics, extramedullary disease, and age ≥75 y. Higher ORR (80.2% vs 53.4%) and complete response or better (26.7% vs 8.9%) were seen with MeziKd. Deaths were reported in 21.5% (MeziKd) vs 26.7% (Kd) of pts, mostly due to progressive disease. Grade (Gr) 3–4 treatment-emergent adverse events were seen in 83.7% vs 56.5% of pts, neutropenia in 61.1% vs 9.1%, and infections in 34.0% vs 15.6% with MeziKd and Kd, respectively; Gr 5 infections in this high-risk population were few (2.4 vs 1.1%). **Conclusions:** MeziKd showed a clinically meaningful PFS benefit as early as first relapse in predominantly triple-class-exposed, anti-CD38 mAb- and LEN-refractory pts, a population with significant unmet need. These data support Mezi, a potent oral tx with a predictable and manageable safety profile, as a readily accessible, potential new standard of care for RRMM across multiple settings. Clinical trial information: NCT05552976. Research Sponsor: Bristol Myers Squibb.

LBA8005 Oral Abstract Session

Concurrent thoracic radiotherapy (TRT), platinum/etoposide chemotherapy, and durvalumab immunotherapy in extensive-stage (ES) small cell lung cancer (SCLC): A phase III trial.

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Background: A phase III trial indicated a survival benefit of TRT after chemotherapy in ES SCLC. A synergistic effect of concurrent radiotherapy and immunotherapy has been proposed and retrospective studies suggest that TRT improves survival in ES SCLC patients receiving chemo-immunotherapy (chemo-ICI). The main aim of this phase III trial was to investigate whether adding TRT to chemo-ICI improves overall survival (OS) in ES SCLC. **Methods:** Eligible patients were ≥18 years, had ECOG performance status (PS) 0-1 and disease stage III-IV (TNM 8) ineligible for curative chemoradiotherapy and were randomized 1:1 to chemo-ICI plus TRT («TRT») or chemo-ICI alone («C-I»), stratified by presence of liver and brain metastases. Patients received 4 courses of carboplatin (AUC 5), etoposide (100 mg/m^2 iv day 1-3 or 100 mg/m^2 iv day 1 plus 200 mg/m^2 po days 2-4) and durvalumab 1500 mg q3w, followed by durvalumab 1500 mg q4w until progression, unacceptable toxicity or patients wished to discontinue. TRT of 30 Gy/10 fractions to thoracic lesions started 21-28 days after day 1 of the 1st chemo-ICI cycle. Prophylactic cranial irradiation of 25-30 Gy/10-15 fractions was considered for those responding to chemo-ICI. Primary endpoint was OS, secondary endpoints include overall response rates (ORR), progression free survival (PFS) and toxicity. To show an increase in 1-year survival rates from 53% to 66% with a 2-tailed α of 0.05 and a β of 0.20, 128 patients were required in each group. **Results:** Enrolment started in January 2022 and was prematurely discontinued in September 2025 according to recommendations by the independent Data and Safety Monitoring Committee due to more serious adverse events (AE) in the TRT group and futility. By then, 228 patients from 20 European hospitals were randomized (TRT: n =115, C-I: n =113). Median age was 68 (range 39-84), 50.4% were female, 37.7% had PS 0, 96.1% stage IV disease, 39.9% metastases to the liver and 28.1% to the brain. Treatment groups were well balanced. Mean number of chemo-ICI courses was 3.6, mean number of total durvalumab courses 7.5 (range 1-30) and 91.3% in the TRT group received TRT. TRT did not improve OS (median 10.0 [TRT] vs. 11.1 months, HR 1.12, 95% CI 0.82-1.54, p=0.47), ORR (TRT: 88.5%, C-I: 89.6%, p=0.79) or PFS (median 5.1 [TRT] vs. 5.1 months, HR 1.09, 95% CI 0.83-1.44, p=0.53). Overall, there were more AEs in the TRT group (87.8% vs. 69.9%, p=0.006), but not more grade 3-4 AEs (TRT: 21.1%, C-I: 17.5%, p=0.33). Esophagitis occurred in 47.8% and grade 3-4 esophagitis in 10.4% of the TRT group. There were more deaths from other causes than SCLC in the TRT group (14.8% vs. 3.5%, p=0.003), though not significantly more when excluding deaths occuring before TRT commenced (9.6% vs. 3.5%, p=0.067). **Conclusion:** The addition of TRT after the first cycle of chemo-ICI did not improve treatment outcomes in ES SCLC. Clinical trial information: NCT05223647. Research Sponsor: Clinical therapy research in the specialist health services in Norway; AstraZeneca; Central Norway Health Authority.

LBA8500 Oral Abstract Session

Sunvozertinib monotherapy versus platinum-based chemotherapy as first-line treatment for advanced NSCLC with EGFR exon20ins: Primary analysis of a multinational phase 3 randomized study (WU-KONG28).

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Background: Sunvozertinib has been granted accelerated approval in the US and China for the treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor exon 20 insertion mutations (EGFR exon20ins) who failed platinum-based chemotherapy, based on results from two phase 2 single arm pivotal studies (WU-KONG1B [NCT03974022] and WU-KONG6 [NCT05712902]). WU-KONG28 (NCT05668988) is a multinational randomized confirmatory phase 3 study to compare sunvozertinib versus platinum-based chemotherapy as first-line treatment in advanced NSCLC patients with EGFR exon20ins. Here we reported the primary analysis of WU-KONG28 study results. **Methods:** Eligible patients were randomized in a 1:1 ratio, stratified by baseline brain metastasis status, to receive either sunvozertinib 300 mg once daily or chemotherapy (carboplatin [AUC5] and pemetrexed [500 mg/m^2]) once every 3 weeks for up to 6 cycles, followed by pemetrexed maintenance therapy until disease progression or other discontinuation criteria were met. Patients in the chemotherapy arm could cross over to receive sunvozertinib upon confirmed progressive disease by the blinded independent central review (BICR). The primary endpoint was progression free survival (PFS) assessed by BICR per RECIST 1.1. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), and safety profile. PFS and OS were analyzed using log-rank test and Cox proportional hazards model. The data cutoff date was Jan 16, 2026. **Results:** A total of 324 patients were randomized to receive sunvozertinib (N=163) or chemotherapy (N=161). Baseline characteristics were generally balanced between the two arms. PFS by BICR was significantly longer with sunvozertinib than chemotherapy (median: 10.3 vs 7.5 months; hazard ratio [HR]: 0.65, 95% confidence interval [CI]: 0.50, 0.85, p=0.0008). The PFS benefit was consistent in trends across subgroups. In the chemotherapy arm, 90.2% of patients with BICR-confirmed disease progression crossed over to receive sunvozertinib. The OS data were immature. Patients in the sunvozertinib arm showed higher confirmed ORR (58.9% vs 31.1%) and longer median DoR (11.2 vs 7.1 months). Safety profile of sunvozertinib was similar to what was previously reported. Drug-related treatment emergent adverse events (TEAEs) leading to treatment discontinuation occurred in 7.4% of patients. No drug-related TEAE leading to fatal outcome was reported. **Conclusion:** Sunvozertinib demonstrated significantly superior antitumor efficacy than chemotherapy with a manageable safety profile. These results support sunvozertinib as a first-line treatment for advanced NSCLC harboring EGFR exon20ins. Clinical trial information: NCT05668988. Research Sponsor: None.

LBA8507 Oral Abstract Session

A randomized, open-label, parallel-controlled phase 3 trial of benmelstobart plus chemotherapy and anlotinib for first-line treatment of advanced non-squamous non–small cell lung cancer.

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Background: PD-1/PD-L1 inhibitors plus chemotherapy remain standard first-line therapy for EGFR/ALK/ROS1-wild type advanced non-squamous non-small cell lung cancer (nsq-NSCLC). Pre-clinical data suggest angiogenesis inhibitors may potentiate immune checkpoint inhibitors (ICIs). This phase 3 trial evaluated sequential benmelstobart (anti-PD-L1 mAb) plus chemo followed by benmelstobart plus anlotinib versus standard therapy for PFS improvement in this patient population. **Methods:** TQB2450-III-11 (NCT05346952) is a randomized, open-label, parallel-controlled phase 3 trial. Eligible patients were diagnosed with locally advanced (stage IIIB/C, unfit for surgery or curative-intent chemoradiotherapy) or metastatic nsq-NSCLC. Previous systemic treatment for advanced disease was not allowed. Other key inclusion criteria included ECOG PS of 0-1, aged 18-75 and no EGFR mutations, no ALK or ROS1 rearrangements. Patients were stratified by PD-L1 TPS level (< 1%/1-49%/≥50%) and randomized 1:1 to receive benmelstobart or tislelizumab plus platinum and pemetrexed for 4 cycles, then followed by maintenance with benmelstobart plus anlotinib and pemetrexed or tislelizumab plus pemetrexed until disease progression or unacceptable toxicities. Anlotinib dosing was 10 mg, while benmelstobart or tislelizumab was given at a dose of 1200 mg or 200 mg Q3W. The primary endpoint was PFS by independent review committee according to the RECIST version 1.1. **Results:** From January 24, 2022 to May 8, 2023, 596 eligible patients were randomized 1:1 to benmelstobart group and tislelizumab group. Baseline characteristics were well balanced between two groups. Median PFS was significantly improved in benmelstobart group (14.42 months, 95% CI, 12.35–NE) versus tislelizumab group (8.34 months, 95% CI, 6.97–12.39), HR 0.67 (95% CI, 0.52–0.86; P = 0.0017). The subgroup analysis showed that PFS benefit favored benmelstobart group in almost all subgroups, particularly in patients with ECOG PS 0 (HR 0.36, 0.20-0.65) and PD-L1 TPS < 1% (HR 0.61, 0.43-0.86). OS was immature. Safety profiles were similar in two groups. Treatment-emergent adverse events of any grade was 92.28% (benmelstobart group) and 90.94% (tislelizumab group) respectively. ≥Grade 3 treatment-related adverse events was 56.38% (benmelstobart group) and 48.66% (tislelizumab group). Immune-related adverse events was 19.13% (benmelstobart group) and 18.46% (tislelizumab group). **Conclusions:** Benmelstobart in combination with chemotherapy followed by sequential combination with anlotinib significantly improved PFS compared to tislelizumab in combination with chemotherapy followed by sequential tislelizumab, with a manageable safety profile. It might be a new first-line treatment for nsq-NSCLC. Clinical trial information: NCT05346952. Research Sponsor: None.

LBA8518 Rapid Oral Abstract Session

Phase 3 clinical trial of the combination of erlotinib plus ramucirumab compared with osimertinib in untreated advanced or recurrent non-small cell lung cancer with EGFR L858R mutation: The REVOL858R trial (WJOG14420L).

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Background: Among common EGFR-mutant NSCLC, L858R mutation is suggested to be less sensitive to EGFR-TKIs and associated with poorer prognosis than ex19 del. REVOL858R is the first randomized phase III trial conducted exclusively in patients with advanced/recurrent EGFR L858R–mutant NSCLC, comparing a treatment strategy of erlotinib plus ramucirumab (E+RAM) followed by osimertinib (OSI) upon detection of acquired T790M with first-line OSI monotherapy. **Methods:** Eligible patients were treatment-naive adults (≥20 years) with advanced/recurrent EGFR L858R–positive NSCLC and ECOG PS 0–1. Patients were randomized 1:1, stratified by clinical stage (IIIB/IIIC/IV vs postoperative recurrence), sex, and baseline brain metastasis (BM). Patients received OSI 80 mg once daily (Arm A) or E+RAM (E 150 mg once daily plus RAM 10 mg/kg every 2 weeks; Arm B). In Arm B, tumor rebiopsy or liquid biopsy at termination of E+RAM was mandated; patients with detected T790M subsequently received OSI, whereas those without T790M discontinued protocol treatment. The primary endpoint, time to failure of strategy (TFS), was defined as time from randomization to disease progression or death during OSI, or during the primary treatment when OSI was not administered (in Arm B). **Results:** Overall, 232 patients were randomized (Arm A n=116; Arm B n=116). Baseline characteristics were generally well balanced between the two arms. In the full analysis set, median TFS was 14.8 months in Arm A and 16.6 months in Arm B (HR 1.03; 95% CI 0.78–1.38; log-rank p=0.49). Key secondary endpoints and selected prespecified subgroup analyses of TFS are summarized in Table. The most common AEs (any grade) were diarrhea (41% vs 54%) and acneiform rash (30% vs 71%) in Arm A vs Arm B. Hypertension and proteinuria were observed in 39% and 18% of patients in Arm B, respectively. Interstitial lung disease occurred in 12 patients (10%) in Arm A, and 2 patients (2%) in Arm B. AEs leading to discontinuation of protocol treatment occurred in 21% vs 36% of patients (Arm A vs Arm B). **Conclusions:** A planned E+RAM-to-OSI strategy did not improve TFS compared with upfront OSI in EGFR L858R–mutated NSCLC. Safety findings were consistent with known profiles, with higher discontinuation for tolerability in the strategy arm. Trial information: jRCTs051200142. Clinical trial information: 051200142. Research Sponsor: Eli Lilly Japan K.K.

Key secondary endpoints.

Key secondary endpoint, median (months)	Arm A (OSI)	Arm B (E+RAM)	HR (95% CI)
OS	44.0 (31.1-NR)	38.4 (33.3-NR)	0.98 (0.66-1.45)
3-y OS (%)	56.1%	57.2%	–
ORR (%)	73.2%	66.3%	–
PFS1	14.8	14.9	1.08 (0.81-1.44)
PFS2	23.8	25.1	0.96 (0.70-1.33)
Time to treatment failure	12.6	11.2	1.34 (1.02-1.77)
Key prespecified TFS subgroups			
<65 years / ≥65 years	18.4 / 14.8	21.2 / 16.0	0.90 (0.40-1.99) / 1.06 (0.78-1.45)
With / Without baseline BM	11.8 / 19.2	14.7 / 17.8	0.81 (0.49-1.34) / 1.11 (0.79-1.57)

LBA9503 Oral Abstract Session

Darovasertib plus crizotinib vs investigator's choice as first-line treatment for patients with HLA-A2 negative metastatic uveal melanoma: Primary results from the OptimUM-02 trial.

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Background: Uveal melanoma (UM) is the most common ocular cancer in adults with up to 50% of patients developing metastasis with high mortality. No FDA-approved systemic treatments exist for HLA-A*02:01 (HLA-A2) -negative metastatic UM (mUM), and therapies effective in other melanoma subtypes have limited efficacy. Darovasertib (darova) is a first-in-class, oral PKC inhibitor that showed encouraging clinical outcomes in a prior phase 1/2 study in combination with the MET inhibitor crizotinib (crizo). Here we present primary safety & efficacy results from the nested phase 2/3 OptimUM-02 trial of darova+crizo as first-line treatment for HLA-A2 negative-mUM. **Methods:** OptimUM-02 is an open-label study of HLA-A2 negative first-line mUM patients who were randomized 2:1 to receive darova 300 mg plus crizo 200 mg BID or investigator's choice (IC) of treatment (pembrolizumab, ipilimumab + nivolumab, or dacarbazine). The primary endpoint for efficacy for phase 2 was progression-free survival (PFS) by RECIST (BICR). Other endpoints included investigator assessed PFS (PFS_{inv}), objective response rate (ORR), duration of response (DOR), disease control rate (DCR: CR+ PR + SD $\geq$ 12 weeks), and safety. Overall survival, the phase 3 primary endpoint, will be presented as the data matures. **Results:** Overall 338 patients received at least one dose of study treatment (safety population), 313 comprised the efficacy population. The median PFS by BICR was 6.9 months for darova+crizo (5.6, 8.3) and 3.1 months for IC (1.8, 4.2); HR: 0.42, p<.0001. Median PFS_{inv} was 6.7 months (5.6, 8.2) and 2.7 months (1.7, 4.1) resp; HR 0.36, p< 0.0001. BICR ORR {37.1% [CR 2.4%; PR 34.8%] vs. 5.8% [CR 0%, PR 5.8%], DCR (73.3% vs 31.1%), DOR (median 6.8 months vs. Non-Evaluable) as well as ORR_{inv} [39.5% vs. 1.9%], DCR_{inv} [74.3% vs. 27.2%] and DOR_{inv} (6.8 months vs. NE) all favored darova+crizo (p-value < 0.0001). Preliminary OS is also trending favorably. The most common treatment emergent adverse events (AEs) for darova+crizo were diarrhea (89.5%), nausea (78.2%), peripheral edema (70.7%), & vomiting (53.6%). In the IC arm, these were nausea (41.4%), diarrhea (36.3%), fatigue (33.3%), AST & ALT elevation (31.1%). AEs led to discontinuation & dose reduction of darova in 3.8% & 23.8% and crizo in 10.9% & 27.2% subjects. In the IC arm, 19.2% discontinued due to AEs. The most common Grade 3 or 4 AEs for darova + crizo were diarrhea (10.9%) & syncope (7.9%) and for IC, AST & ALT increase (8.1%), diarrhea (6.1%) & hepatitis (5.1%). Treatment related serious AEs occurred in 9.2% and 25.3% on darova + crizo and IC respectively. One treatment related fatal AE occurred in each arm. **Conclusions:** In patients with HLA-A2-negative-mUM treated in the first-line setting, darova+crizo demonstrated a clinically and significantly longer PFS, and improved ORR and DCR compared with the investigator's choice treatment. AEs were consistent with the previously reported safety profiles in each arm. These results support a potential new therapeutic standard for a disease with limited treatment options and poor prognosis. Clinical trial information: NCT05987332. Research Sponsor: IDEAYA Biosciences.

LBA9504 Oral Abstract Session

ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in patients with Merkel cell carcinoma and lymph node metastases.

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Background: Merkel cell carcinoma (MCC) with lymph node (LN) metastases (mets) is historically associated with high risk of relapse and mortality despite surgery and/or radiation therapy (RT). Previously reported adjuvant trials (ADMEC-O and STAMP) have not shown a clear benefit with adjuvant PD-(L)1 blockade. **Methods:** ADAM trial (NCT03271372) is an investigator-initiated, phase III, multi-center, double-blinded, placebo-controlled study. We enrolled 100 patients (pts) with MCC and LN mets (stage III) treated definitively with surgery and/or RT, and without radiologic evidence of residual MCC. Pts were randomized (1:1), stratified by primary tumor/LN status and RT status, to receive IV avelumab (A; 800 mg/dose) or placebo (P), for up to 2 years (yrs) on a de-escalating schedule. The primary endpoint was relapse-free survival (RFS). 100 patients provide 86% power to observe a statistically significant (2-sided 5%) difference in RFS assuming true hazard ratio (HR) for RFS failure of 0.4. Secondary endpoints included distant metastasis-free survival (DMFS), disease-specific survival (DSS), overall survival (OS), and safety. Point estimates were obtained using Kaplan-Meier or cumulative-incidence methods, and Cox regression (stratified, with pre-specified adjustment of confounding variables as needed) was used to estimate HRs of failure. **Results:** 100 eligible pts (pathologic stage IIIB - 52; IIIA - 48) were randomized to A (N=48) vs P (N=52) between 12/2017 and 01/2024. At the data cutoff date (01/15/2026), median follow-up among relapse-free survivors was 4.2 yrs [range 1.9-7.1]. Median age was 70 yrs overall (A-72 [50-86], P- 67 [35-83]) and 93% of pts had received adjuvant RT. The HRs for RFS, relapse, DMFS, DSS and OS are listed in the Table below. The point estimates for MCC relapse for A vs P arms, respectively, were 12.8% vs 40.4% at 1 year, 21.3% vs 42.3% at 2 years and 28.3% vs 44.5% at 3-, 4- and 5-year timepoints. Grade 3/4 treatment-related adverse events (TRAE) rate was 15% (n=7) in A and 0% in P arms; no grade 5 TRAEs occurred. **Conclusion:** In this study, adjuvant avelumab was associated with reduced risk of MCC relapse in pts with LN mets. High MCC-specific survival in both arms points to effectiveness of PD-(L)1 blockade in adjuvant and metastatic settings. These data will inform future discussions regarding adjuvant therapy in clinical practice. Clinical trial information: NCT03271372. Research Sponsor: EMD Serono; Kuni Foundation.

Efficacy endpoints.

Endpoint	HR for Failure, Avelumab vs Placebo (95% CI, p-value) Stratified / Adjusted stratified	Number of events Avelumab/Placebo
RFS	0.61 (0.32-1.16, p=0.132) / 0.54 (0.28-1.05, p=0.069)	16/24
Relapse*	0.51 (0.26-1.00) / 0.47 (0.23-0.94)	13/23
DMFS	0.93 (0.44-1.97) / 0.89 (0.41-1.94)	13/15
DSS	1.81 (0.43-7.55) / **	5/3
OS	2.37 (0.73-7.73) / **	9/5

*Not a pre-specified analysis; **Not enough events to accommodate adjustment.

LBA9505 Oral Abstract Session

Updated outcomes from STAMP: Surgically treated adjuvant Merkel cell carcinoma with pembrolizumab, a phase III trial—ECOG-ACRIN EA6174.

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Background: EA6174 (STAMP) is the first randomized phase III trial of adjuvant pembrolizumab (pembro) in resected Merkel cell carcinoma (MCC), a rare, aggressive skin cancer with high relapse risk after surgery. This abstract presents new analyses of MCC-specific outcomes and radiation therapy (RT) effects. **Methods:** Patients (pts) with resected stage I without a sentinel lymph node biopsy to IIIB MCC were randomized 1:1 to pembro 200 mg IV q3 weeks ×17 doses (n = 147) or standard of care (SOC) (n = 146). Randomization was stratified by stage (I/II vs III) and intended RT. Co-primary endpoints were relapse-free survival (RFS) and overall survival (OS). MCC-specific outcomes were captured as relapse due to recurrence or death due to any cause (RFS_a), and MCC-specific recurrence and death (RFS_b). Distant metastasis-free survival (DMFS) was defined as time to distant recurrence or death from MCC. 280 pts provided 80% power with one-sided type 1 error rate of 0.05 to evaluate the hazard ratio (HR) of 0.56 hierarchically (RFS before OS). One-sided p-values from the log-rank test are reported in the analysis (data as of 2/19/26, median follow-up 47 months). **Results:** 293 pts enrolled (67.9% male; 84.3% stage III, median age 69, > 50% accrued during the COVID-19 pandemic). Overall RFS (RFS_a) was numerically improved with pembro but not statistically significant between arms (p = 0.10). DMFS was improved in pts treated with pembro (p = .05). Significant improvement was observed in MCC-specific outcomes (RFS_b) in pts treated with pembro, with HR = 0.66 [90%CI (0.45,0.96)], resulting in 1-year and 2-year RFS_b rates of 84% [90% CI(78,88)] and 77% [90%CI(70,82)] in the pembro arm, compared with 73% [90%CI(67,79)] and 67% [90%CI (60,74)], in the SOC arm (p = 0.032). The impact of pembro on RFS_b was maintained (p = 0.039) among the subset that received any RT (n = 131 pembro, n = 123 SOC). For pts treated concurrently with RT, pembro did not affect outcomes; however, for pts treated sequentially with RT prior to randomization (n = 68 pembro and n = 65 SOC), pembro improved RFS_a (P = 0.014), RFS_b (p = 0.009), and DMFS (p = 0.004). **Conclusions:** EA6174 demonstrates that pts treated with pembro experienced significantly fewer MCC-related events than pts who received SOC and that adjuvant pembro improves DMFS. RFSa may have been influenced by the average age of enrolled pts and by disruptions and morbidity associated with patient enrollment during the COVID-19 pandemic; as such RFSb may be a more accurate indicator of pembro efficacy. These findings support a meaningful impact of pembro on MCC-specific outcomes, particularly for distant relapse. Pembro may be of particular benefit when RT is delivered sequentially rather than concurrently with pembro, similar to other studies of RT and immunotherapy in solid tumors. Mature OS and MCC-specific survival data will further guide use of adjuvant immunotherapy for MCC. Clinical trial information: NCT03712605. Research Sponsor: Conquer Cancer, the ASCO Foundation.

LBA9509 Clinical Science Symposium

A multicenter, randomized, controlled, open-label, phase II trial of autologous tumor-infiltrating lymphocytes (GC101 TIL) in patients with advanced melanoma.

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Background: Tumor-infiltrating lymphocyte (TIL) therapy is effective in advanced melanoma but hampered by toxicity from high-dose IL-2 and lymphodepletion (cyclophosphamide/fludarabine). We explored a modified TIL therapy (GC101) featuring an IL-2-free protocol and a low-intensity preconditioning regimen. This phase II study evaluates the modified GC101 TIL therapy in anti-PD-1-resistant melanoma. **Methods:** MIZAR-003 (NCT06703398) is a multicenter, phase II, randomized, open-label trial across 25 sites in China enrolling advanced melanoma patients resistant to PD-1 antibodies. Key eligibility: ECOG 0–1, adequate organ function. Exclusion: uveal melanoma, prior cellular therapy within 6 months. A total of 98 patients will be randomized 1:1 to Arm A (GC101 TIL) or Arm B (investigator-choice chemotherapy). GC101 therapy consists of tumor resection, low-intensity preconditioning (cyclophosphamide 20 mg/kg/d, pre-infusion d -5 to- 3; hydroxychloroquine 600 mg, pre-infusion d -5), followed by infusion of IL-2-free TIL and sintilimab (100 mg at infusion, then 100 mg Q6W $\times$ 4). Patients in Arm B with IRC-confirmed disease progression may cross over to receive GC101 TIL. The primary endpoint is IRC-assessed PFS per RECIST v1.1. Secondary endpoints include IRC-assessed ORR, CR rate, DOR, and OS; investigator-assessed ORR, PFS, CR rate, DOR, and PFS2; and safety. **Results:** In this exploratory interim analysis (70% of expected events), 84 patients were randomized (Arm A: 44; Arm B: 40) between 02/2025 and 01/2026, with a median follow-up of 5.2M (range 1.1-12.0). Baseline characteristics were balanced. As assessed by IRC, Arm A significantly improved mPFS (4.1M [95% CI 2.8–5.6] vs 1.6M [95% CI 1.3-4.0]; HR 0.53 [95% CI 0.30-0.94], p=0.0310), ORR (45.2% vs 5.4%; p=0.0018), and DCR (80.6% vs 43.2%; p=0.0017). OS data are immature. In mucosal melanoma (n=6 per arm), mPFS was not reached vs 1.3M, with DCR of 100.0% vs 33.3%. Grade $\geq$3 treatment-related AEs (TRAEs) occurred in 36.8% (Arm A) vs 27.5% (Arm B); treatment-related SAEs in 13.2% vs 7.5%. No new safety signals were observed, and no TRAEs led to treatment discontinuation or death. **Conclusions:** GC101 TIL significantly improved PFS and ORR versus investigator-choice chemotherapy in anti-PD-1-resistant melanoma, with manageable safety, supporting its potential as a new later-line therapy. Clinical trial information: NCT06703398. Research Sponsor: None.

LBA9514 Rapid Oral Abstract Session

MATRiX: A randomized phase II trial of tuvusertib (ATR inhibitor) with or without avelumab in advanced anti-PD(L)-1 refractory Merkel cell carcinoma.

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Background: Advanced Merkel cell carcinoma (MCC) often responds to anti-PD-(L)1, but patients (pts) with immune checkpoint inhibitor (ICI)-refractory disease have poor outcomes and few therapy options. MCC has defects in G1 checkpoint control, proliferates rapidly, and is reliant on S/G2 checkpoints such as ATR (ataxia telangiectasia mutated and Rad3-related). Inhibiting ATR can promote immunogenic cell death. MATRiX (MCC refractory to immunotherapy treated with ATR inhibitor ± avelumab) is a multicenter, NCI-sponsored, randomized, open-label phase II trial evaluating tuvusertib, an ATR inhibitor, alone (Arm 1) or in combination with avelumab (Arm 2) in anti-PD-(L)1-refractory MCC, NCT05947500. **Methods:** Pts were randomized 1:1 using a permuted-block design. Arm 1 received tuvusertib 180 mg PO on days 1-14 of each 21-day cycle. Arm 2 received tuvusertib as in Arm 1, plus avelumab 1600 mg IV every 21 days. Pts with disease progression in Arm 1 were eligible to cross over to Arm 2. The planned sample size (N=50; 25 per Arm) provided >80% power to observe a statistically significant (1-sided level of 0.15) difference in the primary endpoint, progression-free survival (PFS), assuming a hazard ratio of 0.5. Secondary endpoints were overall response rate (ORR), duration of response, and overall survival (OS). Data cutoff: January 20, 2026. **Results:** From 5/2024 to 9/2025, 35 subjects (median age 73) received therapy: Arm 1, n=10; Arm 2, n=25. One pt was deemed ineligible post-randomization and excluded from all analyses. 18 pts (53%) had primary ICI-refractory disease, and 22 (65%) had ≥2 prior systemic therapies. Arm 1 met prespecified futility criteria (0/10 responses) and was closed early. No objective responses were observed among 4 pts who crossed over to Arm 2. Among 24 eligible pts in Arm 2, 1 complete and 4 partial responses [ORR 20.8% (95% CI: 7.1-42.2%)] were observed, including 4 primary and 1 acquired ICI-resistant cases. 4 of 5 responders remained progression-free at cutoff (182-273 days from treatment initiation); 1 relapsed at 479 days. One-year estimates were PFS 0% (Arm 1) and 26.4% (Arm 2; 95% CI: 10.8-45.1%) and OS 29.2% (Arm 1; 1.5-69.8%) and 36.5% (Arm 2; 7.8-67.2%), respectively. Grade ≥3 treatment-emergent adverse events occurred in 80% of pts in Arm 1 and 58% in Arm 2; the most common were lymphopenia (20% vs 21%), anemia (50% vs 17%), fatigue (20% vs 17%), pain (10% vs 17%), and infection (0% vs 17%). Safety profiles were consistent with previous reports for these agents. **Conclusions:** Tuvusertib with avelumab demonstrated antitumor activity in anti-PD-(L)1-refractory MCC, inducing durable clinical benefit in ICI-resistant metastatic pts with limited salvage options. No signal of anticancer efficacy was observed with ATRi monotherapy. These findings warrant further investigation of ATRi in combination with immunotherapy in ICI-refractory MCC. Clinical trial information: NCT05947500. Research Sponsor: EDDOP Leadership Award-P30 Administrative Supplement: The MATRiX Study; CA015704.

LBA9517 Rapid Oral Abstract Session

Neoadjuvant intralesional daromun (L19IL2/L19TNF) in resectable locally advanced melanoma: An update on the primary outcome and sensitivity analyses (EFS) from the PIVOTAL phase 3 trial.

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Background: PIVOTAL (NCT02938299) is an open-label, randomized, multicenter, phase 3 trial evaluating daromun as a neoadjuvant intralesional (IT) therapy for resectable, locally advanced stage III melanoma. The trial enrolled 256 efficacy-evaluable patients (pts) in the EU and met its primary endpoint, demonstrating a statistically significant improvement in recurrence-free survival (RFS; HR = 0.59; p = 0.005) for daromun versus upfront surgery, at a median follow-up (FU) of 21 months from randomization (Kähler et al, Ann Onc 2025, 36, 1166). **Methods:** Pts with skin and/or lymph node metastatic melanoma amenable to complete surgical resection were randomized (1:1) to receive 4 weekly IT injections of daromun (13 Mio IU of L19IL2 and 400 μg of L19TNF) followed by surgery or upfront surgery alone. Prior surgery, radiotherapy (RT) and/or systemic therapies (ST) were permitted, as well as any approved adjuvant treatment post-surgery.The primary endpoint was RFS, the secondary endpoints included DMFS, OS and safety. An event-free survival (EFS) sensitivity analysis was conducted, considering progression to unresectable melanoma before surgery, recurrence of the disease, or death due to melanoma or treatment as events. **Results:** An updated primary outcome analysis at a median FU of over 36 months from randomization (database cut-off Nov. 29, 2025) confirmed a clinically relevant improvement in RFS (HR = 0.60; p = 0.003) for daromun versus upfront surgery. The EFS sensitivity analysis carried out in the overall population was consistent with the RFS results (HR = 0.66; 95% CI = 0.47-0.92).The PIVOTAL trial included two clinically distinct subgroups: pts with newly diagnosed disease (n = 32; 12%) and pts with recurrence(s) after surgery and/or systemic (neo)adjuvant treatment (n = 224; 88%). Among the recurrent cohort, 86 pts (38.3%) had received and failed previous ST, while 138 pts (61.6%) had only received surgery/RT. Sensitivity EFS analyses were also performed in i) the recurrent cohort (HR = 0.59; 95% CI = 0.41-0.85), ii) the subgroup of pts in the recurrent cohort who had only received previous surgeries and/or RT (HR = 0.55; 95% CI = 0.34-0.89), and iii) the pts subgroup in the recurrent cohort who received prior ST (HR = 0.63; 95% CI = 0.36-1.08). The rate and type of treatment-related adverse events at a longer FU were consistent with previous reports, and no new safety risks were identified. **Conclusions:** With longer FU the highly significant reduction in the risk of recurrence or death with neoadjuvant daromun in pts with locally advanced stage III melanoma is confirmed. The sensitivity EFS analyses provide consistent, confirmatory evidence of daromun's efficacy across the entire trial population and, more importantly, in the subgroup of pts with recurrent disease, regardless of any prior ST. No new safety signals were reported. Clinical trial information: NCT02938299. Research Sponsor: Philogen S.p.A.

LBA10509 Rapid Oral Abstract Session

Safety and performance results from PATHFINDER 2, a registrational study of a multi-cancer early detection (MCED) test in an intended-use population.

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Background: The MCED test (Galleri) detects a shared cancer signal from cell-free DNA in blood and predicts a cancer signal origin (CSO) to guide diagnostic (dx) workup. PF2 (NCT05155605) is a large, prospective, multicenter, interventional study of the MCED test's performance and safety in a diverse US intended-use population. **Methods:** PF2 enrolled participants aged ≥50y without clinical suspicion of cancer or cancer diagnosis/treatment within 3y of enrollment. Primary objectives were MCED performance and safety in terms of dx testing triggered by a positive (cancer signal detected) MCED test result. Participants with a positive MCED test underwent targeted dx workup guided by the predicted CSO(s). Participant-reported anxiety was assessed with the State Trait Anxiety Inventory. **Results:** PF2 enrolled 35,878 participants; 32,007 with a 12m cancer assessment were analyzable for performance. Of 287 (0.9%) with a positive MCED test, 173 were diagnosed with cancer within 12m, for a cancer detection rate of 0.5% (95% CI 0.5-0.6%) and positive predictive value of 60.3% (54.5-65.8%). Specificity was 99.6% (99.6-99.7%). 12m episode sensitivity was 69.8% (62.8-76.0%) in a prespecified subgroup of 12 cancers responsible for $^{2}/_{3}$ of US cancer deaths, 66.2% (55.1-75.8%) in a subgroup of 6 aggressive cancers with low 5y survival, and 39.3% (34.9-44.0%) across all cancers. Overall CSO prediction accuracy was 91.3% (86.2-94.7%) across all cancers. The MCED test detected 151 new primary and 22 recurrent cancers; additional cancers detected by screening were those with USPSTF A/B (n=31) and C (n=60) recommended screening. Of 151 MCED-detected new primaries, 80 (53.0%) were clinical stage I-II; 107 (70.9%) were stage I-III. Of 80 MCED-detected stage I-II cancers, 71.2% had no USPSTF A/B screening recommendation. Of 35,335 participants analyzable for safety, 213 (0.6%) had invasive procedure(s) to evaluate a positive MCED test result, of which 90% were nonsurgical and 1.8x more likely for participants with vs without cancer diagnosis. Most (87.6%) had a CSO-guided dx evaluation. There were 5 study-related adverse events during the time of dx workup; none were serious. Anxiety temporarily increased for participants with a positive MCED test and cancer diagnosed, and returned to baseline by 12m. Of participants with a positive MCED test, median time from test result to dx resolution was 48d (95% CI 43-56). Few participants (7/63 [11.1%]) had cancer found by dx PET/CT after a targeted dx workup that did not reveal cancer. **Conclusion:** The MCED test demonstrated robust performance with a favorable safety profile. When MCED testing was added to USPSTF A/B screening, 6.5x more cancers were detected by screening, most at early stages. The diverse, representative PF2 participant population supports the generalizability of these findings to the US intended-use population. Clinical trial information: NCT05155605. Research Sponsor: GRAIL, Inc.

LBA12001 Oral Abstract Session

Gabapentin plus tramadol versus tramadol alone for chemoradiotherapy-induced oral mucositis pain in head and neck cancer: Results of a randomized phase III trial.

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Background: Oral mucositis-related pain during concurrent chemoradiation (CTRT) for head and neck squamous cell carcinoma (HNSCC) significantly impairs quality of life (QoL) and frequently necessitates opioid escalation. Despite tramadol-based analgesia, up to one-third of patients require stronger opioids. Gabapentin may improve pain control by targeting the neuropathic component of mucositis-related pain. We conducted a randomized phase III trial evaluating whether the addition of gabapentin to tramadol improves mucositis pain control during CTRT. **Methods:** In this single-center, open-label, randomized phase III superiority trial, 154 patients with HNSCC receiving radical or adjuvant CTRT who developed CTCAE v5.0 grade ≥1 mucositis with pain [Visual Analogue Scale (VAS) ≥1] were enrolled. Eligible patients were aged 18–70 years with ECOG performance status 0–2. Patients were randomized 1:1 to tramadol plus topical anaesthetic (Arm A) or gabapentin plus tramadol and topical anaesthetic (Arm B). Gabapentin was escalated from 300 mg/day to a maximum of 1,800 mg/day. The primary endpoint was pain control measured as the area under the curve (AUC) of VAS pain scores following the first dose of analgesic. Secondary endpoints included analgesic escalation at day 7, weight loss at the end of CTRT, QoL, treatment compliance, adverse events, and treatment delays. With 154 patients, the study had 80% power to detect an effect size of 0.5 at a two-sided α of 0.05. The study was registered with the Clinical Trials Registry-India (CTRI/2020/03/024269). **Results:** A total of 154 patients were randomized. Median age was 49 years (IQR 42–57), and most patients had locally advanced disease (T3–4 77.3%, N2–3 69.5%, stage IVA–B 83.1%). The primary endpoint, pain control measured by AUC of VAS scores following the first dose of analgesic, was similar between the two arms [median AUC 1170 (95% CI 727–1638) vs 1080 (95% CI 802–1800)]. However, analgesic escalation requiring morphine occurred significantly more frequently in the tramadol arm compared with the gabapentin arm (37.3% vs 12.0%, $p < 0.001$), corresponding to an absolute risk reduction of 25.3%. Grade ≥2 weight loss occurred in 33.8% vs 27.3% of patients ($p = 0.382$), and radiotherapy interruptions occurred in 6.5% vs 1.3% ($p = 0.096$), favoring the gabapentin arm. QoL scores were comparable between arms. Gabapentin-related toxicities were mostly grade 1–2 and manageable. **Conclusion:** Addition of gabapentin to tramadol during CTRT significantly reduced the need for opioid escalation for mucositis-related pain in patients with head and neck cancer. Although early pain scores were similar, gabapentin demonstrated a clinically meaningful opioid-sparing effect, suggesting it may be an effective strategy for managing CTRT-induced mucositis pain. Clinical trial information: CTRI/2020/03/024269. Research Sponsor: Tata Memorial Centre Research Administration Council (TRAC); Cadila Pharmaceuticals.

LBA12002 Oral Abstract Session

Ramelteon for prevention of postoperative delirium in elderly cancer patients: A randomized, double-blind, placebo-controlled multicenter trial, JORTC-PON02/J-SUPPORT2103/NCCH2103.

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Background: Delirium is a common and serious complication after major cancer surgery in older adults. Current guidelines, including the American Psychiatric Association guideline, do not recommend routine pharmacological prevention because of insufficient high-quality evidence. Ramelteon, a melatonin receptor agonist with a favorable safety profile, has suggested potential benefit in critically ill populations but has shown inconsistent results for prevention of postoperative delirium. **Methods:** This randomized, double-blind, placebo-controlled multicenter phase III trial enrolled cancer patients aged ≥65 years undergoing surgery under general anesthesia. Patients received ramelteon 8 mg or placebo nightly from 4–8 days before surgery through postoperative day 4. Randomization used minimization with prespecified stratification factors (age ≥75 years, surgical duration ≥6 h, benzodiazepine use, and study site). Guideline-based multicomponent delirium prevention care was implemented in all patients. The planned sample size was 678 patients aged ≥75 years (primary analysis set) plus 88 aged 65–74 years. The primary endpoint was DSM-5–defined delirium within 5 days after surgery. Between-group differences were analyzed using a Cochran–Mantel–Haenszel test adjusted for stratification factors. **Results:** Among patients aged ≥75 years, postoperative delirium occurred in 22.47% (71/316) of patients receiving ramelteon and 22.76% (71/312) receiving placebo, with no significant difference between groups (adjusted risk difference, ramelteon minus placebo, 0.05%; 95% CI, -6.50% to 6.59%; P = 0.9881). Among patients aged ≥65 years, delirium occurred in 22.54% (80/355) in the ramelteon group and 21.19% (75/354) in the placebo group (adjusted risk difference, ramelteon minus placebo, 1.57%; 95% CI, -4.52% to 7.65%; P = 0.6098). **Conclusion:** In this phase III randomized controlled trial, ramelteon did not reduce the incidence of postoperative delirium in older adults undergoing major cancer surgery, and these findings do not support routine pharmacological prevention with ramelteon in this setting. Clinical trial information: jRCTs031210673. Clinical trial information: jRCTs031210673. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

Delirium within 5 days after surgery.

Item	Description
Primary endpoint result (≥75 y)	22.47% (71/316) with ramelteon vs 22.76% (71/312) with placebo
Secondary endpoint result (≥65 y)	22.54% (80/355) with ramelteon vs 21.19% (75/354) with placebo

LBA12003 Oral Abstract Session

Nationwide randomized, phase III, placebo-controlled trial of bupropion for cancer-related fatigue: Primary outcome results.

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Background: Fatigue is common and debilitating among people with cancer. Treatment options for cancer-related fatigue are limited. Methylphenidate demonstrates limited efficacy and low tolerability. Behavioral interventions include exercise and cognitive-behavioral therapy, which many individuals may be unwilling or unable to adopt. Additional therapies are needed. Bupropion has been shown to reduce two hypothesized mechanisms of cancer-related fatigue (CRF), systemic inflammation and hypothalamic pituitary adrenal (HPA) axis functioning. A large-scale, placebo-controlled evaluation of bupropion is needed to offer a potential new therapeutic option for CRF. **Methods:** The trial was conducted through the University of Rochester Cancer Center National Cancer Institute Community Oncology Research Program (URCC NCORP) Research Base and member sites across the U.S. Eligible patients were adults with any stage or site of disease who reported moderate to severe worst fatigue (i.e., score of 4 or above on 0-10 scale) in past week and had no reported or documented contraindication to bupropion. They completed surgery, radiation, and/or intravenous (IV) anticancer therapy at least two months prior to enrollment. Individuals receiving oral therapies or IV supportive therapy were eligible. Participants were randomized 1:1 to receive over-encapsulated 150 mg bupropion or a placebo. They were instructed to take one capsule in week 1, two capsules in weeks 2-12, and one capsule in week 13. The primary outcome was group differences in the FACIT-F fatigue subscale score at week 12. ANCOVA was conducted with group as the main factor and baseline FACIT-F score as a covariate. Study site was included as a random effect independent of residual error. The study was designed with a statistical power of 90% to identify a difference of 0.30 SD in the FACIT-F score, which corresponds to a clinically meaningful change. **Results:** Participants (N = 428) had a mean age of 61 years (SD = 12). Most were female (83%), white (86%), non-Hispanic (93%), and/or diagnosed with breast cancer (73%). There were no baseline group differences in demographic, clinical, or fatigue variables (p values$>$0.13), except the bupropion group was less likely to have received radiation (65% vs. 74%, p= 0.05). Intent-to-treat analyses indicated that bupropion significantly reduced fatigue (Cohen's d= 0.23, p= 0.03) relative to placebo. Prespecified moderator analyses indicated that bupropion was associated with significant improvements in fatigue in women (Cohen's d= 0.33, p= 0.006) but not men (p= 0.24). **Conclusions:** In this large, phase III, community-based trial, bupropion resulted in modest reductions in fatigue relative to placebo, particularly among women. Bupropion should be considered in the pharmacologic management of CRF. Clinical trial information: NCT03996265. Research Sponsor: U.S. National Institutes of Health.

LBA12008 Oral Abstract Session

SUPPORT+ digital self-management and clinical support for advanced cancer: A randomized controlled trial.

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Background: Patients with advanced cancer often experience distressing symptoms that impair HRQoL and lead to emergency department (ED) visits and hospitalizations. Digital symptom-monitoring tools enable earlier detection of symptoms, yet evidence in palliative care remains limited. This study evaluated whether SUPPORT+, a mobile app incorporating weekly symptom reporting using the Integrated Palliative Care Outcome Scale (IPOS), automated self-management guidance, and nurse follow-up for severe symptoms, improves outcomes when added to usual care for community-dwelling patients with advanced cancer. **Methods:** A multi-centre RCT was conducted across 6 palliative care clinics in Hong Kong (Jan 2023–Feb 2025). Patients with advanced cancers no longer receiving systemic treatment were randomized 1:1 to SUPPORT+ or usual care for 18 weeks. The primary outcome was change in HRQoL (EQ-5D-5L). Secondary outcomes included ECOG PS, ED visits, and hospitalizations. **Results:** A total of 633 patients were enrolled (315 intervention; 318 control), median age 79 (range 31–103), with 47.4% male. HRQoL was better maintained in SUPPORT+: EQ-5D-5L index declined from 0.59 at baseline to 0.52 at week 18 vs. 0.62 to 0.37 in usual care (mean difference −0.18; $p<0.001$). EQ-VAS remained more stable (68.7 to 65.8 vs. 68.9 to 59.5; mean difference −6.54, $p<0.001$). ECOG PS deterioration was less common (12.4% vs. 18.9%; $p=0.016$). ED visits were similar. Hospitalization outcomes favoured SUPPORT+, with more reductions in admissions and shorter lengths of stay (both $p\leq0.001$). **Conclusions:** SUPPORT+ maintained HRQoL, preserved PS, and reduced hospitalizations in advanced cancer. Digital symptom monitoring with automated self-management and timely healthcare support is a promising strategy to strengthen community-based supportive care. Clinical trial information: HKUCTR-3116. Research Sponsor: Health and Medical Research Fund.

Proportion of patients in the SUPPORT+ arm and control (usual care) arm with changes in HRQoL, self-efficacy, emergency department visit, hospitalization episodes and duration.

		Intervention Group N=315		Control Group N=318		P-value
		no.	%	no.	%	
Primary Endpoint:						
EQ-5D-5L index (change ≥0.11)	Improved	59	18.73%	14	4.4%	<0.001
	No change	137	43.49%	129	40.57%	
	Worsen	119	37.78%	175	55.03%	
EQ-5D-5L VAS (change ≥6)	Improved	80	25.40%	48	15.09%	0.002
	No change	114	36.19%	112	35.22%	
	Worsen	121	38.41%	158	49.69%	
Secondary Endpoints:						
Self-efficacy	Improved	121	38.41%	65	20.44%	<0.001
	No change	18	5.71%	26	8.18%	
	Worsen	176	55.87%	227	71.38%	
Emergency Department Visits	Reduced	85	26.98%	76	23.90%	0.167
	No change	171	54.29%	163	51.26%	
	Increased	59	18.73%	79	24.84%	
Hospitalization Episodes	Reduced	89	28.25%	70	22.01%	0.001
	No change	174	55.24%	157	49.37%	
	Increased	52	16.51%	91	28.62%	
Hospitalization Days	Reduced	98	31.11%	70	22.01%	<0.001
	No change	162	51.43%	136	42.77%	
	Increased	55	17.46%	112	35.22%	
ECOG	Improved	6	1.90%	13	4.09%	0.016
	No change	270	85.71%	245	77.04%	
	Worsen	39	12.38%	60	18.87%	