DXC006, a first-in-class CD56-targeting antibody-drug conjugate, in advanced solid tumors: A first-in-human, phase I dose escalation clinical trial.

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Background: DXC006 is an antibody-drug conjugate of a humanized anti-CD56 antibody linked to the topoisomerase I inhibitor CPT113 with DAR=4 through a cleavable peptidyl bis-linker by CrossConju technology. DXC006 demonstrated strong antitumor activity *in vivo* and *in vitro*, here we report the safety and preliminary efficacy of first-in-human phase I trial of DXC006. **Methods:** Patients with metastatic/locally advanced solid tumors after at least one line of systemic standard therapy were enrolled. For dose escalation (D-ESC), DXC006 was administered intravenously at doses of 1.2, 2.4, 4.8, 6.0mg/kg Q2W or 6.0, 7.2 mg/kg Q3W with BOIN design and 3+3 design. A subset of pts was enrolled into dose-expansion (D-EXP) at recommended dose regimen. The primary objectives were to evaluate the safety and tolerability (dose limiting toxicities, DLTs; maximum tolerated dose, MTD) of DXC006. **Results:** Data cutoff at December 26th, 2025, 72 patients were enrolled and received at least one dose(D-ESC n=16,D-EXP n=56) , including SCLC (n=44), lung adenocarcinoma (n=11), lung squamous cell carcinoma (n=3), neuroendocrine neoplasm (n=14). No DLTs occurred and MTD was not reached. D-EXP was carried out at 4.8mg/kg Q2W and 6.0mg/kg Q3W regimens. Treatment related adverse events (TRAEs) rate (all grade/≥G3) was 97.2% and 27.8%, TOP5 most common TRAEs (all grade/≥G3) were decreased appetite (54.2%/0%), nausea (52.8%/0%), anemia (48.6%/20.8%), asthenia (37.5%/1.4%), sensory disturbance (33.3%/0%). No interstitial lung disease (ILD) was observed. TRAEs led to dose interruption/discontinuation were observed in (23.6%/1.4%) of the patients. RP2D is 6.0mg/kg Q3W. Totally, 59 patients were eligible for efficacy analysis. For all patients, the objective response rate (ORR) and disease control rate (DCR) were 52.5 % and 81.4% (including confirmed and pending confirmation PR); for SCLC patients, were 69.4% and 91.7%; for lung adenocarcinoma, were 45.5% and 72.7% (details in table). Encouraging anti-tumor activity was observed for DXC006 treatment in SCLC at 2nd line (ORR 85.7%, confirmed 64.3%). PK, PD and PFS results will be updated in the upcoming meeting. **Conclusions:** DXC006 demonstrated a manageable safety profile and adequate tolerability, and showed encouraging efficacy in pretreated advanced solid tumors, especially in SCLC. Clinical trial information: NCT06224855. Research Sponsor: Hangzhou DAC Biotechnology Co., Ltd.

	Small cell lung cancer	Small cell lung cancer (2nd Line)	Neuroendocrine Neoplasm	Lung Adenocarcinoma	Lung Squamous cell carcinoma
N	36	14	10	11	2
Median prior treatment line (range)	2(1, 6)	1(1, 1)	2(1, 6)	2(1, 3)	5(5, 5)
cPR	14	9	1	4	0
PR	25	12	1	5	0
SD	8	2	6	3	0
PD	3	0	3	3	2
ORR % (95% CI)	69.4 (53.1, 82.0)	85.7 (60.0, 96.0)	10.0 (1.8, 40.4)	45.5 (21.3, 72.0)	0.0
DCR % (95% CI)	91.7 (78.2, 97.1)	100 (78.5, 100)	70.0 (40.0, 89.2)	72.7 (43.4, 90.3)	0.0

Phase I study of BL-M14D1, a novel DLL3-directed antibody-drug conjugate (ADC), in patients with locally advanced or metastatic small-cell lung cancer (SCLC), neuroendocrine carcinoma (NEC), and other solid tumors.

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Background: BL-M14D1 is a novel DLL3-directed ADC with a potent topoisomerase I inhibitor Ed-04. Results for safety and efficacy from a phase I study on BL-M14D1 in patients with locally advanced or metastatic (LA/M) SCLC and NEC are presented. **Methods:** Patients who had LA/M solid tumors were enrolled in dose escalation and dose expansion phase and treated with BL-M14D1 at 0.66, 2.0, 3.5, 4.0, 4.5, 5.0, and 6.0mg/kg on Day 1 every 3 weeks (D1 Q3W). SCLC and NEC patients enrolled in dose expansion phase were treated at 4.0 and 4.5mg/kg D1 Q3W. **Results:** As of Nov 30, 2025, a total of 127 patients were enrolled, including 87 SCLC and 40 NEC. Median prior line of therapy was 2 (range 1-5). Treatment-related AEs (TRAEs) rate was 98.4% and grade≥3 TRAEs rate was 74.0%. The most frequent grade≥3 TRAEs were hematologic, including thrombocytopenia (54.3%), neutropenia (53.5%), leukopenia (46.5%) and anemia (32.3%), which were able to be effectively managed with standard supportive measures including dose reductions, as demonstrated by a low rate (1.6%) of TRAEs leading to discontinuation. One grade 3 ILD and one treatment-related death was reported. Efficacy data at 4.0 and 4.5mg/kg was presented below. BL-M14D1 has demonstrated a promising efficacy with an ORR/cORR of 71.1%/57.8% and mPFS of 7.2 months in heavily pre-treated SCLC. Furthermore, BL-M14D1 has shown encouraging activity in other gastrointestinal and gynecological NECs. **Conclusions:** BL-M14D1 has demonstrated promising antitumor activity with a tolerable safety profile at dose levels of 4.0mg/kg and 4.5mg/kg D1 Q3W in heavily pretreated patients with SCLC and NEC, supporting further clinical development of BL-M14D1 in SCLC and other less common NECs. Phase III studies assessing BL-M14D1 in SCLC and NEC are in preparation. Clinical trial information: NCT06505824. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	SCLC Total* (N=83)	SCLC 4.0mg/kg (N=34)	SCLC 4.5mg/kg (N=37)	NEC† Total* (N=22)	NEC† 4.0mg/kg (N=3)	NEC† 4.5mg/kg (N=19)
Median prior LoT (range)	2 (1-5)	2 (1-3)	2 (1-5)	2 (1-3)	2 (1-2)	2 (1-3)
ORR, % (95% CI)	71.1 (60.1, 80.5)	73.5 (55.6, 87.1)	70.3 (53.0, 84.1)	40.9 (20.7, 63.6)	33.3 (0.8, 90.6)	42.1 (20.3, 66.5)
cORR, % (95% CI)	57.8 (46.5, 68.6)	61.8 (43.6, 77.8)	56.8 (39.5, 72.9)	27.3 (10.7, 50.2)	33.3 (0.8, 90.6)	26.3 (9.1, 51.2)
DCR, % (95% CI)	94.0 (86.5, 98.0)	97.1 (84.7, 99.9)	91.9 (78.1, 98.3)	90.9 (70.8, 98.9)	100 (29.2, 100)	89.5 (66.9, 98.7)
mFU for PFS (mo) (95% CI)	6.8 (5.5, 7.2)	7.7 (5.6, 8.2)	4.4 (4.1, 5.5)	3.0 (1.6, 4.3)	NR (1.8, NR)	3.0 (1.4, 3.9)
mPFS (mo) (95% CI)	7.2 (5.6, 12.7)	7.2 (5.6, NR)	6.9 (4.2, NR)	5.3 (3.9, NR)	4.6 (3.9, 5.3)	NR (2.6, NR)

†Sites of NEC included cervix, esophagus, stomach and others.
*Efficacy analysis included pts at 4.0 and 4.5 mg/kg who received BL-M14D1 and had at least one post-baseline scan.

First-in-human study of SYS6043, a novel B7-H3–targeting antibody-drug conjugate, in patients with advanced pan-tumor malignancies.

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Background: B7-H3, a tumor-associated immune checkpoint, is broadly overexpressed in multiple solid tumors and associated with aggressive disease biology and treatment resistance. SYS6043, a novel ADC targeting B7-H3, is designed to selectively deliver a cytotoxic payload to B7-H3 expressing tumors. Preclinical trials showed potent antitumor activity across diverse solid tumor models. Here, we report safety and efficacy results from a phase 1/2 trial of SYS6043 in patients with advanced solid tumors. **Methods:** Eligible patients (18–75 years) had advanced solid tumors refractory to or progressing after standard therapies. The study included a phases 1 dose-escalation and PK expansion phase, followed by a phase 2 cohort expansion. Phase 1 used a BOIN design to evaluate SYS6043 at a dose of 1.2-10.0 mg/kg Q3W and 4.0-6.0 mg/kg Q2W, with PK expansion at selected doses. Phase 2 evaluated SYS6043 at 8.0 mg/kg Q3W and 6.0 mg/kg Q3W and Q2W across tumor-specific cohorts. Primary endpoints were safety, tolerability, and determination of the RP2D in Phase 1, and objective response rate (ORR) in Phase 2. **Results:** As of November 28 2025, 502 patients were enrolled, including ovarian cancer (OC, *n*= 68), small cell lung cancer (SCLC, *n*= 57), breast cancer (BC, *n*= 55), cervical cancer (CC, *n*= 42), nasopharyngeal carcinoma (NPC, *n*= 40), non-squamous non-small lung cancer (nsq-NSCLC, *n*= 34), endometrial cancer (EC, *n*= 21), and other solid tumors (*n*= 185). Dose-limiting toxicities (grade 3 gastrointestinal disease, and grade 4 febrile neutropenia) occurred at 10.0 mg/kg Q3W. Treatment-related adverse events (TRAEs) occurred in 94.2% of patients, with ≥grade 3 TRAEs in 28.5%. The most common TRAEs were anemia (52.0%), nausea (44.4%), fragile (42.8%), leukemia (41.6%), neutropenia (36.9%), decreased appetite (35.3%), and hypoalbuminemia (25.3%). Efficacy analyses focused on Q3W cohorts. SYS6043 demonstrated rapid and deep antitumor activity across multiple tumor types. In heavily pretreated SCLC (*n*= 50), ORR was 64.0% (95% CI, 49.2-77.1) with DCR of 92.0% (95% CI, 80.8-97.8). At 6 mg/kg Q3W (*n*= 28), ORR reached 75.0% (95% CI, 55.1-89.3), including one complete response. In OC, ORR and DCR were 46.2% and 87.2%, respectively with median PFS of 5.6 months at 6 mg/kg Q3W. Notably high response rates were also observed in BC (ORR 83.8%, DCR 100%), nsq-NSCLC (ORR, 57.1%), CC (ORR, 38.5%), NPC (ORR, 37.9%), and EC (ORR, 30.0%), indicating broad and consistent antitumor activity. **Conclusions:** SYS6043 demonstrated a manageable safety profile and robust, cross-tumor antitumor activity in a large population of patients with advanced solid tumors. The magnitude and consistency of responses across multiple histologies, including treatment-refractory tumors such as SCLC, support SYS6043 as a promising therapeutic candidate warranting further clinical and translational investigation. Clinical trial information: ChiCTR2400094683. Research Sponsor: CSPC Megalith Biopharmaceutial Co., Ltd.

T-Bren (BL-M07D1) in patients with recurrent or metastatic (R/M) ovarian cancer: Results from two phase II studies.

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Background: T-Bren is a HER2-directed antibody-drug conjugate (ADC) consisting of an anti-HER2 monoclonal antibody linked to a potent topoisomerase I inhibitor (Ed-04). In phase I studies, T-Bren demonstrated encouraging anti-tumor activity with a manageable safety profile in patients (pts) with solid tumors. Results of safety/efficacy from two phase II studies in pts with R/M ovarian cancer (OC) are presented. **Methods:** Two studies evaluated T-Bren as monotherapy in pts with R/M platinum-resistant (disease progression within 6 months of the last dose of platinum-based chemotherapy) and platinum-sensitive OC. Pts with R/M OC were treated at 3.8mg/kg or 4.4mg/kg D1 Q3W. Primary endpoints include ORR and RP2D. Pts were selected for HER2 expression (ultra-low/1+/2+/3+). **Results:** As of Nov 30, 2025, a total of 65 pts were enrolled at 3.8 (N = 51), or 4.4mg/kg (N = 14) D1Q3W. Of all pts, 28 (43.1%) pts previously received ≥3 lines of therapy. The most common grade 3 and above hematologic TRAEs were thrombocytopenia (41.5%), leukopenia (35.4%), neutropenia (35.4%), and anemia (29.2%); the most common grade 3 and above non-hematologic TRAEs were asthenia (6.2%), lymphocyte count decrease (6.2%). Grade 3 and above TRAEs, which were predominantly hematologic in nature, were able to be effectively managed with standard supportive measure including dose reductions, as demonstrated by the TRAE leading to discontinuation rate of 3.1%. No ILD was observed. No new safety signals were identified. Median follow-up was 7.8 mo. Among pts at 3.8mg/kg D1 Q3W, confirmed ORR (cORR) was 88.9% in platinum-sensitive OC and 47.5% in platinum-resistant OC. mPFS had not reached and 9-mo PFS rate was 85.7% in platinum-sensitive OC and 61.2% in platinum-resistant OC. Efficacy results are summarized in the table below. **Conclusions:** T-Bren has demonstrated promising anti-tumor activity with a manageable safety profile in heavily pre-treated pts with R/M OC. Dose 3.8mg/kg D1 Q3W was chosen as the RP3D. Phase III study of platinum-resistant OC is in preparation. Clinical trial information: NCT06031584; NCT06131450. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	Total (N=63)	3.8mg/kg Total (N=49)	3.8mg/kg Platinum-sensitive (N=9)	3.8mg/kg Platinum-resistant(N = 40)
Median prior LoT (range)	2 (1-8)	2 (1-6)	2 (1-4)	2 (1-6)
ORR, % (95% CI)	57.1 (44.0, 69.5)	59.2 (44.2, 73.0)	88.9 (51.8, 99.7)	52.5 (36.1, 68.5)
cORR, % (95% CI)	49.2 (36.4, 62.1)	55.1 (40.2, 69.3)	88.9 (51.8, 99.7)	47.5 (31.5, 63.9)
DCR, % (95% CI)	88.9 (78.4, 95.4)	89.8 (77.8, 96.6)	100 (66.4, 100)	87.5 (73.2, 95.8)
mPFS (mo) (95% CI)	9.3 (7.0, NR)	NR (7.0, NR)	NR (5.6, NR)	NR (7.0, NR)
9-mo PFS rate, % (95% CI)	50.1 (24.0, 71.6)	67.5 (46.0, 81.9)	85.7 (33.4, 97.9)	61.2 (34.5, 79.7)

*All pts who received at least one dose of T-Bren, excluding those still ongoing with insufficient follow up were used for efficacy analysis.

3004 Oral Abstract Session

Analysis of spatial atlas of ADC targets in immunotherapy-treated NSCLC to link compartment-specific target expression with tumor immune contexture, clinical outcome, and on-treatment remodeling.

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Background: The spatial distribution, co-expression patterns, immune contexture associations, and on-treatment evolution of ADC targets in NSCLC is unknown. **Methods:** The samples of 100 NSCLC patients treated with PD-1/PD-L1–based immunotherapy (STING NCT04932525) were analyzed using multiplex immunofluorescence with three 7-plex panels assessing ADC targets (Claudin18.2, TROP2, B7-H3, B7-H4), receptor co-expression (HER2, EGFR, MET, STEAP2), and immune contexture (CD8, PD-1, TIM3, LAG3, TIGIT), with PanCK and CD45 for compartment assignment. Digital pathology enabled single-cell segmentation into tumor (PanCK+), stromal, and immune (CD45+) compartments. Immune contexture was defined as Desert, Excluded, or Infiltrated by CD8 distribution. ADC target expression was quantified as the proportion of PanCK+ tumor cells expressing each target or combination. Associations with objective response (ORR), progression-free survival (PFS), and overall survival (OS) were assessed. Paired baseline/on-treatment biopsies (n = 21 pairs) evaluated treatment-induced remodeling. **Results:** Spatial profiling quantified 30 tumor-cell ADC target phenotypes. Across NSCLC, epithelial target coverage was broad, with $>$ 80% of tumor cells expressing EGFR or MET and $>$ 60% co-expressing both. Co-expression patterns were histology-dependent: EGFR/MET (±HER2) predominated in adenocarcinoma, whereas TROP2/B7-H3 co-expression was enriched in squamous carcinoma. Immune contexture shaped the ADC landscape: Infiltrated tumors showed higher tumor-cell fractions expressing EGFR, MET, TROP2, HER2, STEAP2, and B7-H3 compared with Desert tumors (all $p \leq 0.01$), while PanCK+/B7-H4 and PanCK+/CLDN18 were not contexture-associated. Clinically, B7-H4 showed a striking compartment-specific association with outcome. High abundance of B7-H4–expressing immune/stromal cells was the only phenotype replicated across ORR, PFS, and OS (stromal B7H4+: ORR 65.0% vs 38.6%, p = 0.010; PFS 12.0 vs 4.0, p = 0.013; OS 36.4 vs 13.1, p = 0.016). In contrast, tumor-cell B7-H4 predicted resistance and poor survival (tumoral B7H4+: PFS 3.5 vs 10.2, p = 0.007; OS 10.9 vs 35.6, p = 0.047). On treatment, paired biopsies demonstrated target remodeling, with increased B7-H3 expression and a concordant reduction of tumor CLDN18 by composition and membrane intensity. **Conclusions:** ADC target abundance and co-expression in NSCLC tumor cells are immune-contexture dependent and dynamically remodeled under ICI. Distinct, histology-specific co-expression patterns inform rational mono- and dual-ADC strategies. A novel, clinically actionable finding is the opposite prognostic impact of B7-H4 by spatial compartment, supporting spatially resolved biomarkers and histology- and timepoint-aware ADC±ICI selection for precision treatment in NSCLC. Research Sponsor: None.

3005 Oral Abstract Session

Clinical utility of discordances between histomorphology and molecular biomarkers in precision oncology.

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Background: Conventional molecular biomarkers guide treatment selection in precision oncology, yet therapeutic benefit remains variable even within biomarker-defined populations. Deep learning (DL) models can infer biomarker status from hematoxylin and eosin (H&E) histopathology, but systematic discordances arise between conventional biomarker assays and their histomorphology-based (HM) predictions. We hypothesized that such discordances reflect biologically meaningful tumor functional states rather than model error and may have clinical relevance. **Methods:** DL models were trained to predict 15 clinically relevant biomarkers from H&E images across six cancer types using public datasets. Discordant cases, defined as disagreement between assay-based biomarker labels and their DL prediction from H&E, were quantified and analyzed for alignment with functional gene expression states and clinical outcomes. Clinical utility was assessed in two landmark randomized trials: FINHER (HER2 prediction; N = 1010; trastuzumab randomized in HER2+ patients), and TAILORx (Oncotype DX recurrence score [RS] prediction; N = 10,273; chemotherapy randomization within RS 11–25). Adjusted Cox models tested added prognostic value and treatment benefit interactions. Primary endpoint was distant recurrence. **Results:** Models achieved strong performance for predicting the biomarkers (median AUC 0.78; range 0.65–0.87). Discordance rates ranged from 8% (MSI in colon) to 32% (KRAS in lung). In discordant cases, HM predictions correlated more strongly with functional gene expression states than the biomarker status they were trained to predict (mean Spearman r = 0.52 vs 0.31; $p < 0.001$). In FINHER, predicted HER2 status added prognostic value beyond HER2 status (p = 0.01) and predicted trastuzumab benefit in HER2+ patients (p-interaction = 0.026). In HER2+ patients, trastuzumab benefit was observed in those predicted as HER2+ (HR = 0.35, 95% CI: 0.15–0.83), but not in those predicted as HER2- (HR = 1.17, 95% CI: 0.45–3.02). In TAILORx, predicted RS added prognostic value over true RS in the no-chemo group (p = 0.005) and showed treatment interaction beyond RS within RS 11–25 (N = 1629; p-interaction = 0.021), as well as when restricted to postmenopausals (p = 0.029). Discordant patients (RS 11–25 predicted as RS > 26) derived chemotherapy benefit (HR = 0.30, 95% CI: 0.13–0.77), whereas those predicted as RS < 26 did not (HR = 0.95, 95% CI: 0.71–1.29). **Conclusions:** Discordances between molecular biomarkers and HM predictions are not random errors but reflect underlying tumor functional states. HM biomarkers may capture relevant information missed by standard assays that can improve therapeutic benefit prediction. This framework enables reinterpretation of DL pathology predictions, supports integrating H&E models to complement biomarkers, and enables derivation of functional information without outcome data. Research Sponsor: the Israel Innovation Authority - Kamin; the Zimin Institute for Artificial Intelligence Solutions in Healthcare grant; the Israel Precision Medicine Partnership program (IPMP) grant; the Israel Cancer Research Fund (ICRF).

Clinical activity and safety of RNK08954 in advanced non–small cell lung cancer (NSCLC) patients with *KRAS* G12D mutation (NCT06667544).

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Background: KRAS G12D is the most prevalent subtype of KRAS mutations across solid tumors. RNK08954 is a potent and selective KRAS G12D small molecule oral inhibitor. It inhibited proliferation of KRAS G12D-mutant cells and demonstrated significant tumor regressions in mouse xenograft models. Here we report the results of RNK08954 from Phase 1 first-in-human study. **Methods:** This ongoing multicenter open-label trial of RNK08954, comprises of: Phase 1a dose-escalation (U-BOIN design, 5 dose levels: 200, 400, 800, 1000 and 1200 mg RNK08954 single agent QD) and Phase 1b dose optimization and expansion cohorts (NSCLC, Pancreatic, and other tumor types). Key endpoints were determining the recommended doses for expansion (RDE), safety, tolerability, antitumor activity (objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression free survival (PFS)), pharmacokinetics and pharmacodynamics. Patients (pts) enrolled into the study had solid tumors not amenable to standard therapy; 0 or 1 ECOG PS; and KRAS G12D mutation. **Results:** At data cutoff (Jan 20, 2026), 106 pts were enrolled, with 47 pts presenting with NSCLC. The median age was 65 years, and 91.5% of pts had ECOG 1. Prior lines of therapy ranged between 1 and 3, with a median of 14 mo since NSCLC diagnosis. The ORR was 38.5% (15/39; 95% CI: 23.4, 55.4), DCR was 94.9% (37/39; 95% CI: 82.7%, 99.4%), median DoR was not reached (NR) at the time of analysis (Q1, Q3: 4.8, NR) and median PFS will be reported with mature data. ctDNA analysis demonstrated correlation with clinical benefits. RNK08954 demonstrated a near-dose dependent exposure across dose levels. Both 1000 and 1200 mg were chosen for RDE, and the recommended Phase 2 is considered as 1200 mg QD. Overall, treatment was tolerated, with diarrhea (78.7%), nausea (61.7%) and vomiting (55.3%) being the most frequent treatment related events (TRAEs) and were mainly Grade 1. Grade 3 TRAEs occurred in 23.4%, with diarrhea most frequent TRAEs (10.6%). No Grade 3 or higher transaminase elevation (ALT/AST) was observed, only one patient experienced Grade 3 neutropenia.There were no fatal events. Further updated results will be presented at the meeting. **Conclusions:** RNK08954 was well tolerated and displayed promising antitumor activity in pts with KRAS G12D-mutant NSCLC. The study supports further evaluation either as monotherapy or in combination with standard of care and/or novel agents. Clinical trial information: NCT06667544. Research Sponsor: None.

Phase I/IIa study of DN022150, a novel selective noncovalent small molecule KRAS G12D inhibitor in patients with advanced KRAS G12D–mutant solid tumors.

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Background: The KRAS G12D mutation is ranks among the most common RAS mutations across human cancers and is closely linked to poor clinical outcomes. DN022150 is a novel highly selective KRAS G12D inhibitor, that exerts potent antitumor effect by specifically binding to the switch-II pocket of the mutant KRAS G12D protein, this binding mechanism blocks the interaction of GDP and GTP with the mutant protein, thereby abrogating activation of the downstream of the RAS-MAPK signaling pathway. We report preliminary findings from the first-in-human study of DN022150 in patients with advanced KRAS G12D-mutant solid tumors. **Methods:** This Phase I/IIa study evaluates the safety, tolerability, pharmacokinetics (PK), and efficacy of DN022150 in patients with locally advanced or metastatic solid tumors harboring KRAS G12D mutations who have progressed following prior standard therapies. The study includes three sequential parts: dose escalation, dose expansion, and indication exploration. During dose escalation, patients receive fixed doses of DN022150. Based on integrated analysis of safety, tolerability, PK, and efficacy data from escalation phase, approximately 1-3 dose/frequency cohorts will be selected for the subsequent dose-expansion phase. The primary objective is to evaluate the safety, tolerability, and preliminary antitumor activity of DN022150 in patients with KRAS G12D-mutated advanced solid tumors. **Results:** As of January 22, 2026, a total of 56 patients were enrolled. Among them, 83.9% (47/56) had an ECOG PS of 1 and 66.1% (37/56) diagnosed with pancreatic cancer. Approximately 80% had received ≥2 prior lines of systemic therapy. Safety analysis included 49 participants (dose levels: 20-650 mg). Notably, no dose-limiting toxicities occurred across all dose levels. Grade ≥3 TEAEs were observed in 44.9% (22/49) of patients, with TRAEs in 30.6% (15/49). No grade 4-5 TRAEs were documented. TRAEs led to dose delays in 14.3% (7/49) of patients and treatment interruptions in 16.3% (8/49). The most common grade ≥3 TRAEs (≥5%) were neutropenia, anemia, and leukopenia. Tumor assessments were conducted every 8 weeks (±7 days). Among the 31 evaluable patients, treated at dose levels of 200 mg to 650 mg, an impressive 96.8% (30/31) achieved target lesion reduction at first post-baseline assessment, including 71% (22/31) with ≥20% reduction. ORR was 37.5% (3/8) at 450 mg and 31.3% (5/16) at 650 mg, with DCR of 87.5% (7/8) and 93.8% (15/16). **Conclusions:** DN022150 demonstrated favorable safety and tolerability profiles in patients with KRAS G12D-mutated advanced solid tumors, with no dose-limiting toxicities observed and manageable TRAEs. The agent showed potent antitumor activity, confirming its precise targeting of the KRAS G12D mutation. These results position DN022150 as a promising novel therapy for this molecularly defined population. Clinical trial information: CTR20242749. Research Sponsor: None.

Preliminary efficacy of GFH375 in patients with advanced cholangiocarcinoma or colorectal cancer harboring KRAS G12D mutation.

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Background: Kirsten rat sarcoma (KRAS) G12D is the most prevalent RAS mutation in human cancers, accounting for 10.6-19.2% and 5.8-10.8% of cases in colorectal cancer (CRC) and cholangiocarcinoma (CCA), respectively. Currently, the later-line therapies for metastatic CCA and CRC remain very limited. The KRAS G12D mutation is associated with poor prognosis and confers resistance to conventional chemotherapy. GFH375, a potent, selective, orally bioavailable KRAS G12D inhibitor, has demonstrated antitumor efficacy in pancreatic cancer and non-small cell lung cancer. Here we report the preliminary efficacy results of GFH375 in patients (pts) with advanced KRAS G12D mutant CCA and CRC. **Methods:** This is a phase I/II study (NCT06500676) evaluating the safety, tolerability, pharmacokinetics and efficacy of GFH375 in pts with advanced solid tumors harboring KRAS G12D mutations. Pts with locally advanced or metastatic CCA and CRC who had failed prior therapies were also enrolled. Tumor assessments were performed every 6 weeks during the first 48 weeks, and every 12 weeks thereafter. All efficacy endpoints, including objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS) were evaluated according to RECIST v1.1. Circulating tumor DNA (ctDNA) samples were collected at baseline and at the end of treatment for exploratory analyses. **Results:** As of 31 Oct 2025, twenty CCA and 41 CRC pts were treated with GFH375 once daily (400, 600 or 750 mg). Among the CCA pts (median age: 59.5 yrs; 80.0% male), 17 (85.0%) had metastatic disease at baseline, and the median prior lines of therapy were 2 (range: 1-6). ORR was 35.0% (7/20), and DCR was 95.0% (19/20). Nine out of 12 pts with stable disease (SD) had tumor shrinkage. Median PFS was 6.3 months, and median overall survival (OS) was not reached. Among those CRC pts (median age: 56 yrs; 61.0% male), all had metastatic disease at baseline, and the median prior lines of therapy were 3 (range: 1-6). Among 35 pts who had at least one post-treatment tumor assessment, ORR was 11.4% (4/35), and DCR was 77.1% (27/35). Median PFS was 4.1 months and median OS was not reached. Baseline ctDNA results were available in 19 CCA pts and 36 CRC pts. KRAS G12D mutations were detected in 14 (73.7%) CCA pts and 31 (86.1%) CRC pts. The common co-mutated genes (≥15%) in CCA were TP53, BCL2L11 and APC, while in CRC were TP53, APC, RUNX1, SMAD4 and PIK3CA. The safety profile in the 61 pts was similar to that of the whole population as previously reported. The most common treatment-related adverse events (TRAEs) (≥30%) included diarrhea, nausea, vomiting, aspartate aminotransferase increased, anemia and decreased appetite. **Conclusions:** GFH375 monotherapy has demonstrated promising antitumor activities in heavily treated pts with CCA and CRC. GFH375 monotherapy in CCA and in combination with other anti-tumor therapies for CRC is under development. Clinical trial information: NCT06500676. Research Sponsor: GenFleet Therapeutics (Shanghai) Inc.

Integrin $\alpha_v\beta_3$-targeted radionuclide therapy with ^{177}Lu-AB-3PRGD$_2$ in multiple advanced metastatic solid tumors: A prospective, single-arm, single-center, investigator-initiated clinical trial.

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Background: Tumor angiogenesis drives progression and metastasis in solid malignancies. Integrin $\alpha_v\beta_3$ is selectively overexpressed on multiple tumor cells and neovasculature with limited normal tissue expression, offering a promising therapeutic target. Our previous dose-escalation study investigated the safety and maximum tolerated dose of the integrin $\alpha_v\beta_3$-targeted radiopharmaceutical ^{177}Lu-AB-3PRGD$_2$. Building on this foundation, the current study aims to evaluate its therapeutic efficacy in patients with various advanced metastatic solid tumors. **Methods:** In this prospective, single-arm, single-center investigator-initiated clinical trial, eligible patients had histologically confirmed advanced metastatic solid tumors with documented progression after exhaustion of standard systemic therapies. Tumor integrin $\alpha_v\beta_3$ expression was confirmed by ^{68}Ga-3PRGD$_2$ PET/CT imaging. Patients received up to four cycles of ^{177}Lu-AB-3PRGD$_2$ at 3.7 GBq per cycle. The primary endpoint was ORR by RECIST 1.1. The secondary endpoints included DCR, PFS, OS, and safety. The sample size was calculated based on the primary endpoint of ORR. Assuming a null ORR of 10% and an alternative ORR of 30%, a one-sided binomial test with a significance level (α) of 0.05 and 80% power required approximately 20 evaluable patients. **Results:** From December 2023 to December 2025, 20 patients were enrolled. Of these, 5 received three treatment cycles and 5 received four cycles. The median age was 62 years (range 38–75) and 30% were female. Tumor types included radioiodine-refractory thyroid cancer (20%), breast cancer (15%), lung cancer (10%), cholangiocarcinoma (10%), renal cancer (10%), and others. At baseline, 65% of patients had ECOG performance status $\geq$2. Among 13 patients received $\geq$ 2 cycles of treatment, the ORR was 23% (3/13) and DCR was 92% (12/13), including 3 PR and 9 SD. With a median follow-up of 11.9 months, median PFS was 7.3 months and median OS was 18.5 months. Patients achieving disease control had significantly longer PFS and OS compared to those with progressive disease ($P< 0.001$). Dosimetry analysis, available for 18 patients (90%), showed a mean tumor absorbed dose of 6.8 $\pm$ 5.4 Gy/GBq. Grade 3/4 treatment-related adverse events occurred in 20% of patients (4/20), primarily hematologic toxicities including thrombocytopenia (n = 4), leukopenia (n = 2), and anemia (n = 2). **Conclusions:** Integrin $\alpha_v\beta_3$-targeted radionuclide therapy with ^{177}Lu-AB-3PRGD$_2$ demonstrated promising efficacy in disease control and tumor response, and it was generally well tolerated in patients with advanced metastatic solid tumors. These findings justify further investigation in prospective, multicenter, randomized clinical trials. Clinical trial information: NCT06375564. Research Sponsor: None.

Phase Ib results from the phase Ib/II study of [^{177}Lu]Lu-DOTA-TATE in combination with standard of care as a first-line treatment for pts with extensive-stage small cell lung cancer.

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Background: Most pts with newly diagnosed extensive-stage small cell lung cancer (ES-SCLC) relapse after initial response to standard of care (SOC; platinum/etoposide + anti–programmed death-ligand 1 [PD-L1] therapy); novel combination strategies are needed. This Phase Ib/II study (NCT05142696) assessed [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-DOTATATE) – a radioligand therapy with high affinity for somatostatin receptor 2 (SSTR2; a poor prognostic biomarker expressed in ~50% of SCLC tumors) – plus SOC. Here, we report Phase Ib data (cutoff 20 Nov 2025). **Methods:** Phase Ib was a dosage escalation study to determine the recommended dosage (RD) of ^{177}Lu-DOTATATE – alongside carboplatin AUC 5 + etoposide 100 mg/m^2 + anti–programmed cell death protein 1 (PD-1)/PD-L1 therapy (pre/post protocol amendment: tislelizumab 200 mg/atezolizumab 1200 mg, respectively) Q3W in the induction phase, and alongside anti–PD-1/PD-L1 therapy Q3W in the maintenance phase – in pts aged ≥18 y with newly diagnosed SSTR+ (by PET/CT) ES-SCLC. Cohorts of 3–6 pts were enrolled to increasing dosage levels (DLs) of ^{177}Lu-DOTATATE (backfill allowed to ≤10 pts); escalation was guided by dosage-limiting toxicity (DLT) rate (Bayesian Optimal Interval design) and other safety data. The primary endpoint was DLTs (^{177}Lu-DOTATATE–related adverse events within the 42-day DLT period). **Results:** Of 57 pts screened, 29 received treatment (median [range] age 62 [43–73] y; white 89.7%; male 44.8%; ECOG PS 0/1/2 37.9%/58.6%/3.4%; smoking history 100%; bone/brain/liver metastases 51.7%/13.8%/48.3%); 93.1% completed the induction phase (DL1 [3.7 GBq] 9/9; DL2a [5.55 GBq] 11/11; DL3a [7.4 GBq] 7/9). Median treatment duration between first/last dosage and cutoff was 14.2/9.4 months. For ^{177}Lu-DOTATATE, median (range) number of doses was 4.0 (1.0–7.0), duration was 4.1 (1–6) months, and cumulative activity was 22.7 (7.1–44.4) GBq. There were no DLTs in 17 evaluable pts. The table reports safety and preliminary efficacy data. **Conclusions:** The observed safety profile was consistent with expected toxicity; the RD for Phase II was 7.4 GBq. Clinical trial information: NCT05142696. Research Sponsor: Novartis Pharmaceuticals.

Safety and preliminary efficacy (N=29).

AEs, %	
Any: all grades; Grade ≥3	100; 100
Treatment related	100
^{177}Lu-DOTATATE related	86.2*
Serious	72.4[†]
Leading to discontinuation	24.1[‡]
Deaths due to AEs, n	2[§]
Confirmed best overall response, %	82.8[¶]
6-month duration of response rate, %	28.5 (95% CI 11.8, 47.7)
6-month progression-free survival rate, %	36.1 (95% CI 19.0, 53.6)

*Most commonly reported: thrombocytopenia (58.6) and anemia (44.8).
[†]66.7 DL1, 63.6 DL2a, 88.9 DL3a.
[‡]33.3 DL1, 27.3 DL2a, 11.1 DL3a.
[§]DL1: cardiac failure, large intestinal hemorrhage (on-treatment death); not treatment related.
[¶]100 DL1, 90.9 DL2a, 55.6 DL3a.
AE, adverse event; CI, confidence interval; DL, dosage level.

An open-label, first-in-human study of SKB500 in patients with locally advanced or metastatic solid tumors.

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Background: SKB500 is an antibody drug conjugate (ADC) composed of an antibody targeting the B7 homolog 3 (B7-H3), which is overexpressed in many types of solid tumors, conjugated to a topoisomerase I inhibitor payload via a cleavable pyrimidine-tripeptide linker. We hereby report initial results of the FIH study (NCT06736327). **Methods:** This phase 1 study comprised dose-escalation, dose-expansion, and indication-expansion phases to evaluate the safety, tolerability, pharmacokinetics, and efficacy of SKB500. Patients (pts) with unresectable solid tumors refractory to standard treatment will be enrolled and receive SKB500 at doses ranging from 2 to 18 mg/kg every three weeks (Q3W) until disease progression or unacceptable toxicity. The primary efficacy endpoint was objective response rate (ORR) assessed by investigators per RECIST v1.1. **Results:** As of Dec 23, 2025, 150 pts were treated with SKB500 across all dose levels (2-18 mg/kg). No dose-limiting toxicities (DLT) were observed during dose escalation. Based on preliminary data, the recommended phase 2 dose (RP2D) was established as 12 mg/kg. Among 97 pts treated at 12 mg/kg, the median treatment duration was 6.7 weeks. Treatment-related adverse events (TRAEs) occurred in 70 pts (72.2%), with most frequent (≥20%) being anemia (35.1%), nausea (34.0%), and white blood cell count decreased (24.7%). Grade ≥3 TRAEs occurred in 16 pts (16.5%), with most frequent being anemia, lymphocyte count decreased, pneumonia, and asthenia (each 3.1%). Pneumonitis occurred in 2 pts (2.1%; both grade 1). Both pneumonitis and grade ≥ 3 hematologic toxicities demonstrated low occurrence rates. No TRAEs led to treatment discontinuation or death. Among 55 pts treated at 12 mg/kg who had at least 6 weeks of follow-up (≥2 prior lines: 34.5%; prior platinum: 98.2%; prior IO therapy: 76.4%), the ORR was 54.5% (30/55) and the DCR was 92.7% (51/55). In tumor-specific subgroups, the small cell lung cancer (SCLC) cohort (n = 21) achieved an ORR of 71.4% (15/21) and a DCR of 100% (21/21), while the esophageal squamous cell carcinoma (ESCC) cohort (n = 18) showed an ORR of 55.6% (10/18) and a DCR of 88.9% (16/18). **Conclusions:** SKB500 demonstrated a manageable safety profile and promising antitumor activity in patients with treatment-refractory advanced solid tumors, with notable efficacy in SCLC and ESCC cohorts, supporting further clinical development. Clinical trial information: NCT06736327. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

First-in-human study of BG-C9074 (B7-H4–targeting ADC) in advanced solid tumors: Dose escalation and safety expansion.

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Background: B7-H4, a transmembrane glycoprotein, has limited expression in normal tissue, but is upregulated in a variety of solid tumors. BG-C9074 is an investigational topoisomerase I inhibitor antibody-drug conjugate (ADC) that targets B7-H4. We present results of monotherapy dose escalation and safety expansion from the ongoing phase 1 study. **Methods:** BG-C9074-101 (NCT06233942) is a first-in-human, multicenter study of BG-C9074 as monotherapy and in combination with other anticancer therapies in patients (pts) with advanced solid tumors. Pts with advanced solid tumors, irrespective of B7-H4 expression, received BG-C9074 IV every 3 weeks in escalating doses from 1 to 9 mg/kg. Endpoints included safety, preliminary antitumor activity (per RECIST v1.1) and pharmacokinetics. **Results:** As of Dec 29, 2025, 123 pts with advanced solid tumors received BG-C9074 monotherapy in phase 1a (ovarian [OC], n = 62; HR+/HER2- breast cancer, n = 28; triple negative breast cancer [TNBC], n = 18; cholangiocarcinoma, n = 11; endometrial, n = 3; squamous non-small cell lung cancer, n = 1). Median (range) prior lines were 4 (0-13). 8 pts experienced DLTs (thrombocytopenia [n = 2, 6.5 mg/kg; n = 1, 7 mg/kg], febrile neutropenia [n = 1, 6.5 mg/kg; n = 1, 7 mg/kg], neutropenic infection [n = 1, 7 mg/kg], fatigue [n = 1, 6 mg/kg], nausea [n = 1, 9 mg/kg], and unexplained death [n = 1, 9 mg/kg]). Treatment-related adverse events (TRAEs) occurred in 113 pts (91.9%); grade (gr) ≥3 in 30.1%. The most common TRAEs were nausea (53.7%; gr ≥3, 4.1%), neutrophil count decreased/neutropenia (44.7%; gr ≥3, 18.7%), and fatigue (37.4%; gr ≥3, 2.4%). Hematologic and gastrointestinal toxicities were manageable with dose modifications and/or supportive care. Among 114 efficacy-evaluable pts, confirmed ORR (cORR) was 28.1% (95% CI: 20.1-37.3), including 2 CRs (1 OC, 6.5 mg/kg, 1 TNBC, 5 mg/kg) and 30 PRs (Table); unconfirmed ORR was 33.3% (24.8-42.8; 3 CRs, 35 PRs). Responses were observed across doses and levels of B7-H4 expression, without consistent association of response with B7-H4 expression across tumor types. Median (range) study follow-up was 6.0 (0.3-17.7) months. ADC and free payload concentrations decreased in a biexponential manner with a half-life of ~7 days for ADC. Exposure for ADC and free payload increased approximately dose proportionally. **Conclusions:** BG-C9074 demonstrates a tolerable safety profile in pts with advanced solid tumors. Encouraging antitumor activity was observed in OC and TNBC. Dose expansion and optimization are ongoing. Clinical trial information: NCT06233942. Research Sponsor: BeOne Medicines Ltd.

	OC (n=55)	TNBC (n=16)	HR+/HER2- BC (n=28)	Total (N=114)
cORR, % (95% CI)	34.5 (22.2-48.6)	31.3 (11.0-58.7)	17.9 (6.1-36.9)	28.1 (20.1-37.3)
CR, n (%)	1 (1.8)	1 (6.3)	0 (0.0)	2 (1.8)
PR, n (%)	18 (32.7)	4 (25.0)	5 (17.9)	30 (26.3)
SD, n (%)	32 (58.2)	5 (31.3)	16 (57.1)	60 (52.6)
PD, n (%)	4 (7.3)	5 (31.3)	7 (25.0)	17 (14.9)
Not evaluable, n (%)	0 (0.0)	1 (6.3)	0 (0.0)	5 (4.4)

First-in-human trial of BH-30643, a novel macrocyclic, non-covalent, mutant-selective OMNI-EGFR inhibitor, in *EGFR*-mutant (*EGFR*m) NSCLC.

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Background: Macrocyclic next-generation tyrosine kinase inhibitors (TKIs) have transformed outcomes in ALK- and ROS1-positive NSCLC; such creatively designed medicines are similarly needed to improve outcomes in EGFR-mutant NSCLC. Using a novel, mutant-selective macrocyclic structure, BH-30643 was designed for super-potency against driver EGFRm, largely sparing wildtype (WT) EGFR, and with unique invulnerability to resistance from C797S with or without T790M. Here we report emerging first-in-human dose-escalation data from the SOLARA trial (NCT06706076). **Methods:** Phase 1 dose escalation used a BOIN design with backfill at potentially efficacious doses. Expansion cohorts targeted populations of interest. Patients (pts) had advanced NSCLC with EGFR and/or HER2 mutations detected on local testing (tissue or plasma). Measurable disease was required; asymptomatic untreated brain metastases (BM) were permitted. Objectives included safety, PK, and RECIST response rate (ORR). Plasma NGS was performed at baseline and on treatment. **Results:** As of 01/05/2026, 72 pts enrolled into dose escalation and backfill across 7 dose levels at a total daily dose of 20mg -160mg, median age 62, 44% Asian, 65% with history of BM, median of 3 prior lines of treatment (range 1-12). EGFR mutations included classical (38 pts), exon20ins (14 pts) and other/atypical (18 pts) or HER2 mutations (2 pts). Plasma exposures at doses of 40mg BID and above achieved $>$ 10x coverage over target EC90 and exceeded exposure levels of most contemporary EGFR TKIs. Common TRAE ($>$ 10%) were WT EGFR-associated, including diarrhea (38%), rash (28%), fatigue (15%), stomatitis (13%), and were predominantly grade 1. Bilirubin elevation was seen in 26 pts (36%) related to off-target UGT1A1 inhibition (Gilbert's-like). Grade 3 TRAE were seen in 15 pts (18%), most commonly bilirubin (8/15); DLTs included bilirubin increase and mucositis, occurring at doses $\geq$ 60mg BID. No pneumonitis was observed. Responses were observed across diverse EGFRm subsets, including in CNS. Including expansion pts, 28 pts enrolled with C797S on their most recent informative molecular testing (6 with concurrent MET+ or KRAS+), with 23 still on therapy. Of 17 with on-treatment scans, partial responses (confirmed or ongoing) were seen in 10 (59%); ORR was comparable with (50%) or without (66%) T790M. Of 9 pts with baseline C797S detected in ctDNA (3 with T790M), 7 had $>$ 99% reduction of C797S VAF on treatment. **Conclusions:** Leveraging a novel macrocyclic scaffold, BH-30643 is the first TKI monotherapy to demonstrate clinical responses against C797S both with or without T790M. High plasma exposures combined with super-potency, CNS activity, and favorable safety offers potential for deep and durable EGFR inhibition. Enrollment into backfill and expansion cohorts is ongoing to better characterize activity in both TKI-naïve and resistant pts. Clinical trial information: NCT06706076. Research Sponsor: BlossomHill Therapeutics.

Genomically personalized radiation dose de-escalation: A phase II basket radiation study in patients with pathogenic mutations in *ATM*.

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Background: *ATM* (ataxia-telangiectasia mutated) is a key DNA damage response gene, and pathogenic variants are known to cause a rare hereditary syndrome notable for extreme radiosensitivity. Somatic *ATM* inactivation is associated with markedly improved tumor control following RT. We hypothesized that *ATM*-mutant tumors could achieve effective local control with substantially lower RT doses, reducing normal tissue toxicity. This concept of genomically personalized radiation dose de-escalation was tested in a phase II trial. **Methods:** We conducted a single-arm phase II trial of low-dose RT in patients with metastatic solid tumors harboring pathogenic *ATM* mutations. Eligible patients had radiographic progression suitable for palliation and all patients received 4Gy x 2 fractions- 60% reduced compared to conventional 4Gyx5 palliation- delivered to a target lesion. The primary endpoint was 6-month local failure rate (radiographic progression or re-irradiation) and benchmarked against historical local failure control rates of 82% for 4Gyx5 standard palliation, with pre-specified analysis conducted at this initial dose level. Toxicity was graded by CTCAE criteria. **Results:** Twenty-one patients (across 9 histologies; 3 germline *ATM*, 18 somatic) were enrolled. At 6 months, 12 patients were evaluable; 10 of 12 (83.3%) achieved local control with the 4Gyx2 regimen. Notably, this included a 4.4cm angiosarcoma with a complete response by 6 months- an exceptional outcome with such a low dose. Two patients (16.7%) had local failure by 6 months. Both of these tumors retained ATM protein expression by immunohistochemistry and harbored concurrent pathogenic *TP53* mutations. In contrast, molecular analysis confirmed biallelic *ATM* loss in four patients, including the top three responders. No grade $\geq$2 toxicities or other significant RT-related side effects were observed. **Conclusions:** *ATM*-mutant tumors were effectively controlled with markedly reduced RT dose (4Gyx2), achieving local control in 83% of lesions at 6 months, comparable to historical response rates with standard palliation (4Gyx5), but with minimal toxicity. Additionally, FACETS analysis showed a stronger correlation with treatment response than germline vs. somatic mutation status, suggesting that FACETS analysis could be more informative in determining eligibility criteria for future clinical trials. These preliminary findings establish *ATM* as a novel biomarker for personalized RT dose de-escalation and compel further investigation into ATM as a therapeutic target. Clinical trial information: NCT05010031. Research Sponsor: Imaging and Radiation Sciences Program (IMRAS); U.S. National Institutes of Health.

A phase 1 study of BGB-B2033 (GPC3 x 4-1BB bispecific antibody) monotherapy in patients with selected advanced or metastatic solid tumors: First disclosure of clinical data.

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Background: GPC3 is a tumor-specific antigen that is highly expressed in hepatocellular carcinoma (HCC) and squamous non-small cell lung cancer. 4-1BB is a co-stimulatory receptor on activated T cells that promotes proliferation, survival and cytolysis of T cells. BGB-B2033, a novel, IgG-based GPC3 x 4-1BB bispecific antibody with Fc region engineered to prevent FcγR binding and increase half-life, activates T cells while minimizing systemic toxicity. BGB-B2033 is being studied as monotherapy or in combination in patients (pts) with advanced GPC3-expressing solid tumors in a first-in-human phase 1 trial (NCT06427941). Here we report initial results from the monotherapy dose escalation and safety expansion (part A). **Methods:** In part A, eligible pts with ≥1 prior systemic therapy received ascending dose levels of BGB-B2033. The primary objective was safety. Secondary objectives were preliminary antitumor activity (per investigator-assessed RECIST v1.1), pharmacokinetics, and immunogenicity. Dose escalation followed the Bayesian mTPI-2 design. **Results:** As of December 10, 2025, part A enrolled 61 pts; 60 (98.4%) had HCC and 56 (91.8%) were Asian. Median (range) prior lines of therapy were 2.0 (1-6). The median (range) study follow-up was 3.9 (0.3-14.9) months. Treatment-emergent adverse events (TEAEs) were reported in 63.9% of pts across the 8 dose levels; 27 (44.3%) pts had treatment-related (TR)-TEAEs. Six grade ≥3 TR-TEAEs occurred in 5 (8.2%) pts: alanine aminotransferase (ALT) increased, aspartate aminotransferase increased, blood bilirubin increased, drug eruption, lymphopenia and neutrophil count decreased (1.6% each). One dose-limiting toxicity (ALT increased) resolved after dose reduction. Immune-mediated adverse events (imAEs) were reported in 4 (6.6%) pts; all were grades 1-2. One pt reported a grade 1 infusion-related reaction. In the 59 efficacy-evaluable pts with HCC, confirmed ORR was 20.3% (95% CI: 11.0-32.8), with 12 partial responses; 23 pts had stable disease, 23 had progressive disease, and 1 pt was not evaluable. Ten of the 12 responders had ongoing response at data cutoff. A preliminary dose response was observed; at doses above the predicted target efficacious dose, confirmed ORR was 28.9% (11/38). Serum concentration profiles of BGB-B2033 exhibited target-mediated drug disposition at lower dose levels and decreased in a more biexponential manner at higher dose levels. Soluble 4-1BB, a pharmacodynamic marker, showed a greater increase at higher dose levels. **Conclusions:** BGB-B2033 was generally well tolerated, with limited imAEs in this predominantly 2L+ HCC population. Durable responses were observed in pts with advanced HCC, including pts with prior PD-(L)1-based treatment. Triplet dose escalation with tislelizumab and bevacizumab as well as monotherapy dose expansion are ongoing. Clinical trial information: NCT06427941. Research Sponsor: BeOne Medicines Ltd.

3017 Rapid Oral Abstract Session

Luvometinib in adults with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas: A randomized, double-blind, placebo-controlled, phase 3 trial.

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Background: Neurofibromatosis type 1 (NF1) related plexiform neurofibromas (PNs) is associated with significant morbidity, including pain, disfigurement and functional impairment. Surgical treatment for PNs may be limited due to tumor size, location and extent. A randomized, double-blind, placebo-controlled, phase 3 trial (NCT05913037) was conducted to evaluate the efficacy and safety of Luvometinib in adults with inoperable NF1 PN causing significant morbidities. **Methods:** Adults (≥18 yrs) with NF1 and symptomatic, inoperable PNs were randomized in a 2:1 to receive oral Luvometinib (8 mg daily) or placebo in 28-day cycles, stratified by baseline (BL) NRS-11 tumor pain score (≥2 or < 2). An interim analysis was performed at 16 months after the last patient randomization. The primary endpoint was confirmed objective response rate (ORR) by Blinded Independent Review Committe (BIRC) per REiNS criteria. Key secondary endpoints included ORR by the investigator (INV), duration of response (DOR), time to response (TTR) by BIRC and INV, pain severity and safety. **Results:** 167 adults were randomized to receive luvometinib (n = 112) or placebo (n = 55). As of the data cutoff on Aug 19, 2025, the median follow-up was 19.7 months(range: 1.4-25.5). The confirmed ORR assessed by BIRC was 43.8% (95% CI, 34.4-53.4) with luvometinib, compared with 10.9% (95% CI, 4.1-22.3) with placebo (p < 0.0001). Luvometinib led to a rapid response (median 3.9 months). The median DOR was 15.1 months (95% CI, 14.8-NE), with a 85.2% rate of DOR ≥12 months with luvometinib. A greater proportion of patients with BL overall tumor pain scores ≥2 experienced a reduction in pain score of at least 2 points with luvometinib compared to placebo (81.0% vs. 53.6%). The most common treatment-emergent adverse events (TEAEs) were folliculitis, increased CPK, mouth ulcer, diarrhea. Serious AEs occurred in 14.3% (luvometinib) versus 7.3% (placebo) of pts. TEAEs led to discontinuation was 1.8% in both groups. **Conclusions:** Our study demonstrated that luvometinib achieved a statistically significant ORR per BIRC compared with placebo, with rapid and durable response, significant reductions in pain severity, and an overall manageable safety profile. These findings suggest that luvometinib may emerge as a new standard treatment for patients with NF1 and symptomatic, inoperable PNs. Clinical trial information: NCT05913037. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

The efficacy and safety of azvudine (FNC) in phase 1 investigator-initiated study in patients with advanced solid tumors.

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Background: Azvudine has been approved in China for treatment of AIDS and COVID-19. Serial preclinical studies demonstrated remarkable anti-tumor activity, especially in combination with anti-PD-1 therapy. The mechanistic studies have shown that FNC could significantly reduce myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment. This ongoing phase 1 investigator-initiated study aims to further confirm the nonclinical findings of FNC in cancer patients. **Methods:** Patients with advanced solid tumors who had progressed on standard of care (SoC) therapies were eligible in this single-arm, single-center, open-label study with the primary objective of safety and clinical efficacy. All subjects received the SoC of physician's choice in combination with FNC which was administered orally once daily, with dose escalated across six dose levels: 3mg, 4mg, 5 mg, 6 mg, 7 mg, and 8 mg. **Results:** As of 31 Oct, 2025, 25 subjects were enrolled, including 22 subjects with pMMR/MSS CRC, 3 subjects with NSCLC. All CRC subjects received the triple-combination regimen of FNC, penpulimab, and fruquintinib. Among the CRC subjects, the total ORR was 18.2%, DCR was 72.7%, the mPFS was 4.3 months (95%CI: 3.32,6.31) and the mOS was 7.6 months (95% CI: 5.09,NR). Four subjects achieved the radiographic response (PR), 2 subjects from the 6 mg dose group, and one subject each from the 5 mg and 7 mg dose groups. A subgroup analysis based on liver metastasis status was performed for the 15 subjects enrolled in the 5 mg, 6 mg, and 7 mg dose groups. The ORR for the 7 subjects without liver metastases was 57.1%, the DCR was 100%, and the mean treatment duration was 33.6 weeks. In contrast, among the 8 subjects with liver metastases, the ORR was 0%, the DCR was 87.5%, and with a mean treatment duration of 16.7 weeks. No DLTs occurred in the 16 evaluable subjects during the DLT observation period. TEAEs were reported in 96.0% of patients, with a TRAE incidence of 36.0%. Most TRAEs were Grade 1/2, including hepatic dysfunction (12.0%), γ-GTP increased (8.0%), weight decreased (4.0%), diarrhoea (4.0%), insomnia (4.0%), and ALP increased (4.0%). One Grade ≥3 TRAE weight decreased occurred in the 3 mg group. SAEs were reported in 24.0% (6/25) of subjects, with only one case of weight decreased in 3 mg group considered possibly related to FNC. Two subjects (8.0%) discontinued treatment due to TEAEs, one of which was abnormal liver function, possibly related to FNC. No treatment related deaths, dose interruptions, or dose reductions were reported. **Conclusions:** Overall, the combination of FNC with PD-1 and VEGFR inhibitors was safe and well-tolerated, with encouraging clinical activity in advanced/metastatic pMMR/MSS CRC. Clinical trial information: chiCTR2600116125. Research Sponsor: None.

Discovery from single-cell RNA sequencing profiles of 18 CPTAC glioblastoma patients and validation in bulk profiles of 138 TCGA patients and two human-derived cell lines of a whole-transcriptome predictor of overall survival and drug targets by using quantum mechanics–based AI/ML.

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Background: Single-cell, more than bulk, multi-omic data, are small-cohort, noisy, and high-dimensional, and extremely difficult to model. We have developed artificial intelligence and machine learning (AI/ML) to overcome these challenges [doi: 10.1073/pnas.0530258100]. We have shown that our algorithms are uniquely able to discover accurate, precise, actionable, and mechanistically interpretable predictors, applicable to the general population, from the bulk multi-omes of as few as 19 patients [doi: 10.1158/1538-7445.AM2025-CT227]. We have demonstrated that these predictors of overall survival (OS) and drug targets consistently validate across laboratories and sometimes across indications, in federated and imbalanced studies and over time, and outperform all others where they exist [doi: 10.1063/1.5099268, 10.1200/JCO.2024.42.16_suppl.10043]. Here, we demonstrate our AI/ML in single-cell data. **Methods:** We used our algorithms to derive models from the single-cell RNA sequencing profiles of 18 glioblastoma (GBM) Clinical Proteomic Tumor Analysis Consortium (CPTAC) patients, and tested them in the bulk profiles of 138 patients in the Cancer Genome Atlas (TCGA). CPTAC and TCGA both profiled the core primary tumor of each patient, but CPTAC also sampled the peritumoral brain tissue. The two cohorts are indistinguishable in terms of their gender, age, and OS distributions, but they significantly differ in terms of race. **Results:** A whole-transcriptome model was discovered that is correlated with OS among the 18 CPTAC patients, with a Kaplan-Meier median OS difference of 30 months between the two groups of predictor-stratified patients, and a Cox hazard ratio of 4.6 and a concordance index of 87% (log-rank and Wald P-values $< 5.0\times10-2$). When tested in the TCGA cohort, the model was a similarly significant predictor of OS. In both cohorts, despite the differences in profiling protocols and cohort demographics, the predictor outperformed the best standard-of-care indicator of OS in GBM, i.e., age. Consistent with a previous whole-genome predictor, which was derived from bulk DNA profiles, and validated in a clinical trial [doi: 10.1063/1.5142559], shorter OS was associated with overexpression of such anterior/posterior pattern specification genes as the Notch ligand *DLL3*. We experimentally validated, in two human-derived cell lines, that its putative activator, *METTL2A*, is required for GBM cells' proliferation and viability [doi: 10.1158/1538-7445.AM2025-3686]. **Conclusions:** Our algorithms can discover predictors of patients' OS and drug targets, in real-world small-cohort, noisy, and high-dimensional — single-cell — in addition to bulk multi-omic data, and the predictors experimentally validate. Research Sponsor: NIH/National Cancer Institute (NCI) Physical Sciences in Oncology Project, "Multi-Tensor Decompositions for Personalized Cancer Diagnostics and Prognostics," U01 CA-202144; NSF/American Institute of Mathematics (AIM) Quantum Research Community Project, "AIM Q"; The Musella Foundation in partnership with StacheStrong; Utah Science, Technology, and Research (USTAR) Initiative.

Quantum mechanics-based multi-tensor AI/ML as predictor of patients' overall survival, gene targets, and drug responses from their glioblastoma tumors' whole genomes.

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Background: The drug failure rate has increased to ~95%, despite the growth in targeted therapies. As clinical trials demonstrated, a targeted gene alone does not predict whether patients have longer life expectancy in response to the drug. As studies with model organisms showed, the effect of the drug, and the mechanisms underlying it, depend on the entire multi-ome. But multi-omic data are small-cohort, noisy, and high-dimensional, i.e., extremely difficult to model. **Methods:** We have developed our artificial intelligence and machine learning (AI/ML) to overcome these challenges [doi: 10.1073/pnas.0530258100, 10.1158/1538-7445.AM2025-CT227]. We demonstrated our algorithms in the unsupervised modeling of, e.g., whole genomes of 85 astrocytoma patients. Mechanistic interpretation showed that the modeling blindly removed batch effects, separated normal demographic variations, and discovered a disease-specific genome-wide pattern of DNA copy-number alterations. This pattern was used to derive an actionable predictor of patients' overall survival (OS) and gene targets to sensitize their tumors. We computationally validated both the predictor and the modeling in federated studies of mutually-exclusive sets of 59–251 patients. The modeling repeatedly discovered a representation of the predictor in every study, across astrocytoma grades II, III, and IV, i.e., glioblastoma (GBM), patients. We experimentally validated the predictor in a clinical trial of 79 GBM patients, initially retrospectively, and, in a four-year follow up, also prospectively [doi: 10.1063/1.5142559, 10.1145/3624062.3624078, 10.1200/JCO.2024.42.16_suppl.e14028]. In all the cohorts, the predictor, with 75–95% concordance with OS, was more accurate than all standard-of-care indicators. With 100% reproducibility among Complete Genomics, Illumina, and Ultima whole-genome sequencing, and $>$ 99% when including Affymetrix and Agilent DNA microarrays, the predictor was also the most precise. **Results:** Here, we describe functional genomic experimental validation of both a predicted gene target and the predicted tumors' responses to the targeting. Guide RNAs were designed and a lentiviral CRISPR-Cas9 all-in-one vector was utilized to knock out the modeling-predicted target *METTL2A*. Knockout validation at the protein level was performed using Western blot. Knockout in the patient-derived GBM cell lines U-87 MG and U-118 MG resulted in significantly attenuated cell viability and proliferation. The level of attenuation was significantly different between the cell lines, consistent with their whole genome-based predicted responses. **Conclusions:** Our quantum mechanics-based multi-tensor AI/ML solved the 75-year-old problem of correctly predicting — patients' OS, drug responses, and gene targets — from their GBM tumors' whole genomes. Research Sponsor: NIH/National Cancer Institute (NCI) Physical Sciences in Oncology Project, "Multi-Tensor Decompositions for Personalized Cancer Diagnostics and Prognostics," U01 CA-202144; NSF/American Institute of Mathematics (AIM) Quantum Research Community Project, "AIM Q"; The Musella Foundation in partnership with StacheStrong; Utah Science, Technology, and Research (USTAR) Initiative.

Development and clinical utility of an H&E-based tumor origin prediction model.

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Background: Tumor of unknown primary origin remains a critical unmet need in oncology, as histologic and anatomic diagnoses are essential for ensuring effective and timely therapies. We previously developed the Tempus Tumor Origin (TO) Laboratory Developed Test (LDT), an RNA sequencing-based machine learning algorithm that discriminates between clinically relevant cancer subtypes. However, RNA-sequencing data is not always available, with a failure rate that can be $>$ 20% in the literature. In this study, we develop and assess the accuracy of a hematoxylin and eosin (H&E)-based machine learning algorithm to predict tumor origin. We also explore combining predictions from H&E and RNA models to improve accuracy further. **Methods:** We curated a cohort of 93,770 H&E whole slide images (WSIs) of tumor biopsies and surgical resections across 67 cancer subtypes from 73,634 patients. The cohort was split into 60/20/20 for training, validation, and testing, stratified by cancer subtypes and clinical covariates. We extracted tile embeddings from WSIs using a foundation model, H-optimus-0, and trained an attention-based multiple instance learning model to predict cancer subtype labels derived from clinically abstracted documents. Using a subset of 54,878 samples that also have predictions from the RNA-based Tempus TO algorithm, we trained and evaluated a multilayer perceptron multimodal model that takes the prediction scores from the H&E model and the RNA model as input. **Results:** On 7,092 test set samples that had both modalities available, the H&E, RNA, and multimodal models achieved top-1 accuracies of 0.85, 0.91, and 0.92 and top-3 accuracies of 0.94, 0.97, and 0.97, respectively. Among subtypes with at least 30 samples in the test set, the multimodal model statistically significantly outperformed the RNA model on five subtypes and underperformed on two. In addition, the H&E model had a top-1 accuracy of 0.77 and a top-3 accuracy of 0.90 on 3,028 samples in the test set that failed RNA sequencing due to quantity insufficient (QNS). Table 1 presents H&E model performance on the RNA QNS samples by diagnosis subtypes. **Conclusions:** We developed a high-performing H&E-based algorithm to predict tumor origin. With shorter turnaround time and wider availability, the H&E model can potentially deliver accurate tumor origin predictions faster and, critically, in cases where RNA-seq is unsuccessful or unavailable. Furthermore, leveraging both H&E and RNA in a multimodal model may improve the performance of future tumor origin algorithms.
Research Sponsor: None.

H&E model performance on RNA QNS test set samples in the five most prevalent diagnosis subtypes and other subtypes combined.

Diagnosis subtype	N	Top-1 accuracy (%)	Top-3 accuracy (%)
Lung adenocarcinoma	497	84	94
Prostatic adenocarcinoma	387	92	95
Breast carcinoma	348	83	95
Colorectal adenocarcinoma	327	85	93
Pancreatic adenocarcinoma	272	78	94
Other	1,197	64	83

Prospective prediction of alisertib-induced Aurora-A kinase resistance mutations in patients with metastatic ER+ breast cancer using an innovative artificial intelligence approach.

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Background: Pharmacological blockade of Aurora-A mitotic kinase (AURKA) oncogenic pathway represents a promising therapeutic strategy to inhibit breast cancer plasticity and progression. However, treatment with the selective AURKA inhibitor alisertib is followed by acquired on-target mutations in a subset of patients that are linked to alisertib resistance and tumor progression. Current resistance mechanisms are typically identified retrospectively after therapeutic failure. We evaluated whether Dynaptive, a structure- and evolution-aware artificial intelligence (AI) platform, could prospectively predict treatment-induced AURKA resistance mutations prior to experimental observation. **Methods:** We identified acquired on-target mutations in patients from the alisertib Phase-II clinical trial. These mutations were cross-matched against Dynaptive predictions that had been generated independently of any experimental resistance data. Dynaptive integrates protein conformational ensembles and evolutionary sequence constraints to predict mutational hotspots and assess their functional and drug-binding impact. Identified mutations were evaluated against large-scale population datasets to determine natural occurrence. **Results:** Several AURKA mutations observed in patients that showed resistance to alisertib were prospectively predicted by Dynaptive despite being entirely absent from prior population datasets. These mutations were not observed previously in either healthy or cancer cohorts described in the public domain. Significantly, the most frequently occurring AURKA resistance mutation occurred at a residue ranked second among predicted mutational hotspots and were predicted to reduce alisertib binding affinity by $\geq$10-fold. Across all variants, absence from population datasets and emergence only following treatment support a treatment-induced resistance mechanism. **Conclusions:** A structure-aware AI platform prospectively identified clinically relevant, treatment-induced AURKA resistance mutations prior to experimental detection. These findings demonstrate the feasibility of predictive modeling to anticipate resistance mechanisms and support the development of next-generation AURKA inhibitors optimized to overcome mutations-driven resistance and to improve therapeutic efficacy, safety and durability. Research Sponsor: None.

Light-activated EGFR antibody–drug conjugate: Analysis of selectivity and translational profile for first-in-human evaluation.

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Background: Conventional antibody–drug conjugates (ADCs) are limited by systemic toxicity and narrow therapeutic windows. Cetuximab-I21-2 is a first-in-class, EGFR-targeted ADC conjugated to a Heloporfin-derived photosensitizer engineered for activation exclusively at the tumor site using red-light irradiation. This approach enables biologically targeted delivery with externally controlled cytotoxic activation, designed to improve the therapeutic index and support safe translation into first-in-human studies. **Methods:** In vitro cytotoxicity was evaluated across EGFR-high, intermediate, and low tumor cell lines (A431, HCC827, Huh7, NCI-N87, MIA-PaCa-2) with or without red-light activation (1–5 J/cm^2). Cellular ROS generation, mitochondrial membrane potential disruption, and photodynamic injury were assessed by live-cell imaging. In vivo activity was tested in A431 xenograft-bearing B-NDG mice following a single intravenous dose of Cetuximab-I21-2 (35.3 mg/kg) and localized tumor irradiation at 100 or 200 J. Safety evaluation included body-weight trends and clinical observations. **Results:** Cetuximab-I21-2 showed negligible dark toxicity up to several μg/mL, confirming that the payload remains inactive without illumination. Upon irradiation, the ADC demonstrated potent, energy-dependent cytotoxicity (IC50: 0.05 μg/mL in A431 and 0.14 μg/mL in HCC827 at 5 J/cm^2), with reduced effects in EGFR-low models, supporting a target- and activation-dependent mechanism. Illumination triggered rapid singlet-oxygen and ROS production and immediate mitochondrial depolarization. In vivo, Cetuximab-I21-2 achieved irradiation-dependent tumor suppression, reaching 22.2% inhibition at 200 J, and produced histologic photodynamic injury localized to the tumor. Treatment was well tolerated: animals exhibited only transient (<10%) weight loss and no systemic toxicity. **Conclusions:** Cetuximab-I21-2 demonstrates a strong translational profile with selective activation, robust preclinical antitumor activity, and a favorable safety margin. The spatial control offered by light activation may enable dose-sparing strategies and reduce systemic adverse events typically associated with ADCs. These findings support advancement toward IND-enabling studies, including optimization of clinical illumination parameters, device–drug integration, and early feasibility planning for first-in-human evaluation in EGFR-expressing solid tumors. Research Sponsor: Shanghai Biophy Biological Pharmaceutical Co., Ltd.

First-in-human study of ALK201, a FGFR2b-targeting antibody-drug conjugate (ADC) for patients (pts) with advanced solid tumors.

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Background: ALK201 is a novel ADC comprising of an anti-FGFR2b humanized monoclonal antibody conjugated to topoisomerase I inhibitor Exatecan via a cleavable and highly hydrophilic linker. ALK201 exhibited potent anti-tumor activities in preclinical studies with a tolerable safety profile. Here we report the preliminary results of ALK201 monotherapy for pts with advanced solid tumors from the first-in-human phase I/II trial (NCT06656390). **Methods:** This is an ongoing, multicenter, open-label study being conducted in the US, China, and Australia, which consists of two parts, dose-escalation (Part A) and dose-expansion (Part B). The Part A employs the Bayesian optimal interval (BOIN) with backfilling (BF) design to determine the MTD and recommended doses for Part B. In Part A, pts with advanced solid tumors refractory to standard therapies were treated with ALK201 at 1.5-9.6 mg/kg Q3W. Part B was dose expansion at effective doses identified in Part A. The primary endpoint was safety. Secondary endpoints included efficacy and pharmacokinetics (PK). **Results:** As of December 31, 2025, 38 pts with advanced solid tumors were enrolled in Part A and dosed at 1.5 mg/kg (n=4), 3.0 mg/kg (n=3), 4.8 mg/kg (n=5) ,7.2 mg/kg (n=12), 8.4 mg/kg (n=5) and 9.6 mg/kg (n=9). The median age was 58 years (range 25-74). All pts progressed after receiving a median of 3 prior lines of standard anti-cancer therapy (range 1-8). 28 (73.7%) were Asian and 10 (26.3%) were White. No dose-limiting toxicities (DLTs) have been observed at doses up to 9.6 mg/kg. MTD was not reached. Treatment-related adverse events (TRAEs) occurred in 78.9% pts. The most common TRAEs (incidence ≥10%) were nausea (44.7%), anemia (21.1%), vomiting (21.1%), decreased appetite (13.2%), white blood cell count decreased (13.2%), neutrophil count decreased (10.5%), platelet count decreased (10.5%), AST increased (10.5%), hypoalbuminemia (10.5%) and fatigue (10.5%). Grade ≥3 TRAEs occurred in 23.7% pts and were exclusively reversible hematologic toxicities. Treatment related ocular adverse events limited to grade 1 in 4 pts (10.5%) with minimal clinical impact. Among 25 pts who were evaluable for response, 6 achieved a partial response (PR), 11 achieved stable disease (SD) in best of response. The objective response rate (ORR) and disease control rate (DCR) were 24% (95% CI: 9.4, 45.1) and 68% (95% CI: 46.5, 85.1), respectively. The ORR and DCR in ≥ 7.2mg/kg groups were 35.7% (5/14) and 100% (14/14), respectively. PK analysis showed a dose-dependent ADC and total antibody exposure at doses of 1.5-9.6 mg/kg. ALK201 elimination half-life was approximately 6-11 days. **Conclusions:** ALK201 demonstrated a favorable safety profile in pts with pretreated advanced solid tumors. Promising anti-cancer activity was observed at doses of 7.2 mg/kg and above, warranting further investigation in those effective dose levels. Clinical trial information: NCT06656390. Research Sponsor: Shanghai Allink Biotherapeutics.

Trastuzumab deruxtecan (T-DXd) for pretreated patients in China with HER2 IHC 3+ solid tumors: DESTINY-PanTumor03 Part 1 primary analysis.

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Background: Treatment options in China are limited for patients with late-line, HER2-expressing advanced solid tumors. In Part 1 of DESTINY-PanTumor02, T-DXd showed clinically meaningful antitumor activity in HER2-expressing advanced solid tumors, with the greatest benefit observed in HER2 IHC 3+ tumors. Based in part on these findings, T-DXd has been approved in multiple countries worldwide, including the US, as treatment for patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and/or have no satisfactory alternative therapies. Following the results from DESTINY-PanTumor02, DESTINY-PanTumor03 is evaluating T-DXd in patients in China with HER2-expressing advanced solid tumors. The primary analysis of Part 1 of DESTINY-PanTumor03 is presented here. **Methods:** DESTINY-PanTumor03 is an open-label, Phase 2 study (NCT06271837). Part 1 is evaluating T-DXd (5.4 mg/kg IV Q3W) in patients in China with HER2 IHC 3+ (by central testing), locally advanced, unresectable, or metastatic solid tumors (excluding breast and gastric cancers) after ≥1 prior systemic treatment for advanced disease or without treatment options. The primary endpoint is confirmed objective response rate (ORR) by independent central review (ICR) per RECIST 1.1. Secondary endpoints include ORR by investigator assessment (INV) per RECIST 1.1; duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) by INV and ICR per RECIST 1.1; overall survival (OS); and safety. **Results:** At primary analysis data cutoff (November 28, 2025), 50 patients with biliary tract (n = 11), colorectal (n = 6), cervical (n = 10), endometrial (n = 7), ovarian (n = 5), non-small cell lung (n = 7), or other cancers (n = 4) had received T-DXd. Median follow-up duration was 9.9 (range 1.1–18.3) months. Median number of prior treatment regimens was 2 (range 1–10). By ICR, ORR (95% CI) was 58.0% (43.2, 71.8), median DOR (95% CI) was 15.4 (12.5, not evaluable [NE]) months, DCR (95% CI) at Week 6 was 88.0% (75.7, 95.5), and median PFS (95% CI) was 15.7 (7.2, NE) months. By INV, ORR (95% CI) was 56.0% (41.3, 70.0). Median OS was not reached. Grade ≥3 drug-related adverse events occurred in 31 (62.0%) patients, and adjudicated drug-related interstitial lung disease / pneumonitis occurred in 4 (8.0%) patients (Grade 2 n = 3 [6.0%], Grade 3 n = 1 [2.0%]). **Conclusions:** T-DXd demonstrated durable and clinically meaningful antitumor activity in pretreated patients in China with HER2 IHC 3+ advanced solid tumors. Safety was generally consistent with the established T-DXd profile. Results from DESTINY-PanTumor03 Part 1 support T-DXd as a tumor-agnostic treatment for patients in China with HER2 IHC 3+ solid tumors. Clinical trial information: NCT06271837. Research Sponsor: AstraZeneca.

Extrapulmonary small cell carcinoma treated with conventional or tumor-targeted topoisomerase I inhibition plus ATR blockade: Clinical outcomes and molecular correlates.

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Background: Extrapulmonary Small Cell Carcinoma (EPSCC) is a rare (0.1–0.4% of all cancers), aggressive neuroendocrine cancer with poor outcomes (Median PFS 2-4 months), no established second-line standard, and limited prospective data. We evaluated ATR inhibition with berzosertib combined with topoisomerase I (TOP1) inhibition with topotecan or sacituzumab govitecan (SG) and explored molecular correlates of response. **Methods:** Given the rare nature of EPSCC, patients were pooled from 3 prospective phase II trials evaluating topotecan or SG with berzosertib (NCT03896503, NCT02487095, NCT04826341) without intent for direct regimen comparison. Eligible patients had platinum-refractory EPSCC and received treatment at recommended phase II doses. Endpoints included efficacy and safety, with exploratory molecular correlates including somatic mutations, copy number alterations, circulating tumor DNA, tumor RNA sequencing, and pharmacogenomic analyses. **Results:** Of the 41 patients enrolled, 34 were evaluable (topotecan+berzosertib, n=20; SG+berzosertib, n=14). ORR based on RECIST was 10% (95% CI, 2.8–30.1) with topotecan+berzosertib and 21.4% (95% CI, 7.6–47.6) with SG+berzosertib; disease-control rates were 45% and 86%, respectively. Durable clinical benefit was observed in subsets of patients, with PFS $\geq$6.8 months and OS up to 19.7 months in the SG cohort, and OS $>$18 months in patients treated with topotecan+berzosertib. Patients with prolonged PFS represented multiple primary sites, including bladder, prostate and laryngeal. Grade 3–4 hematologic adverse events were more frequent with topotecan+berzosertib, whereas gastrointestinal toxicity and alopecia were more common with SG+berzosertib; no unexpected safety signals were observed. In the SG cohort, UGT1A1 intermediate and poor metabolizers experienced higher rates (90%) of grade 3–4 toxicities than normal metabolizers (10%). Early ctDNA declines correlated with radiographic response, while rising ctDNA preceded progression; baseline ctDNA correlated with tumor burden ($r = 0.83$; $P = 0.006$). Transcriptomic analyses demonstrated enrichment of E2F-driven and neuroendocrine lineage programs in responders (NES = 1.64–1.67; $P < 0.001$). **Conclusions:** In relapsed or refractory EPSCC targeting tumor replication stress through combined ATR and TOP1 pathway inhibition yielded clinically meaningful activity. Tumor-targeted TOP1 delivery with SG plus berzosertib achieved disease-control rate and a manageable safety profile. UGT1A1 phenotype was associated with toxicity in the SG cohort, supporting the relevance of pharmacogenomic-guided risk stratification. Correlative analyses identified E2F-driven transcriptional programs, neuroendocrine lineage signatures and early ctDNA suppression as promising biomarkers for future trials. Clinical trial information: NCT03896503, NCT02487095, NCT04826341. Research Sponsor: None.

First-in-human phase I/II study of MRG006A, a first-in-class Glypican-3 (GPC3)–targeted antibody-drug conjugate (ADC), in patients (pts) with advanced hepatocellular carcinoma (HCC).

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Background: Pts with advanced HCC face limited treatment options beyond immunotherapy and anti-angiogenic agents. GPC3, a surface antigen overexpressed in HCC and associated with poor prognosis, represents a promising therapeutic target due to its tumor-specific expression. MRG006A, a potential first-in-class GPC3-targeted ADC, demonstrated potent pre-clinical anti-tumor activity. Here we report the preliminary safety and efficacy of MRG006A in advanced HCC with intermediate/high GPC3 expression from a phase I/II trial. **Methods:** MRG006A-001 (NCT07093970) is an ongoing first-in-human, open-label, multi-center phase I/II study. The phase I study comprises dose escalation (Ia) and dose optimization/expansion (Ib) stages. The dose-escalation employed an accelerated titration plus 3+3 design. Eligible pts who had failed standard treatment received MRG006A intravenously at 1.6-6.4 mg/kg every three weeks (Q3W). GPC3 expression was only required for dose expansion cohorts. The primary endpoints were safety and tolerability. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), clinical benefit rate (CBR), etc. **Results:** As of Dec 19, 2025, the maximum administered dose was established as 6.4 mg/kg Q3W, with ≥ G3 treatment-related adverse event (TRAE) of platelet count decreased reported in all six pts at this dose level and dose-limiting toxicity (G4 platelet count decreased) observed in one patient. During dose escalation, tumor response was observed at 3.2 mg/kg and 4.8 mg/kg. Accordingly, dose optimization in phase Ib proceeded with three levels (3.2, 4.0, and 4.8 mg/kg Q3W). Twenty-six HCC pts with intermediate or high GPC3 expression were enrolled across three cohorts; 61.5% had BCLC stage C disease; median 2 (range 1-4) prior lines of therapy, and 25 (96.2%) had received immune checkpoint inhibitors and anti-angiogenic agents. Among 25 efficacy evaluable pts, ORR, DCR and CBR were 23.1%, 68.0% and 32.0%, respectively. In pts with high GPC3 expression (n=12), ORR, DCR and CBR increased to 33.3%, 75.0% and 50.0%, respectively; median PFS and DOR were 7.0 and 4.2 months (median follow-up 5.7 months). Most pts (24 [92.3%]) experienced TRAE of any Grade. TRAEs of ≥ G3 were reported in 11 (42.3%) pts . The most common TRAEs were platelet count decreased (88.5%), blood bilirubin increased (50.0%), AST increased (46.2%), white blood cell count decreased (38.5%), and nausea (30.8%). No treatment-related permanent discontinuations or deaths occurred. **Conclusions:** MRG006A demonstrated manageable safety and promising anti-tumor activity in heavily pretreated pts with GPC3-expressing advanced HCC. Our findings support the therapeutic potential of GPC3-directed ADC and merits further clinical investigations. Clinical trial information: NCT07093970. Research Sponsor: None.

Consideration of adjusted ideal body weight dosing in BG-C9074 (B7-H4–targeting ADC) from pharmacokinetics, efficacy, and safety perspectives.

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Background: B7-H4 is a transmembrane glycoprotein that is upregulated in a variety of solid tumors. BG-C9074 is an investigational topoisomerase I inhibitor antibody-drug conjugate (ADC) that targets B7-H4. We present results of the pharmacokinetic (PK) and exposure-response (ER) analyses supporting the implementation of adjusted ideal body weight (AiBW)-based dosing in the ongoing phase 1 study. **Methods:** BG-C9074-101 (NCT06233942) is a first-in-human, multicenter study designed to assess BG-C9074 as monotherapy and in combination with other anticancer therapies in patients (pts) with advanced solid tumors. Total body weight (TBW) and AiBW-based dosing were evaluated at 1-7 mg/kg and 6.5-9 mg/kg, respectively, administered intravenously every 3 weeks. PK samples were collected to measure serum ADC and plasma free P1021 payload analytes at Cycle 1 and steady state (Cycle 5). A population PK model, incorporating both ADC and payload, was developed and used to evaluate safety and efficacy ER relationships. **Results:** As of October 30, 2025, PK, safety, and efficacy data were available for 107 pts with advanced solid tumors. TBW dosing of BG-C9074 led to a maximum tolerated dose < 7 mg/kg. The ADC and free payload exposures increased with BW for TBW dosing, while ADC clearance moderately increased with BW leading to higher exposure in high BW patients (Table 1). Higher ADC exposure was associated with an increased incidence of Grade ≥ 3 treatment-related adverse events (TRAEs), predominantly neutropenia. Early dose modifications and use of granulocyte colony-stimulating factor were more frequent at higher doses and exposures. Increased and sustained tumor shrinkage observed in pts with ovarian cancer (OC) with higher ADC exposure. AiBW enabled a higher tolerable dose at 8 mg/kg, by normalizing ADC and payload exposure across all bodyweight ranges. **Conclusions:** AiBW dosing effectively reduced PK variability compared with TBW dosing, providing more consistent exposure across BW. Higher ADC exposure was associated with increased efficacy, but also with a higher incidence of manageable TRAEs. AiBW optimizes the risk-benefit profiles across BW. Clinical trial information: NCT06233942. Research Sponsor: BeOne Medicines Ltd.

	Underweight (<18.5 kg/m^2)	Normal (18.5-24.9 kg/m^2)	Overweight (25-29.9 kg/m^2)	Obese (≥30 kg/m^2)
Simulated Cycle 1 Median ADC exposure at 7 mg/kg TBW (ng/mL)	352	464	533	626
Simulated Cycle 1 Median ADC exposure at 7 mg/kg AiBW (ng/mL)	411	448	464	481
ADC Exposure Tertile	1	2	3	
Grade ≥3 TRAE	16.2% (6/37)	27.8% (10/36)	37.8% (14/37)	
Grade ≥3 Neutropenia	10.8% (4/37)	19.4% (7/36)	27% (10/37)	
Dose modifications	16.2% (6/37)	19.4% (7/36)	27% (10/37)	
Median tumor shrinkage in OC at Week 24 Tumor Assessment (N=25)	−28.9%	−33.3%	−48%	

Phase I study of BL-M05D1, a novel Claudin18.2-directed antibody-drug conjugate (ADC), in patients with locally advanced or metastatic Claudin18.2–expressing solid tumors.

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Background: BL-M05D1 is a novel Claudin18.2-directed ADC with a potent topoisomerase I inhibitor Ed-04. Results for safety and efficacy data from a phase I study on BL-M05D1 in patients (pts) with locally advanced or metastatic (LA/M) Claudin18.2-expressing solid tumors are presented. **Methods:** Pts who had LA/M solid tumors enrolled in dose escalation and dose expansion phase, and treated with BL-M05D1 at 0.66, 2.0, 3.0, 4.0 or 5.0mg/kg on Day 1 every 3 weeks (D1 Q3W). Gastric cancer/gastroesophageal junction cancer (GC/GEJ), biliary tract cancer (BTC), and pancreatic cancer (PanC) patients with Claudin18.2-expressing enrolled in dose expansion phase were treated at 2.0, 3.0 or 4.0mg/kg D1 Q3W. **Results:** As of Nov 30, 2025, a total of 245 pts were enrolled (87 GC/GEJ, 53 BTC, 104 PanC) and 1 other). The most frequent grade≥3 TRAEs were all hematological, including thrombocytopenia (33.9%), neutropenia (32.7%), leukopenia (31.8%) and anemia (14.3%); non-hematologic TRAEs were relatively low. One pt at 5.0mg/kg group experienced grade 3 febrile neutropenia as a DLT. No treatment-related deaths or ILD were reported. In PanC, BL-M05D1 has demonstrated a promising efficacy with an ORR of 35.7% and mPFS of 5.6 mo at 4.0mg/kg in CLDN18.2-positive pts; in the second line pts, ORR was 50.0% with a mPFS of 5.7 mo. Furthermore, BL-M05D1 has shown promising efficacies in CLDN18.2-positive GC and BTC with an ORR of 39.2% and 37.9%, and mPFS of 5.4 mo and 5.9 mo, respectively, at 4.0mg/kg. Efficacy results are summarized below. **Conclusions:** BL-M05D1 has demonstrated a promising antitumor activity with a tolerable safety profile in pts with pretreated Claudin18.2-positive PanC, GC, and BTC. 4.0mg/kg D1 Q3W was chosen as RP2D. The data support further development of BL-M05D1 in Claudin18.2-positive PanC, GC, and BTC. Phase III studies are in preparation. Clinical trial information: NCT06349811. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	PanC-Total*	PanC CLDN 18.2 +# 4.0 mg/kg	PanC CLDN 18.2 +# 1 Prior Chemo in 4.0mg/kg	GC-Total*	GC CLDN 18.2 +# 4.0 mg/kg	GC CLDN 18.2 +# 1 Prior Chemo in 4.0 mg/kg	BTC-Total*	BTC CLDN 18.2 +# 4.0 mg/kg	BTC CLDN 18.2 +# 1 Prior Chemo in 4.0 mg/kg
	N = 81	N = 28	N = 16	N = 79	N = 51	N = 29	N = 40	N = 29	N = 20
Median prior LoT (range)	2 (1-4)	2 (1- 3)	/	2 (1-4)	1 (1-3)	/	1 (1-3)	1 (1-3)	/
ORR, % (95% CI)	17.3 (9.8-27.3)	35.7 (18.6-55.9)	50.0 (24.7-75.3)	35.4 (25.0-47.0)	39.2 (25.8-53.9)	44.8 (26.4-64.3)	37.5 (22.7-54.2)	37.9 (20.7-57.7)	45.0 (23.1-68.5)
DCR, % (95% CI)	74.1 (63.1-83.2)	89.3 (71.8-97.7)	100 (79.4-100)	88.6 (79.5-94.7)	88.2 (76.1-95.6)	86.2 (68.3-96.1)	92.5 (79.6-98.4)	93.1 (77.2-99.2)	90.0 (68.3-98.8)
mFU for PFS (mo)	2.8	5.5	4.2	4.4	4.4	4.3	2.8	2.7	2.7
mPFS (mo)	4.0	5.6	5.7	4.4	5.4	7.7	6.9	5.9	5.9

*Efficacy analysis included all pts who received at least one dose of BL-M05D1 and with at least one post baseline scan.
#PanC CLDN 18.2 +: IHC 2+/3+ ≥ 50%; GC CLDN 18.2 +: IHC 2+/3+ ≥ 40%; BTC CLDN 18.2 +: IHC1+/2+/3+≥30%.

HER2-independent antitumor and pharmacodynamic responses to trastuzumab deruxtecan in patients with advanced solid tumors.

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Background: Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody conjugated to topoisomerase 1 inhibitor, deruxtecan, payload that is an effective treatment strategy across several tumor types and various HER2 expressions. The relative contributions of each of the underlying mechanisms driving the broad clinical activity require further elucidation for the ongoing rational development of this promising agent. To this end, our pilot study (NCT04294628) evaluates the pharmacodynamics (PD) of T-DXd in patients (pts) with solid tumors displaying a variety of HER2 expression levels. **Methods:** This multicenter pilot study enrolled pts with HER2-expressing advanced solid tumors as defined by HER2 immunohistochemistry (IHC) score of 1+ or greater or *ERBB2* amplifications (amp) or mutations (mut). Baseline HER2 expression was evaluated by Ventana PATHWAY immunohistochemical (IHC) analysis. T-DXd was administered at 5.4 mg/kg intravenously once every 3 weeks, in 21-day cycles (C), with mandatory tumor biopsies collected at baseline, post-dose C1, and pre-dose C3. Blood samples for biomarker analyses were collected throughout the study. PD biomarkers for topoisomerase 1 (TOP1) target engagement, consequent DNA damage repair (DDR), and tumor immune microenvironment changes were analyzed. Overall response was also evaluated. **Results:** Sixty-one pts received T-DXd. Eligibility HER2 (eHER2) status was determined from pt records: 21 IHC 1+, 22 IHC 2+, 7 IHC 3+, 8 *ERBB2* amp, 3 *ERBB2* mut. Of the 41 pts with baseline biopsies centrally assessed for HER2 (bHER2) by IHC, 13 had bHER2 scores discordant with eHER2, including 8 patients who were eHER2 1-2+ but were bHER2 null. No new safety signals were observed. One pt had a complete response (cervical, bHER2 3+), 14 pts had confirmed partial responses (PR), including 3 who were bHER2 null (2 ovarian, 1 uterine), and 5 pts had unconfirmed PR (uPR). Of the 21 paired biopsies assessable for PD response, 15 demonstrated TOP1 target modulation and 14 of those 15 also demonstrated DDR induction. Substantial tumor infiltration and activation of CD8+ T cells at baseline and/or following T-DXd administration occurred in several patients and were particularly prevalent in those with response. In the one responding patient where lesion-specific analyses were possible, we observed significant diameter reduction (3.9 cm to 1.9 cm) and PD responses in a bHER2 null lesion. **Conclusions:** Clinical responses and target modulation were observed in pts irrespective of bHER2 expression. Lesion-specific analyses provide evidence of antitumor activity and target engagement even in a bHER2-null lesion. Genomic analyses to identify additional molecular determinants of response or resistance to T-DXd are ongoing. This project was funded in part by the National Cancer Institute, National Institutes of Health, under Contract No. 75N91019D00024. Clinical trial information: NCT04294628. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

First-in-human phase 1 study of TQB6411, an EGFR/c-Met bispecific antibody-drug conjugate (ADC), in patients with advanced solid tumors.

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Background: EGFR and c-Met overexpression are common across various solid tumors. TQB6411 is a novel ADC binding to both EGFR and c-Met with a valency of 1:2 to enhance the affinity to c-Met. Here we report the preliminary results of this first-in-human phase 1 study of TQB6411(NCT07043751). **Methods:** Patients (pts) with advanced malignant tumor who had failed or were intolerant to standard treatment were eligible. TQB6411 was administered intravenously once every 3 weeks. An accelerated titration design was used for the initial dose level (0.8 mg/kg), followed by a conventional 3+3 dose escalation design for the remaining dose levels. The primary endpoints were dose-limiting toxicity (DLT), recommended phase II dose and safety. **Results:** As of December 31, 2025, 26 pts were enrolled and received research treatment (median age [range], 60[33–75] years; 46.2% female). The most common diagnosis was non-small cell lung cancer (NSCLC, 21 pts), followed by esophageal cancer (EC, 3 pts) and colorectal cancer (CC, 2 pts). All pts had received at least one previous line of systemic treatment. Dose group assignments were as follows: 1 in 0.8mg/kg, 3 in 2.4mg/kg, 13 in 4mg/kg, 6 in 5.3mg/kg, and 3 in 6.6mg/kg. By the data cutoff date of January 9, 2026, the dose had been escalated to 6.6mg/kg, with no DLT occurring. The median treatment duration was 3 cycles (rang:1-9). In 22 pts who were followed up for at least 21 days, 19 (86.4%) experienced at least 1 treatment-related adverse event (TRAE). The most common TRAEs included asthenia (54.5%), infusion reaction (50.0%, decreasing to 38.9% in the ≥4 mg/kg dose group after prophylaxis modification), myalgia (27.3%), alopecia (22.7%), and neutrophil count decreased (22.7%). No interstitial lung disease occurred. Only 4 cases of grade 3 AEs (two of neutrophil count decreased, one of allergic shock, one of white blood cell count decreased) were observed in 3 pts and were all attributed to TQB6411. No ≥ grade 4 AEs occurred. In the ≥4 mg/kg dose group, 8 pts received at least one imaging assessment, 4 achieved a partial response (PR), giving an objective response rate of 50.0%. The disease control rate was 100%. The details of efficacy results are shown in the table below. **Conclusions:** In this ongoing phase 1 study. TQB6411 showed an impressive safety profile, with a lower incidence of higher-grade TRAEs (especially lower haematological toxicities), and encouraging efficacy, with tumor responses could be observed even in the relatively lower dose group. Clinical trial information: NCT07043751. Research Sponsor: None.

	4mg/kg (N = 6)	5.3mg/kg (N=2)
PR, n	3 (NSCLC: 2, EC:1)	1(NSCLC)
SD, n	3 (NSCLC)	1 (NSCLC)

Clinical outcomes in phase 1 study of EBC-129, a first-in-class, anti–N256-glycosylated CEACAM5 and CEACAM6 antibody-drug conjugate (ADC), in patients with gastroesophageal adenocarcinomas.

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Background: Gastro-oesophageal adenocarcinoma (GEA) is an aggressive malignancy with limited treatment options. EBC-129 is a first in class MMAE-linked ADC against both, N256-glycosylated CEACAM5 and 6. Previously reported dose escalation data identified 1.8 and 2.2 mg/kg Q3W as the RP2Ds. Here we report pooled safety and efficacy data of GEA patients enrolled in dose escalation (DEs) and expansion (DEx) cohorts of the Phase 1 study (NCT05701527). **Methods:** This study consisted of DEs and DEx cohorts. Previously treated patients with histologically confirmed, locally advanced or metastatic GEA with centrally confirmed immunohistochemistry (IHC) positivity at ≥20% at 2^+ and/or 3^+ on archival samples were enrolled. Objectives were to evaluate safety, efficacy, PK of EBC-129, administered every 3 weeks. **Results:** A total of 21 GEA patients were enrolled (4 in DEs and 17 in DEx). Pre-screening data shows that 57% and 77% are positive in IHC at cut-offs of ≥20% at $2/3^+$ and ≥1% at 3^+, respectively. Patients received 1.2 (n=1), 1.8 (n=9), 2.0 (n=1) or 2.2 (n=10) mg/kg EBC-129 Q3W. 81% were male; mean age 59.0 years; median 3 (range 1-9) lines of previous treatments with 62% prior taxane treated. At data cut-off (9^{th} Jan 2026), 3 patients are continuing treatment, 12 patients had radiological progression, 3 had clinical progression, and 3 patients withdrew from treatment. Among the 17 evaluable patients, the ORR, DCR and median PFS are outlined in the table below. ORR of 50% was seen in patients with an IHC ≥50%. 65% of patients had any tumour shrinkage overall. Infusion related reactions (IRRs) were seen in 43% of patients most being Grade 1/2 and resolved or reduced with premedication; except for 1 patient who had Grade 3 IRR. The other ≥3 Grade TRAEs (CTCAE v5) included neutropenia (52.4%), anaemia (14.3%), WBC count decreased (9.5%), diarrhoea (9.5%); and amylase increase, vomiting, anorexia, nausea in 1 patient each (4.8%). 4 patients (19.0%) experienced peripheral neuropathy (3 grade 1, 1 grade 2). Other than the 1 patient with Grade 3 IRR, no other drug-related discontinuations occurred in this cohort. Higher antigen expression levels correlated with better response. **Conclusions:** EBC-129 shows promising clinical activity in heavily treated GEA patients with a manageable tolerability profile. Further evaluation in 2L GEA is planned. Clinical trial information: NCT05701527. Research Sponsor: National Research Foundation.

Efficacy results from EBC-129-01, GEA cohort.

Dose	IHC status*	ORR^	DCR	mPFS (wks)
1.8 mg/kg	≥20% (n=7)	28.5%	85.7%	18.1
1.8 mg/kg	≥50% (n=4)	50%	100%	29.2
2.2 mg/kg	≥20% (n=8)	25.0%	75.0%	10.1
2.2 mg/kg	≥50% (n=5)	40%	80%	9.3
Overall (All doses)	≥20% (n=17)#	29.4%	82.4%	17.86
Overall (All doses)	≥50% (n=10)#	50%	90%	21.4

*Centrally confirmed IHC positivity at 2^+ and/or 3^+ on archival samples were enrolled; ^Includes one patient with unconfirmed response; #1 patient each at 1.2 mg/kg and 2.0 mg/kg.

3034 Poster Session

Real-world effectiveness of sacituzumab govitecan (SG) versus trastuzumab deruxtecan (T-DXd) in HER2-negative (HER2-) metastatic breast cancer (MBC) in China: A propensity-score–matched study.

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Background: SG and T-DXd are both antibody-drug conjugates (ADC) approved in China for HER2- MBC patients. However, direct real-world comparisons between these two therapies in HER2- MBC patients in China remain limited. This study aimed to evaluate and compare clinical outcomes of SG and T-DXd in Chinese patients with HER2- MBC in real-world practice. **Methods:** This retrospective study included 306 HER2- MBC patients, with 151 treated with SG and 155 treated with T-DXd. Separate propensity score matching (PSM) was performed for the triple-negative (TN) and hormone receptor-positive (HoR+) cohorts, respectively. Matching variables for both cohorts included age, HER2 expression, prior ADC use, number and site of metastases (liver, brain), and prior lines of therapy. For TN cohort only, DFI, prior taxane and PD-1/PD-L1 inhibitor use were additionally matched (caliper = 0.1). Clinical outcomes included real-world progression-free survival (rwPFS), overall survival (OS), objective response rate (ORR) and disease control rate (DCR). **Results:** Median follow-up was 13.4 mo (SG-TN), 12.0 mo (SG-HoR+), 12.4 mo (T-DXd-TN), and 12.0 mo (T-DXd-HoR+). After PSM, 33 TN patients and 28 HoR+HER2- patients were matched in each treatment group. Baseline clinical characteristics were well-balanced. In TN patients, rwPFS was comparable between SG and T-DXd (5.0 vs 5.7 mo, HR=0.63, P=0.138). The comparable effectiveness of SG and T-DXd was also observed in both HER2-null (P=0.498) and HER2-low (P=0.250) subgroup. Meanwhile, SG showed a trend toward improved rwOS (NR vs 13.1 mo, HR=1.75, P=0.216). However, T-DXd demonstrated significantly higher ORR (18.2% vs 45.5%, P=0.017) and DCR (45.5% vs 75.8%, P=0.012) compared to SG. In HoR+HER2- patients, T-DXd showed significantly longer rwPFS compared to SG (9.8 vs 5.5 mo, HR=0.41, P=0.010), especially among those with HER2-low disease (8.4 vs 5.3 mo, HR=0.36, P=0.007); OS data were immature. ORR (14.3% vs 39.3%, P=0.035) and DCR (42.9% vs 85.7%, $P<0.001$) favored T-DXd, as well. Subgroup analyses indicated that T-DXd in those with DFI >12 months prolonged rwPFS than SG (10.2 vs 3.5 mo, HR=0.46, P=0.036). In HoR+ patients, the median rwPFS was significantly longer in T-DXd group than SG group in the majority of subgroups. **Conclusions:** In this real-world PSM analysis, T-DXd showed improved rwPFS compared with SG in HoR+HER2- MBC patients, while both regimens had generally comparable effectiveness in TN patients. These findings suggest that treatment selection may be influenced by hormone receptor status and the duration of DFI. Further prospective studies are warranted to validate these observations. Research Sponsor: None.

BC3195, a novel ADC targeting cadherin-3 (CDH3): Preliminary results of a phase I study in patients with advanced solid malignancies (study BC3195-102).

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Background: Cadherin-3 (CDH3), a calcium-dependent adhesion glycoprotein, is overexpressed on lung, breast, ovarian, colorectal, pancreatic, head-neck and other malignancies, but expression on nonmalignant tissue is negligible. CDH3 is essential for cancer cell proliferative signaling and is associated with aggressiveness, invasiveness and poor prognosis. BC3195 is an antibody-drug conjugate (ADC) comprised of an antibody targeting CDH3, a cleavable linker and a monomethyl auristatin E (MMAE) payload. **Methods:** Two phase Ia/Ib studies of BC3195, whose objectives are to evaluate the safety, pharmacokinetics (PK) and preliminary antitumor activity of the ADC, are enrolling patients (pts) with advanced solid malignancies in the US (BC3195-102) and China (BC3195-101). In both studies, BC3195 is administered as a 1-hour (h) IV infusion every 3 weeks. In BC3195-102, dose escalation uses a BOIN design with pre-selected dose levels (DLs) of 1.8 and 2.4 mg/kg and an algorithm to explore lower or intermediate DLs based on safety. **Results:** As of data cut-off (Dec 30, 2025), 16 pts have been enrolled at DLs of 1.2 (3 pts), 1.5 (3 pts), 1.8 (9 pts), and 2.4 mg/kg (1 pt). Fourteen (87.5%) pts had received ≥3 prior treatment. Fatigue (81.3%) and stomatitis (62.5%) were the main adverse events (AEs). Three pts (18.8%) had Grade ≥3 AEs, two of which were Grade 3 stomatitis in the first week post-treatment of Cycle 1 at the 1.8 mg/kg DL of Cohort 1. The dose of BC3195 was subsequently de-escalated to 1.2 mg/kg and then re-escalated to 2.4 mg/kg along with preventative measures, which included ice chip mouth rinses, dexamethasone mouthwash, and B vitamins in the peri-treatment period, and topical steroids for any skin rash. There was no further stomatitis of Grade 3 severity after implementation of these measures; 1 pt had a Grade 3 rash in Cycle 2 at 1.5 mg/kg that responded rapidly to oral steroids. Neither ocular nor neurotoxicity have been noted. Of 16 pts evaluable for tumor response (RECISTv1.1), 3 partial responses occurred in heavily pretreated pts with HER+ breast cancer, prostate cancer, and fibrosarcoma, all of whom were treated at the 1.8 mg/kg DL. Preliminary PK results (1.2-1.8 mg/kg) include med T_{max} values of 1 h for both ADC and total antibody (TA), whereas med T_{max} values for free MMAE range from 65 to 89 h. At 1.8 mg/kg, mean $t_{1/2}$ values are 58 h, 92 h, and 95 h for the ADC, TA and MMAE, respectively. ADC exposure has been highest at 1.8 mg/kg, with mean C_{max} and AUC_{last} values of 31.8 μg/mL and 1297 μg*h/mL, respectively. **Conclusions:** BC3195 has a manageable safety profile, favorable PK characteristics and demonstrated preliminary antitumor activity in several types of heavily pretreated advanced solid malignancies. Based on shared safety data, enrolment in both BC3195-102 (US) and BC3195-101 (China), which is in dose expansion, is converging on the 2.1 mg/kg DL (NCT06548672). Clinical trial information: NCT06548672. Research Sponsor: Biocity Biopharmaceutics Co. Ltd.

XNW27011, a Claudin 18.2(CLDN18.2) targeted antibody-drug conjugate (ADC), in patients with CLDN18.2-positive gastric/gastroesophageal junction adenocarcinoma (G/GEJA): A phase 2 study.

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Background: The prognosis of G/GEJA remains poor, especially in late line patients (pts). mPFS for G/GEJA pts who received ≥ 2 prior lines of standard therapy is 1.6 - 2.6 months (mos). XNW27011 is a novel antibody-drug conjugate (ADC) targeting CLDN18.2, a promising therapeutic target that is aberrantly expressed in patients with G/GEJA. **Methods:** This phase 2 study aims to evaluate the efficacy and safety of XNW27011. Adult pt with advanced solid tumors who has failed standard therapy or is intolerable to available standard therapy/without available standard therapy, and with CLDN18.2 expression in ≥5% tumor cells (TC) with IHC staining ≥2+ (IHC≥2+, TC≥5%, EPR19202) were enrolled, including G/GEJA pts. All patients had measurable disease (RECIST v1.1) and ECOG 0-1. Patients received XNW27011 at 2.4-4.8 mg/kg Q3W. Endpoints included ORR for efficacy, TRAE events for safety and PK parameters. **Results:** As of Dec 29, 2025, a total of 86 eligible G/GEJA pts were enrolled at 2.4-4.8 mg/kg. IHC≥2+, TC≥20% was chosen as the CLDN18.2 expression criteria for further development of XNW27011. Here, we report the results in G/GEJA pts with CLDN18.2 expression of IHC≥2+, TC≥20%. Safety: 71 enrolled pts had CLDN18.2 expression of IHC≥2+, TC≥20%. The median age was 57.0 years, 87.3% of the pts had received ≥2 lines of systemic therapy, 85.9% of the pts had received immune checkpoint inhibitors. The common TRAEs (≥20%) included anemia, nausea, white blood cell count decreased, decreased appetite, neutrophil count decreased, vomiting, weight loss, hypoalbuminemia, asthenia, platelet count decreased, lymphocyte count decreased and hypokalemia. Efficacy: At 3.0 mg/kg, 26 patients were evaluable for efficacy, with 23 and 3 pts had received ≥2 and 1 prior lines of systemic therapy, respectively. The median follow-up(mFU) was 11.3 mos, cORR and cDCR were 65.4% and 84.6%, respectively. mPFS was 5.7 mos and mOS was 11.7 mos. Among the 23 pts who had ≥2 prior lines of therapy, the mPFS was 6.8 mos and mOS was 11.9 mos, with the mFU of 11.5 mos. Notably, one patient previously treated with CLDN18.2-targeted therapy still demonstrated durable clinical benefit, with PFS of 11.3 mos and still remains on treatment as of data cutoff date. Pharmacokinetics: At doses from 0.6 - 6.0 mg/kg in pts with solid tumors including G/GEJA, XNW27011 exposure (C_{max} and $AUC_{0-\infty}$) increased in an approximately dose proportional manner with a half-life of 5~7 days. Across all dose levels, circulating blood payload concentrations were low with 3.3% ADA positive rate. **Conclusions:** XNW27011 demonstrated promising anti-tumor activity and a manageable safety profile in CLDN18.2-positive G/GEJA. A pivotal phase 3 study evaluating XNW27011 as a ≥3 line therapy in G/GEJA pts is currently ongoing. Clinical trial information: NCT06792435. Research Sponsor: Evopoint Biosciences Co., Ltd.

First-in-human study of DM002, an anti-MUC1/HER3 bispecific antibody-drug conjugate, in patients with advanced solid tumors.

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Background: DM002 is a bispecific ADC (BsADC) conjugated to BLD1102, a linker/payload system composed of a linker and a DNA topoisomerase I inhibitor (BCPT02), targeting MUC1 and HER3 with an average DAR value of 8. MUC1 and HER3 are highly co-expressed in several types of solid tumors, for which DM002 has demonstrated robust anti-tumor activity in PDX/CDX models. **Methods:** This is a First-in-human dose-escalation study (NCT06751329). Patients (pts) with advanced solid tumors received DM002 by IV administration from 1 to 6.0 mg/kg Q3W. The classical "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. Tumor response was evaluated by the Investigators based on RECIST v 1.1. A Safety Monitoring Committee (SMC) was established to determine the dose levels, dose regimen, and the maximum tolerated dose (MTD)/ recommended dose for expansion (RDE). **Results:** As of 28 Dec 2025, a total of 29 pts from China, United states of America and Australia were enrolled and received ≥1 dose of DM002 across 5 dose cohorts. Median age was 61 years (range 45-80). Baseline ECOG scores were 0 (n=8), 1 (n=21) with all pts progressed after an average of 2.5 (range 1-5) prior lines of available standard therapy. There were three dose-limiting toxicities observed in 2 patients at 6.0 mg/kg. The MTD is 4.5mg/kg. Nineteen pts (65.5%) experienced treatment-related adverse events (TRAEs), mainly manifested as hematological toxicity and gastrointestinal reactions. the most common TRAEs (≥15%) including: nausea (37.9%), neutropenia (37.9%), thrombocytopenia (34.5%), anemia (31%), vomiting (27.6%), leukopenia (20.7%), hyponatremia (20.7%), diarrhea (17.2%), alanine aminotransferase increased (17.2%), hypoalbuminemia (17.2%). Most TRAEs were Grade 1-2 and Grade ≥3 TRAEs reported in 12 pts (9 neutropenia, 5 leukopenia, 4 thrombocytopenia, 3 anemia, 2 lymphocytopenia, hyponatremia and febrile neutropenia, 1 aspartate aminotransferase increased, blood bilirubin increased, monocyte count decreased, myelosuppression, hypocalcemia, malaise and infection). No ILD was observed. Among 15 pts having imaging tumor assessment by RECIST v1.1, there were 3 PRs, including 1 pt with prostate cancer and 1pt with ovarian cancer at 3.0 mg/kg, and 1 pt with pancreatic cancer at 4.5 mg/kg, and 8 pts with stable disease (SD). In the 3.0/4.5/6.0 mg/kg dose groups, a total of 8 pancreatic pts underwent imaging tumor assessment, with 1 pt achieving PR, and 5 pts achieving stable disease (SD). **Conclusions:** DM002 is safe and tolerable up to 4.5 mg/kg dose level. In pancreatic cancer, prostate cancer and ovarian cancer, DM002 has demonstrated an encouraging efficacy with a manageable safety profile. The putative RDEs are 3.0 and 3.5 mg/kg which will be further evaluated in phase II trials. Clinical trial information: NCT06751329. Research Sponsor: None.

A phase 1b/2 study of JK06, a 5T4-targeted antibody-drug conjugate (ADC), in patients with unresectable locally advanced or metastatic cancer.

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Background: 5T4, a Type I transmembrane glycoprotein, is over expressed in a broad spectrum of solid tumors. It modulates the CXCR4 & WNT signaling pathways contributing to epithelial to mesenchymal transition contributing to metastatic progression & correlates with poor clinical outcomes among a range of cancers, such as NSCLC, CRC & ovarian. JK06 is a tetravalent, biparatopic DAR2 MMAE ADC targeting 5T4, providing picomolar affinity & enhanced internalization to compensate for generally lower 5T4 expression levels & poor intrinsic internalization kinetics. **Methods:** Pts with advanced relapsed/refractory solid tumors, unselected for 5T4 expression, receive IV JK06 monotherapy once every 3 wks. Dose escalation has been completed, and the study is currently enrolling multiple tumor-specific cohort expansions with randomization across two doses of JK06 to identify an RP2D in NSCLC & breast cancer. Fresh & archival tumor biopsies are being collected for retrospective correlation of 5T4 expression to efficacy & safety. Responses are assessed every 9 wks per RECIST v1.1. Exploratory evaluations of changes in quality of life after JK06 treatment are included in cohort expansions. **Results:** To date, 80 refractory metastatic solid tumor pts (n = 39 in dose esc; n = 41 in cohort expansions) have been treated, median age of 60 yrs, >70% treated with ≥ 3 prior lines of therapy, including >75% of treated pts with prior taxane exposure. Treatment has been well-tolerated with predominantly low-grade treatment-related adverse events (TRAEs) (Gr 1 & 2), such as fatigue (35%), alopecia (18%), decreased appetite (18%), dry eye (10%) & peripheral sensory neuropathy (PSN) (9%). Among 70 pts have sustained JK06-related Gr 3 adverse events (AEs): fatigue, malaise, gait disturbance, keratitis, vomiting, corneal ulcer, & PSN, that resolved, with two continuing treatment with dose reduction; no Gr 4 JK06-related AEs have been observed to date. Four pts underwent dose reductions, and five additional pts were discontinued due to TRAEs. Among 19 response-evaluable NSCLC pts to date, a 32% ORR has been observed, with 1 confirmed complete response (cCR), 4 confirmed partial responses (cPR) (one with CNS response) & 1 with unconfirmed partial responses (uPR), with the longest continuing therapy for 51 wks. Responses have been observed in adenomatous, squamous & EGFR mutant NSCLC pts. One of seven evaluable breast cancer pts (14% ORR) achieved a cPR and remained on treatment for >27 wks. **Conclusions:** To date, JK06 demonstrates promising emerging clinical activity in refractory NSCLC & breast cancer at multiple dose levels while being well tolerated without significant drug-related toxicities. Updated safety & clinical activity data from both dose escalation & expansion cohorts, including the initial assessment of dose randomization, will be presented. Clinical trial information: NCT06667960. Research Sponsor: None.

3039 Poster Session

Efficacy and safety of XNW27011, a Claudin-18.2 targeted (CLDN18.2) ADC, in advanced pancreatic ductal adenocarcinoma: A phase 2 study.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a historically poor prognosis, the median overall survival (mOS) for PDAC patients (pts) who received ≥ 1 prior lines of standard treatments is only 6.2 to 7.4 months(mos). XNW27011 is a novel and potent Topoisomerase inhibitor (TOP1i)-based ADC targeting CLDN18.2. In preclinical studies, XNW27011 demonstrated antitumor activities in PDAC, supporting its progression into clinical development. Here, we report results of XNW27011 in pts with PDAC. **Methods:** The objectives of this phase 2 study were to evaluate the efficacy and safety of XNW27011 in PDAC, and to optimize doses for subsequent confirmatory trials. Pts with PDAC expressing CLDN18.2 (defined as ≥5% tumor cells with ≥2+ IHC staining) who had received prior systemic therapy were treated with XNW27011 at doses from 2.4 - 4.8 mg/kg, Q3W. The primary endpoint was ORR, secondary endpoints included TRAEs for safety, DCR, PFS, OS, and PK parameters. **Results:** As of Dec 29, 2025, a total of 48 pts had been enrolled with majority of them being enrolled in 3.0 mg/kg group. Among the 48 pts, the ECOG PS was 0 or 1, the median age was 59.0 years. 18 pts (37.5%) had received 1 prior line of systemic therapy. 22 pts (45.8%) had been treated with TOP1i. Efficacy: A total of 30 PDAC pts in the 3.0 mg/kg dose group were evaluable for efficacy. The ORR and DCR was 26.7% and 83.3%, respectively. mPFS and mOS was 4.1 and 10.0 mos, respectively. Among the 13 pts who had received only one prior line of therapy, the ORR was 46.2% and the DCR was 100.0%, mPFS was 4.4 mos, OS was not mature yet. However, the current mOS was 10.1 mos with the median follow-up of 8.1 mos. Detailed efficacy data are presented in the table. Among the pts who were previously treated with TOP1i, the median follow-up was 7.9 mos, the mPFS and mOS were 5.2 and 10.0 mos, respectively. Safety: Among the 48 PDAC pts, the incidence of treatment-related adverse events (TRAEs) was100.0%. The incidence of Grade ≥3 TRAEs and serious TRAEs were 77.1% and 58.3%, respectively. 35.4% and 6.3% of the TRAEs led to dose reduction and discontinuation, respectively. The most common TRAEs included nausea (77.1%), vomiting (64.6%), decreased appetite (64.6%) and anemia (62.5%). Pharmacokinetics: At doses of 0.6-6.0 mg/kg in patients with solid tumors including PDAC, the XNW27011 exposure (C_{max} and $AUC_{0-\infty}$) increased in an approximately dose proportional manner with a half-life of 5~7 days. Across all dose levels, circulating payload blood concentrations were low with 3.3% ADA positive rate. **Conclusions:** XNW27011 showed a manageable safety profile and encouraging survival outcome in pts with PDAC expressing CLDN 18.2, supporting its further clinical development as a promising therapeutic option for patients with PDAC expressing CLDN 18.2. Clinical trial information: NCT06792435. Research Sponsor: Evopoint Biosciences Co., Ltd.

Safety, efficacy, and pharmacokinetics of XNW28012, a tissue factor antibody-drug conjugate (ADC) with topoisomerase 1 inhibitor (TOP1i) payload, in patients with advanced solid tumors: Results from a phase I/II study.

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Background: Tissue factor (TF) is overexpressed in a broad range of solid tumors including pancreatic ductal adenocarcinoma (PDAC). XNW28012 is the first TF ADC with a novel TOP1i payload. Here we report the safety and PK of XNW28012 in patients (pts) with solid tumors, and the efficacy in PDAC from a Phase I/II study. **Methods:** Eligible pts who failed standard therapy received XNW28012 Q3W. TF expression was not required for enrollment. The primary endpoints for dose escalation and expansion were safety and ORR, respectively. BOIN design was used for dose escalation. Eligible pts with PDAC and other solid tumors were enrolled at 2.0 and 2.4 mg/kg for dose expansion. **Results:** As of Nov. 21, 2025, 313 pts were enrolled (escalation: 16; expansion: 297), with median age of 56.3 yrs; 77.0% of ECOG 1; and 56.9% received ≥2 lines of prior systemic therapy. TEAEs in ≥20% pts were anemia (62.0%), stomatitis (60.1%), nausea (49.5%), WBC count decreased (47.0%), appetite decreased (43.1%), neutrophil count decreased (39.9%), vomiting (39.6%), asthenia (35.5%), weight decreased (30.7%), conjunctivitis (29.4%), rash (28.1%), hypokalemia (23.3%), hyponatremia (21.4%), and hypoalbuminemia (21.1%). ≥Grade 3 TEAEs in ≥5% pts were stomatitis (17.6%), neutrophil count decreased (14.4%), WBC count decreased (12.8%), anemia (11.5%), and lymphocyte count decreased (8.3%). Dose interruption, reduction and discontinuation due to TEAE occurred in 60.7%, 22.0%, and 3.8% of the pts, respectively. Grade 3 conjunctivitis was reported in 2.9% pts across the doses. Most common bleeding AE was epistaxis (12.1%), all grade 1/2. 1 pt at 3.6 mg/kg experienced DLT (grade 4 neutropenia, grade 3 stomatitis). 16 pts were enrolled in dose escalation from 0.6 to 3.6 mg/kg. ORR and DCR were 46.7% and 100%, respectively in 15 evaluable pts including PDAC, ovarian cancer, cervical cancer, and head and neck squamous cell carcinoma. In dose expansion, 45 and 48 PDAC pts were efficacy evaluable at 2.0 and 2.4 mg/kg, with a median follow up of 4.4 m and 6.0 m, respectively. Efficacy data in PDAC pts in dose expansion were summarized in the Table. PK data showed dose proportionality and very low payload exposure in the system indicating stable linker. **Conclusions:** XNW28012 demonstrated a manageable safety profile in heavily treated advanced solid tumor pts and promising anti-tumor activity in PDAC patients. The data support further development of XNW28012 in a broad range of solid tumors including PDAC. Clinical trial information: NCT06799637. Research Sponsor: Evopoint Biosciences Co., Ltd.

Prior line	2.0 mg/kg, 1L (N=25)	2.0 mg/kg, 2L+ (N=20)	2.4 mg/kg, 1L (N=21)	2.4 mg/kg, 2L+ (N=27)
ORR, n (%)	7 (28.0%)	3 (15.0%)	10 (47.6%)	7 (25.9%)
DCR, n (%)	23(92.0%)	18(90.0%)	19 (90.5%)	23 (85.2%)
mPFS, (months)	4.2	4.5	6.4	5.2
mOS, (months)	NC	10.7	14.6	9.0
KM OS rate at 9m (%)	64.5%	51.6%	54.2%	50.5%
KM OS rate at 12m (%)	NC	NC	54.2%	22.9%

NC: Not Calculated.

Non-invasive MRD monitoring and profiling of clonal evolution by ctDNA in patients with advanced cancers treated within molecular tumor boards.

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Background: Profiling of targetable genetic alterations within molecular tumor boards (MTB) guides for personalized treatment selection in patients with advanced cancers. During therapy, response is typically assessed by CT scans or MRI, which often have suboptimal sensitivity and specificity. Circulating tumor DNA (ctDNA) from blood plasma has emerged as a promising biomarker for noninvasive profiling of tumor mutational landscapes and disease monitoring. Here, we applied a pan-cancer next-generation sequencing (NGS) technology to assess the role of ctDNA for comprehensive tumor genotyping, early response prediction, and characterization clonal heterogeneity in patients receiving MTB recommended therapies. **Methods:** We developed and applied a custom targeted NGS approach (ExTARGET), which covers 266 genes across a 540 kb genomic region, to 157 plasma samples obtained at distinct milestones from 57 patients with diverse solid cancers. Plasma samples from healthy individuals (n= 24) were used to determine the specificity of our technology. **Results:** We identified variants in 96% of baseline plasma samples by ctDNA profiling, with a median of 7 mutations per patient (range: 1-41). Most frequently mutated genes included *KRAS* (35%), *BRAF* (24%), *ERBB2* (22%) and *TP53* (22%). Targetable tumor variants that led to treatment recommendations within the MTB were found non-invasively in 69% of patients. Longitudinal monitoring of baseline ctDNA variants in on-treatment samples, obtained early during therapy (n= 21), revealed that ctDNA dynamics were predictive of disease progression and preceded radiological/clinical progression in 8/19 (42%) patients. All patients with increasing ctDNA levels early during treatment showed radiologic disease progression in subsequent CT scans. On the other hand, an early decrease of ctDNA levels was associated with durable disease control in most patients and significantly favorable progression-free survival (p= 0.008; HR = 0.1, 95%CI: 0.02-0.6). Next, we explored temporal clonal heterogeneity in plasma samples collected from 16 patients with disease progression following MTB-recommended therapies. We observed substantial clonal evolution over time, with all samples harboring at least one emerging variant. Among these emerging alterations, 19% were classified as 'oncogenic' and 5% were identified as potentially targetable. **Conclusions:** We here developed an NGS-based technology for ctDNA profiling in heavily pretreated patients receiving MTB-recommended therapies. Non-invasive genotyping from plasma robustly identifies targetable aberrations and allows comprehensive tumor genotyping. Monitoring of ctDNA during treatment and at disease progression facilitates early prediction of treatment response and profiling of temporal clonal heterogeneity that could enable subsequent treatment selection. Research Sponsor: German Cancer Consortium (DKTK).

Performance of a tissue-free, molecular residual disease assay in colorectal, breast, and lung cancers from circulating tumor DNA.

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Background: The Latitude test is a methylation-based, tissue-free molecular residual disease (MRD) test. In this study, we describe the improved performance of the assay in colorectal cancer (CRC) and its performance in an expanded set of indications including breast and lung cancer. **Methods:** The methylation-based, tissue-free ctDNA assay uses next-generation sequencing to query differentially methylated genomic regions in patients with CRC, breast, and lung cancer compared to cancer-free individuals in order to classify plasma samples as MRD positive (MRD+) or MRD negative (MRD-). Performance was evaluated in patients with cancer: CRC (N = 214), breast (N = 153), and lung (N = 148) with known ctDNA-positive results from Signatera (tumor-informed ctDNA testing) across a range of variant allele frequency (VAF) ranges, and cancer-free individuals (training set N = 531, validation set N = 200). Performance metrics, such as percent positive agreement (PPA) and specificity, were evaluated using cross validation in the cancer and cancer-free cohorts, respectively. **Results:** Among 214 CRC patients (VAF range: 0.003%-4.5%), PPA was 95.94% and specificity among all 200 cancer-free individuals was 99.50%. Among 153 breast cancer patients (VAF range: 0.002%-7.8%), PPA was 91.81%, which was maintained across subtypes, including HR+ (94.75%, N = 40), HER2+ (94.45%, N = 20), and triple-negative (87.94%, N = 29). Among the 164 cancer-free females, specificity of the breast tissue-free assay was 98.18%. Among 148 lung cancer patients (VAF range: 0.003%-5.8%), PPA was 92.63%, maintained across subtypes, including non-small cell lung cancer (92.54%, N = 112) and small cell lung cancer (95.23%, N = 25). Among all 200 cancer-free individuals, specificity of the lung tissue-free assay was 99.50%. **Conclusions:** These data demonstrate a high concordance between the Latitude tissue-free MRD assay and a clinically validated tumor-informed ctDNA assay across CRC, breast, and lung cancers, supporting the use of methylation-based biomarkers for informing prognosis and patient management. Research Sponsor: None.

Extracellular matrix-derived liquid biopsy for predicting response in patients with biliary tract cancer treated with nivolumab with or without ipilimumab combined with stereotactic body radiotherapy: Insights from the CheckPAC trial.

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Background: Biliary tract cancer (BTC) is a rare malignancy with limited treatment options and poor prognosis. Although combined chemotherapy and immune checkpoint inhibitors are first-line treatment for advanced BTC, durable response is uncommon. Current immunotherapy biomarkers, such as PD-L1 expression, have limited utility and treatment response biomarkers are urgently needed. BTC is characterized by a fibrotic extracellular matrix, where widespread tumor fibrosis has been linked to immunosuppression and treatment resistance. In this study, we used Nordic ProteinFingerPrint Technology to evaluate the pharmacodynamic and predictive value of the FDA supported fibrosis biomarker NordicPRO-C3 (type III collagen pro-peptide) and the T-cell infiltration biomarker NordicC4G (granzyme B degraded type IV collagen) in patients with metastatic BTC treated with nivolumab with or without ipilimumab plus stereotactic body radiotherapy (SBRT). **Methods:** PRO-C3 (NordicPRO-C3) and C4G (NordicC4G) were measured at baseline and 60 days after treatment initiation in serum from 61 patients with BTC from the CheckPAC trial (NCT02866383). Patients received SBRT combined with nivolumab (n = 19) or nivolumab/ipilimumab (n = 42). The primary endpoint was clinical benefit rate (CBR; CR+PR+SD vs. PD) assessed by RECIST 1.1. Biomarker levels at baseline and biomarker changes during therapy were evaluated relative to response using Fisher's exact test; overall survival (OS) was assessed using uni- and multivariate Cox regression. **Results:** CBR was 0% in patients with high baseline PRO-C3 (243 ng/mL) versus 31% in patients with low PRO-C3 ($p < 0.05$). High PRO-C3 was associated with poor OS after adjusting for CA19-9, performance status, and modified Glasgow Prognostic Score (HR = 3.1, 95% CI 1.5-6.6, p = 0.004). Longitudinally, C4G increased significantly at day 60 in patients with clinical benefit ($p < 0.001$). CBR was 44% in patients with increased C4G versus 0% in those with decreased C4G (p = 0.007), and increased C4G was associated with improved OS (p = 0.01). All patients with clinical benefit had both increased C4G and low PRO-C3 at day 60. Among patients without clinical benefit, patients with increased C4G and low PRO-C3 and showed a trend towards improved OS (Median OS 8.3 months vs. 3.6 months, p = 0.08). **Conclusions:** High pretreatment tumor fibrosis, quantified by elevated serum PRO-C3, is associated with poor response and OS in patients with BTC treated with SBRT plus immunotherapy. Changes in PRO-C3 and the T-cell infiltration biomarker C4G reflect pharmacodynamic changes, with increased C4G linked to improved outcome, particularly in patients with low PRO-C3. Together, these biomarkers may help to predict treatment response and guide clinical decision-making in BTC.
Research Sponsor: None.

Prognostic impact of MRD positivity at ultra-sensitive ctDNA levels using a WGS-based personalized assay: A pan-cancer analysis from MONSTAR-SCREEN-3.

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Background: While circulating tumor DNA (ctDNA) demonstrates promise as a molecular residual disease (MRD) biomarker, its clinical implementation has been primarily limited to tumors with favorable ctDNA shedding characteristics. The MONSTAR-SCREEN-3 evaluates a whole-genome sequencing (WGS)-based MRD assay to assess MRD positivity at ultra-sensitive level beyond conventional WES-based MRD, including traditionally low-shedding tumors. **Methods:** MONSTAR-SCREEN-3 is a prospective multicenter study targeting 1,100 patients with solid tumors undergoing curative-intent treatment. Personalized panels were constructed using Precise MRD (Myriad Genetics), incorporating up to 1,000 tumor-specific alterations identified through WGS of matched tumor tissue. Serial plasma samples were collected at baseline, post-neoadjuvant treatment (NAT) (when applicable), 1-month (1M) post-surgery, every 3 months in year 1, and every 6 months thereafter up to 2 years. Assay performance was evaluated across multiple cancer types for ctDNA detection and recurrence monitoring. **Results:** Between May 2024 and November 2025, 1,088 patients across over 20 cancer types were enrolled, including colorectal (n=250), breast (n=156), cervical (n=95), gastric (n=88), and pancreatic (n=69) cancers. Treatment strategies included upfront surgery (n=704), NAT (n=296), and definitive chemoradiotherapy (n=96). Median follow-up was 5.3 months (range, 0–18.1). Baseline ctDNA detection was achieved in 96.2% (684/711), with 16.4% at ultra-sensitive levels (tumor fraction <100 parts per million [ppm]). Post-operative MRD positivity was 26.4% (163/617) at 1M and 23.8% (120/504) at 3M, with 46.0% and 41.7% detected at ultra-sensitive levels, respectively. Among 91 patients who received NAT and underwent pathological assessment, post-NAT MRD status demonstrated a sensitivity of 74.3% (55/74) and a specificity of 100% (17/17) for predicting pathological complete response ($P<0.01$). Among patients with available survival data, post-1M MRD positivity was associated with significantly worse disease-free survival (DFS) compared with MRD negativity (HR, 16.9; 95% CI, 8.2–34.8; $P < 0.001$). Furthermore, post-1M MRD positivity at levels below 100 ppm was associated with significantly inferior DFS compared with MRD negativity (HR, 8.2; 95% CI, 3.4–19.4; $P < 0.001$), whereas post-1M MRD positivity at levels ≥100 ppm was associated with significantly worse DFS compared with MRD positivity below 100 ppm (HR, 3.4; 95% CI, 1.7–6.7; $P < 0.001$). **Conclusions:** The WGS-based MRD assay demonstrated high baseline detection sensitivity and robust ultra-sensitive detection across diverse cancer types. Our findings show that post-1M MRD positivity below 100 ppm at ultra-sensitive level is prognostic for recurrence risk. Updated molecular and clinical outcome data will be presented. Clinical trial information: UMIN000053975. Research Sponsor: SCRUM-Japan Funds (https://www.scrum-japan.ncc.go.jp/index.html); Myriad Genetics.

Comprehensive genomic profiling of matched ctDNA and tissue from patients with four common cancers enrolled to the NCI-MATCH trial.

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Background: In the NCI-MATCH trial (NCT02465060), tumor tissue from 5,954 patients with advanced cancers underwent next-generation sequencing using the Oncomine Comprehensive Assay v2 (OCAv2) to determine eligibility. Most tumors lacked a qualifying mutation of interest (MOI) for assignment. Plasma from 1,301 patients with common cancers – [colorectal (COAD-READ), breast (BREAST), non–small cell lung (NSCLC), and prostate (PRAD) (OncoTree codes are shown in parentheses)] was analyzed to characterize circulating tumor DNA (ctDNA) and assess its utility for detecting clinically relevant MOIs. **Methods:** Cell-free DNA was extracted from plasma collected in Streck tubes at enrollment. ctDNA profiling was performed using the NCI ctDNA Research v2 assay (523 genes) on the Illumina NovaSeq 6000. Matched tumor tissue was analyzed using OCAv2 (143 genes). Positive percent agreement (PPA) was calculated using tissue as the reference. Blood-based microsatellite instability (bMSI) was assessed across ~2,400 loci, with bMSI-high (bMSI-H) defined as sum Jensen-Shannon Distance (sumJSD) ≥0.2. Blood-based tumor mutation burden (bTMB) was defined as total SNVs and indels per Mb. **Results:** Of 1,301 patients, 1,148 (88%) yielded evaluable ctDNA results (COAD-READ, n=487; BREAST, n=367; NSCLC, n=220; PRAD, n=74). Overall PPA with matched tissue was 90.3%. Discordant samples had significantly lower median tumor fraction by maximum somatic allele frequency (MSAF; 0.39%) than concordant samples (12.04%). Median MSAF by histology was 14% (COADREAD), 7% (BREAST), 8% (NSCLC), and 5% (PRAD). Clinically relevant fusions detected exclusively in ctDNA included *RET* (1% NSCLC), *EML4::ALK* (2% NSCLC), *FGFR2* (1% COADREAD; 2% BREAST), and *NTRK1* (<1% COADREAD and BREAST), corresponding to actionable NCI-MATCH arms [*FGFR2/3* - arm K (erdafitinib), *ALK* - arm F (crizotinib), *NTRK* - arm Z1E (larotrectinib)]. Actionable ctDNA-only mutations in PRAD included *ATM* and MLH1. Twenty-eight cases were bMSI-H (MSAF ≥0.02; sumJSD ≥0.2), of which 13 were mismatch repair-deficient by tissue testing (MLH1/MSH2 nuclear stain-negative). bMSI-H was most frequent in COADREAD (7%). Ten cases (seven COADREAD, two NSCLC, one PRAD) were MMR-proficient by tissue but bMSI-H by ctDNA. Twenty-four cases had high bTMB (≥20 mut/Mb; MSAF ≥0.02), all of which were also bMSI-H. **Conclusions:** ctDNA - tissue concordance NCI-MATCH in these four cancer histologies was high (90.3%), supporting liquid biopsy as a practical alternative when tissue is unavailable. Detection of ctDNA-only alterations highlights tumor heterogeneity in advanced cancers and identifies additional therapeutic opportunities. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Incremental clinical yield of serial large NGS panel liquid biopsies in routine care: Analysis of the STING study.

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Background: Plasma ctDNA profiling is increasingly repeated over the disease course to capture tumor evolution and newly targetable alterations. However, the incremental clinical yield of serial ctDNA profiling in routine practice remains incompletely characterized. **Methods:** This analysis was conducted within the prospective STING study (ClinicalTrials.gov identifier: NCT04932525), a program that aims to identify actionable molecular targets in patients with advanced solid tumors. Eligible patients were adults with advanced solid tumors and provided written informed consent for molecular analyses. Circulating tumor DNA (ctDNA) profiling was performed using an FDA-approved hybrid-capture next-generation sequencing assay, enabling to analyze over 300 genes, and assessment of tumor mutational burden (TMB) and microsatellite instability (MSI) from plasma samples. All molecular results were reviewed during a weekly institutional Molecular Tumor Board to assess clinical relevance and therapeutic implications. For the present study, patients with ≥2 FMI liquid biopsies were included. The earliest ctDNA test was defined as baseline (BL1), and the second earliest as BL2. Actionable alterations were classified according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). The primary objective was to determine the proportion of patients in whom repeat ctDNA testing identified new actionable alterations not detected at BL1, and their ESCAT tier distribution. **Results:** Among 1,565 patients (3,494 liquid biopsies), the median number of tests per patient was 2 (range 2–6). The most common tumors were lung (26.4%), breast (13.1%), prostate (10.9%), colorectal (CRC) (8.0%), pancreas (6.7%), and thyroid (4.1%). The median BL1→BL2 interval was 313.5 days (range 2–2,279). At BL1, 470 patients (30.0%) harbored ≥1 actionable alteration (ESCAT I–III); excluding TMB-high, 23.9%. Repeat testing identified ≥1 *new* actionable alteration in 316 patients (20.2%); excluding TMB-high, 10.7%. Notably, 227 patients (14.5%) converted from no actionable alteration at BL1 to ≥1 actionable alteration on later testing (8.1% excluding TMB-high). Newly detected actionable alterations were distributed as ESCAT II (54.3%), ESCAT I (26.1%), and ESCAT III (19.7%); 93 patients (5.9%) gained at least one new ESCAT I alteration. The yield of new actionable alterations varied by tumor type (~29% CRC, 25.9% breast, 23.5% lung, 14.6% prostate). **Conclusions:** In a large real-world cohort, serial ctDNA testing provided clinically meaningful incremental detection of actionable alterations in ~1 in 5 patients, including new ESCAT I findings in ~6%. These data support serial ctDNA profiling to capture evolving tumor genomics and expand therapeutic opportunities. Prospective studies should define optimal timing and confirm downstream clinical impact. Research Sponsor: None.

Cell-free DNA (cfDNA) methylation-based multi-cancer early detection (MCED) assay to enable subtyping of lung cancer, breast cancer, and non-Hodgkin lymphoma (NHL).

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Background: Given that distinct pathological and molecular subtypes of most cancers correspond to different treatment strategies, accurate cancer subtyping is clinically critical. Currently, pathological and molecular subtyping relies primarily on tissue biopsy—a procedure that is not always clinically feasible. Additionally, tumor heterogeneity may compromise the accuracy of subtyping via this approach. Prior studies have shown that cfDNA methylation-based detection is tissue-independent and outperforms mutation-based assays in cancer subtyping. Here, we employed a previously developed targeted methylation MCED assay to further classify the subtypes of lung cancer, breast cancer, and NHL. **Methods:** Pretreatment blood samples from lung cancer, breast cancer, and NHL patients enrolled in a MCED study were analyzed via the targeted methylation assay. Only samples with detected circulating tumor DNA (ctDNA) were included. The training cohort comprised lung cancer (n=529: 227 adenocarcinomas, 191 squamous cell carcinomas, 111 small cell carcinomas), breast cancer (n=359: 92 triple-negative breast cancers [TNBC], 267 non-TNBC cases), and NHL (n=157: 145 B-cell lymphomas, 12 T-/NK-cell lymphomas). The validation cohort included lung cancer (n=194: 87 adenocarcinomas, 82 squamous cell carcinomas, 25 small cell carcinomas), breast cancer (n=87: 26 TNBC, 61 non-TNBC cases), and NHL (n=60: 48 B-cell lymphomas, 12 T-/NK-cell lymphomas). cfDNA methylation profiles were analyzed to further classify the subtypes of these three malignancies. **Results:** In the validation cohort, the lung cancer classification model exhibited high overall accuracy 91.8% (178/194), with subtype-specific accuracies of 94.3% (82/87) for adenocarcinoma, 89.0% (73/82) for squamous cell carcinoma, and 92.0% (23/25) for small cell carcinoma. The breast cancer model achieved an overall accuracy of 80.5% (70/87), including 65.4% (17/26) for TNBC and 86.9% (53/61) for non-TNBC. For NHL, the model yielded an overall accuracy of 96.7% (58/60), with 97.9% (47/48) for B-cell lymphoma and 91.7% (11/12) for T-/NK-cell lymphoma. **Conclusions:** The cfDNA methylation-based MCED assay facilitates accurate subtype prediction for common malignancies without the need for invasive tissue biopsy procedures. This assay achieves high accuracy in lung cancer and NHL, whereas relatively lower accuracy is observed for breast cancer, particularly TNBC, owing to its reliance on molecular subtyping. Future studies will validate this assay in larger cohorts and extend its utility to a broader spectrum of cancer types. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

Correlation of presurgical circulating tumor DNA (ctDNA) levels with pathologic (p) stage and lymph node (LN) burden in localized colon cancer.

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Background: Accurate preoperative staging is vital for tailoring neoadjuvant therapy (NAT) in localized colon cancer. However, clinical staging often diverges from pathological findings due to limitations of imaging modalities in assessing pathologic LN (pLN) involvement and inter-observer variability. This study evaluated the association between presurgical ctDNA levels, microsatellite instability (MSI) status, and pLN burden across pStages I–III in colon cancer. **Methods:** This retrospective study included patients (pts) with pStage I-III colon cancer from the GALAXY study with available presurgical ctDNA levels (mean tumor molecules/mL; MTM/mL) assessed by a personalized tumor-informed assay (Signatera, Natera, Inc). Key exclusions included receipt of NAT, inconsistent pLN classification, pN1c disease, and missing MSI status. Conditional inference tree modeling was used to hierarchically evaluate clinicopathologic and molecular risk factors for their association with presurgical ctDNA levels. **Results:** Of the 3,473 pts (14.4%, 43.1% and 42.5% with pStage I, II and III, respectively) included, 90.2% had microsatellite stable (MSS) tumors. The conditional inference tree partitioned the cohort into five subgroups of distinct presurgical ctDNA level distributions defined by pStage, pLN burden, and MSI status, and demonstrated the pStage to be the strongest determinant of presurgical ctDNA levels. pStage I pts had uniformly low MTM/mL. In contrast, pStage II–III pts had higher and more variable MTM/mL levels, which were stratified by pLN burden and further differentiated by MSI status within each nodal category. Presurgical ctDNA levels were significantly higher in pLN-positive vs pLN-negative pts (median 2.52 vs 1.23 MTM/mL, $p < 0.0001$) and in pStage IIB-III vs pStage I-IIA pts (median 2.64 vs 1 MTM/mL, $p < 0.0001$). While presurgical ctDNA levels did not differ significantly based on MSI status alone, within both MSS and MSI-H subgroups, they were significantly higher in pLN-positive pts vs pLN-negative pts (MSI-H: median 4.40 vs 1.19 MTM/mL; MSS: median 2.41 vs 1.25 MTM/mL). Similar results were observed when grouped based on pStage I/II vs III. Specifically among pLN-positive pts, presurgical ctDNA levels increased with higher pLN burden (MSI-H: median 15.13 vs 3.75 MTM/mL for ≥4 vs 1-3 LN, $p=0.049$; MSS: median 3.70 vs 1.96 MTM/mL for ≥4 vs 1-3 LN, $p<0.0001$). **Conclusions:** Presurgical ctDNA levels reflect a hierarchical interplay of pathologic stage, lymph node burden, and MSI status rather than any single clinicopathologic factor. High presurgical ctDNA levels reliably correlated with pStage and pLN positivity in localized colon cancer, supporting the development of models incorporating presurgical ctDNA quantification to better select pts for NAT and their evaluation in prospective trials. Clinical trial information: 000039205. Research Sponsor: None.

Clinical utility of liquid *KRAS*-mutation screening in advanced pancreatic cancer patients referred for early-phase trials.

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Background: Approximately 90% of pancreatic ductal adenocarcinomas (PDAC) harbor a KRAS mutation. Clinical trials targeting oncogenic *KRAS* mutations, including mutant-specific, pan-KRAS/-RAS inhibitors, have shown promising activity. As tissue next-generation sequencing (NGS) is a multi-step process that can affect turnaround time (TAT), a liquid biopsy (LB) approach is of interest. We investigated the clinical utility of LB testing for common *KRAS* variants to facilitate matching pts with PDAC to early phase trials. **Methods:** In this single-center, prospective enrollment/retrospective analysis study, we included pts with locally advanced (LA) or metastatic PDAC seen at Princess Margaret Cancer Centre (PM) phase I clinical trials and gastrointestinal (GI) cancer clinics between Jan 2025 - Jan 2026. Medical records were reviewed to collect clinicopathologic characteristics and treatment data. Plasma ddPCR assessed 4 *KRAS* codon 12 variants (G12C/D/R/V) at the CAP-CLIA-accredited Advanced Molecular Diagnostics Laboratory at PM. TATs for KRAS ddPCR vs tissue NGS were compared using the Wilcoxon signed-rank test. **Results:** Of 98 pts with LA/metastatic PDAC, the median age was 67 years, 59% were male, and 67 pts were ECOG 1 (88%). 84 pts had disease stage IV (86%), 43 (44%) pts were chemotherapy-naïve, and 33 (34%) pts had 1 prior L of therapy. Median number of metastatic sites was 2 (range [r] 1-5), and median CA19-9 was 343 (IQR 35-1767). *KRAS* G12 mts were detected by ddPCR in 38% (37/98) of pts: G12D (46%), G12V (46%), G12R (5%), G12C (2.7%). The median ddPCR VAF was 4.8% (r: 0.4 - 42.2), median TAT of 5 days (r: 1 - 8). Among pts with *KRAS* detected by ddPCR, 4 (11%) were enrolled in phase I trials targeting *KRAS*. Tissue NGS was performed in 40 pts (41%), KRAS was detected in 90% (36 pts), with a median VAF of 45% (r: 5-90), and median TAT of 54 days (r: 10-92; $p<0.0001$ compared to ddPCR TAT). Reported *KRAS* variants: G12D (50%), G12V (19.4%), G12R (19.4%), Q61H (8.3%), G12C (2.8%). Co-mts in TP53 were seen in 22/36 pts (61%). Concordance between ddPCR and tumor NGS metrics are shown in Table 1. Median NGS VAF of concordant vs discordant cases: 48% vs 21% ($p=0.047$). **Conclusions:** Plasma-based *KRAS* screening using ddPCR was significantly faster than tissue NGS in advanced PDAC. A liquid-first strategy can accelerate matching pts to RAS-targeted trials, but intense competition for trial allocations limits access to these agents. ddPCR has excellent specificity and PPV across *KRAS* variants but limited sensitivity, thus serves as a rapid rule-in assay. Tissue NGS remains relevant, especially in ddPCR negative pts, and to assess co-mutations. Research Sponsor: None.

N=36 pts	ddPCR(+/-)	NGS (+/-)	Sens	Spec	PPV	NPV	Concordance	Discordance
G12C	1 / 35	1 / 35	100%	100%	100%	100%	100%	0%
G12D	11 / 25	18 / 18	61%	100%	100%	72%	81%	19%
G12R	1 / 35	7 / 29	14%	100%	100%	83%	84%	16%
G12V	5 / 31	6 / 30	83%	100%	100%	97%	97%	3%
All 4 variants	19 / 17	32 / 4	59%	100%	100%	24%	64%	36%

ctDNA kinetics throughout first-line AI and palbociclib using a tumor-informed structural variant-based ctDNA assay: Retrospective analysis of PADA-1 samples.

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Background: With standard assays (Limit of Detection [LoD95] at or >100 PPM), most patients with ER+/HER2- mBC show ctDNA "clearance" within a few weeks after initiating first- line AI+CDK4/6i, with ctDNA becoming detectable again only at or shortly before progression. To gain a more comprehensive view of ctDNA kinetics in response to therapy, we analyzed serial plasma samples from PADA-1 using a tumor-informed assay with a 100-1,000-fold higher sensitivity (LoD95 <10PPM). **Methods:** PADA-1 allowed the collection of plasma at baseline and every two months during first-line AI+palbociclib (PAL). A total of 489 serial plasma samples from 45 patients in PADA-1 were analyzed using an ultrasensitive structural variant-based ctDNA assay. WGS was performed on tumor material from archival primary or metastatic biopsies, and personalized multiplex dPCR assays tracking up to 16 somatic structural variants were used for ctDNA monitoring. **Results:** At baseline, before AI+PAL start, ctDNA was detected in N=40/41 evaluable patients (98%). ctDNA remained detectable in 381/489 (78%) samples during therapy. ctDNA was persistently detectable and quantifiable (i.e. detected at all time-points) throughout first-line therapy in most initially positive patients (24/40, 60%). With this ultra-sensitive assay, we report, for the first time, that ctDNA follows a recurrent kinetic pattern: (1) a steep decrease during the first 6 months of treatment, (2) a nadir reached at 6–12 months, and (3) a continuous increase until radiological disease progression (or discontinuation of follow-up). In some patients (15/40, 38%), ctDNA became undetectable at some point during therapy despite the high sensitivity of the assay, with sustained ctDNA clearance associated with no risk of impending tumor progression. **Conclusions:** Serial analyses with a highly sensitive ctDNA test uncover the molecular trajectory of tumor response to first line AI+PAL. The presence of an early ctDNA nadir, followed with a later slow and continuous increase of ctDNA, prior to radiological progression, highlights the dynamic nature of ER+ HER2- mBC response to therapy. This approach can complement imaging-based disease monitoring, extends the clinical utility of ctDNA monitoring beyond individual mutations, and opens new perspectives of therapeutic interventions and treatment adaptation. Clinical trial information: NCT03079011. Research Sponsor: Pfizer; SAGA Diagnostics.

Tumor-of-origin prediction using methylation signals from plasma cell-free DNA (cfDNA): Real-world experience in Asia and the Middle East (AME).

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Background: Accurate identification of tumor tissue of origin (TOO) is essential for guiding treatment decisions in advanced cancers; however, tissue biopsies may be limited by accessibility, sample adequacy, or diagnostic delays. Plasma cfDNA-based methylation profiling provides a non-invasive approach for TOO determination and has demonstrated high agreement with clinicopathologic diagnoses in prior studies. However, real-world data from AME remains limited. We evaluated the real-world performance of a methylation-based TOO classifier using plasma cfDNA in this population. **Methods:** We retrospectively analyzed plasma cfDNA samples from patients with advanced solid tumors tested across AME using the Guardant360 Liquid assay through December 2025. The assay interrogates epigenomic signals from >19,000 methylated regions. The TOO classifier assigns a ranked cancer signal of origin (CSO) based on tumor-specific methylation patterns, reporting a primary CSO prediction and, when confidence is intermediate, a secondary CSO prediction. CSO confidence is quantified algorithmically based on methylation signal strength and classification certainty. Only samples with medium (50–80%) or high (>80%) confidence predictions were included. All tests were ordered as part of routine clinical care, and available clinicopathologic diagnoses (CPD) served as the reference standard. **Results:** Among 1,782 cfDNA-profiled samples, 1,230 (69%) yielded a CSO prediction with medium or high confidence. The primary CSO prediction matched CPD in 85% of cases overall, increasing to 91% when secondary CSO predictions were included. Tumor-type–specific accuracy varied, with the highest performance observed for colorectal, breast, and prostate cancers (94% each). Agreement with CPD was lower for gastroesophageal (72%) and kidney cancers (68%). Among 114 cancer of unknown primary (CUP) cases, a suspected clinical diagnosis was available for 48. Medium- or high-confidence CSO predictions were generated in 42 (87%). CSO predictions aligned with subsequent clinicopathologic consensus or confirmatory biopsy in 35 (83%), spanning 13 tumor types, most commonly lung cancer (24%). Therapy response evaluation was available for 12 patients, with partial response in 9 (75%) and stable disease in 3 (25%). **Conclusions:** In this real-world AME cohort, the TOO classifier identified probable tumor tissue of origin in most advanced cancer patients. CSO predictions showed high agreement with CPD across multiple tumor types. This approach demonstrated potential value in resolving CUP cases, with the predicted origin confirmed in 83% of evaluable patients. These findings support the clinical feasibility of methylation-based tumor-of-origin testing in AME and warrant further studies to evaluate its impact on clinical decision-making. Research Sponsor: Guardant Health Pte. Ltd., Singapore.

Tissue-free minimal residual disease evaluation and clinical utility in early breast cancer: A real-world study.

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Background: Minimal residual disease (MRD) detected using circulating tumor DNA (ctDNA) is associated with increased breast cancer (BC) relapse risk in patients (pts) with early BC after curative-intent surgery. However, the clinical utility of ctDNA-based MRD testing for post-surgical surveillance and risk stratification remains incompletely defined. We used real-world data to evaluate the performance of Guardant Reveal, a tissue-free epigenomic assay for MRD detection, and the clinical significance of a positive MRD test (+MRD) in pts with resected early BC. **Methods:** Data of pts with resected stage I-IIIA BC in the Guardant InfinityAI Data Library who underwent Guardant Reveal testing between February 2023 and September 2025 was analyzed. Pts with ≥1 post-surgical MRD were included if they had either no distant metastatic BC recurrence with ≥1 year of follow up after the last MRD test or a documented distant metastatic BC postoperatively; pts with a new non-breast primary malignancy were excluded. Sensitivity was assessed by site of distant metastasis and interval from MRD test to recurrence; nodal recurrences were excluded due to claims data limitations. Specificity was assessed using all tests from pts without recurrence and ≥1 year of follow up after the last post-treatment MRD test. Claims data were used to infer treatment changes following +MRD. **Results:** A total of 822 pts was analyzed. 114 pts with real-world clinico-genomics data were evaluable for sensitivity and 708 for specificity. One-year sensitivity for distant metastatic recurrence was 71%, and was highest for bone-only (97%, 35/36 cases) or lung (89%, 8/9 cases) recurrences and lowest for brain-only recurrences (33%, 1/4 cases). Sensitivity within 12 months of recurrence was higher in hormone receptor-positive (HR+)/HER2-negative BC (79%) and stage IIIA BC (81%) and for multiple-organ versus single-organ metastasis (83% versus 69%). Sample-level specificity was 94%. Following +MRD, 41 pts did not initiate or switch systemic therapy; 29 had distant BC recurrence, including 24 within 90 days after +MRD. Twenty pts switched therapy within 90 days of +MRD; 19 recurred, including 17 within 90 days after +MRD. Among 10 pts with post-recurrence MRD testing, only 3 had +MRD. **Conclusions:** In a real-world cohort of pts with resected early-stage BC, a tissue-free epigenomic ctDNA MRD assay demonstrated high specificity and clinically meaningful sensitivity for distant metastatic recurrence, particularly for bone-only and lung metastases and in pts with HR+ BC. These findings support ctDNA-based MRD testing as a noninvasive tool for postsurgical surveillance and risk stratification in early BC. Research Sponsor: None.

Early ctDNA dynamics assessed by a personalized whole-genome sequencing-based assay as a predictor of outcomes with immune checkpoint blockade in advanced melanoma.

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Background: Circulating tumor DNA (ctDNA) is an emerging biomarker for assessing treatment outcomes and monitoring disease recurrence in melanoma. However, evidence supporting its clinical utility at very early on-treatment timepoints remains limited. We evaluated whether ctDNA dynamics relative to a single cycle of immune checkpoint blockade (ICB) are associated with treatment outcomes in patients (pts) with advanced melanoma. **Methods:** In this prospective, single-center cohort, pts with unresectable stage III or IV melanoma were enrolled. Treatment included anti-PD1 monotherapy (n=22, 40%) or anti-PD1+anti-CTLA-4 therapy (n=33, 60.0%). ctDNA analysis was performed using a personalized, tumor-informed assay (Signatera Genome, Natera, Inc.) designed from WGS of matched tumor and normal pairs. ctDNA (reported in mean tumor molecules per mL, MTM/mL) was subsequently tracked in the pts' longitudinal blood samples, which were collected at baseline (T0) and prior to cycle 2 (T1; 3-4 weeks after ICB initiation). ctDNA dynamics were categorized as favorable (ctDNA clearance at T1 or >10-fold decrease from T0 to T1) or unfavorable (rising ctDNA or <10-fold decrease from T0 to T1). Associations between these categories and progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier estimates and Cox proportional hazards models. **Results:** A total of 55 pts with unresectable stage III (n=12, 21.8%) or stage IV (n=43, 78.2%) melanoma were included. Median follow-up was 36.43 months (mo) (range, 31.47-41.39). ctDNA-positivity was 83.6% (46/55) at baseline and 80.0% (44/55) at T1. Table 1 summarizes survival outcomes per ctDNA profile. Pts with an unfavorable profile (UP) of ctDNA dynamics experienced worse PFS and OS in contrast to those with a favorable profile (FP). Median PFS was 2.1 mo in the UP group versus 28.8 mo in the FP group; median OS was 19.3 vs 37.8 mo, respectively. All pts (n=21, 100%) with progressive disease had an UP, including 52.3% (11/21) with rising ctDNA and 47.7% (10/21) with <10-fold decrease. Median ctDNA levels at T1 were also higher in pts without objective response compared with responders (56.69 vs 0.38 MTM/mL; p<0.001). **Conclusions:** ctDNA dynamics assessed by a personalized WGS-based assay after a single cycle of ICB were strongly associated with response and survival outcomes in advanced melanoma. These findings support the evaluation of treatment-adaptation strategies based on early ctDNA dynamics in pts receiving immunotherapy. Research Sponsor: None.

ctDNA profile	median PFS (mo)	6-mo PFS	12-mo PFS	PFS HR (95%CI) p-value	median OS (mo)	6-mo OS	12-mo OS	OS HR (95%CI) p-value
Favorable N=24	28.8	100% (24/24)	91.7% (22/24)	Reference	37.8	100% (24/24)	100% (24/24)	Reference
Unfavorable N=31	2.1	22.6% (7/31)	22.6% (7/31)	5.29 (2.39–11.75) p<0.001	19.3	80.6% (25/31)	67.7% (21/31)	9.96 (2.66–37.37) p<0.001

A population tumor kinetics analysis for early-cycle ctDNA-guided therapy decisions in DLBCL.

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Background: Early circulating tumor DNA (ctDNA) kinetics may be instrumental in identifying patients with DLBCL who can safely discontinue therapy after three cycles, as well as those who are less likely to benefit from completing the full six cycles. However, the optimal timing for ctDNA measurement, added value of early cycle data, and influence of assay sensitivity remain uncertain. Through population tumor kinetics (pop-TK) modeling of Pola-R-CHP (Pomeroy et al., Blood Cancer Discovery, 2025), we evaluated how adding data from cycles 1 and 2 enhances risk stratification beyond the assessment conducted after cycle 3. **Methods:** A 5-drug pop-TK model calibrated to Pola-R-CHP single-agent sensitivity distributions and clinical outcomes simulated tumor cell populations and patient-level parameters. Predicted residual disease after each cycle was mapped to ctDNA titers under assays of varying detection thresholds, representing conventional ctDNA, high-sensitivity ctDNA, and PET. We evaluated (1) ctDNA negativity at cycle three only, (2) adding cycles 1 and 2 for prediction, and (3) using cycles 1 and 2 to identify non-responders. For detection thresholds, representative values were selected to reflect overall trends. **Results:** Among ctDNA-negative patients at cycle 3 (n=557), stopping therapy at cycle 3 led to a recurrence rate of 0.172, while completing six cycles eliminated all recurrences. Adding ctDNA from cycles 1 and 2 separated cycle 3-negative patients into a high-risk group with much higher recurrence (90/121; 0.744) and a low-risk group with very low relapse risk (6/436; 0.014). Across assay sensitivities, high-sensitivity ctDNA reduced recurrence after cycle 3 cessation to 0.093 (43/464), whereas PET-level sensitivity showed a higher recurrence rate (0.288; 171/593), and adding data from cycles 1 and 2 consistently improved sensitivity. Early-cycle ctDNA (C1, C2) stratified patients into a high-risk non-responder group (5-year PFS 0.009), who can benefit from transferring treatment plans, and a low-risk group with favorable outcomes (5-year PFS 0.961). **Conclusions:** Pop-TK modeling suggests that although most patients with cycle 3 ctDNA negativity do not relapse when treatment is continued through cycle 6, some patients may still experience relapse that might not have occurred if treatment had been completed through cycle 6. Adding early cycles produces a large low-risk subgroup, supporting safer de-escalation, while still identifying patients who will consistently relapse if therapy is stopped early. Higher assay sensitivity reduces false negatives, but early-cycle ctDNA remains very informative. Furthermore, early cycle ctDNA enables identification of non-responding patients before completion of therapy. These findings support the addition of early cycle ctDNA into response-adapted de-escalation and early treatment switching in trials for DLBCL treated with Pola-R-CHP. Research Sponsor: None.

Multi-omics discovery and clinical validation of COL1A2 alternative splicing isoforms as liquid biopsy markers for metastasis surveillance in osteosarcoma.

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Background: Osteosarcoma (OS) is characterized by early metastatic dissemination, yet the lack of sensitive and tumor-specific tools for real-time surveillance remains a major barrier to improving patient outcomes. **Methods:** We performed an integrative multi-omics analysis of 424 OS patients, incorporating whole-exome sequencing, bulk RNA sequencing, short-read single-cell RNA sequencing, and single-cell long-read transcriptomics to resolve isoform-level AS alterations at single-cell resolution. Candidate isoforms were evaluated across plasma and peripheral blood datasets from 346 healthy controls to assess tumor specificity. Translational utility was tested in a prospective clinical trial (ChiCTR2400079438), comparing COL1A2 isoform–based circulating tumor cells (CTCs) detection with conventional VIM/TWIST1-based CTC assays and tumor-informed circulating tumor DNA (ctDNA) profiling. **Results:** OS exhibited widespread alternative splicing dysregulation across both tumor and stromal compartments, with extensive isoform remodeling revealed by single-cell long-read transcriptomics. Two metastasis-associated COL1A2 isoforms were detected in 98% of OS tumor cells but were entirely absent in healthy controls, demonstrating high tumor specificity. COL1A2 isoform–based CTCs detection significantly outperformed VIM- or TWIST1-based assays for predicting metastasis (AUC 0.833 vs. 0.531, $P < 0.01$) and achieved accuracy comparable to circulating tumor DNA (ctDNA) assays (AUC 0.833 vs. 0.861, $P = 0.78$). Notably, COL1A2 isoform–based CTCs detected metastatic progression 5.11 months earlier than conventional imaging, approximately two months earlier than ctDNA. Longitudinal analyses further revealed frequent loss of primary tumor–derived mutations during metastatic evolution, limiting the sensitivity of tumor-informed ctDNA assays, whereas COL1A2 isoform–based CTC detection remained robust. **Conclusions:** Collectively, this study provides the first systematic comparison of CTCs- and ctDNA-based surveillance strategies in OS and establishes COL1A2 isoform-based CTCs detection as a sensitive, specific, and mutation-agnostic liquid biopsy strategy. Clinical trial information: ChiCTR2400079438. Research Sponsor: None.

Integrating tumor mutation profiles, preoperative circulating tumor DNA (ctDNA), and clinical features to a predicting model for early peritoneal recurrence in stage II-III gastric cancer following curative gastrectomy.

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Background: Peritoneal recurrence is the common failure pattern after curative gastrectomy and is most consequential within the first 2 years. Early risk identification can alter treatment strategy. Conventional clinicopathologic models are inadequate for individualized early detection. Tumor-informed circulating tumor DNA (ctDNA) enables detection of minimal residual disease (MRD) and may help refine risk stratification. **Methods:** We conducted a prospective cohort study of 134 patients with stage II–III gastric adenocarcinoma undergoing curative-intent gastrectomy (MRD cohort). Clinicopathologic variables, tumor mutation profiles, and ctDNA metrics were integrated to train and internally validate machine-learning models using logistic regression, random forest, and XGBoost for the primary endpoint of peritoneal recurrence within 12 months and 24 months after surgery. External validation was performed using the Yang et al. dataset. **Results:** Among 134 MRD patients with complete molecular and clinical data, 19 (14.2%) and 35 (26.1%) developed peritoneal recurrence within 12 months and 24 months, respectively. ctDNA positivity and higher max variant allele frequency (max VAF) were strong predictors of early peritoneal relapse, with additional contributions from pathologic stage and preoperative CEA, PI3K–AKT or EMT pathway genes. Across algorithms, ctDNA-integrated models consistently outperformed clinical-only baselines, with XGBoost showing the best overall discrimination on cross-validation. Findings generalized on external validation with the Yang et al. dataset, supporting model transportability. **Conclusions:** Integrating tumor-informed ctDNA with clinical and genomic features enables actionable prediction of early peritoneal recurrence after curative gastrectomy. This tool can trigger strategy modification of either stricter follow-up, adjuvant therapy intensification, or consideration of neoadjuvant approaches, in selected high-risk patients. Multicenter validation and prospective utility studies are warranted. Clinical trial information: NCT05029869. Research Sponsor: None.

A prospective study of tumor-informed ctDNA minimal residual disease detection in bone and soft tissue sarcomas.

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Background: The high recurrence and metastasis rates lead to poor survival of patients with sarcoma. Conventional imaging often detects relapse at a relatively late stage. In our previous study, circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) detection demonstrated strong prognostic value in osteosarcoma, enabling earlier detection of recurrence compared with radiographic surveillance. However, whether this approach is applicable to soft tissue sarcomas and the broader sarcoma population remains unclear. **Methods:** Between August 2020 and March 2024, patients with sarcoma were prospectively enrolled at a single center. Tumor-informed MRD assays were designed using whole-exome sequencing of paired tumor–normal samples. Longitudinal postoperative plasma samples were collected for ctDNA analysis. Survival outcomes were assessed using Kaplan–Meier analysis with log-rank tests. Multivariable Cox proportional hazards regression was performed adjusting for age, sex, tumor necrosis score, and histologic subtype (osteosarcoma vs non-osteosarcoma). **Results:** A total of 121 patients were included, comprising 74 bone-origin sarcomas (72 osteosarcomas) and 47 soft tissue sarcomas; 77 patients were male and 44 were female. With a median follow-up of 21.7 months, postoperative ctDNA positivity was strongly associated with inferior survival. Median relapse-free survival was 6 months in ctDNA-positive patients versus 43 months in ctDNA-negative patients ($P < 0.001$). This prognostic separation remained significant across early (≤1 month), intermediate (1–6 months), and late (>6 months) postoperative time windows. In multivariable Cox analysis, postoperative ctDNA status remained an independent prognostic factor (HR = 5.20, 95% CI: 2.07–13.08; $P < 0.001$). In 19 patients, ctDNA positivity preceded radiographic evidence of recurrence, with a mean lead time of approximately 3 months. Notably, 56 patients with persistently negative postoperative ctDNA experienced no recurrence or metastasis during follow-up. **Conclusions:** Tumor-informed ctDNA-based MRD detection is applicable to a broad range of sarcoma subtypes and provides robust prognostic information following surgery. These findings support the role of ctDNA as an early biomarker for disease recurrence in sarcoma. Clinical trial information: ChiCTR2400083045.
Research Sponsor: None.

Leveraging a hybrid tumor-informed and tumor-agnostic ctDNA assay for optimal ctDNA-MRD detection: A real-world study in Southeast Asia.

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Background: While tumor-informed ctDNA assays are the gold standard for minimal residual disease (MRD) detection, their utility is frequently limited by suboptimal tissue quality and quantity. This study evaluated a hybrid strategy combining personalized tumor-informed mutations and a tumor-agnostic hotspot panel to improve ctDNA-MRD detection in a real-world patient cohort. **Methods:** We retrospectively analyzed 1015 blood samples of 577 patients diagnosed with stage I-IV lung (n=222), colorectal (n=172), and breast (n=143) cancers. The hybrid assay (K-4CARE, Gene Solutions) integrated patient-specific variants with a cancer-specific tumor-agnostic hotspot panel (K-4CARE, Gene Solutions). ctDNA status was correlated with clinical outcomes in 200 early-stage patients (median follow-up >6 months) and 59 metastatic-stage patients. **Results:** The hybrid approach significantly outperformed the tumor-informed method, increasing pre-treatment ctDNA detection rates by 33.3–48.8% in cases with suboptimal tissue quality. In the early stage, post-operative ctDNA was detected in 93.5% (29/31) of the patients having recurrence, with the median lead time of 8.4 months; while 97.6% (165/169) of those with no recurrence had negative results. ctDNA positivity was an independent prognostic factor ($p<0.001$) that increased recurrence risk in lung (HR=145.4; 95% CI: 37.4-564.5), colorectal (HR=173.6; 95% CI: 19.7->300.0), and breast (HR=147.8; 95% CI: 26.3->500.0) cancers. In the metastatic stage, at 12 weeks after therapy initiation, 85.3% (29/34) of the molecular responders, who had ctDNA cleared or reduced by >50% of baseline VAF level, achieved clinical partial response or stable disease; while 88.0% (22/25) of the molecular non-responders had confirmed progressive disease. Notably, the tumor-agnostic hotspot panel helped identify new and resistance mutations, including EGFR T790M in lung (20.0%), ESR1 Y537N (7.1%), ESR1 Y538G (3.6%), ESR1 P535H (1.8%) in breast (12.5%), and KRAS G12D in colorectal (25.0%) cancers. **Conclusions:** This hybrid approach improved sensitivity to detect ctDNA-MRD, and the capability to identify emergent resistance mutations provides expanded clinical utility for longitudinal monitoring. Research Sponsor: Gene Solutions JSC, Ho Chi Minh city, Vietnam.

Cell-free DNA fragmentomics as an enabler of tumor-of-origin classification using a commercial targeted cfDNA panel.

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Background: Analysis of cell-free DNA (cfDNA) fragmentation patterns (“fragmentomics”) has emerged as a powerful approach for cancer detection and classification, but most prior studies rely on whole-genome or research-grade sequencing. The feasibility and performance of fragmentomics using commercial targeted cfDNA next-generation sequencing (NGS) panels used in routine clinical care remain unclear. We evaluated whether fragmentomics metrics derived from the Tempus xF targeted cancer exon panel could accurately classify tumor type. **Methods:** We analyzed cfDNA sequencing data from 1,950 patients across 10 cancer types sequenced on the Tempus xF clinical NGS panel (105 genes), split a priori into training (n=1,455) and validation (n=495) cohorts. Exon-level fragmentomics features were extracted, including fragment size distributions, Shannon entropy, normalized read depth, proportions of short fragments, fragment size bins, motif diversity, and chromatin-context–specific entropy metrics. Elastic-net regression models were trained to classify tumor type using 10-fold cross-validation, with area under the receiver-operating characteristic curve (AUROC) as the primary endpoint. Model performance was independently evaluated in the validation cohort, including stratification by circulating tumor DNA (ctDNA) fraction. **Results:** In cross-validation of the training cohort, a combined fragmentomics model achieved a median AUROC of 0.790 across cancer types. In independent validation, the combined model maintained robust performance with a median AUROC of 0.794. Prostate, breast, and ovarian cancers demonstrated the highest discrimination (validation AUROCs up to 0.952 and 0.936 for prostate and breast cancer, respectively). Performance improved substantially in samples with higher tumor burden: among validation samples with ctDNA fraction ≥10% (85.2% of cases), the median AUROC increased to 0.815 compared with 0.719 in low ctDNA samples. **Conclusions:** Fragmentomics analysis applied to an existing commercial targeted cfDNA panel enables accurate tumor-of-origin classification without additional sequencing or assays. These findings demonstrate a scalable strategy to extend the diagnostic capabilities of routine clinical cfDNA testing and support the integration of fragmentomics into real-world liquid biopsy workflows, particularly in patients with sufficient ctDNA fraction. Research Sponsor: None.

Ultrasensitive tumor-informed ctDNA MRD detection to identify metastatic relapse and as predictor of recurrence-free survival following resection of early-stage NSCLC.

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Background: After curative-intent resection of non-small cell lung cancer (NSCLC), patients remain at risk for metastatic relapse and development of second primary malignancies. Circulating tumor DNA (ctDNA) molecular residual disease (MRD) detection has prognostic value, but sensitivity in early-stage disease has been limited. We evaluated an ultrasensitive tumor-informed whole-genome sequencing (WGS) assay that leverages phased variants (PVs) for longitudinal MRD detection in a cohort from the ctDNA Lung DETECT study (NCT05254782). **Methods:** Patients with clinical stage I NSCLC treated with upfront surgery were enrolled at Princess Margaret Cancer Centre/University Health Network. Resected tumor tissue underwent WGS to generate personalized tumor-informed assays tracking up to 5000 somatic variants, including prioritized PVs prioritized (CLARITY, Foresight Diagnostics). Plasma samples (pre-operative, 3-6 weeks post-operative landmark, 6 months, 12 months, and at recurrence) were analyzed retrospectively with labs blinded to outcomes. Endpoints were MRD detection, recurrence free survival (RFS), MRD clearance patterns. **Results:** Of 128 clinical stage I patients with banked samples, 121 (95%) had sufficient tumor for WGS. Pathologic stage distribution AJCC 8th Ed. was stage 0/I/II/III/IV (n=1/86/22/1). Among 121 patients, 16 (13%) experienced distant recurrence and 15 (12%) developed second primary malignancies: lung, breast, ovarian, prostate and sarcoma. MRD detection at pre-operative (HR 5.6, p=0.002) and post-operative landmark (HR 4.2, p=0.002) was significantly associated with RFS. MRD+ at 12 months post-resection demonstrated stronger prognostic value, as 97% (91/94) MRD-negative patients remained recurrence free compared to 15% (2/13) MRD+ patients (HR 48.3, $p<0.0001$). We assessed MRD clearance between post-op landmark and later samples in patients who received adjuvant therapy. In total, 34 received adjuvant therapy; of these, 10 were MRD+ post-operatively with at least 1 subsequent sample. MRD clearance during or after adjuvant therapy was significantly associated with improved RFS (p=0.019). Patients with MRD clearance at any time after adjuvant therapy had 0% recurrence (0/4), while 83% (5/6) patients who failed to clear MRD despite adjuvant therapy had recurrence. In recurrence, MRD was detected in 94% (15/16) prior to or at recurrence. Only 1 MRD-negative patient recurred, >2 years after the last assessed sample. **Conclusions:** Ultrasensitive tumor-informed ctDNA MRD detection identifies patients at high risk for metastatic relapse following NSCLC resection, including pathologic Stage I, and may provide substantial lead time over conventional imaging. Clearance of post-surgical MRD with adjuvant therapy may inform post-resection surveillance and future studies of adjuvant therapy. Clinical trial information: NCT05254782. Research Sponsor: Princess Margaret Cancer Foundation; Ontario Institute for Cancer Research.

cfDNA sequencing as a cutting-edge technology to identify pathogenic germline variants from 8353 patients with advanced tumors at the Gustave Roussy Institute.

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Background: Large cfDNA panels used for somatic profiling can incidentally reveal pathogenic variants of potential germline origin, with implications for patient management and hereditary cancer risk assessment. **Methods:** Between December 18th, 2020 and July 22nd, 2025, a weekly molecular tumor board reviewed cfDNA sequencing data from 8353 patients with advanced solid tumors treated at Gustave Roussy using the FoundationOne Liquid CDx panel, within the prospective STING trial (NCT04932525). We evaluated the yield, clinical relevance, and confirmatory outcomes of an MTB-governed workflow to flag putative germline pathogenic variants (PGPVs) from routine cfDNA profiling in advanced cancers. Across the 324 covered genes, we selected a list of 31 known hereditary cancer genes and 7 emerging candidates. Patients without prior germline confirmation were referred for genetic counseling and confirmatory testing on an independent sample. Turnaround times were compared with the conventional germline pathway. **Results:** Among 8,353 patients (mean age 62 years), 445 (5.3%) carried 471 PGPVs, including 23 patients with more than 2 variants. The most frequently implicated genes were *BRCA2* (n=101), *MUTYH* (n=81) and *BRCA1* (n=62). Overall, 54.6% of PGPVs were incidental findings (257/471); among incidental findings, 51.0% were clinically actionable (131/257), corresponding to 27.8% of all PGPVs (131/471). Germline status was confirmed in 172 patients (86 known prior to cfDNA profiling and 86 confirmed following cfDNA-guided referrals, including 60 incidental findings of which 52 were actionable; 14 variants (11 patients) were not confirmed and 6 were pending. For variants first flagged through cfDNA, the mean interval from liquid biopsy prescription to confirmatory germline report was 2 months, compared with 6 months through the conventional pathway. In evaluable paired cases, cfDNA showed high diagnostic performance for identifying germline findings (sensitivity 98.3%, specificity 97.4%). **Conclusions:** In an advanced pan-cancer real-world cohort, an MTB-governed cfDNA workflow identified PGPVs in 5% of patients, with over half representing incidental findings and 28% of all PGPVs being actionable. cfDNA profiling can accelerate referral and confirmation of hereditary cancer risk when coupled with expert interpretation and confirmatory germline testing, while acknowledging limitations for certain alterations. Research Sponsor: None.

ESR1 mutation longitudinal dynamics in RWD cohort of HR+/HER2− metastatic breast cancer patients treated with standard-of-care hormonal therapy.

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Background: *ESR1* mutations (*ESR1*m) are known drivers of resistance to aromatase inhibitors. While *ESR1*m has been linked to worse survival outcomes, clonal complexity over time has not been well-evaluated in a real-world context. Here we characterized longitudinal dynamics of *ESR1*m, including rare point mutation emergence and polyclonality in hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC) patients (pts) treated with aromatase inhibitor (AI) plus CDK4/6 inhibitor (CDK4/6i). **Methods:** We identified a cohort for longitudinal analysis from the Tempus real-world database (RWD). Eligible pts had HR+/HER2- mBC (diagnosed before 01/2023), received AI+CDK4/6i therapy in mBC, and had comprehensive genomic profiling from tissue/liquid biopsy (Tempus xT/Tempus xF) within 2 yrs of treatment, with ≥1 on-treatment xF tests. We analyzed *ESR1* clonal dynamics, starting from first *ESR1*m detection in a subset of pts who had multiple xF tests. Polyclonality was also assessed, defined as presence of at least 2 distinct *ESR1*m in a sample. **Results:** Of 301 HR+/HER2- mBC pts on AI+CDK4/6i therapy, 102 (33.9%) developed an *ESR1*m. In the *ESR1*m group, 72 pts (70.6%) had 2+ on-treatment liquid biopsies (Tempus xF/xF+), comprising the final cohort for observation. At *ESR1*m detection, 64.8% pts had a single detectable *ESR1*m, most commonly D538G (31.9%) and Y537S (12.5%). In contrast, 34.7% had polyclonal mutations (19.7% with 2 distinct mutations; 15.3% with 3+). Recurrent detection of D538G (52.8%), Y537S (20.8%), and Y537N (16.7%) was noted in repeat xF testing. Detection of additional *ESR1*m (26.4%) over time confirmed known common mutations such as Y537N (8.3%), D538G (5.6%), and Y537S (5.6%). However, longitudinal testing also found rare mutations such as V422del and H524L. Mutational dynamics shifts were also revealed by longitudinal testing. In 36.1% pts, a previously detected *ESR1*m was no longer found, often in those who initiated a SERD. D538G (5.6%) and Y537N (4.2%) were the most commonly lost mutations. Recurrent and new *ESR1*m detection occurred in pts who continued AI+CDK4/6i (44.4%). Many pts showed a combination of these dynamics. **Conclusions:** Multimodal RWD analyses demonstrate valuable clinical insights on *ESR1*m patterns detected from longitudinal molecular surveillance testing in HR+/HER2- mBC pts treated with AI+CDK4/6i. We observed shifting dynamics in *ESR1*m burden, including detection of rare mutations and polyclonality. These findings show the value of monitoring *ESR1*m longitudinally over disease course and prompt further research into clinical impacts of clonal dynamics. Research Sponsor: None.

Quantitative assessment of tumor shedding using AI-derived radiographic tumor burden and quantified liquid biopsy in advanced gastrointestinal cancers.

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Background: Radiographic imaging remains the clinical standard for assessing cancer treatment response; however, it lacks sensitivity to detect early biological shifts and spatially heterogeneous tumor behavior. Methylated circulating tumor DNA (mctDNA) provides a complementary molecular measure of disease burden, yet the quantitative relationship between radiographic tumor burden and DNA shedding remains poorly characterized. In this cohort study, we evaluated whether early changes in shed rate predict progression-free survival (PFS) and overall survival (OS) in patients with advanced gastrointestinal (GI) cancers. **Methods:** Patients with advanced GI malignancies receiving systemic therapies underwent paired longitudinal radiographic and liquid biopsy assessments. Radiographic tumor burden was quantified (OSCAR AI platform). Tumor contours were independently blinded reviewed by two radiologists. Up to 15 target lesions per organ were selected, and the total tumor burden was calculated analogous to longitudinal RECIST assessment. Tumor Methylation Score (TMS) from the Northstar Response assay quantified mctDNA. Tumor shed rate (TSR) was defined as the ratio of TMS to the AI-derived radiographic tumor volume and calculated at baseline and at the first on-treatment landmark using the closest-paired CT scan and blood drawn within 120 days. Fold-change in TSR from baseline was compared with PFS and OS. Undetectable tumor volume cases were excluded. **Results:** Forty patients were evaluable, with both baseline and landmark timepoints available within the 120-day window. TSR ranged from a min of 0 methylated molecules per mm^3 (m4) to a max of 1.0 m4 with a median of 0.06 m4. TSR significantly differed between tumor types (p=0.013, ANOVA), with CRC having the highest median shed rate (0.13 m4) and EGA and pancreatic having the lowest median shed rates (0 m4). TMS was significantly associated with tumor volume at baseline (Rsq=0.15,p=0.01, Deming) and on-treatment (Rsq=0.6, p<0.001, Deming). An increased TSR was associated with OS (HR=5.8, 95% CI 1.7-19.2, <0.01) and PFS (HR=3.5, 1.4-8.6, <0.01). **Conclusions:** TSR represents a novel, multidimensional integration of AI-driven volumetrics and liquid biopsy. Our findings suggest that an increasing shed rate is a predictor of PFS and OS, potentially serving as a lead-time indicator of tumor-host homeostatic decompensation. Future analysis will determine if TSR captures critical transitions in tumor biology that precede and perhaps drive radiographically detectable progression. Research Sponsor: U.S. National Institutes of Health; UF Health Cancer Institute; Florida state appropriations provided in Fla. Stat. § 381.915; BillionToOne.

Breast cancer screening is heating up: A novel thermophysics-based AI modality for screening subjects with BIRADS 4 or 5 mammograms.

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Background: Although mammography is an effective cancer detection modality, limited specificity at population scale leads to unnecessary biopsies, highlighting a need for adjunctive approaches. Cancer exhibits increased metabolic activity, leading to temperature differentials when compared with benign tissue. In this study, ultra-high sensitivity infrared imaging (IRI) was utilized with a novel thermophysics-based AI neural network to leverage temperature differentials for cancer screening. **Methods:** This prospective validation pilot study enrolled 14 patients with BI-RADS 4 or 5 breast lesions on diagnostic imaging prior to biopsy. IRI and optical images were acquired using an infrared imaging device at angular intervals, encoding the breast surface. Thermal and optical data were processed using a 3D reconstruction algorithm to generate breast surface thermal-spatial point-clouds, encoding temperature values at corresponding locations. Tumor presence or absence was predicted using an AI physics-informed neural network (PINN) that solves inverse bioheat transfer equations to identify heat sources associated with increased metabolic activity and blood perfusion. The PINN result was then compared to diagnostic mammography and to histologic findings on pathology. **Results:** 14 patients aged 42-83 years were included in a prespecified salient interim analysis approved by the study committee to assess feasibility. Histologic outcomes ranging from normal breast tissue to benign and premalignant/malignant conditions as outlined in Table 1. The PINN accurately predicted the presence and location of all premalignant/malignant lesions, including all incidences of IDC (n=3), DCIS (n=3), and ADH (n=2). Histologically benign lesions (n=6) were not detected by the PINN as a heat source. The mean size error for the PINN was 1.3 cm compared to size on pathology. **Conclusions:** Infrared imaging combined with a thermophysics-based AI neural network was able to localize and detect premalignant/malignant breast lesions with 100% sensitivity and specificity. Our findings suggest that IRI adjunctive screening may have the potential to both accurately detect breast cancer and minimize unnecessary biopsies. Research Sponsor: None.

Comparison of PINN assessment with histological outcome.

Number of Patients	Breast Tissue Type	PINN Assessment	PINN Diameter (cm)	Histologic Assessment	Histologic Diameter (cm)
2	SF	+	1.2, 2.2	ADH	2.1,3.0
3	SF	+	1.1, 1.4, 1.4	DCIS	2.1, 2.0, 2.8
3	SF	+	1.0, 1.2, 1.6	IDC	0.5, 3.0, 5.0
1	SF	–		Fibrosis	
1	SF	–		Cystic Fluid	
1	SF	–		Fibrocystic	
1	SF	–		Fibroadenoma	
1	SF	–		Duct Ectasia	
1	HD	–		Normal Breast	

Breast tissue density classifications: scattered fibro-glandular (SF), heterogeneously dense (HD). Histology subtypes: invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH). PINN=physics-informed neural network.

^{68}Ga-NODAGA-SNA014 whole-body PET imaging to detect Claudin18.2–positive pancreatic cancer lesions.

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Background: ^{68}Ga-labeled nanobody (^{68}Ga-NODAGA-SNA014) is a PET radiotracer based on a single-domain antibody. We conducted a first-in-human (FIH) evaluation of ^{68}Ga-NODAGA-SNA014 to characterize in vivo biodistribution, metabolism, radiation dosimetry, and safety, and to explore its ability to noninvasively quantify Claudin-18.2 (CLDN18.2) expression in patients with gastrointestinal cancers. **Methods:** ^{68}Ga-NODAGA-SNA014 was synthesized and first assessed preclinically in human pancreatic cancer cell lines and xenograft mouse models to evaluate affinity, specificity, and pharmacokinetics. We then performed a translational pilot study in 15 patients with pancreatic cancer imaged on a total-body (panoramic) PET/CT system. Whole-body biodistribution, organ dosimetry, and the association between lesion uptake and CLDN18.2 expression were analyzed and compared with ^{18}F-FDG, where available. **Results:** ^{68}Ga-NODAGA-SNA014 was produced reliably with favorable radiochemical characteristics. In preclinical studies, the tracer exhibited rapid blood clearance, high affinity for CLDN18.2, and specific uptake in CLDN18.2-positive cells and xenografts. In patients, physiologic uptake was highest in the stomach and kidneys, with mild uptake in the pancreas. Lesion uptake varied by CLDN18.2 expression level, and ^{68}Ga-NODAGA-SNA014 demonstrated more precise differentiation of CLDN18.2-high versus CLDN18.2-low lesions than ^{18}F-FDG. **Conclusions:** PET uptake (SUV) of ^{68}Ga-NODAGA-SNA014 correlated with CLDN18.2 expression, supporting its potential as a noninvasive companion diagnostic to guide and optimize CLDN18.2-targeted therapies. Research Sponsor: None.

Comprehensive profiling and clinical utility of CSF-derived cell-free DNA/RNA for evaluation of solid and hematologic malignancies affecting the central nervous system.

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Background: Diagnosis and risk stratification of brain lesions is challenging when tissue biopsy is contraindicated due to anatomic or clinical factors. Cerebrospinal fluid (CSF)–based liquid biopsy using cell-free DNA (cfDNA) and RNA (cfRNA) offers a minimally invasive approach to detect neoplastic disease and inform management. We evaluated the clinical utility of a commercially available cfDNA/cfRNA next-generation sequencing assay applied to CSF specimens from patients with CNS lesions of uncertain etiology. **Methods:** Between 2023 and 2025, cfDNA, cfRNA, and CSF cell pellet RNA profiling using next generation sequencing (NGS) was performed on CSF samples from 1,559 patients, including 1,209 evaluated for suspected primary or secondary solid CNS malignancies and 350 evaluated for CNS involvement by hematologic malignancies. The assay interrogated single-nucleotide variants, insertions/deletions, copy number alterations, gene fusions, lymphocyte clonality, and tumor mutational burden. The depth of sequencing was between 25,000x and 30,000x for cfDNA. For quality control purposes, more than 80 million reads were required for accepting RNA results, while the required percentage of spliced RNA reads was above 20%. Clinical utility and actionability was further assessed in a single-institution cohort of 90 patients by correlating cfDNA/cfRNA results with cytology, flow cytometry, tissue biopsy, and clinical decision-making. **Results:** Among patients evaluated for solid malignancies in the entire cohort, the most common alterations involved TP53, KMT2C, PIK3CA, EGFR, and DNMT3A, while hematologic cases frequently harbored PIM1, TP53, MYD88, CD79B, TET2, and DNMT3A alterations. In the institutional cohort (median age 57 years), neoplastic cfDNA was detected in 40/90 samples, with recurrent alterations mirroring those of the larger panel. cfDNA profiling demonstrated 100% sensitivity for neoplastic DNA detection compared with current standard-of-care cytology and flow cytometry and identified neoplastic DNA in 37% of cytology-negative and 42% of flow-negative cases. Concordance with contemporaneous tissue biopsy yielded a positive predictive value of 89%, with a sensitivity of 68%, reflecting reduced detection in intraparenchymal lesions with limited CSF exposure. cfDNA results directly influenced treatment decisions in patients evaluated for new intracranial malignancy and for CNS metastasis or recurrence. **Conclusions:** CSF cfDNA/cfRNA profiling significantly enhanced diagnostic yield in CNS lesions of uncertain etiology, particularly when conventional cytology is negative, or biopsy is infeasible, while also providing actionable molecular information to guide therapy. Research Sponsor: None.

Application of long-read sequencing to resolve cryptic genomic instability across cancer types.

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Background: Computational mutational signatures can identify tumors with homologous recombination deficiency (HRD), mismatch repair deficiency (MMRD), and focal tandem duplication (FTD) phenotypes, nominating patients for PARP inhibitors or immune checkpoint blockade. However, many signature-positive cases lack identifiable causative alterations by conventional sequencing, forcing patients toward empiric therapy or clinical trial enrollment without molecular confirmation. We evaluated whether long-read nanopore sequencing could provide definitive molecular diagnoses to guide evidence-based treatment selection. **Methods:** We analyzed 768 patients with advanced prostate (n=505), breast (n=246), and ovarian (n=17) cancers enrolled in the MiOncoSeq precision oncology program. Computational signature analysis identified cases with HRD, MMRD, or FTD phenotypes. Cases unresolved by standard short-read sequencing underwent long-read nanopore sequencing with integrated structural variant detection, methylation profiling, and haplotype phasing. **Results:** Signature analysis identified 164 cases (21.3%) with genomic instability phenotypes. Short-read sequencing resolved 118/164 cases (71.9%), leaving 46 patients without molecular confirmation. Long-read sequencing achieved mechanistic resolution in 32/46 cases (69.6%), with complete resolution of MMRD (5/5, 100%) and FTD (7/7, 100%). Secondary signature analysis reclassified 11/14 unresolved HRD cases as non-classical, likely reflecting alternative DNA repair defects or replication stress, refining diagnostic yield to 86.9% (20/23) for credible HRD. Cryptic mechanisms included promoter hypermethylation (*BRCA1*, *MLH1*, *RAD51C*), balanced structural rearrangements (*CDK12*, *PMS2*), and deep intronic splice variants (*PALB2*, *BARD1*). Long-read sequencing also uncovered 3 previously undetected pathogenic germline variants (*BARD1*, *BRIP1*, *PALB2*) with direct implications for hereditary cancer risk assessment and family screening. Combined analysis identified actionable findings enabling targeted therapy selection in 19.5% of patients. **Conclusions:** Long-read sequencing provides definitive molecular diagnoses for patients with signature-positive tumors, enables evidence-based therapy selection over empiric treatment, and uncovers cryptic germline variants informing hereditary cancer risk. Research Sponsor: National Cancer Institute.

CLERAD-PROBE: Dosimetric analysis of I-124 PET–guided remnant radioiodine ablation in differentiated thyroid carcinoma.

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Background: The role of adjuvant radioiodine therapy (RIT) in differentiated thyroid carcinoma (DTC) remains controversial due to a lack of long-term data from randomized controlled trials. Consequently, international guidelines diverge; while some advocate broad application, others prioritize a restrictive, risk-adapted approach. The CLERAD-PROBE trial aims to bridge this gap by comparing both strategies regarding blood dose — as an established surrogate for secondary malignancy risk — and oncological outcomes. **Methods:** CLERAD-PROBE is a prospective, randomized, bicentric study (NCT01704586) in adult DTC patients, excluding those with unifocal papillary microcarcinomas $\leq$ 10 mm limited to the thyroid. Following thyroidectomy, patients in Arm 1 underwent I-124 PET for staging and dosimetry. Adjuvant RIT was administered if one or multiple of the following risk factors were present: incomplete surgical resection, tumor size >4cm or extrathyroidal extent, lymph node metastases and age $\geq$ 45 years, distant metastases, and/or iodine-avid lesions on I-124 PET. In Arm 2, adjuvant RIT was generally performed. Follow-up was performed every 4–6 months using thyroglobulin measurements and cervical ultrasound. The primary endpoint was the mean blood dose after complete remission or 18 months. Secondary endpoints included progression- and recurrence-free survival at 3 and 10 years. **Results:** The primary endpoint was evaluable in 315 patients, enrolled from May 2015 to May 2021 (148 in Arm 1, 167 in Arm 2). Study arms were matched with regards to histology, age, and tumor/nodal stage, though Arm 1 had significantly fewer men (22% vs. 34%, p = 0.02). I-124 PET identified lymph node metastases in 49 patients and distant metastases in 13 patients. RIT was performed in 68 of 148 (46%) patients in Arm 1. Of these, 13 patients with low-risk carcinoma underwent RIT because of new metastases found on I-124 PET. The mean absorbed blood doses (252 mGy vs 447 mGy, range: 4 - 3217 mGy vs. 48 - 2520 mGy; $p < 0.001$) and administered I-131-activities (2.3 GBq vs. 4.9 GBq; range: 0 – 18.6 GBq vs. 1.0 – 26.2 GBq; $p < 0.001$) were lower in Arm 1. **Conclusions:** I-124 PET identifies persistent, iodine-avid disease in patients who would not routinely receive adjuvant RIT pursuant to ATA Guidelines, while enabling individualized selection in the others to minimize secondary malignancy risk. The impact on long term oncological outcomes has yet to be determined. Three years follow-up analyses evaluating recurrence rates and overall oncological safety are currently in progress and will be presented at the congress. Clinical trial information: NCT01704586. Research Sponsor: German Cancer Aid; 110751.

iPREDICT: Phase II study of CD8 PET in patients with immunoresponsive solid tumors—Imaging characteristics and correlation with RECIST response.

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Background: CD8 T cells mediate antitumor effects of immune checkpoint blockade (ICB); their histologically-determined abundance prior to or during therapy (Rx) appears to correlate with ICB response in melanoma (MEL) and other solid tumors. We performed this Phase IIb study to assess CD8 targeted PET imaging with ^{89}Zr-crefmirlimab berdoxam prior to and during ICB Rx to study its potential as a marker for Rx selection, enhancement or even replacement of existing tumor measurement systems, and correlation of clinical outcomes. **Methods:** 70 patients (pts) with MEL or Merkel cell cancer (MCC) (27), renal cell cancer (RCC) (35) or lung cancer (NSCLC) (8) who were eligible for first or second-line single- or double-agent ICB or ICB plus an oral kinase inhibitor (TKI) were enrolled. ^{89}Zr-crefmirlimab berdoxam (1 mCi,1.5 mg protein), was administered intravenously ≤2 weeks prior to cycle 1 of ICB Rx, followed by a PET/CT scan 24 (+/-3) hours later (baseline, BL). The 2nd tracer injection and associated PET/CT scan occurred 4-6 weeks after ICB Rx initiation, prior to cycle 3 (on treatment, OT). Standard of Care imaging and RECIST 1.1 were used to assess response to Rx. **Results:** All 70 pts were evaluable for safety analysis; none experienced an SAE related to imaging agent. 65 pts (21 MEL, 2 MCC, 34 RCC and 8 NSCLC) were included in the primary endpoint analysis of correlating CD8 PET scans with best confirmed overall response (BOR) by RECIST 1.1. MEL and MCC pts received single (6/23) or double ICB (17/23), RCC pts received single ICB with/without TKI (21/34) or dual ICB (13/34), and all NSLCL pts received single ICB. In the RCC cohort, multiple CD8 PET metrics showed statistically significant association with either individual BOR or Binary Response at BL, OT or as delta, including: Tumor Standard Uptake Value (SUV), Lymph Node (LN) SUV, relative percentage of CD8 negative or positive lesions and normal organ SUV. Normalization to reference organs improved the correlation with BOR for the combined cohorts and for the MEL/MCC cohort. Depending on clinical objectives, different classification rules to predict BOR were applied, prioritizing specificity for non-responders and sensitivity for responders (Table). These results were cohort-dependent, as each cohort exhibited a distinct distribution of SUVs. **Conclusions:** PET imaging can quantitate CD8 T cells with sufficient specificity and sensitivity to support further study in selection of pts for Rx regimens and assessing early response to therapy. Clinical trial information: NCT05013099. Research Sponsor: Imaginab.

Prediction of BOR by CD8 PET.

Cohort	Response	Parameter	Timepoint	AUC	95% CI	Sensitivity	Specificity
MEL + MCC	CR+PR vs SD+PD	Spleen SUVmean	BL	0.67	0.44,0.90	87.5	60.0
MEL + MCC	CR+PR vs SD+PD	Tumor SUVmax normal. to thyroid	Delta	0.70	0.46, 0.95	85.7	64.3
RCC	CR+PR vs SD+PD	Hottest LN SUVmax	OT	0.84	0.65, 1.00	71.4	90.9
RCC	CR vs PR+SD+PD	% CD8 negative lesions	Delta	0.96	0.87, 1.00	100.0	92.3

Cell-free DNA methylation profile–based fusion epigenotyping to enhance *ALK* fusion detection in NSCLC patients.

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Background: Short read lengths in next-generation sequencing and targeted panel probe design pose challenges to fusion detection by impairing the resolution of complex genomic rearrangements and the accurate mapping of intronic breakpoints. To address these limitations, we developed a cell-free DNA (cfDNA) methylation-based fusion epigenotyping method that leverages fusion-associated tumor epigenetic signatures to complement genomic-based methods and increase the fusion detection sensitivity of our liquid biopsy. We validated *EML4-ALK* fusion detection by this algorithm in non-small cell lung cancer (NSCLC) using paired clinical tumor tissue and cfDNA samples. **Methods:** We trained a binary classifier to discriminate *EML4-ALK* fusion-positive from fusion-negative NSCLC using cfDNA methylation signal and genomic molecule support. To validate the epigenotyping classifier, an independent cohort of 577 clinical NSCLC samples was selected with paired tumor tissue and Guardant360 Liquid (Guardant Health, Palo Alto, CA) cfDNA for each patient (with epigenomic tumor fraction $>$ 0.03%). The cohort included 94 tissue-confirmed fusion-positive samples (78 cfDNA genomic positives and 16 cfDNA genomic false negatives) with *EML4-ALK* detected in tumor tissue, and 483 tissue-confirmed fusion-negative samples (*ALK* fusion negative in both tissue and paired cfDNA). The epigenotyping classifier predictions in cfDNA were evaluated against tissue-based orthogonal truth. **Results:** Among tissue-confirmed fusion-positive samples, tissue-liquid assessment showed a high positive percent agreement (PPA) / sensitivity of 89.36% (84/94), as well as 100% concordance with genomic caller positives (78/78). The rate of rescued fusions by the epigenotyping classifier from genomic false negative liquid cases was 38% (6/16). Among tissue-confirmed fusion-negative samples, tissue-liquid assessment showed a high negative percent agreement (NPA) / specificity of 99.38% (480/483). The false positive rate (FPR) of high confidence calls (probability exceeding a 99.7% specificity threshold or with partial genomic evidence) was 0.0% (0/483). **Conclusions:** cfDNA methylation-based fusion epigenotyping substantially increased detection of actionable *ALK* fusions while maintaining high specificity, as demonstrated by tissue-liquid concordance. The results of this approach showed the clinical value of giving NSCLC patients an increased likelihood to receive more effective, less toxic ALK inhibitor therapy, while the minimized FPR helps ensure appropriately matched treatment decisions. Research Sponsor: Guardant Health.

Multicenter clinical study of [^{18}F]AlF-HER2-BCH PET/CT as a molecular pathology tool for linear quantification of HER2 expression levels in breast cancer.

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Background: Determining the human epidermal growth factor receptor 2 (HER2) status is essential in metastatic breast cancer (MBC) management. To establish the clinical validity of [^{18}F]AlF-HER2-BCH PET/CT (HER2-PET), we assessed the diagnostic accuracy of qualitative and quantitative HER2-PET assessment to predict HER2 expression by immunohistochemistry (IHC), including HER2-negative and -low breast cancer. **Methods:** This prospective multicenter trial enrolled treatment-naïve patients with newly diagnosed, non-rapidly progressive breast cancer across all molecular subtypes. Paired HER2 PET and [^{18}F]FDG PET/CT (FDG-PET) scans were acquired within a standardized 7-day. Tumor uptake was quantified using maximum standardized uptake value (SUVmax) and target-to-background ratios (TBR), and analyzed via general linear mixed models. **Results:** Between 2020 to June 2025, 240 patients were analyzed. Comparative analysis revealed superior diagnostic performance of whole-body HER2-PET versus FDG-PET for malignant lesion detection: sensitivity (97.6% vs 89.9%), specificity (83.9% vs 77.4%%), and overall accuracy (96.4% vs 88.9%). Quantitative HER2-PET analysis revealed significantly different SUVmax values across HER2 expression categories (median [IQR]: HER2-positive 13.1 [9.2-20.7] vs HER2-low 7.3 [5.1-8.9] vs HER2-negative 3.2 [2.7-4.5]; P<0.001), demonstrating strong correlation with IHC/FISH-defined HER2 status. In contrast, FDG-PET uptake showed no association with HER2 status (P=0.5). Among 10 discordant cases between HER2-PET and standard IHC/FISH: eight (80%) represented confirmed biological heterogeneity, with differing HER2 status across metastatic sites; two (20%) IHC 1+ cases exhibited PET-positive/FISH-amplified patterns, suggesting potential IHC false-negative results. **Conclusions:** [^{18}F]AlF-HER2-BCH PET/CT provides comprehensive HER2 profiling beyond single-biopsy IHC, offering new therapeutic insights for HER2-low/negative metastatic breast cancer through whole-body molecular visualization. Clinical trial information: NCT04547309. Research Sponsor: None.

Diagnostic performance of Al^{18}F-HER2-BCH PET/CT and ^{18}F-FDG PET/CT, in the detection of primary and metastatic lesions in the evaluable imaging core population (N participant=240, N Biopsy-proven lesion=359).

	HER2 PET	FDG PET	Difference^	P Value*
Participants				
True positive	207	199	–	–
True negative	26	22	–	–
False positive	2	4	–	–
False negative	5	15	–	–
Sensitivity	97.6% (94.7 to 99.1)	93.0% (88.6 to 95.9)	4.65% (0.32 to 8.98)	0.036*
Specificity	92.8% (77.9 to 99.0)	84.6% (66.4 to 94.7)	8.24% (-6.8 to 23.3)	0.342
Positive predictive value	99.0% (96.6 to 99.9)	98.0% (95.2 to 99.4)	1.0 (-1.1 to 3.1)	0.398
Negative predictive value	83.9% (67.2 to 93.7)	59.5% (43.3 to 74.1)	24.4 (6.8 to 42)	0.009**
Accuracy	97.1% (94.2 to 98.7)	92.1% (87.8 to 95.2)	5.0 (1.3 to 8.7)	0.008**

FAPI-CUP: A prospective cohort study of patients with cancer of unknown primary (CUP) to evaluate a novel radiotracer, fibroblast activated protein (FAPI), targeting cancer-associated fibroblasts for primary site detection.

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Background: Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumours for which standardised diagnostic work-up fails to identify the site of origin at diagnosis. ^{18}F-FDG-PET/CT aids in identifying a putative primary site in ~30-50% of CUP patient (pts); however, has limited sensitivity for detecting cancers with high stromal content. Fibroblast activation protein (FAP) is a type II transmembrane serine protease and highly expressed by cancer-associated fibroblasts abundant in desmoplastic tumours such as CUP. ^{68}Ga-FAPI-46 is a FAP-targeting PET tracer but has not been directly compared to ^{18}F-FDG-PET/CT in CUP. Aims: We aimed to determine if the addition of ^{68}Ga-FAPI-46 detects more primary sites compared with ^{18}F-FDG-PET/CT and CT CAP (standard of care; SoC) in CUP pts and if there is an association between the level of FAPI avidity and response to systemic treatment. **Methods:** A prospective cohort study recruiting CUP pts across four sites in Australia. Key inclusion criteria: 1) pts considered CUP after diagnostic work-up, pathological review and gender appropriate tests; 2) adequate haematologic and organ function; 3) not commenced current line of systemic treatment (exception palliative radiotherapy for symptom control); 4) ECOG $\leq$ 2 and life expectancy $>$ 3months. 5) $\leq$1 prior line of systemic treatment. Pts undergo SoC imaging (CT CAP, ^{18}F-FDG-PET/CT) and ^{68}Ga-FAPI-46 PET/CT scan which are reviewed at a multidisciplinary meeting to determine primary site. Clinicopathological review and genomic analysis (if available) were used to determine final primary site. Pts start systemic treatment and have SoC follow-up with data regarding RECIST 1.1 response, survival outcome and further lines of treatment for 12 months. **Results:** At interim analysis 60 pts were recruited from 03/2022 to 06/2025. Median age was 68 years [30-83] with 89% being ECOG 0-1 and 80% classified as having an unfavourable CUP subtype. A primary site was detected in 37/60 (62%) and 33/60 (55%) pts with ^{68}Ga-FAPI-46 PET/CT and SoC and SoC alone, respectively. Cholangiocarcinoma (9/37; 24%) and lung (7/37; 19%) were the commonest primary sites detected. 46/60 (77%) pts commenced systemic treatment with a best overall response rate of 9/38 (24%) in RECIST evaluable pts. There was no association between RECIST response and baseline FAPI avidity for either average SUVmax top 3 lesions (p=0.653) or highest SUVmax (p=0.416). **Conclusions:** ^{68}Ga-FAPI-46 PET/CT in addition to SoC detected a primary site in more patients compared to SoC imaging alone. There was no association between RECIST response and baseline FAPI avidity. Clinical trial information: NCT05263700. Research Sponsor: MRFF.

Integrated imaging cytology profiling system for rapid point-of-care molecular diagnosis of leptomeningeal metastasis in breast cancer.

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Background: Leptomeningeal metastasis (LM) from breast cancer has a poor prognosis (median survival ~4 months). Early and accurate diagnosis and phenotyping enable timely therapeutic intervention, particularly with emerging targeted agents such as antibody–drug conjugates (ADCs), to improve clinical outcomes. Yet, MRI and CSF cytology often lack sensitivity. We developed iSCOPE, an integrated imaging cytology platform that rapidly enriches and detects tumor cells in CSF via single-cell immunomolecular profiling. **Methods:** Breast cancer patients with neurological symptoms and/or suspicion for LM were enrolled in the study (IRB: KNUCH 2020-08-015). CSF (5–10 mL) was obtained by lumbar puncture for iSCOPE testing, and the rest was for conventional cytology examination. iSCOPE (integrated single-cell on-chip point-of-care evaluation) enriches large epithelial cells from unprocessed CSF at single-cell capture sites in a microfluidic chip while smaller blood cells pass through. Captured cells are then immunolabeled with QUAD markers (a four-marker combination overexpressed in breast cancer), as well as HER2 and ER/PR, for phenotyping. Automatic quantitative fluorescence imaging using a miniaturized imager reports the total cells, QUAD-positive cells, and their phenotypes in 1 hour. iSCOPE was validated using FNA cytology samples and then applied to CSF samples. Results were compared with conventional CSF cytology. **Results:** In the validation study using FNA cytology samples, iSCOPE demonstrated excellent breast cancer detection accuracy based on QUAD-positive cell counts (area under the curve/AUC = 0.995), and receptor phenotyping showed concordance with clinical pathology (AUC $>$ 0.9). In CSF testing, iSCOPE correctly discriminated between LM (n = 7) and control CSF samples from patients with normal pressure hydrocephalus (n = 5). In serially collected CSF testing due to inconclusive diagnoses, iSCOPE detected LM in two cases, a few months earlier than conventional cytology when a suspicious finding was initially made (Table 1). **Conclusions:** This study demonstrates the clinical feasibility of iSCOPE for CSF-based diagnosis of LM in breast cancer. iSCOPE addresses current challenges in cytology analysis by incorporating a microfluidic chip to enrich for scant, suspicious cells and by using immunomolecular profiling to detect tumor cells. The CSF study results highlight the potential clinical use of iSCOPE for detecting LM in a point-of-care setting. Research Sponsor: National Institute of General Medical Sciences (NIGMS); R01GM138778; National Cancer Institute; R33CA281794; Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI); HR - 2022 - KH130591.

CSF analysis for LM diagnosis.

ID	Primary subtype	LM diagnosis (MRI)	LM diagnosis (Cytology)	LM diagnosis (iSCOPE)
S1	TNBC	2/8/2025	2/10/2025	2/10/2025
S2	HR+ HER2-	Negative	2/18/2025	Suspicious
S3	HR+ HER2-	4/2/2025	3/31/2025	8/14/2024
S4	HR+ HER2-	2/28/2025 (suspicious)	8/28/2025	2/17/2025
S5	TNBC	12/26/2025 (suspicious)	Negative	Negative

Diagnostic performance, safety, and biodistribution of [^{68}Ga]Ga-OncoACP3 for PET imaging in prostate cancer: A phase I clinical trial.

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Background: Acid Phosphatase 3 (ACP3) is an emerging promising theranostic target in prostate cancer (PCa), expressed on PCa cells across most primary and metastatic lesions. ACP3 shows higher, more homogeneous expression than PSMA in low- and high-ISUP-grade tumours and in metastases, while not being expressed in healthy organs such as salivary glands, kidneys, and gastrointestinal tract. We present data from a multicentre, prospective phase I clinical trial investigating safety, dosimetry, pharmacokinetics, and diagnostic performance of [^{68}Ga]Ga-OncoACP3, a high-affinity ligand of ACP3 discovered from DNA-Encoded Chemical Libraries, in PCa. **Methods:** Twenty patients with a confirmed diagnosis of PCa were planned for enrolment in the study in two cohorts: Cohort A, 5 patients with primary tumour only; Cohort B, 15 patients with or without metastatic disease. Each patient received a single intravenous injection of [^{68}Ga]Ga-OncoACP3. PET/CT acquisitions were performed at 0, 10, 60 and 120 minutes after the injection with multiple blood and urine samples collections for pharmacokinetic and dosimetric analysis. Adverse events were recorded and graded according to CTCAE v5.0. [^{68}Ga]Ga-OncoACP3 PET findings were compared with PSMA PET (performed by all patients, according to clinical practice) and, when available, with follow-up data and histopathological findings. **Results:** All 20 patients completed [^{68}Ga]Ga-OncoACP3 PET imaging: 8 for initial staging, 10 for biochemical relapse, and 2 for advanced disease evaluation. No adverse events occurred. The tracer showed mixed hepatobiliary/renal excretion, with no uptake in salivary glands. PET-positive lesions showed rapid and selective tumour uptake shortly after injection, with increasing signal intensity at 60 and 120 minutes. All confirmed PSMA-positive lesions were evident at [^{68}Ga]Ga-OncoACP3 PET, in most cases with a higher tumour-to-background compared to PSMA PET. In three cases, [^{68}Ga]Ga-OncoACP3 PET detected additional PCa lesions, all confirmed by follow-up data or histopathology. No area of unspecific bone uptake at PSMA PET was evident at [^{68}Ga]Ga-OncoACP3. **Conclusions:** [^{68}Ga]Ga-OncoACP3 has an excellent safety profile and favourable pharmacokinetics, as well as promising tumour-targeting properties in PCa. [^{68}Ga]Ga-OncoACP3 may outperform current PSMA-targeting modalities across the whole natural history of the disease, and particularly in theranostic applications. Clinical trial information: NCT06840535. Research Sponsor: Philogen S.p.A.

Diagnostic performance, safety, and biodistribution of [^{68}Ga]Ga-OncoCAIX for PET/CT imaging: A first-in-human phase I clinical trial in clear cell renal cell carcinoma.

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Background: Conventional imaging techniques are routinely used in clear cell renal cell carcinoma (ccRCC). However, their ability to accurately characterise tumour biology and stage the disease remains limited. An attractive target for theranostic applications is represented by carbonic anhydrase IX (CAIX), which is overexpressed in ccRCC. [^{68}Ga]Ga-OncoCAIX is a novel small-molecule radiopharmaceutical for positron emission tomography (PET) imaging. The compound has been discovered by DNA-Encoded Chemical Libraries and designed to selectively bind to CAIX, allowing for tumour-specific uptake and favourable biodistribution in preclinical models. This multicentre, prospective, phase I study provides the first-in-human assessment of [^{68}Ga]Ga-OncoCAIX PET/CT in patients with kidney lesions. **Methods:** Twenty patients with suspected primary or recurrent ccRCC based on conventional imaging were planned for enrolment in the study. Each patient received a single intravenous injection of [^{68}Ga]Ga-OncoCAIX. PET/CT acquisitions were performed at 0, 10, 60 and 120 minutes after the injection with multiple blood and urine samples collections for pharmacokinetic and dosimetric analysis. Adverse events were recorded and graded according to CTCAE v5.0. Where available, PET findings were correlated with histopathology. **Results:** Twenty patients were included. Seventeen patients were evaluated for incidentally detected renal masses, and three for suspected recurrence identified on CT or MRI. [^{68}Ga]Ga-OncoCAIX was well tolerated, with no drug-related AEs reported. The tracer demonstrated mixed renal and hepatic clearance, favourable biodistribution, and low background activity in healthy tissues, including the kidneys. Physiological uptake was mainly observed in the gastrointestinal tract, particularly the stomach. PET-positive lesions showed rapid and selective tumour uptake shortly after injection, with increasing signal intensity at 60 and 120 minutes. Eight patients had positive PET findings, eleven scans were negative and one patient presented a lesion with mild tracer uptake. Available histopathological confirmation showed concordance with PET results, including three PET-positive ccRCCs, three PET-negative oncocytomas, and one PET-negative chromophobe RCC; the one lesion with mild tracer uptake corresponded to a papillary RCC with mild CAIX expression on histology. Dosimetric analyses are ongoing. **Conclusions:** [^{68}Ga]Ga-OncoCAIX shows an excellent safety profile and favourable biodistribution, as well as promising tumour-targeting properties in ccRCC lesions. These preliminary findings support its potential role for the detection and characterisation of ccRCC. Complete data on histopathology will confirm the diagnostic accuracy and potential clinical utility in patients with suspected ccRCC. Clinical trial information: NCT06840548. Research Sponsor: Philogen S.p.a.

Molecular characteristics and outcomes of a real-world cohort of carcinoma of unknown primary determined by tissue-of-origin assays.

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Background: Carcinoma of unknown primary (CUP) increasingly intersects with precision oncology as molecular profiling becomes integrated into diagnostic algorithms. However, published CUP cohorts and guideline-based series remain anchored to clinical and pathologic criteria and do not characterize patients whose tissue-of-origin (TOO) predictions remain low probability despite comprehensive molecular analysis. This population—where molecular data fail to resolve lineage—is poorly described. We evaluated clinical, molecular, and outcome features of CUP defined as < 90% probability for all predicted lineages. **Methods:** A retrospective chart review of TOO tests ordered at a single academic center between 2021-2025 was conducted. Demographics, pathology, molecular features including Tumor Mutational Burden (TMB), mutational profiles, predicted lineages, and treatments were abstracted from the TOO report and electronic health record. Survival status was assessed as of 12/31/2025. **Results:** Among 132 patients evaluated for CUP, 50 met the study definition (TOO probability <90% for a single lineage). Median age was 66 years, 56% were female and 76% were Black. Predicted lineages spanned gastrointestinal, pancreaticobiliary, lung, breast, melanoma, and genitourinary tissues, reflecting heterogeneity and lack of dominant lineage signal. Many tumors demonstrated overlapping immunophenotypes consistent with molecular ambiguity. High TMB (≥10 mut/Mb) was reported in 16% with PD-L1 positive in 4%, limiting eligibility for tissue-agnostic immunotherapy. Most patients received empiric systemic therapy rather than site-directed or molecularly targeted regimens. Targetable alterations reported included BRAF, KRAS, HER2, ATM, CHEK2, and PIK3CA. TOO primary site predictions were in concordance with final pathology in only 22 cases (44%). At last follow-up, 29 patients (57%) were deceased. **Conclusions:** This study characterizes a precision-oncology–relevant subset of CUP in which molecular classifiers fail to assign high-confidence lineage, a population not represented in prior CUP publications. Tumors in this cohort showed broad predicted lineages across multiple organ systems with low rates of high TMB, reflecting substantial molecular heterogeneity. Many displayed nondistinct histology with overlapping immunophenotypes, consistent with diagnostic ambiguity. Concordance between predicted TOO and final pathology was limited, underscoring the challenges of relying solely on molecular classifiers. Actionable targets and markers for immunotherapy were infrequent, and most patients received empiric chemotherapy. Outcomes were poor, underscoring the unmet need for improved integrative molecular approaches and novel precision-oncology strategies in CUP subsets that remain unresolved despite comprehensive molecular assessment. Research Sponsor: None.

Analytical validation of a plasma-based cfDNA NGS assay (Guardant360 Liquid CDx) for comprehensive solid tumor profiling.

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Background: NGS-based profiling of circulating cell-free DNA (cfDNA) enables accurate and sensitive tumor genotyping from blood. Guardant360 Liquid CDx is intended as a companion diagnostic for comprehensive tumor mutation profiling across >700 genes in patients with malignant neoplasms. Analytical performance was evaluated per FDA IVD standards and guidelines across five variant classes: single-nucleotide variants (SNVs), insertions/deletions (indels), gene rearrangements, gene amplifications (CNA), and copy-number losses (CNLs) – with emphasis on accuracy, precision, specificity (limit of blank [LoB]), and limit of detection (LoD). **Methods:** Analytical Validation tested >4000 samples from nearly 2,000 unique patients across 29 cancer types, as well as contrived materials. Concordance was evaluated against FDA-approved Guardant360 CDx and an externally developed ctDNA assay, where applicable. Primary endpoints were positive percent agreement (PPA) and negative percent agreement (NPA) by variant class and category (clinically significant vs panel-wide). LoD was established at both low and high input levels. No minimum cfDNA ng input cutoff was required; low-input performance was evaluated at minimum molecule coverage (QC threshold). Precision was assessed across workflow components and blood collection tube (BCT) lots. Specificity was assessed using healthy donor cfDNA sequenced with multiple replicates at high input. **Results:** Clinical samples demonstrated a high QC pass rate of 99.1%. Clinically significant variants showed high concordance: SNV PPA 94.9% with NPA 99.86%, and indel PPA 96.24% with NPA 99.98%. Panel-wide specificity was near-perfect (SNV NPA 99.99966%; indel NPA 99.99991%). Rearrangements achieved PPA 94.64% and NPA 99.76%; CNA PPA 91.67% and NPA 99.97% ; CNL PPA 100% and NPA 97.56%. High-input LoD was established in silico and confirmed with clinical samples: 0.2% mutant allele frequency (MAF) for all clinically relevant SNVs, indels and most rearrangements, with selected variant LoD as low as 0.1% (KRAS G12C). At the minimum input, panel-wide LoD was 1.0% for clinically relevant SNVs and 0.9% for indels; 0.5-1.6% for rearrangements, 2.3-2.4 copies for CNAs, and 22.7% tumor fraction for CNL. Precision studies showed ≥98.6% agreement across conditions at near-LoD variant levels; within-lot and between-lot BCT precision yielded >97% analytical positive/negative agreement (targeted variants ≥1× LoD). In LoB, no false positive variants were detected in any healthy donor replicates (0% FPR per sample and per variant), validating in-silico CHIP detection methods. **Conclusions:** The assay demonstrates high accuracy, precision and specificity across all reportable variant classes, with LoD at or below 0.2% MAF for key variant types. These data support its use for comprehensive, pan-cancer tumor genomic profiling in routine oncology practice. Research Sponsor: None.

Farnesyl transferase inhibitor (FTI) darlifarnib (KO-2806) in combination with adagrasib in *KRAS* G12C mutated (mut) advanced solid tumors: Preliminary results from the FIT-001 phase 1 first-in-human trial.

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Background: Clinical response to RAS inhibitors (RASi) is often limited by inherent/adaptive resistance mediated by persistent mTORC1 signaling. RHEB is a farnesylation-dependent protein required for mTORC1 activation. Darlifarnib, a potent next-generation FTI, selectively inhibits mTORC1 pathway activation and demonstrates synergistic antitumor activity in combination with the KRAS G12C inhibitor adagrasib (ada) in preclinical models, supporting potential to improve clinical activity in *KRAS* G12C mut tumors. **Methods:** FIT-001 (NCT06026410) is an ongoing, multicenter, open-label Ph1 dose escalation/expansion study of darlifarnib in advanced solid tumors. Darlifarnib 3, 5 or 8 mg QD D1–7, D15–21 + ada 400 mg BID in 28d cycles was evaluated in heavily pretreated pts with *KRAS* G12C mut NSCLC, PDAC or CRC. Primary objectives: safety/tolerability; key secondary objective: antitumor activity. **Results:** Dose escalation resulted in candidate darlifarnib doses of 3 and 5 mg. As of 15 Dec 2025, 30 pts (median age 61y; 63% male; 83% White; 93% baseline [BL] Karnofsky performance status 80–100%) received ≥1 darlifarnib 3 (n=15) or 5 mg (n=15) + ada dose. Primary tumor types: 30% NSCLC, 20% PDAC, 50% CRC. Pts were heavily pretreated: 43% had ≥3 prior systemic therapies; 40% had prior KRASi. Both darlifarnib 3 and 5 mg + ada were well tolerated; most common (≥30%) any-grade (Gr) treatment-emergent AEs (TEAEs): 63% diarrhea, 57% nausea, 50% anemia, 43% vomiting, 40% neutropenia, 40% thrombocytopenia. Most common (≥15%) Gr ≥3 TEAEs: 30% neutropenia, 17% anemia. 1 dose limiting toxicity occurred (anemia, darlifarnib 5 mg + ada). Most common treatment (trx) discontinuation reason was progressive disease (n=10). With a median follow-up of 23 wks, 13 pts remained on trx. Preliminary results from 25 response-evaluable pts (≥1 darlifarnib dose + post BL scan) included confirmed + unconfirmed responses. Antitumor activity was observed in all tumor types. Across darlifarnib 3 and 5 mg + ada dose levels, ORRs (95% CI) were 67% (22.3–95.7) for NSCLC, 60% (14.7–94.7) for PDAC, 14% (1.8–42.8) for CRC (Table); DCRs (CR+PR+SD): 83% (35.9–99.6) for NSCLC, 100% (47.8–100) for PDAC, 71% (41.9–91.6) for CRC. Updated data across all doses to be presented. **Conclusions:** Darlifarnib 3 and 5 mg + ada were well tolerated with encouraging antitumor activity in heavily pretreated *KRAS* G12C mut NSCLC, PDAC and CRC. These preliminary data support further investigation of darlifarnib + KRASi, such as ada, to address mTORC1-mediated resistance and potentially improve clinical outcomes for pts. Clinical trial information: NCT06026410. Research Sponsor: Kura Oncology, Inc.; Bristol Myers Squibb.

n (%)	Darli 3 mg + ada	Darli 5 mg + ada	Total
NSCLC	3	3	6
ORR[a]	1 (33)	3 (100)	4 (67)
DCR	2 (67)	3 (100)	5 (83)
PDAC	2	3	5
ORR[a]	2 (100)	1 (33)[b]	3 (60)[b]
DCR	2 (100)	3 (100)	5 (100)
CRC	6	8	14
ORR[a]	0	2 (25)	2 (14)
DCR	3 (50)	7 (88)	10 (71)

[a]Confirmed+unconfirmed responses.
[b]1 uPR post datacut.

A phase 2 multi-center pharmacodynamic study of the fatty acid synthase (FASN) inhibitor TVB-2640 in advanced *KRAS*-mutant non–small cell lung cancer.

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Background: Preclinical and translational studies demonstrate that KRAS-mutant NSCLC has a unique metabolic dependence on de novo fatty acid synthesis, mediated by fatty acid synthase (FASN) and downstream lipid metabolism pathways that support saturated fatty acid production, enabling rapid tumor growth, survival, and resistance to lipid peroxidation. TVB-2640 is an orally bioavailable and selective FASN inhibitor that blocks the β-ketoacyl reductase step of fatty acid synthesis and has demonstrated antitumor activity in *KRAS* mutant NSCLC models. **Methods:** This single-arm trial (NCT03808558) enrolled patients with previously treated, advanced *KRAS* mutant NSCLC. Eligible patients had progressed on prior platinum-based chemotherapy (100%) and immune checkpoint inhibition (95%), had measurable disease by RECIST v1.1, ECOG performance status 0–1, and adequate organ function. One patient had received prior KRAS directed therapy. TVB-2640 100 mg/m^2 (equivalent to two to four 50-mg tablets) was administered orally once daily in continuous 28-day cycles. Exploratory correlative analyses included ^{11}C-acetate PET, plasma lipidomics, sebaceous lipid profiling, and quality-of-life measures. **Results:** Among 18 enrolled patients, the median age was 69 years, 12 (67%) were male, 14 (78%) were white and 13 (72%) had a history of smoking. Median number of prior lines of therapy was 4. The most common *KRAS* mutations were G12V (44%), G12C (17%), and G12D (17%). No patients had a radiographic response, 7 (39%) had stable disease, 9 (50%) had disease progression, and 2 (11%) were non-evaluable. Five patients (28%) had radiographic shrinkage of target lesions but did not achieve partial response due to the magnitude of decrease (n = 3) or progression of non-target lesions (n = 2). Median progression-free survival was 1.8 months (95% CI, 1.7-1.8 months). Overall, 84% of patients had adverse events (AE). Most common AEs were xerostomia (50%), dry skin (44%), and fatigue (39%). Most common grade ≥ 3 AEs (44%) were fatigue, dermatological toxicities, xerostomia, ocular toxicities and anemia (11% each). **Conclusions:** Single-agent FASN inhibition with TVB-2640 in heavily pretreated *KRAS* mutant NSCLC did not meet the primary endpoint of response. Since FASN is a downstream effector of mutant KRAS, combination regimens with KRAS inhibitors can be considered as a future approach in NSCLC. Ongoing correlative studies may further inform the use of this agent. Despite not meeting its primary endpoint, this clinical trial highlights a novel therapy targeting energy metabolism in lung cancer. Clinical trial information: NCT03808558.
Research Sponsor: Gateway Foundation for funding the clinical trial; Sagimet for provision of product/material.

Pan-cancer landscape and real-world management of BRAF non-V600E and MAP2K1 alterations: Analysis from the WAYFIND-R registry.

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Background: While targeted therapies have revolutionized the management of BRAF V600E-mutant tumors, non-V600E BRAF and MAP2K1 alterations remain a clinical "gray zone." These variants represent a functionally diverse group of drivers with no established treatment guidelines, often leading to heterogeneous care and suboptimal outcomes. We used the multinational WAYFIND-R registry to map the prevalence and functional landscape of these rare alterations and to evaluate real-world treatment patterns. **Methods:** We retrospectively analyzed 4,774 patients with solid tumors from the multinational WAYFIND-R registry (NCT04529122). Patients with BRAF and MAP2K1 alterations identified via Next-Generation Sequencing (NGS) were included. Variants were categorized by functional class (Class I-III). Clinical characteristics, co-mutation profiles, and treatment sequences were analyzed to correlate molecular features with management strategies and outcomes. **Results:** Rare alterations were identified in 38 (0.8%) patients, predominantly in colorectal (29%), lung (13%), and melanoma (13%) cancers. Genomic analysis revealed a complex landscape. Among BRAF-altered patients (n=30), while Class I (V600E/K) accounted for 63.3% (n=19), the remaining 36.7% comprised non-V600E variants distributed between functional Class II (20.0%) (e.g., G469A, L597S) and Class III (13.3%) (e.g., D594N, G466R). MAP2K1 alterations (n=9) were distributed across RAF-dependent Class I (44.4%), RAF-regulated Class II (44.4%), and RAF-independent Class III (11.1%) variants (e.g., E102_I103del). Treatment patterns were highly inconsistent. While first-line therapy typically consisted of standard chemotherapy or anti-PD-1 monotherapy, there was no consensus for subsequent lines. This lack of targeted approach correlated with poor outcomes in lung and colorectal cohorts. However, in contrast to unselected treatments, we observed durable responses with biology-guided MEK inhibitor plus Immunotherapy combinations in two index cases. A patient with MAP2K1 Class III (E102_I103del) NSCLC achieved a near-complete metabolic response with cobimetinib + nivolumab. Similarly, a BRAF Class II (G469A) NSCLC patient achieved a complete metabolic and molecular response (confirmed by ctDNA clearance) with trametinib + pembrolizumab. **Conclusions:** This analysis confirms that >35% of BRAF-altered patients (nonV600 mutants) and all MAP2K1-altered patients in real-world settings currently lack standardized treatment protocols. The observed clinical heterogeneity highlights a significant unmet need. Our findings suggest that integrating functional subclassification into clinical decision-making and utilizing targeted combinations is necessary and may offer a viable strategy. Clinical trial information: NCT04529122. Research Sponsor: F. Hoffmann-La Roche Ltd.

First data disclosure from the first-in-human phase 1/2 trial of SMP-3124LP, the first investigational pegylated liposome CHK1 inhibitor, in patients with selected advanced solid tumors.

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Background: Checkpoint kinase 1 (CHK1) is a critical in the DNA damage response pathway and an important target for anticancer therapy. However, clinical development of CHK1 inhibitors has been limited by myelosuppression and a narrow therapeutic window. The use of liposomal technology potentially widens the therapeutic window by lowering rates of hematologic toxicities minimizing drug exposure to healthy tissues and maximizing delivery to tumors. SMP-3124 is a structurally distinct CHK1-selective inhibitor designed to be optimally delivered in a PEGylated liposome formulation. SMP-3124LP is being developed for malignancies with high replication stress. **Methods:** This ongoing Phase 1/2 study evaluated the safety, tolerability, PK, and preliminary antitumor activity of SMP-3124LP given intravenously (NCT06526819). The dose escalation included patients (pts) with selected advanced solid tumors. **Results:** As of 28 Nov 2025, 42 pts were enrolled at 20, 40, 60, and 90 mg/m^2 every 2 weeks. 23 pts (55%) had ≥4 prior lines of therapy. No dose-limiting toxicities (DLTs) were observed at 20 or 40 mg/m^2. A DLT of Grade (G) 4 thrombocytopenia was noted at 60 mg/m^2 and one pt had 2 DLTs of reversible G4 thrombocytopenia and G3 febrile neutropenia at 90 mg/m^2. Most common treatment-related adverse events (≥20%) were neutropenia (45%), infusion-related reactions (IRR, 38%), thrombocytopenia (36%), anemia (24%) and leukopenia (21%). Treatment-related G3/4 neutropenia was 33%, G3/4 thrombocytopenia and G3 anemia were 9.5% each. Cytopenias were generally transient and none led to treatment discontinuation. All IRRs were G1/2 and manageable with premedications, supportive care, and/or slower infusion rates. Dose-proportional increases in C_{max} (4.3-fold) and AUC (6.0-fold) were observed from 20 to 90 mg/m^2 with low volume of distribution (1.99 to 2.68 L) and a geometric mean half-life of 23 to 31 hours. As of 13 Jan 2026, disease control rate (DCR) was 49%, with 5 RECIST v1.1 partial responses (PR) + 12 RECIST v1.1 stable disease (SD) out of 35 efficacy evaluable patients. Among the PRs, 2 platinum-resistant ovarian cancer (PROC, one with prior PARPi), 2 anal SCC, and 1 colorectal cancer with FBXW7 mutation. 2 other advanced PROC pts had SD with tumor shrinkage 20% or more (one with -88% CA125 response). The anal SCC and rectal cancer pts all received ≥4 prior lines of therapy. Duration of response has not been reached. **Conclusions:** SMP-3124LP was generally well tolerated and had a manageable safety profile. The liposomal formulation appears to reduce the incidence of cytopenias compared to historical data with non-liposomal CHK1 inhibitors. Dose-proportional increases in PK were observed. Promising signals of antitumor activity were observed with 5 RECIST v1.1 PRs and 49% DCR in pts with heavily pretreated cancers. Clinical trial information: NCT06526819. Research Sponsor: Sumitomo Pharma America, Inc.

Real-world characterization of SEZ6, a transmembrane protein expressed in various solid tumors.

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Background: Seizure-related homolog 6 (SEZ6) is a transmembrane protein involved in neuronal development that is downregulated in normal adult tissues outside the central nervous system (CNS). It is overexpressed in various solid tumors such as small cell lung cancer (SCLC), neuroendocrine neoplasms (NENs), and CNS tumors, with strong correlations between mRNA and protein expression. In SCLC, limited data suggest that *SEZ6* expression is greater in molecular subtypes with neuroendocrine (NE)-high gene signatures (i.e., SCLC-A and SCLC-N) than in non-NE subtypes (i.e., SCLC-P). However, *SEZ6* expression in tumor tissues remains poorly understood and existing data are limited by small sample sizes. This study aimed to characterize *SEZ6* expression in a large patient population, across multiple tumor types. **Methods:** Pan-tumor data from a real-world database (Tempus AI, Inc.) were analyzed for *SEZ6* mRNA expression in 37,645 samples, with a focus on lung, brain, and NE tumor types. In SCLC, *SEZ6* expression was compared between SCLC-A, -N, -P, and -I samples via hierarchical clustering. Gene expression was reported as $\log_2$(transcripts per million [TPM]+1). **Results:** Across the 37,645 samples analyzed, tumor types with the highest median ($\log_2$[*SEZ6* TPM+1]) expression were astrocytoma (5.8; n=354), glioma (5.8; n=502), NENs (5.7; n=2794), and glioblastoma (5.6, n=2833). Among NENs, the highest *SEZ6* expression was seen in prostate neuroendocrine carcinoma (NEC) (6.6; n=176), SCLC (6.5; n=2018), and bladder small cell NEC (6.5; n=139). Median *SEZ6* expression was 3–45-fold higher than other biomarkers of interest in SCLC (*B7-H3*, 3-fold; *DLL3*, 3-fold; *CD274* [PD-L1], 28-fold; *PDCD1* [PD-1], 45-fold). In SCLC samples, median *SEZ6* expression was stable across primary (6.4) and metastatic (6.5) tumors and stage II to IV disease (6.6–6.5). Among SCLC molecular subtypes, median *SEZ6* expression was lower in non-NE SCLC-P tumors (3.8; n=85) than in SCLC-I (6.0; n=175), or in NE-high SCLC-N (6.7; n=339) and SCLC-A (7.3; n=224) tumors. *SEZ6* expression was 6–7-fold higher in prostate NEC than in non-NE metastatic prostate adenocarcinoma (castration resistant, 6-fold; castration sensitive, 7-fold). **Conclusions:** *SEZ6* is highly expressed in SCLC and tumors of NE origin, particularly prostate and bladder NEC. In SCLC, *SEZ6* expression is higher than other targets of antibody–drug conjugates (ADCs) approved or in development for SCLC, supporting SEZ6 as a promising therapeutic target. *SEZ6* expression is highest in SCLC-A and SCLC-N molecular subtypes. High *SEZ6* expression is also seen in SCLC-I, a subtype associated with platinum resistance, suggesting SEZ6 may be a potential therapeutic target in certain patients with platinum-refractory SCLC. Taken together, these results suggest cross-indication applicability of targeting SEZ6, highlighting its potential as a multi-tumor ADC target warranting further investigation. Research Sponsor: Whitehawk Therapeutics.

Convenience vs. complexity: Adoption of subcutaneous PD-(L)1s in lung cancer in EU4+UK.

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Background: Subcutaneous (SC) PD-(L)1 formulations represent a significant step towards simplifying treatment administration by reducing treatment time, compared to intravenous (IV) preparations. To date, the EMA has approved three SC PD-(L)1s: atezolizumab, nivolumab, and pembrolizumab. Here, we evaluate how the availability of SC formulation is affecting physicians' prescribing behaviour, the drivers of the switch from IV to SC, and potential barriers affecting decisions in the treatment of lung cancer in EU4+UK. **Methods:** The Ipsos' Global Oncology Monitor is a physician-reported syndicated patient record database. This analysis comprises 2,537 cancer-treating physicians in EU4+UK, screened for seniority and caseload, submitting data on 36,383 lung cancer patients, online, from January 2024 to November 2025. Physicians who treated lung cancers also completed a perceptual questionnaire on SC PD-(L)1 usage in lung cancer. Responses were collected from 150 physicians in EU4+UK, online, from October to December 2025. **Results:** Adoption of SC PD-(L)1 in lung cancer in EU4+UK is at 6% in the 3 months ending November 2025 compared to 94% of the IV format. We observed that SC PD-(L)1 was more likely used as monotherapy while the IV formulation in combination therapy (Table 1). Among patients receiving the IV version, 13% have a planned switch to SC, 71% do not, while 16% remained classified as the physician being undecided. Of those who would switch/ undecided, the switch was estimated to happen after a mean of 4.5 cycles on the IV formulation. **Conclusions:** In this study, the uptake of SC PD-(L)1 reflects its clear benefit in reducing treatment time; however, the IV formulation remains dominant, suggesting physician hesitancy toward the SC format. While shorter administration time is beneficial, it does not yet outweigh concerns regarding patient comfort. Crucially, SC usage is notably lower in combination therapies compared to monotherapy. This suggests that when IV chemotherapy is required, the convenience of an SC add-on is diminished. Furthermore, the perception that SC offers 'no additional value' over the established IV contributes to this inertia. To drive adoption and improve patient experience, manufacturers must address administration-related discomfort and effectively communicate the comparative efficacy and workflow benefits of the SC formulation, particularly for patients who have yet to switch. Further investigation to assess any country differences and patient point of view will be beneficial. Research Sponsor: None.

Usage of PD-(L)1 by formulation.

	Subcutaneous n=123	Intravenous n=1,914
Monotherapy	72%	41%
Combination	28%	59%

Targeting cancer stem cells with a novel virus-like drug conjugate.

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Background: Belzupacap sarotalocan (bel-sar) is a novel virus like-drug conjugate in clinical stage development for multiple solid tumors. The virus-like particle component of the drug is derived from the papillomavirus and specifically binds to heparan sulfate proteoglycans (HSPGs) and chondroitin sulfate proteoglycans (CSPGs) with unique sulfation modifications on the surface of cancer cells. Upon activation with near-infrared light, cell associated bel-sar causes immediate cell death and induces an anti-tumor immune response, with a single administration leading to elimination of solid tumors accompanied by long-term protective immunity in a number of animal tumor models. Cancer stem cells (CSCs) represent a distinct subpopulation of tumor cells that possess stem-like characteristics, including self-renewal. These cells are thought to drive disease persistence and are intrinsically more resistant to conventional cancer treatment, such as chemotherapy, radiotherapy, and immunotherapy. CSC-mediated resistance remains a major obstacle to achieving durable clinical responses and the elimination of this cell population is hypothesized to be essential for long-lasting tumor control. **Methods:** We developed and characterized a panel of human-derived CSC models (bladder, breast, oropharyngeal, prostate cancers, glioblastoma, uveal melanoma) using a SORE6 lentivirus reporter in which stem-like transcription factors SOX2 and OCT4 drive GFP expression to identify CSC subpopulations. Bel-sar binding and potency was compared between CSC and the more differentiated non-cancer stem cells (nCSC) populations. Additionally, chemotherapy resistant tumor lines were established from the CSC panel and were similarly tested for bel-sar targeting and cytotoxicity. **Results:** CSC populations were validated by SOX2/OCT4 co-expression, CSC surface marker expression (CD24, CD44, EpCAM-1, CXCR4), ALDH activity, and tumorsphere formation. Bel-sar was capable of binding CSCs with equal or enhanced efficiency as compared to nCSCs through cell surface HSPGs and CSPGs as demonstrated by heparin and chondroitin sulfate inhibition. Additionally, bel-sar was able to kill CSCs and nCSCs with equal efficiency in vitro. Following chemotherapy-induced enrichment of CSCs, bel-sar maintained its therapeutic effect on chemotherapy-resistant CSC populations, reinforcing previous data demonstrating complete responses in animal models. **Conclusions:** This study highlights bel-sar's distinctive capacity to target and eradicate CSCs across diverse tumor types. These results support bel-sar's clinical development for local tumor control and suggest bel-sar treatment may be effective against recurring or chemotherapy-resistant tumors. Research Sponsor: Aura Biosciences; National Cancer Insitute.

Targeting TP53 pathologic variants for cancer immunotherapy using a self-replicating mRNA vaccine strategy.

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Background: *TP53* pathogenic variants (PVs) are highly prevalent in human malignancies as a whole and especially in patients with pancreatic ductal adenocarcinoma (PDAC). Approximately 80% of TP53 PVs are missense mutations that may be targeted for cancer therapy. **Methods:** We have developed a self-replicating mRNA (srRNA) vaccine (TMG-mut *TP53* srRNA SA-LNP) encoding concatenated p53 mutant peptides encompassing 14 hotspot *TP53* missense mutations in PDAC, encapsulated in sialic acid (SA)-modified lipid nanoparticles (LNPs). These 14 hotspot TP53 PVs were selected by examining four public available datasets and from our previous studies. **Results:** TMG-mut *TP53* srRNA SA-LNPs incorporated Venezuelan equine encephalitis virus replicase which enabled higher and prolonged *in vivo* protein expression compared to conventional mRNA construct. Encapsulation with SA-modified LNPs led to significantly better efficiency in targeting dendritic cells (DCs) *in vitro* and *in vivo* compared to conventional LNPs. We used *in vitro* (cell lines) and *in vivo* assays (PDX and human engineered mouse genetic models) to test the efficacy of our RNA vaccine. We validated the detection of TP53 neoantigen by mass spectrometry generated by our srRNA vaccine. We then tested its anti-tumor immunity by itself alone and in combination with anti-PD1 inhibition using multiple cell lines and PDX that carry different TP53 PV (R175H and R273H). TMG-mut *TP53* srRNA SA-LNP stimulated potent and specific anti-tumor $CD8^+$ T cell responses in *in vitro* and *in vivo* assays using autologous DCs, T cells and cancer cells from multiple PDAC patients. Using both Panc02 syngeneic PDAC cell line and patient-derived PDAC xenografts (PDX), we show that TMG-mut *TP53* srRNA SA-LNP stimulated potent and specific anti-tumor immunity against PDAC tumors that harbor different corresponding p53 PVs. Panc02-$TP53^{R175H}$ tumor-bearing transgenic mice expressing human HLA-A*02:01 treated with TMG-mut *TP53* srRNA SA-LNP showed significantly suppressed tumor growth and prolonged survival with increased tumor infiltration of activated $CD8^+$ T cells as well as increased production of cytokines including type II interferon, TNFalpha, and other biomarkers. We also show our vaccine stimulates increased tumor cell apoptosis. In addition, TMG-mut *TP53* srRNA SA-LNP dramatically enhanced the anti-tumor immunity of anti-PD1 by synergistically suppressing tumor growth and prolonging the survival of tumor-bearing mice in both low and high-tumor burden animal model. **Conclusions:** Our results demonstrate for the first time that missense p53 PVs are valid targets for developing novel cancer immunotherapy using srRNA vaccine approach enhanced by SA-LNPs encapsulation. Our data potentially opens a new approach for developing mRNA vaccine-based immunotherapy for a large population of cancer patients as TP53 PVs are highly prevalent in nearly every type of malignant tumors. Research Sponsor: None.

TSY-310, a novel bispecific EGFR×ROR1 ADC: Assessment of antitumor activity in heterogeneous breast tumors through enhanced internalization and bystander cytotoxicity.

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Background: Epidermal growth factor receptor (EGFR) is a clinically validated target and is highly expressed in various solid tumors, including triple-negative breast cancer (TNBC). Clinical efficacy of EGFR-directed therapies in TNBC, however, is often limited by intratumoral heterogeneity, acquired resistance, and mutations conferring insensitivity to tyrosine kinase inhibitors. TSY-310 is a novel bispecific EGFR×ROR1 nanobody-Fc fusion antibody–drug conjugate (BsADC) designed to address these challenges by simultaneously targeting EGFR and receptor tyrosine kinase-like orphan receptor 1 (ROR1). TSY-310 carries an average of 3.6 molecules of monomethyl auristatin E (MMAE) via a protease-cleavable valine–citrulline linker, enabling potent and tumor-selective cytotoxicity, and induces strong tumor regression across multiple NSCLC PDX models representing a range of EGFR and ROR1 expression levels. **Methods:** Cytotoxicity was evaluated in cell lines with distinct EGFR/ROR1 expression profiles. Bystander killing was assessed in co-culture systems of antigen-positive and antigen-negative cells. Cellular internalization and trafficking were analyzed by immunofluorescence microscopy. In vivo efficacy and bystander activity are investigated in xenograft models with heterogeneous antigen expression. **Results:** TSY-310 exhibited sub-nanomolar cytotoxicity (IC_{50} = 0.45 nM) against MDA-MB-468 ($ROR1^+/EGFR^+$) TNBC cells in correlation with dual receptor expression levels, and demonstrated robust bystander killing, eliminating neighboring antigen-negative A427-Luc and MDA-MB-453-Luc cells through MMAE diffusion in co-culture systems. Rapid internalization of TSY-310 was observed in dual-positive MDA-MB-468 cells within 6 hours, consistent with enhanced cytotoxic activity. In a $EGFR^+/ROR1^+$ HBCx-28 TNBC PDX model, it achieved complete and sustained tumor regressions in all treated mice (5/5) and demonstrated superior efficacy compared with the monospecific ROR1-directed ADC on a payload-equivalent basis. In vivo studies to assess bystander activity and efficacy in heterogeneous tumor models are ongoing. **Conclusions:** These findings highlight TSY-310 as a first-in-class bispecific ADC capable of overcoming tumor heterogeneity through dual binding and bystander killing, supporting its potential as an effective therapeutic agent for heterogeneous solid tumors such as TNBC, where existing EGFR-targeted therapies have shown limited benefit. Research Sponsor: Formosa Pharmaceuticals, Inc.

Influence of genetic ancestry on UV mutational signatures linked to immunotherapy response in melanoma, beyond TMB.

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Background: Melanoma is a UV-driven malignancy with substantial biological heterogeneity, yet genomic profiling efforts have historically underrepresented diverse ancestral backgrounds, limiting insights into population-level differences in tumor biology and treatment response. **Methods:** In this retrospective study, a supervised machine learning framework was developed to infer genetic ancestry across 483,454 tumors profiled by tumor-only whole-exome sequencing (WES) at Caris Life Sciences (Phoenix, AZ), using 36,962 ancestry-informative variants derived from globally diverse Genome Aggregation Database (gnomAD) reference individuals (n=4,150). Survival outcomes inferred from claims data were evaluated using Cox proportional hazard ratios (HR) with 95% confidence intervals (CI) and log-rank p-values. Associations between features were evaluated using standard statistical tests and regression models. **Results:** We applied this framework to cutaneous melanoma (N=8,872). The UVB-related COSMIC mutational signatures SBS7a and SBS7b were markedly enriched in tumors from patients (pts) of European (EUR) ancestry (93.2% and 75.6%, respectively) but were uncommon in African ancestry tumors (6.9% and 5.2%). Within EUR ancestry pts, higher EUR ancestry fraction was associated with higher SBS7a and SBS7b prevalence ($p=9.0x10^{-4}$ and $1.5x10^{-4}$), consistent with known differences in pigmentation biology and melanoma etiology. Among 3,587 melanoma pts treated with first-line immune checkpoint inhibitors (ICI), SBS7a positivity was strongly associated with improved overall survival (OS HR [95% CI] = 0.55 [0.46–0.66]) and time to next treatment (TTNT HR=0.58 [0.49–0.69]; all $p<0.001$), outperforming tumor mutational burden (TMB) as a prognostic biomarker. SBS7a+ remained prognostic in a multivariable Cox analysis accounting for TMB, age, sex, and the first two ancestry principal components. Furthermore, both SBS7a+ TMB-high and SBS7a+ TMB-low tumors demonstrated superior outcomes compared to SBS7a– TMB-low tumors (OS HR=0.49 [0.41–0.60] and 0.62 [0.51–0.74], respectively; all $p<0.001$). Similar patterns were observed in cutaneous squamous cell carcinoma. To assess specificity for UV-driven biology, we evaluated two non-sun-exposed malignancies: uveal melanoma and renal cell carcinoma (RCC). SBS7a was virtually absent in uveal melanoma and RCC (6.7% and 6.9%, respectively, among EUR ancestry pts) and did not stratify ICI outcomes in either cancer. These negative controls suggest that SBS7a does not arise without UV exposure and is not a general immunotherapy biomarker. **Conclusions:** These findings establish a scalable genetic ancestry framework, reveal ancestry-linked differences in melanoma mutagenesis, and demonstrate that SBS7a provides clinically meaningful, TMB-independent prognostic information specific to UV-driven tumors. Research Sponsor: None.

A phase 1, first-in-human study of OP-3136, a novel oral selective KAT6A/B inhibitor, as monotherapy in advanced solid tumors and in combination with endocrine therapy in ER+, HER2− advanced breast cancer (ABC): Preliminary results.

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Background: Histone lysine acetyltransferases (KATs) control oncogenic transcription and are frequently dysregulated in cancer. OP-3136 is a potent, selective, oral small-molecule inhibitor of KAT6A/B with preclinical antitumor activity, including in combination with endocrine therapy (ET) (Palanisamy et al, 2024). This phase 1 study evaluates the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of OP-3136 as monotherapy in advanced solid tumors and in combination with fulvestrant or palazestrant (a novel oral complete estrogen receptor antagonist [CERAN] and selective estrogen receptor degrader [SERD]) in ER+, HER2− ABC (NCT06784193). **Methods:** Patients (pts) with ABC, metastatic castration-resistant prostate cancer (mCRPC), or non-small cell lung cancer (mNSCLC) received OP-3136 once daily (QD) as monotherapy (no limit on prior lines of therapy), and a separate cohort of ABC pts received OP-3136 + fulvestrant in a phase 1 study using a Bayesian Optimal Interval dose-escalation. **Results:** As of 26 November 2025, 32 pts ABC, n=23; mCRPC, n=8; and mNSCLC, n=1) received OP-3136 (monotherapy, n=25; in combination with fulvestrant, n=7) across doses of 2–45 mg QD. All ABC pts received prior endocrine therapy and CDK4/6 inhibitors, all mCRPC pts received prior androgen receptor–targeted therapy. The median (min – max) of prior anticancer systemic therapy lines was 3 for ABC (1–5) and 5 (1–8) for mCRPC pts. The median time on treatment was approximately 2 months (max 47 months). In the monotherapy cohort, treatment-related adverse events (TRAEs) were mostly grade (G)1–2. The most common (≥25%) TRAEs included dysgeusia (72%; G2, 24%), anemia (40%; G3, 8%), fatigue (32%; G2, 16%), and neutropenia (28%; G3, 20%). In the combination cohort, TRAEs were predominantly G1–2 with one G3 neutropenia and leukopenia. No dose-limiting toxicities (DLTs), G4-5 TRAEs or treatment discontinuations due to TRAEs were reported. Across monotherapy dose levels, among 14 pts with measurable disease, reduction of target lesions occurred in 64% (9/14) and 2 pts (1 with ABC and 1 with mCRPC) had partial responses (unconfirmed). Among 17 pts with evaluable disease,10 had stable disease. PK analyses showed dose-proportional exposure of OP-3136 with rapid absorption and sustained systemic exposure over the dosing interval supporting QD administration. **Conclusions:** OP-3136 demonstrated a manageable safety profile and favorable PK, both as monotherapy and in combination with fulvestrant. Preliminary evidence of antitumor activity in ER+ HER2- ABC and mCRPC was observed in these heavily pretreated pts. Dose escalation and enrollment in combination with fulvestrant or palazestrant are ongoing and updated data will be presented. Clinical trial information: NCT06784193. Research Sponsor: Olema Oncology.

A phase 1a/b study of RGT-61159, an oral MYB splicing modulator, in patients with advanced adenoid cystic carcinoma and colorectal cancer.

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Background: MYB is a master regulator of cell proliferation, self-renewal, and differentiation processes and its aberrant expression is found in multiple forms of human cancer including adenoid cystic carcinoma (ACC), acute myeloid leukemia, T-cell acute lymphoblastic leukemia, colorectal cancer (CRC), small cell lung cancer, and breast cancer. RGT-61159 is an orally available small molecule designed to selectively modulate splicing of the oncogenic transcription factor MYB, resulting in downregulation of MYB protein levels and tumor cell death. **Methods:** This ongoing Phase 1a/b, multi-center, open-label clinical trial evaluates RGT-61159 in patients (pts) with advanced, relapsed or refractory ACC or CRC. Pts with ACC must have disease progression within 12 months of study entry. The study employs a 3+3 dose-escalation design with daily oral dosing in 21-day cycles, starting at 6 mg and escalating using a Fibonacci scheme. Primary objectives are to assess safety and tolerability and determine the recommended Phase 2 dose (RP2D). Secondary objectives include characterization of pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity. **Results:** As of 22 December 2025, 44 pts (86% ACC, 14% CRC) were treated across 8 dose levels (6–144 mg). In pts with ACC, median age was 61 years (range: 33–77) and median prior lines of therapy was 1 (range: 0-6); 47% were female. In pts with CRC, median age was 63 years (range: 44–72) and median prior lines of therapy was 5.5 (range: 4-8); 50% were female. Dose-limiting toxicities (DLTs) occurred in three pts: G3 nausea and muscle weakness, G3 fatigue, and missed doses due to G2 atrial flutter. Treatment-emergent adverse events (TEAEs) observed in ≥20% of pts were diarrhea, nausea, fatigue, dyspnea, and anemia. One G3 vasculitis (144 mg) and dose-related inflammatory edema events (G2 at 108/144 mg; G1 at lower doses) occurred; none were protocol-defined DLTs. Overall, RGT-61159 was well tolerated at or below the provisional RP2D of 84mg. 19 pts remain on treatment, including 9 pts (all with ACC) treated from 24 to 60mg who have been on study for more than 6 months with durable stable disease. In 35 evaluable pts, 18 have had tumor regressions with one partial response (RECIST v1.1) observed in a pt with ACC treated at 60mg. After the data cut, another pt with ACC treated at 84mg also achieved a partial response. Dose-dependent, robust knockdown of MYB in the peripheral blood was observed (up to 75% at 84mg). Plasma exposure increased approximately dose-proportionally with low to moderate variability. **Conclusions:** RGT-61159 is well tolerated at doses at or below the provisional RP2D. Robust peripheral knockdown of MYB was observed in a dose-dependent fashion at clinically relevant doses. Clinical activity manifested as prolonged stable disease and a partial responses primarily in pt with ACC. Clinical trial information: NCT06462183. Research Sponsor: Rgenta Therapeutics.

Genomic landscape of *ERBB3* alterations in 5,416 metastatic solid tumors: Real-world evidence regarding biomarker-agnostic ADC strategies.

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Background: While ERBB2 (HER2) is a well-established therapeutic target, the clinical significance and genomic landscape of ERBB3 (HER3) across diverse solid tumors are less defined. As HER3 emerges as a critical mediator of resistance and a target for novel antibody-drug conjugates (ADCs), characterizing its genomic alterations in a real-world setting is essential to refine therapeutic positioning. **Methods:** We analyzed clinical next-generation sequencing (NGS) data (Illumina TSO 500 or Oncomine Comprehensive Assay Plus) from 5,416 patients with metastatic solid tumors at a single tertiary center (Samsung Medical Center) between 2019 and 2025. ERBB3 alterations were categorized into mutations (SNVs/indels, VAF $\geq$2%) and amplifications (copy number [CN] $\geq$4). **Results:** ERBB3 alterations were identified in 12.9% (697/5,416) of patients. The prevalence was overwhelmingly driven by mutations (12.3%), while amplifications were rare (0.6%). The highest mutation frequencies were observed in: Urothelial carcinoma, 18.2%; Malignancy of unknown origin, 16.3%; and Biliary tract cancer, 15.7%. The most frequent variants were K498I (Domain IV) and R1127H (C-terminal tail). Known oncogenic hotspots (V104, A232V, G284R, E928G) were present but not dominant. Notably, the ERBB3-mutated cohort exhibited high co-mutation rates with canonical drivers: TP53 (66%), APC (35%), and KRAS (31%). In common GI cancers, ERBB3 mutations frequently co-occurred with APC and KRAS, suggesting they often act as "passenger" or secondary events rather than primary drivers. High-level amplifications (CN $\geq$8) were rare ($<$0.1%) and appeared in isolated cases across various histologies. **Conclusions:** ERBB3 alterations are relatively common (12.9%) in metastatic solid tumors but are characterized by a diverse mutational landscape rather than focal amplifications. The high frequency of co-occurring canonical drivers suggests that HER3 primarily functions as a resistance hub or facilitator in these tumors. These real-world data provide a strong genomic rationale for biomarker-agnostic ADC strategies (targeting HER3 protein expression) rather than mutation-specific approaches in most ERBB3-altered solid tumors. Research Sponsor: None.

Phase Ib expansion and dose optimization study of CX-5461 in patients with solid tumours enriched for DNA-repair deficiencies.

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Background: G-quadruplexes (G4) are guanine-rich DNA/RNA structures that contribute to DNA damage and genomic instability. Pidnarulex (CX-5461) is a first-in-class G4 stabilizer that induces synthetic lethality in Homologous Recombination-deficient (HRD) cells. Previous phase 1 study showed safety and preliminary activity. Here we report dose optimization for recommended phase 2 dose (RP2D) of CX-5461 and confirm safety. **Methods:** CX-5461 was administered intravenously on Days 1 and 8 of a 28-day cycle at 2 dose levels (250 and 325 mg/m^2) in patients (pts) with advanced pancreatic adenocarcinoma (PA), breast cancer (BC), or ovarian cancer (OC). The main cohort (Arms A: 250 mg/m^2 & B: 325 mg/m^2) included pts with HRD or DNA damage response (DDR) alterations and has completed accrual. An exploratory cohort (Arms C: 250 mg/m^2 & D: 325 mg/m^2) of OC pts with BRCA or other HRD genes enrolled simultaneously. Primary objective is to determine RP2D of CX-5461 using Relative Dose Intensity (RDI). Secondary objectives are safety, tolerability and efficacy. **Results:** 54 pts were treated and evaluable for toxicity (Arm A = 18, Arm B = 18, Arm C = 10, Arm D = 8). Patients' characteristics and efficacy results are detailed in table 1. The median number of prior lines of treatment were 6 (1-14). The median number of CX-5461 cycles received were 2 (1-30) and weeks on treatment were 8 (4-120). Grade ≥3 Treatment-Related Adverse Events (TRAEs) occurred in 12 pts (22%), including proteinuria, thrombocytopenia, and fatigue; 6 (11%) were AEs of special interest: 1 (2%) palmar-plantar erythrodysesthesia, 4 (7%) photosensitivity, and 1 (2%) phototoxic drug eruption. Among 29 response-evaluable pts in main cohort, 1 had PR (3%) and 10 had SD (34%),median duration 16 weeks (wks) (8-84). In evaluable OC (n=29), 2 had PR (7%), 13 SD (44%), median duration 16 wks (8-84). OC pts with BRCA mutations (n=25) had 2 PR (8%) and 11 SD (44%); all had prior PARPi exposure. 3/ 5 non-BRCA HRD had SD (60%). Prolonged clinical benefit was observed in 4 pts with treatment durations of 14 (OC, gBRCA1), 17 (OC, gBRCA2), 21 (OC, sBRCA1) and 30 cycles (PA, gPALB2). RDI was 91% in Arm A and 88% in Arm B. RDI and clinical data support 250 mg/m^2 as the RP2D. **Conclusions:** CX-5461 was tolerable and showed evidence of durable disease control in heavily pretreated pts, enriched for HRD/DDR alterations and post exposure to PARPi. The 250 mg/m^2 dose is established as the RP2D based on clinical data and RDI. Correlative studies are ongoing. Clinical trial information: NCT04890613. Research Sponsor: None.

		Arm A (N=18)	Arm B (N=18)	Arm C (N=10)	Arm D (N=8)
Tumor Type	BC	7 (39%)	2 (11%)	-	-
	OC	5 (28%)	9 (50%)	10 (100%)	8 (100%)
	PC	6 (33%)	7 (39%)	-	-
Molecular alterations	gBRCA1/2	12 (67%)	9 (50%)	3 (30%)	3 (38%)
	sBRCA1	0 (0%)	1 (6%)	6 (60%)	3 (38%)
	Other	6 (34%)	8 (44%)	1 (10%)	2 (25%)
Efficacy (evaluable pts only)	PR	1/13 (8%)	0 (0%)	0 (0%)	1/7 (14%)
	SD	4/13 (31%)	6/16 (38%)	5/9 (56%)	3/7 (43%)
	Disease control rate	5/13 (39%)	6/16 (38%)	5/9 (56%)	4/7 (57%)

Topoisomerase 1 and DNA damage: Pharmacodynamic responses and mechanism of trastuzumab deruxtecan in HER2- expressing advanced solid tumors.

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Background: Trastuzumab deruxtecan (T-DXd) consists of deruxtecan, a novel topoisomerase 1 (TOP1) inhibitor, covalently bound via a lysosomal protease-cleavable linker to the human epidermal growth factor receptor 2 (HER2)-targeting antibody, trastuzumab. The mechanism(s) underlying the clinical activity seen in multiple tumor types across various HER2 levels is of ongoing, active interest. To investigate the T-DXd mechanism of action, we developed a pilot clinical trial of T-DXd with a detailed pharmacodynamic analysis from TOP1 target engagement to downstream effects of DNA damage in patients with HER2-expressing (IHC 1-3+, HER2 amplified, or HER2 mutated) advanced solid tumors (NCT04294628). **Methods:** Based on preclinical studies modeling the trial, research tumor biopsies from consenting patients were collected at three time points: pre-treatment, post-dose Cycle 1 (48-96 hours) and pre-dose Cycle 3. The biopsies were evaluated for TOP1 inhibition, induction of stabilized TOP1covalent complexes (TOP1cc) and induction of downstream DNA damage repair (DDR) markers (RAD51, pNBS1, RPA32) using validated, quantitative multiplex immunofluorescence assays on fixed tumor sections with image analysis methodology. In addition, a retrospective analysis of Schlafen 11 expression in baseline biopsies was performed to determine its predictive value of tumor responses to T-DXd. **Results:** Twenty-one biopsy pairs (pre-treatment and C1, 48-96h post-dose 1) were evaluable for TOP1 molecular response and downstream DDR marker induction. TOP1 target modulation was detected in 15 (71%) of the on-treatment biopsies and markers of DDR were induced in 18 (86%) biopsy pairs. TOP1 target inhibition, robust induction of downstream DNA damage response including stalled replication fork progression, and DNA breaks were observed in HER2-amplified/2+/3+ tumors, and in HER2 1+ tumors. **Conclusions:** Our results confirm the intended TOP1 molecular mechanism of action of T-DXd in HER2-amplified/2+/3+ and importantly extend that finding to HER2 1+ tumors, resulting in DNA damage in nearly all cases. Pharmacodynamic biomarker studies are poised to yield important insights into the molecular effects of T-DXd in solid tumors. Research Sponsor: This project was funded in part by the National Cancer Institute, National Institutes of Health, under Contract No. 75N91019D00024.

Chemotherapy as a shaper of immune communication in the triple-negative breast cancer microenvironment.

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Background: Triple-negative breast cancer (TNBC) is a highly immunogenic disease and exhibits among the highest levels of immune infiltration compared with other breast cancer subtypes. These characteristics, coupled with the lack of effective targeted therapies, have made TNBC a key candidate for immunotherapy in selected clinical settings. While chemotherapy remains a mainstay of treatment, its immunomodulatory effects on the tumor immune microenvironment (TIME) remain poorly understood. This study computationally models immune cell to immune cell communication using Single-cell RNA sequencing data to identify immune driver cells and their interactions, and how they are altered by chemotherapy in TNBC. **Methods:** Single-cell RNA sequencing data of over 200,000 tumor cells from TNBC patients' tumor samples were obtained from the Gene Expression Omnibus database. They were analyzed to comprehensively characterize the TIME before and after chemotherapy. We also considered healthy breast tissue to establish immune pathways unique to TNBC pathogenesis. We employed unsupervised clustering analysis, reciprocal principal component analysis with annotation from the NIH Center of Immunology for immune cell identifiers. Communication probability, interaction strength, and pathway information flow were computed, and differential signaling was evaluated using Wilcoxon rank-sum tests ($p < 0.05$). Multiple hypothesis testing was also accounted for by Bonferroni-adjusted p-values to control false positives. **Results:** Immune activity within the TIME was minimal in healthy breast tissue, highlighting signaling pathways specific to TNBC pathogenesis. In contrast, there was an increased immune response in tumors after chemotherapy. Pathways with the highest communication activity included MHC-I/II, CCL, MIF, and CD99 signaling. Notably, CD86 signaling, which correlates with PD-L1 expression, and CD45 signaling were significantly activated after chemotherapy in TNBC. Additionally, CD23 signaling, associated with antitumor immunity, was enhanced following chemotherapy. Natural killer cells emerged as the key immune cell type mediating outgoing signals through annexin, IL16, CX3C, and CD99 pathways, which were largely inactive before treatment. **Conclusions:** Our findings demonstrate that chemotherapy reprograms the TIME in TNBC by enhancing intercellular communication among immune cells and upregulating pro-immune signaling pathways. This remodeling of the TIME suggests potential targets for novel immunotherapeutic discoveries and immune-checkpoint modulation in TNBC. Research Sponsor: None.

Sex-associated differences in osimertinib pharmacokinetics among Asian patients with non-small cell lung cancer.

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Background: Osimertinib is an oral, third-generation tyrosine kinase inhibitor (TKI) used in the treatment of epidermal growth factor receptor (EGFR) T790M-positive non-small cell lung cancers (NSCLC). However, therein lies a high interindividual variability in osimertinib trough concentrations at steady state, which may in turn affect clinical outcomes. The study aimed to evaluate factors influencing osimertinib exposure and their potential impact on treatment response. **Methods:** This was a prospective single-institution study of Asian NSCLC patients receiving once daily 80mg osimertinib. Plasma concentrations of osimertinib and its metabolites, AZ5104 and AZ7550 were quantified at steady state using a validated LC-MS/MS method. Pharmacogenetic analysis was conducted using commercially available Taqman SNP genotyping assays. **Results:** A total of 177 Asian patients with Stage I-IV NSCLC tumors were enrolled. Median age was 65 (35-84) years old. Majority of patients were Chinese (90%), female (59%) and non-smokers (82%). Exon 19 deletions were present in 45% of patients. Subgroup analysis of 72 patients with available pharmacokinetic data showed no significant genotypic-phenotypic associations between *CYP3A5*3, ABCB1 1236C>T, ABCB1 3435C>T, ABCB1 2677G>T/A* and *ABCG2 421C>A* and osimertinib pharmacokinetics parameters. Sex was significantly associated with trough osimertinib levels and clearance, with females exhibiting 28% higher osimertinib levels and lower clearance compared with males (P=0.0098). Similar trends were observed with AZ5104 and AZ7550 and osimertinib clearance (P<0.001). No significant differences in overall survival and progression-free survival were observed between sexes. Analysis of best overall response showed that males were more likely to PD compared with females (OR=1.88, 95% CI; 0.54- 6.3) but this was not statistically significant (P = 0.489). **Conclusions:** Our study showed that sex influences osimertinib pharmacokinetics, with females showing higher trough levels and lower clearance. These differences did not, however, translate into significant differences in survival or treatment response between males and females. Research Sponsor: NCC Research Fund; NCCRF-YR2017-JAN-PG2.

NeoRay phase IIa results: A study of [^{177}Lu]Lu-NeoB (^{177}Lu-NeoB) in pts with advanced solid tumors overexpressing gastrin-releasing peptide receptor (GRPR).

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Background: GRPR is overexpressed in many solid tumors. NeoB binds to GRPR with high affinity and can be radiolabeled for theranostics. NeoRay is the first-in-human study of ^{177}Lu-NeoB in pts with advanced solid tumors overexpressing GRPR. Phase (Ph) I reported favorable organ dosimetry and safety, and a recommended Ph II dosage (RP2D) of 9.25 GBq. Here, we report the Ph IIa primary analysis. **Methods:** This Ph IIa, open-label, multicenter, dosage expansion study enrolled 5 adult cohorts with confirmed [^{68}Ga]Ga-NeoB tumor uptake: A) HR+/HER2- breast cancer; B) prostate cancer (PCa); C) gastrointestinal stromal tumor (GIST); D) impaired renal function; and E) pts eligible for Cohorts A–C who also received sacubitril/valsartan (49/51 mg) at Cycle 1 to assess drug-drug interaction (DDI). There was no formal sample size calculation; the target was ~12 pts in Cohorts A–C, ≤6 pts in D, and ~3 pts in E. ^{177}Lu-NeoB 9.25 GBq was to be administered every 6 wks for ≤9 cycles, except in DDI Cohort E (5.55 GBq in Cycle 1, then 9.25 GBq). Primary endpoints (descriptive statistics) were individual response (centrally assessed by RECIST v1.1) in Cohorts A–C, and ^{177}Lu-NeoB PK and dosimetry in Cohort E. Secondary endpoints included safety/tolerability and QoL. **Results:** Overall, 18 pts (A n = 4; B n = 7; C n = 2; D n = 2; E n = 3) received treatment (median age 65 y; 56% male). Median (range) ^{177}Lu-NeoB exposure was 9 (6–60) wks; median (range) cumulative activity administered was 12.1 (5.7–81.4) GBq. At data cutoff (7 Jan 2025), 4 pts (B n = 2; C n = 2) had completed treatment (≥3 cycles); 1 pt (GIST) received 9 cycles. Of 10 pts with centrally assessed post-baseline response data, 1 had partial response (PCa), 5 had stable disease (of whom 2 had stable disease ≥20 wks [GIST]), and 4 had progressive disease. Adverse events (AEs) occurred in 17 (94%) pts (serious AEs in 3 [17%] pts; Gr ≥3 AEs in 6 [33%] pts). Treatment-related AEs (TRAEs) occurred in 7 (39%) pts (all non-serious; Gr ≥3 in 2 [11%] pts). The most common TRAEs were fatigue (n = 5, 28%), anemia (n = 2, 11% [Gr ≥3 in 1 pt, 6%]), and bone pain (n = 2, 11%). One pt died of hepatic failure related to disease progression (not a TRAE). No AEs led to dosage reductions/interruptions/discontinuations. Dosimetry evaluated in 12 pts showed favorable biodistribution, similar to Ph I. Projected cumulative absorbed doses in target organs were below EBRT limits; lesion absorbed doses were generally consistent across cohorts. Mean ± SD EORTC QLQ-C30 global health scores in Cohorts A–C were 70 ± 22 at baseline (n = 12) and 73 ± 16 at Cycle 2 (n = 4), suggesting stable QoL. **Conclusions:** NeoRay Ph IIa data at the ^{177}Lu-NeoB RP2D (9.25 GBq) reinforce Ph I dosimetry and safety results and support further clinical evaluation. Most AEs were mild/moderate and no new safety signals were identified. Despite the limited sample size, preliminary signs of antitumor activity were observed. Clinical trial information: NCT03872778. Research Sponsor: Novartis Pharmaceuticals.

ETCTN 10302: A randomized phase II trial of radium-223 dichloride in combination with paclitaxel in patients with bone metastatic breast cancer.

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Background: Radium-223 dichloride is an alpha particle emitting radiopharmaceutical that mimics calcium and localizes bone metastases inducing double-strand DNA breaks. Tumor cells in M-phase cell cycle arrest from paclitaxel are highly sensitive to alpha-emitting radionuclides. ETCTN 10302 tested the hypothesis that addition of radium-223 to paclitaxel will improve outcomes for bone-dominant metastatic breast cancer. **Methods:** ETCTN 10302 was a randomized, two-arm, multicenter, open-label phase II trial. Patients (pts) were randomized to receive either radium-223 (1.49 microcurie/kg iv day 1 x 6 doses) and paclitaxel (80 mg/kg iv on days 1,8 and 15) of each 28-day cycle (Arm A) or paclitaxel alone (Arm B). Inclusion criteria included HER2-negative metastatic breast cancer with ≥2 bone lesions and limited visceral metastases (five or less and ≤4 cm in size). Primary endpoint was median progression-free survival (PFS). Exploratory analyses included whole exome sequencing and serum alkaline phosphatase dynamics. **Results:** 70 pts were randomized from August 2020 to May 2024. Median age was 58.5 years, 100% were female, 60% were non-Hispanic whites, 14% had triple negative breast cancer, 37% had bone only disease. In the intent-to-treat analysis (37 Arm A, 33 Arm B), there was no significant difference in median PFS (5.8 vs 5.6 months; HR 0.92 p=0.80) but there was a numeric improvement in median OS in radium-223 plus paclitaxel arm (20.2 vs 16.6 months; HR 0.74 p=0.40). Overall response rate (ORR) was 5% in Arm A vs 9% in Arm B. There was no difference in median OS and PFS when analysis was limited to efficacy evaluable pts who completed at least one cycle (37 Arm A, 24 Arm B). Common treatment-related adverse events (TRAE) with the combination of radium-223 plus paclitaxel vs paclitaxel were anemia (78% vs 54%), neutropenia (76% vs 45%), fatigue (49% vs 50%), nausea/vomiting (46% vs 21%), diarrhea (32% vs 25%), peripheral sensory neuropathy (33% vs 30%) and increased ALT (22% vs 4%). Most common ≥grade 3 TRAE was neutropenia in Arm A (43% vs 8% in Arm B). Treatment discontinuation rate due to TRAE was 3%. **Conclusions:** Combination of radium-223 and paclitaxel can be administered safely as most adverse events observed were grade 1 to 2 except for higher incidence of ≥ grade 3 neutropenia. The trial did not meet the primary PFS endpoint but there was a numerical improvement observed in median OS with the combination. Clinical trial information: NCT04090398. Research Sponsor: None.

AKY-2519, a novel B7-H3-targeted radioconjugate, and its biodistribution profile in patients with mCRPC.

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Background: AKY-2519 is a 6.1 kDa B7-H3 (CD276) targeting miniprotein with an N-terminal short polyethylene glycol linker and dodecane tetraacetic acid chelator designed to deliver actinium (Ac)-225 for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and other solid tumors. Miniproteins are a novel radioconjugate therapy (RCT) format affording high affinity, selectivity, deep tumor penetration and internalization prolonging tumor retention and rapid plasma clearance limiting exposure to normal tissues. B7-H3 is highly expressed in multiple solid tumor cancers and absent in normal tissues such as salivary glands. These properties render B7-H3 a promising target specifically for Ac-225 delivering RCT in mCRPC. We evaluated biodistribution and tumor uptake of AKY-2519 relative to PSMA-11 and assessed estimated radiation doses to tumors and normal tissues in 16 mCRPC patients. **Methods:** Sixteen mCRPC patients were imaged with [^{68}Ga]Ga-AKY-2519 and [^{68}Ga]Ga-PSMA-11 PET/CTs to assess biodistribution and tumor uptake by SUV. Patients then received low dose [^{177}Lu]Lu-AKY-2519 (~0.37-0.56 GBq) followed by SPECT/CT at 3, 24, and 144 hours post-injection for normal tissue and tumor dosimetry analyses. SPECT images were reconstructed with MIM SPECTRA Recon Software and mean human absorbed dose coefficients (Gy/GBq) were generated with MIM SurePlan MRT. To assess tumor doses, representative lesions including nodal, skeletal and primary disease sites were analyzed across multiple patients. **Results:** No AEs were reported throughout the imaging assessment. PET and SPECT/CTs showed robust tumor uptake with prolonged retention. High lesion concordance was observed between AKY-2519 and PSMA-11 supporting B7-H3 as a novel target in mCRPC and further suggesting co-expression of B7-H3 and PSMA. No accumulation of AKY-2519 was noted in normal tissues with initial activity in the liver rapidly clearing out. Of the normal tissues of interest including kidneys, salivary glands, liver and bone marrow, the mean absorbed doses were below established clinical thresholds when scaled up to a full therapeutic treatment course. The predicted absorbed tumor doses were within expected therapeutic ranges and exceeded normal tissue exposures indicative of a potentially favorable risk-benefit profile for [^{225}Ac]Ac-AKY-2519. **Conclusions:** These are the first clinical data showing concordance between PSMA and B7-H3 on PET-CT imaging in a substantial cohort of patients supporting B7-H3 as a novel target in mCRPC. The normal tissue to tumor dose ratios observed with AKY-2519 suggest a wide therapeutic window as an Ac-225 delivering therapeutic. The low predicted dose to salivary glands supports its use as an actinium delivering RCT for mCRPC, with dosing under IND expected to start in 2H-2026. Research Sponsor: None.

First-in-human PET/CT imaging with 68Ga-AKY-2519, a B7-H3 targeted mini-protein radioconjugate, to demonstrate tumor uptake and normal tissue exposure across various advanced solid tumors.

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Background: 68Ga-AKY-2519 is a miniprotein radioconjugate developed by Aktis Oncology that targets B7-H3 (CD276) which is overexpressed in several malignancies and is linked with aggressive histology and poor outcomes. AKY-2519 is a high-affinity binder to B7-H3 that internalizes into tumor cells upon binding and thereby maximizes tumor retention. AKY-2519 is also designed to clear rapidly through the kidneys to minimize exposure to normal tissues. To identify potential utility for clinical development of 225Ac-AKY-2519 across various tumor types, here we report the first-in-human evaluation of 68Ga-AKY-2519 using positron emission tomography (PET) in patients with solid tumors. **Methods:** In this prospective, observational study, 18 patients with advanced solid tumors, including prostate cancer (n=7), colorectal cancer (n=4), SCLC (n=3) and NSCLC (n=1) underwent PET/CT imaging following intravenous administration of 68Ga-AKY-2519. Safety, normal tissue distribution and tumor uptake were assessed. Imaging findings were correlated with known disease sites in PSMA and FDG reference PET/CTs as well as available clinical and pathological data. **Results:** 68Ga-AKY-2519 was well tolerated with no adverse events. PET/CT imaging demonstrated favorable tumor uptake, rapid blood pool clearance and low uptake in normal tissues. 68Ga-AKY-2519 uptake (SUVmax) in normal tissues at 120 min post injection (p.i.) was noted in the liver (median 22.9 [interquartile range (IQR) [20.9-30.8]), spleen (7.3 [6.4-11.4]), salivary glands (7.3 [6.4-11.4]), adrenal glands (17.5 [15.9-19.8]) and kidneys (7.3 [6.4-11.4]). No significant bone marrow uptake was noted (median SUVmax 4.1 [3.3-5.1] at 120 min p.i.). High and consistent tumor uptake was observed across various tumor types. The largest cohort was patients with metastatic prostate cancer (n=7), in which the highest 68Ga-AKY-2519 uptake was in bone metastases (median SUVmax 40.4 (120 min p.i.), SUVpeak 25, SUVmean 16.1), followed by lymph node metastases (SUVmax 13.8 (120 min p.i.), SUVpeak 6.5, SUVmean 5.1) and visceral metastases (SUVmax 31.0 (120min p.i.), SUVpeak 22.2, SUVmean 18.7). **Conclusions:** 68Ga-AKY-2519 PET/CT imaging of various malignancies was safe and demonstrated high tumor-to-background uptake and cancerous lesion detection at 120 min p.i. Normal tissue uptake was low, and robust tumor uptake was noted in patients across different solid tumors indicating therapeutic potential. These data warrant further clinical development of 225Ac-AKY-2519.
Research Sponsor: None.

Final results of a first-in-human study of the MC1R-targeting radiopharmaceutical ^{225}actinium MTI-201 (^{225}Ac-MTI-201) in metastatic uveal melanoma (mUM).

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Background: Prognosis in mUM is poor with limited efficacy of currently available therapies. The melanocortin-1 receptor (MC1R) is an attractive target for radiopharmaceutical therapy given high expression in UM. ^{225}Ac-MTI-201 is a novel alpha particle emitting MC1R bound radiopharmaceutical with high biostability, affinity, and MC1R-specific cytotoxicity with defined dosimetry and pharmacokinetics in pre-clinical studies. **Methods:** In this first-in-human study (NCT05496686) of a single IV dose of ^{225}Ac-MTI-201, we enrolled mUM patients (pts) who had disease progression on at least 1 prior therapy. Pts had adequate organ and functional status; prior radiotherapy to >25% of bone marrow was exclusionary. The primary objective was safety and toxicity of ^{225}Ac-MTI-201 with secondary endpoints of pharmacokinetics (PK) and clearance of ^{225}Ac-MTI-201, response rate, progression-free survival (PFS), and overall survival (OS). Up to 12 dose levels [from 4.7 microcurie (μCi) to 1327 μCi] for ^{225}Ac-MTI-201 were planned per a modified continual re-assessment method (CRM) with a cohort size of one based on dose limiting toxicity (DLT) assessment within 28 days of drug administration using CTCAE v5.0. Response was assessed by RECIST 1.1. **Results:** Sixteen pts (8 male, 8 female), median age 63 years (43, 84) have been treated. Median number of prior systemic regimens was 2 (0,4), 8 pts had prior liver directed treatment. Dose of ^{225}Ac-MTI-201 was escalated to level 6 (152 μCi) when one DLT (G4 thrombocytopenia and G4 neutropenia) was observed requiring de-escalation per CRM. A second DLT (G4 neutropenia) at level 5 (76 μCi) required expansions at levels 4 (38 μCi; n=5) and 5 (n=6) where all remaining pts were treated without further DLT with 1 pt currently pending final DLT assessment. Adverse events (AEs) were mostly G1-2 including leucopenia, lymphopenia, neutropenia, thrombocytopenia, anemia, nausea, fatigue and ↑ AST. Reversible myelosuppression [lymphopenia (7), neutropenia (5), thrombocytopenia (2)] was the most common > G3 AE. No non-hematological DLT was seen. Best response was stable disease (4/15; 27%); seen at dose levels 4 and 5. The median PFS was 2.30 months (95% CI: 1.84, 3.65); 6-month PFS was 0.07 (95% CI: 0.0, 0.26) and 12-month OS was 0.39 (95% CI: 0.13, 0.64). Median distribution phase half-life (n=15) was 6.19 minutes followed by a slower median elimination phase half-life of 74.06 minutes with significant positive correlation between fast and slow half-lives (Spearman = 0.696, p= 0.0039), independent of dose level. **Conclusions:** Single dose administration of ^{225}Ac-MTI-201 with dose escalation to 76 μCi appears safe and feasible in mUM. Disease stability in this difficult to treat population is encouraging and a multi-dose study of ^{225}Ac-MTI-201 in mUM is planned pending final pt DLT assessment. ^{225}Ac-MTI-201 has Orphan Drug designation for mUM. Clinical trial information: NCT05496686. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; HHSN261201700035C; Modulation Therapeutics.

First-in-class DIO3 inhibitor as a novel treatment strategy in ovarian cancer.

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Background: Ovarian cancer carries high mortality, driven in part by platinum resistance and a scarcity of actionable therapeutic targets. Thyroid hormone signaling via triiodothyronine (T3) exerts tumor-suppressive effects, including inhibition of proliferative and DNA-damage stress pathways. Iodothyronine deiodinase type 3 (DIO3) is a clinically expressed T3-inactivating enzyme associated with aggressive disease biology, therapeutic resistance, and poor patient outcomes. DioTree Ltd is the first biotech company that developed ITYR-DBRMD, a first-in-class small-molecule DIO3 inhibitor for cancer treatment. **Methods:** DIO3 target engagement was evaluated using enzymatic mimic assays, intracellular T3 quantification (ELISA), and cellular thermal shift assays (CETSA). Pharmacokinetics (PK) were characterized across clinically relevant delivery routes (IV, IP, SC) with development of a dedicated bioanalytical quantification method. Antitumor efficacy was tested in nude mice bearing homologous recombination-proficient (HRP), carboplatin-resistant ovarian cancer xenografts. Mice received vehicle, ITYR-DBRMD, carboplatin, or their combination for three weeks. Tumor growth inhibition (TGI) and safety were assessed. **Results:** ITYR-DBRMD achieved selective and durable inhibition of DIO3 activity with direct cellular binding confirmation, robust increases in intracellular T3 levels, and consistent PK exposure across all administration routes tested. Monotherapy TGI was 43% for carboplatin and 50% for ITYR-DBRMD. Combination therapy produced a clinically meaningful efficacy increase, reaching 68% TGI, with no observed treatment-related toxicity or weight loss, supporting a favorable therapeutic index. Albumin-based tumor delivery and drug retention in tumors was established. **Conclusions:** These data support advancement of ITYR-DBRMD toward early-phase clinical testing, with potential application in ovarian cancer patients, a population lacking targeted therapeutic options. Research Sponsor: Israel Innovation Authority and NGT Incubator.

EIK1003, a PARP1-selective inhibitor, in combination with paclitaxel (PTX): Initial combination and updated monotherapy results from a phase 1/2 study EIK1003-001 in advanced solid tumors.

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Background: Non-selective PARP inhibitors (PARPi) demonstrate efficacy in HRR-mutant tumors but cause myelosuppression, potentially mediated by PARP2 inhibition. Overlapping hematologic toxicities have limited PARPi combinations with chemotherapy, restricting their use largely to the maintenance setting. EIK1003 is a potent and selective PARP1 inhibitor that may enable chemotherapy combinations previously not feasible. Here we report the first clinical data for EIK1003 + PTX and updated results for EIK1003 monotherapy. **Methods:** Cohort 1C evaluated EIK1003 QD (dose level [DL] 1 to 4) + PTX 80 mg/m² QW (Days 1, 8, 15 of 21-day cycles) in patients (pts) with platinum-resistant recurrent ovarian cancer (OC) and HER2(-) breast cancer (BC). Cohort 1A evaluated EIK1003 monotherapy (10 to 160 mg QD). BOIN dose escalation design was used. Primary endpoints were safety and tolerability; secondary endpoints were PK and antitumor activity. **Results:** As of 21-Nov-2025 safety data cutoff, 51 patients were treated in Cohort 1C; 30 remain on treatment. Median age was 59 years (range 25-81), ECOG PS 0/1 (54.9%/43.1%), and 62% pts received ≥ 4 prior lines of therapy. One DLT of febrile neutropenia was reported at DL4. Gr ≥ 3 TEAEs occurred in 62.7% pts and were mainly hematologic (Table 1). All pts with Gr ≥ 3 anemia had baseline anemia. TEAEs led to dose reduction in 10 pts and discontinuation in 8 pts. No deaths occurred due to TEAEs. The ORR was 23.1% (1 CR, 8 PR), with responses in OC (n=5) and BC (n=4). EIK1003 PK in combination was consistent with monotherapy, with target concentrations achieved at all dose levels. In Cohort 1A, 65 pts were treated. Gr ≥ 3 TEAEs were 43.1%, with anemia and neutropenia being most common (Table 1). 3/6 pts with Gr ≥ 3 anemia had baseline anemia. ORR was 14.3% overall, and 31.3% (5/16) in PARP-naïve pts. Median DOR in confirmed responders was > 6 mos in both cohorts (Table 1). Safety, PK/PD, and preliminary efficacy supported advancement of two doses into Part 2 dose optimization. **Conclusions:** EIK1003 + PTX demonstrated a tolerable safety profile in a heavily pre-treated population, with hematologic toxicities comparable to historical PTX use (eg, KN-B96, ESMO 2025). These findings represent the first clinical evidence that PARP1-selective inhibitors can be safely combined with chemotherapy. Extended follow-up of EIK1003 monotherapy confirms durable tolerability with antitumor activity. Clinical trial information: NCT06253130. Research Sponsor: None.

Safety and efficacy summary.

	Cohort 1C (EIK1003 + PTX)	Cohort 1A (EIK1003 monotherapy)
Safety	**N = 51**	**N = 65**
Gr ≥ 3 TEAEs, % (n)	62.7 (32)	43.1 (28)
Neutropenia	43.1 (22)	7.7 (5)
Anemia	15.7 (8)	9.2 (6)
Efficacy*	**N = 39**	**N = 49**
ORR per RECIST 1.1, % (n)	23.1 (9)	14.3 (7)
DCR (CR+PR+SD), % (n)	74.4 (29)	38.8 (19)
DOR, median (range), mos	6.4+ (4.4+, 7.7)	6.2+ (4.2+, 10.4+)

*Efficacy evaluable population as of 17-Dec-2025.

Tucatinib + subcutaneous (SC) trastuzumab (Tuc + Trast SC) in patients (pts) with solid tumors with *ERBB2* alterations (alts): Results from the targeted agent and profiling utilization registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating the antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alts. Combined results of four cohorts of pts with solid tumors with *ERBB2* alts treated with Tuc + Trast SC are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was done in CLIA-certified, CAP-accredited labs. Dosing was 300 mg of Tuc given orally twice daily, 600 mg of Trast and 10,000 units of hyaluronidase SC every 3 weeks (wks), until disease progression. Primary endpoint was disease control (DC) per investigator definition as complete (CR) or partial (PR) response or stable disease (SD) of at least 16 wks duration (SD16+) per RECIST v.1.1. The hypothesized null DC rate of 15% was rejected if the lower limit of a 1-sided 90% CI was >15%. Inferences were based on a beta-binomial model, which accounts for tumor type variance. Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response (OR), duration of response, duration of SD (DOSD), and safety. **Results:** 78 pts (histology-pooled [n=40], lung [n=16], biliary tract [n=11], uterus [n=11]) with 21 tumor types with *ERBB2* alts (*ERBB2* amplification [amp], n=38; mutation [mut], n=32; mut and amp, n=6; overexpression [OE], n=2) were enrolled. All cohorts were combined for analysis. 3 pts were not evaluable. Table shows demographics and outcomes. 1 CR (urothelial carcinoma [UC], *ERBB2* mut), 6 PR (uterus [2], esophagus [1], lung, neuroendocrine [1], ovary [1], UC [1]; *ERBB2* amp [5], mut [1]) and 18 SD16+ (10 tumor types; *ERBB2* amp [7], mut [10], OE [1]) were observed for a DC rate of 33% (1-sided 90% CI, 27 to 100) and an OR rate of 9% (95% CI, 4 to 18). The null hypothesis was rejected. Duration of CR in 1 pt was 87 wks. Median (med) duration of PR was 12 wks (range, 6-72). Med DOSD in pts with SD16+ was 28 wks (range, 12-57). 20 pts (26%) had ≥1 grade 3 tx-related AE or SAE. All were consistent with tx label except back pain, cardiac troponin increase, chronic kidney disease, heart failure, hypomagnesemia, hypophosphatemia, pericardial and pleural effusion, peripheral motor and sensory neuropathy, sinus tachycardia, systemic inflammatory response syndrome and UTI. **Conclusions:** Tuc + Trast SC demonstrated antitumor activity in pts with advanced solid tumors with *ERBB2* alts, warranting additional study. Clinical trial information: NCT02693535. Research Sponsor: Genentech; Pfizer, Seagen (now a wholly owned subsidiary of Pfizer Inc.); AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck, Taiho Oncology.

Demographics (N=78) and efficacy outcomes (n=75).	
Med age, years (range)	**67 (39, 88)**
ECOG PS, No. (%)	
0	29 (37)
1	44 (56)
2	5 (6)
Prior systemic regimens, No. (%)	
0-2	43 (55)
≥3	35 (45)
DC (OR plus SD16+) rate, % (1-sided 90% CI), p-value	33 (27, 100)
OR rate, % (95% CI)	9 (4, 18)
Med PFS, wks (95% CI)	10 (8, 16)
Med OS, wks (95% CI)	44 (30, 55)

3105 Poster Session

Phase II basket trial of brigatinib for *ALK* fusion–positive solid tumors: ALLBREAK trial (WJOG15221M).

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Background: *ALK* fusions occur in approximately 0.2% of solid tumors other than non-small cell lung cancer (NSCLC) and are associated with poor outcomes. Prospective evidence for ALK tyrosine kinase inhibitors in this rare condition is limited. **Methods:** This phase II basket trial evaluated brigatinib (90 mg once daily for 7 days, then 180 mg once daily) using a decentralized clinical trial platform. Eligible patients had advanced solid tumors other than NSCLC with *ALK* fusions detected in tumor tissue or circulating tumor DNA (ctDNA). The initial planned sample size was 14, with an objective response rate (ORR) of 50% considered promising and 12% unacceptable (one-sided $\alpha = 0.025$; $\beta = 0.09$). Enrollment was expanded to 28 patients due to rapid accrual. ctDNA analyses were performed at baseline, cycle 2, and progressive disease (PD). **Results:** Twenty-eight patients from ten hospitals were enrolled from May 2022 to March 2025; one was excluded from the full analysis set (FAS) due to clinical deterioration before treatment initiation. The FAS (n = 27) included patients with biliary tract cancer (BTC), colorectal cancer (CRC), thyroid cancer (TC), inflammatory myofibroblastic tumor (IMT), or other solid tumors (n = 7, 5, 3, 3, and 9, respectively). ECOG PS was 0 or 1 (18/9). The number of prior lines of therapy was 0–2 and ≥3 in 20 and seven patients, respectively. *ALK* fusions were detected by next-generation sequencing (NGS) or fluorescence in situ hybridization (22/5). Among NGS-detected cases, fusion partners included *EML4* (n = 8), *STRN* (n = 2), and others (including *CEP44*, *HOOK1*, *TPM3*, and *RRBP1*; n = 12). The confirmed ORR in the FAS was 63.0% (95%CI, 42.4–80.6), with ORRs of 57% in BTC, 60% in CRC, and 67% each in TC, IMT, and other tumors. For the first 14 patients enrolled as per initial study design, the ORR was 57.1% (95% CI, 28.9–82.3%). In the FAS, the disease control rate was 92.6%, and the median progression-free survival, duration of response, and overall survival were 9.7, 14.4, and 19.5 months, respectively. At data cutoff, 11 patients remained on treatment. ORR varied with fusion partner: 38% for *EML4*, 100% for *STRN*, and 75% for other partners. ORR was comparable between patients with and without baseline ctDNA detection of *ALK* fusions (67% vs. 64%). At PD, acquired *ALK* mutations (G1202R, E1028K, and L1502L) were detected in 23% (3/13) of patients; alterations in *EGFR*, *KRAS*, or *MET* were observed in 23% (3/13) of patients. The most common grade 3–4 adverse events were increased creatine phosphokinase (11%) and hypertension (11%). Interstitial lung disease occurred in 7% of patients (grade 1 only; no grade 3–4). No treatment-related deaths occurred. **Conclusions:** Brigatinib shows a high, durable response rate and manageable toxicity in non-NSCLC *ALK* fusion–positive solid tumors, supporting its use as a tumor-agnostic therapeutic agent in this rare molecular subset. Clinical trial information: jRCT2041210148. Research Sponsor: Takeda.

Zongertinib combined with T-DXd in HER2-positive metastatic gastric, gastro-esophageal junction, or esophageal carcinoma (mGEAC): First results from a phase Ib/II dose-escalation trial.

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Background: Zongertinib, an irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Beamion BCGC-1 (NCT06324357) is an ongoing Phase Ib/II multicohort trial investigating zongertinib, as monotherapy or combined with other agents, in HER2-positive metastatic breast cancer, metastatic colorectal cancer, and mGEAC. Here, we report the first data from Cohort C (Phase Ib), in which patients (pts) with HER2-positive mGEAC received zongertinib combined with T-DXd, as well as supporting preclinical data. **Methods:** Preclinical activity of zongertinib plus T-DXd was assessed in xenograft mouse models of HER2-positive gastric cancer. In Cohort C, pts with histologically/cytologically confirmed, unresectable, HER2-positive mGEAC were enrolled. Pts had documented HER2-positive disease (overexpression/amplification) and disease progression following HER2-directed treatment. Pts received escalating doses of zongertinib once-daily plus a fixed dose of T-DXd (6.4 mg/kg) every three weeks. Dose escalation was guided by a BLRM with overdose control. Pts remained on treatment until any protocol-defined stopping criterion occurred. The primary endpoint was the occurrence of DLTs during the MTD evaluation period. Secondary endpoints included further safety assessments and objective response (investigator-assessed; RECIST v1.1). **Results:** In mouse models, the addition of zongertinib to T-DXd led to increased antitumor activity. In Beamion BCGC-1, as of November 4, 2025, 19 pts had been enrolled to Cohort C and received zongertinib 60 mg (n=4), 120 mg (n=9), 240 mg (n=4), or 300 mg (n=2). Median age was 63 years, 74% male, 74%/26% ECOG PS 0/1. All pts had received prior trastuzumab-based therapy. Treatment-emergent adverse events (TEAEs; any grade [G]/G≥3) were reported in 17/9 (89%/47%) pts. AEs related to zongertinib (any G/G≥3) were reported in 13/2 (68%/11%) pts. There were no zongertinib-related G4/5 AEs. The most-common TEAEs (any G/G≥3) were nausea (53%/0%), decreased appetite (47%/5%), and diarrhea (47%/0%). One pt each had G1 pneumonitis and interstitial lung disease; both recovered. AEs leading to zongertinib dose reduction/discontinuation were reported in 1/2 pts. AEs leading to T-DXd dose reduction/discontinuation were reported in 8/1 pts. The first confirmed responses to zongertinib combined with T-DXd were observed across the different zongertinib dose levels (60 mg: 1 CR, 2 PR; 120 mg: 2 PR, 5 SD; 240 mg: 1 PR, 1 SD). **Conclusions:** No new safety signals were observed for zongertinib in combination with T-DXd; further dose escalation is ongoing. Encouraging clinical activity was observed in pretreated pts with HER2-positive mGEAC who had disease progression following prior trastuzumab-based therapy. Clinical trial information: NCT06324357. Research Sponsor: Boehringer Ingelheim.

Early results from the first-in-human phase 1 study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors (ACESOT-1051).

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Background: WEE1 tyrosine kinase regulates cell cycle checkpoints (G1-S, G2-M) and DNA damage responses. Inhibiting WEE1 can force premature mitotic entry and subsequent apoptosis. APR-1051 is a highly potent, orally bioavailable WEE1 inhibitor (WEE1i) with *in vivo* antiproliferative activity. Low off-target inhibition of APR-1051 on PLK kinases (PLK1, PLK2, PLK3) differentiates it from other WEE1i's and may confer improved safety. **Methods:** This open-label dose escalation (BOIN) and dose selection optimization study is evaluating APR-1051 using a once-daily (QD) regimen. The study is currently enrolling at 220 mg at three US sites (NCT06260514). Primary study objectives are to characterize the safety, dose-limiting toxicity (DLT), maximum tolerated dose/maximum administered dose, and recommended phase 2 dose of APR-1051. Secondary objectives include evaluating APR-1051 pharmacokinetic properties and preliminary efficacy (RECIST v1.1; PCWG3 criteria for mCRPC). Key inclusion criteria are age $\geq$ 18 years with advanced solid tumor and cancer-associated gene alterations, prior standard-of-care systemic treatment, and ECOG PS 0 or 1. Key exclusion criteria are prior WEE1i use, CNS metastases/unstable involvement, secondary malignancies requiring therapy, and concomitant moderate/strong inhibitors/inducers of CYP3A4/5, MDR1, or BCRP. **Results:** As of January 16, 2026, 22 patients (median age 62 years [range: 40–86]; have been enrolled up to the 220 mg dose level. Most (n=13, 59%) cases were colorectal cancers (colon [n=9, 41%], rectal [n=4, 18%]) followed by uterine (n=3, 14%), pancreatic (n=2, 9%), and breast, gastric, oropharyngeal, and soft tissue cancer (each n=1, 5%). The median prior lines of treatments was 3. Any grade adverse event (AE) was report in 21 (95%) patients. Treatment-related AEs were reported in 12 (55%) patients; 10 (45%) patients had non-serious gastrointestinal events. Twelve (55%) patients had 18 unique serious AEs, including one death on treatment unrelated to APR-1051 and one DLT of grade 3 elevated liver enzymes (AST, ALT) probably related to APR-1051 (n=1, 5%). Antitumor activity was observed in one (5%) patient with uterine serous carcinoma treated with APR-1051 150 mg who had an unconfirmed partial response—50% reduction in target lesion size (RECIST v1.1) and $>$ 90% reduction in CA-125 tumor marker—at per protocol 8-week assessment. Five (23%) patients had stable disease: oropharyngeal cancer (APR-1051 70 mg [n=1, 5%]); colon, rectal, uterine cancer (100 mg [n=3, 14%]); colon cancer (150 mg [n=1, 5%]). A dose proportional increase in exposure was observed. **Conclusions:** In the ongoing trial, continuous, oral APR-1051 QD has a manageable safety profile with preliminary signals of antitumor activity in patients with pretreated advanced solid tumors. Clinical trial information: NCT06260514. Research Sponsor: Aprea Therapeutics.

Zidesamtinib efficacy and safety in patients with advanced *ROS1*-positive solid tumors other than NSCLC in the ARROS-1 study.

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Background: *ROS1* fusions are oncogenic drivers in various cancers. Multiple ROS1 tyrosine kinase inhibitors (TKIs) are available for *ROS1*+ non-small cell lung cancer (NSCLC); however, there are limited data on the activity of these agents in patients with other *ROS1*+ tumors. In patients with advanced *ROS1*+ NSCLC (TKI pretreated and TKI-naïve), zidesamtinib has demonstrated encouraging clinical activity, including in patients with CNS disease and/or ROS1 G2032R mutation, and a safety profile consistent with its highly ROS1-selective, TRK-sparing design. Here we report the first data on the activity of zidesamtinib in patients with other *ROS1*+ solid tumors. **Methods:** The global Phase 1/2 ARROS-1 study (NCT05118789) includes a cohort of patients with advanced/metastatic *ROS1*+ solid tumors other than NSCLC, whose disease has progressed on any prior therapy. Key endpoints are objective response rate (ORR, RECIST v1.1 by BICR), duration of response (DOR), and safety. Data cut: 22 September 2025. **Results:** 15 efficacy-evaluable patients with *ROS1*+ solid tumors (10 non-NSCLC tumor types) received zidesamtinib. Patients received a median of 2 prior anticancer therapies (range 1-6): 60% were ROS1 TKI-naïve, 40% were ROS1 TKI pre-treated (range 1-2), 73% had prior chemotherapy (range 1-4). ORR was 40% (6/15, including 1 PR pending confirmation), with no disease progression by BICR among responders (DOR range 3.9+ – 22.8+ months). Responses were observed across multiple tumor types, including cholangiocarcinoma, colorectal, gastric, inflammatory myofibroblastic tumor, ovarian, and pancreatic. 2 ROS1 TKI pre-treated patients had ROS1 resistance mutations (G2032R and F2004I/F2004V) at baseline and both achieved a PR (1 pending confirmation). Treatment-related adverse events (TRAEs) in ≥15% of patients were increased alanine aminotransferase, increased blood creatine phosphokinase, and dysgeusia (n=3 patients each). No patients discontinued due to TRAEs; 1 pt dose-reduced due to TRAE. **Conclusions:** Zidesamtinib demonstrated encouraging activity in patients with diverse *ROS1*+ solid tumors, including those refractory to standard-of-care therapies. Safety was consistent with its ROS1-selective, TRK-sparing design. Enrollment is ongoing. Clinical trial information: NCT05118789. Research Sponsor: Nuvalent, Inc.

First-in-human phase 1/2 study of ETX-19477, an oral, potent, and selective PARG inhibitor, in patients with advanced solid tumors (ERADIC8).

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Background: Poly(ADP-ribose) glycohydrolase (PARG) is an enzyme that catalyzes the removal of poly-ADP-ribose (PAR) chains from proteins during DNA damage repair. PARG inhibition leads to selective cell death in tumors with underlying replication fork defects, including BRCAm tumors, through a mechanism distinct from PARP inhibition. ETX-19477 is an oral, potent, and selective PARG inhibitor that shows robust preclinical activity in mouse models of ovarian, breast, and gastric cancers. **Methods:** ERADIC8 is an open-label, multicenter, Phase 1/2 study, consisting of two parts, dose escalation and dose expansion. A Bayesian Optimal Interval Design was used to enroll patients (pts) into dose escalation cohorts, with enrichment for pts with BRCAm high grade serous ovarian (HGSOC) and breast cancers. The primary objective is to assess safety/tolerability of ETX-19477 and define the maximum tolerated dose (MTD) and recommended Phase 2 dose(s). Secondary and exploratory objectives include pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity per RECIST v1.1. ETX-19477 is given orally once or twice daily in 21-day cycles. **Results:** As of Jan 6 2026, 45 pts were enrolled into the study across 11 dose levels (range: 80-750 mg QD, 190-350 mg BID). Tumor types included ovarian (n=24, BRCAm: 18), breast (n=8, BRCAm: 7), endometrial (n=6, BRCAm: 0), colorectal (CRC, n=3, BRCAm: 1), and other (n=4, BRCAm: 0) cancers. Treatment-related AEs (TRAEs; any grade) occurring in >20% of pts were nausea (53%), vomiting (38%), and fatigue (24%). The only Gr3 TRAE occurring in >5% of pts was neutropenia (16%). There was one Gr4 TRAE of neutropenia in 1 pt (2%) and no Gr5 TRAEs. ETX-19477 exposure is dose proportional, and the BID regimen achieves >85% PARG inhibition throughout the dosing interval in a blood-based PAR accumulation pharmacodynamic assay. As of the data cutoff, dose escalation is ongoing at 350 mg BID (MTD has not been defined) and dose expansion is ongoing at 200-300 mg BID. Among BRCAm, HGSOC pts enrolled at BID dose levels, there were 7 evaluable pts with a median of 4 prior lines of therapy (range 2–11): 2 pts achieved a partial response (PR, 29%) and 3 pts achieved stable disease (SD, 43%). Both pts with PRs were platinum-resistant and received prior PARP inhibitor treatment. 1 pt with BRCAm CRC remains on active therapy (250 mg BID) with SD for 7 months. **Conclusions:** ETX-19477 was well tolerated and showed anti-tumor activity in heavily pretreated pts with BRCAm, platinum-resistant HGSOC during dose escalation. These findings provide the first clinical proof-of-concept of PARG inhibition in HGSOC. ETX-19477 is being further evaluated in the dose expansion phase of the study. Clinical trial information: NCT06395519. Research Sponsor: 858 Therapeutics.

Final analysis of KOMET (NCT04924608), a phase 3 study of selumetinib in adults with NF1-PN.

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Background: In 2025 the EMA and FDA expanded the approval of selumetinib (SELU; ARRY-142886, AZD6244) to adults with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN). We report the final exploratory analysis of SELU efficacy and safety from the Phase 3, randomized, double-blind, placebo (PBO)-controlled KOMET trial. **Methods:** Adults (≥18 yrs) with NF1-PN were randomized 1:1 to 28-day cycles of oral SELU 25 mg/m^2 BID or PBO with crossover to SELU at the end of Cycle (C) 12 or earlier if radiological progression was confirmed by independent central review (ICR). The single-arm objective response rate (ORR) by use of volumetric MRI analysis per ICR REiNS and safety were exploratory endpoints at final DCO (last participant (pt) completed C24; 17 Mar 2025)). Pharmacokinetics (PK) data were collected at steady state C1, Day (D) 8. A planned sample of 73 pts per arm with a 2-sided 5% alpha Fisher's exact test had >99% power to detect the difference between a SELU ORR of 20% and PBO ORR of 0%. **Results:** Overall, 145 pts (SELU: 71; PBO: 74) were randomized; 66 pts in the PBO group crossed over to SELU treatment for the open-label period (SELU period). In the SELU period, 137 pts were treated; 96 pts (66.2%) (SELU: 45, PBO/SELU: 51) completed the study and were judged by the investigators at DCO to have clinical benefit at study completion and, consequently, continued receiving SELU during the post-trial access program. Median actual exposure to SELU during the SELU period was 554 days and maximum exposure to SELU treatment was 1156 days. The median relative dose intensity of SELU treatment was 99.5%. The ORR in the SELU group (N = 71) was 23.9% (95% CI; 14.6, 35.5). Of the 17 pts who achieved objective response, 10 (58.8%) remained in response for ≥12 months while 5 pts (29.4%) had not yet reached 12 months follow-up from onset of response. Median duration of response was not reached in the SELU group by final analysis. During the SELU period (N = 137), 51 pts (37.2%) had a maximum AE severity of ≥Grade 3 (most frequent were known SELU AEs); ≥1 AEs, possibly related to SELU, were experienced by 127 pts (92.7%); of these, 31 pts (22.6%) had ≥Grade 3 AEs. Serious AEs (SAEs) were experienced by 24 pts (17.5%); 6 pts (4.4%) had SAEs possibly related to SELU. AEs of special interest were experienced by 85 pts (62.0%); increased blood creatine phosphokinase (43.1%), increased ALT/AST (13.9% each), and peripheral edema (13.1%) were the most frequent (≥10% of pts). AEs were manageable; the AE-related discontinuation rate for the trial was 9.5%. At C1 D8, 64 pts who received SELU were included in the PK Analysis Set. Median t_{max} was 1.5 h and geometric mean $AUC_{(0-12)}$ was 2986 h × ng/mL for SELU. **Conclusions:** In the first international, randomized, PBO-controlled trial in adults with NF1-PN, SELU achieved a sustained and durable, clinically meaningful reduction in PN volume per ICR REiNS. No new safety concerns were identified and AEs were manageable. Clinical trial information: NCT04924608. Research Sponsor: AstraZeneca as part of an alliance between AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD).

3111 Poster Session

First-in-human trial of the TEAD inhibitor ODM-212 in patients with advanced solid tumors (TEADES).

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Background: The Hippo pathway is implicated in multiple human cancers including mesothelioma and epithelioid hemangioendothelioma (EHE). When Hippo signalling is inactive, Yes-associated protein 1 (YAP1) and WW-domain-containing transcription regulator 1 (TAZ) locate to the nucleus, activating TEA domain family member (TEAD) transcription factors (TEAD1-4) to impact transcription and key oncogenic cellular processes. ODM-212 is a small molecule oral pan-TEAD inhibitor with *in vitro* and *in vivo* antitumour activity in solid tumours. **Methods:** TEADES is a multi-site, open-label, first-in-human trial of ODM-212 enrolling patients ≥18 years of age with various types of advanced, metastatic solid tumours where the Hippo pathway is implicated, with or without relevant genetic alterations. The study followed a Bayesian optimal interval (BOIN) design with a dose escalation with backfill cohorts, followed by expansion in tumour types of interest. Main objectives were safety (including dose-limiting toxicity (DLT)), preliminary efficacy and pharmacokinetics. ODM-212 was administered orally, once or twice daily, in a continuous 4-week cycle. **Results:** Between 7 November 2023 and 5 January 2026, 76 patients (mesothelioma 29, EHE 15, other 32) of mean age 62.1 years and all ECOG 0-1 received ODM-212 at doses between 20-320 mg/day, with 44 continuing on treatment at time of data cut-off. Previous treatment included checkpoint inhibitors (N=38), chemotherapy (N=59) or both (N=36). The longest exposure at data cut-off was 18-months. ODM-212 was well tolerated. No DLTs were reported and the maximum tolerated dose (MTD) was not identified. The most frequent treatment-related adverse event (TRAE) was proteinuria (19.7%), which was reversible and resulted in treatment adjustment in 6 (7.9%) patients. Other common TRAE's were increased lipase (15.8%) and nausea (10.5%). Grade ≥3 TRAE's occurred in 6.6% patients (anemia and increases in amylase, lipase, alanine aminotransferase and aspartate aminotransferase). Treatment responses by RECIST 1.1 were observed across multiple doses (ORR 7/45 = 15.6%), predominantly in patients with mesothelioma (ORR 27.8% in 18 evaluable patients, disease control rate (DCR) 77.8%) and EHE (ORR 22.2% in 9 evaluable patients, DCR 100%). ODM-212 demonstrated a predictable pharmacokinetic profile, with steady state achieved by 15 days and mean elimination half-life of 1-2 days, supporting once or twice daily dosing. **Conclusions:** ODM-212 administration to extensively treated patients with advanced cancer was well tolerated and resulted in some promising tumour responses (particularly in mesothelioma and EHE). The phase 2 portion of TEADES is currently enrolling patients. Clinical trial information: NCT06725758. Research Sponsor: Orion Pharma.

HRS-5041, an androgen receptor degrader, in metastatic castration-resistant prostate cancer: A phase 1, multicenter, first-in-human study.

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Background: ADT plus NHA have been approved for PC of different stages. However, patients (pts) inevitably develop drug resistance, and AR mutations are a common cause of this resistance. HRS-5041 is a novel, oral, highly effective AR degrader that specifically targets the AR wild type (AR WT) and clinically relevant AR LBD mutants. We conducted a phase 1 trial to assess HRS-5041 in NHA-resistant mCRPC. **Methods:** Pts with mCRPC who had progressed on ≥1 NHA and ≥1 taxane chemo (unless refused or not indicated to chemo) were eligible. Pts orally received HRS-5041 at 30–540 mg QD or 240–300 mg BID during dose-escalation (DE), followed by dose or indication expansion at 180–360 mg QD or 240-300 mg BID. 240 mg BID and 360 mg QD were selected for dose optimization. The primary endpoints were DLT, MTD, and RP2D. **Results:** As of Dec. 12, 2025, 156 pts were enrolled, including 77 with AR-LBD mutation and 79 with AR-LBD WT. During DE, no DLT occurred. MTD was not reached. TRAEs were reported in 133 (85.3%) pts; the most common were anemia (38.5%), decreased appetite (25.6%), and diarrhea (24.4%). Grade ≥3 TRAEs and serious TRAEs occurred in 20 (12.8%) and 4 (2.6%) pts. No TRAEs led to death. Among all evaluable pts, rate of PSA reduction ≥50% was 0 for 1 pt at 30 mg QD, 0 for 4 pts at 90 mg QD, 17.4% for 23 pts at 180 mg QD, 32.1% for 53 pts at 360 mg QD, 40.0% for 5 pts at 540 mg QD, 35.7% for 56 pts at 240 mg BID, and 11.1% for 9 pts at 300 mg BID. Data by AR-LBD status for expanded doses are shown in table. Both 360mg QD and 240mg BID groups showed excellent PSA response rates and rPFSs, regardless of AR-LBD status. Among pts with AR-LBD mutations, the 240 mg BID group showed a superior rate of PSA reduction ≥50% and a higher 8-month rPFS rate than the 360 mg QD group. Notably, 2 patients in the 240 mg BID group achieved CR, including 1 with liver metastases. **Conclusions:** HRS-5041 showed tolerable safety and promising antitumor activity in pretreated mCRPC. A phase 3 study is currently underway in mCRPC pts with AR-LBD mutation, with a recommended dose of 240mg BID. Clinical trial information: NCT05942001. Research Sponsor: None.

Efficacy outcomes.

Dose	180 mg QD	180 mg QD	360 mg QD	360 mg QD	240 mg BID	240 mg BID
AR-LBD status	**AR-LBD mutation**	**AR-LBD WT**	**AR-LBD mutation**	**AR-LBD WT**	**AR-LBD mutation**	**AR-LBD WT**
PSA reduction ≥30%*	5 (50.0)	1 (7.7)	15 (48.4)	8 (36.4)	17 (54.8)	7 (28.0)
PSA reduction ≥50%*	3 (30.0)	1 (7.7)	10 (32.3)	7 (31.8)	15 (48.4)	5 (20.0)
rPFS, mo†	NR (2.2–NR)	5.8 (2.1–8.6)	11.0 (5.5–NR)	13.8 (8.2–NR)	11.0 (8.2–NR)	NR (3.5–NR)
8-month rPFS rate†	53.3 (17.7–79.6)	32.6 (5.8–64.3)	58.1 (35.6–75.2)	82.9 (55.7–94.2)	85.3 (60.2–95.1)	71.2 (46.4–86.0)
ORR#	2 (66.7)	0	0	0	3 (42.9)	1 (11.1)

Data are n (%) or median (95% CI).
*Assessed in pts who had at least one post-baseline PSA assessment or who discontinued treatment due to death/clinical progression without post-baseline PSA assessment; N was 10, 13, 31, 22, 31, and 25.
†Assessed in full analysis set; N was 10, 14, 32, 23, 33, and 25.
#Assessed in pts with baseline target lesions; N was 3, 4, 10, 5, 7, and 9.

3113 Poster Session

Safety and efficacy of ifebemtinib (IN10018) combined with garsorasib (D-1553) in $KRAS^{G12C}$ mutant solid tumors from a phase Ib/II study: 2-year follow-up from single-arm of non-small-cell lung cancer (NSCLC).

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Background: Studies have shown that combining RAS inhibitors (RASi) with appropriate partners may enhance efficacy. Ifebemtinib (ifebe) is a potent and selective oral focal adhesion kinase (FAK) inhibitor demonstrating synergy with RASi. D-1553 is a $KRAS^{G12C}$ inhibitor approved in China for $KRAS^{G12C}$–mutant NSCLC. We previously reported encouraging antitumor activity with ifebe plus D-1553. Here we present updated 2-year efficacy and safety results, including exploratory TP53 subgroup analyses. **Methods:** This is a phase Ib/II, open-label study to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of D-1553 in combination with ifebe in patients with locally advanced or metastatic NSCLC harboring $KRAS^{G12C}$ mutations regardless of PD-L1 expression. Patients received ifebe 100 mg once daily (QD) plus D-1553 600 mg twice daily (BID). **Results:** As of January 4, 2026, 33 treatment-naïve NSCLC patients (81.8% stage IV) were enrolled; median follow-up was 24.9 months (Range: 1.05, 31.77). The objective response rate (ORR) was 90.3% (95% CI: 74.2, 98.0) and disease control rate (DCR) was 96.8% (95% CI: 83.3, 99.9). The median progression free survival (PFS) was 22.14 months (95% CI: 9.63, NE) with the 12- and 24-month PFS rates were 67.9% and 40.0%, respectively. The median duration of response (DOR) was 19.38 months (95% CI: 12.85, NE). The 24-month overall survival (OS) rate was 69.7%, and mOS was not reached (95% CI: 27.76, NE). TP53 wild-type patients (n=17) showed more favorable outcomes, with higher ORR (94.1% vs. 81.8%), unreached mPFS (vs. 14.2 months), and unreached mOS (vs. 17.7 months) compared with TP53-mutant patients (n=13). The safety profile of ifebe plus D-1553 was generally comparable to that of each single agent. SAEs were reported in 33.3% of patients, with 18.2% experiencing ifebe-related SAEs. Most TRAEs were grade 1–2; grade ≥3 TRAEs occurred in 24.2% of patients, including one grade 4 event. No treatment-related deaths or discontinuations were reported. **Conclusions:** Ifebe plus D-1553 exhibited robust, durable antitumor activity and a favorable safety profile in treatment-naïve $KRAS^{G12C}$-mutant NSCLC patients regardless of PD-L1 expression. Notably, TP53-wild-type $KRAS^{G12C}$ tumors typically show poor responsiveness and short durability to ICI therapies, likely due to reduced PD-L1 expression and lower tumor mutational burden. The superior outcomes in TP53 wild-type patients suggest this combination may address an unmet need in this distinct population. Further studies are needed to validate these findings and define the regimen's optimal role in the evolving treatment landscape. Clinical trial information: NCT06166836; NCT05379946. Research Sponsor: None.

First-in-human phase I/II study of a highly selective FGFR2 inhibitor 3HP-2827 in patients with advanced solid tumors harboring *FGFR2* alterations.

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Background: Molecular profiling of cholangiocarcinoma (CCA) is highly recommended to guide access to targeted therapies such as FGFR2 inhibitors. 3HP-2827 is a highly selective and potent FGFR2 inhibitor targeting FGFR2 alterations. Here we report the findings of 3HP-2827 in advanced solid tumors harboring FGFR2 alterations. **Methods:** This is a phase I/II study to evaluate the safety, tolerability, PK, and preliminary efficacy of 3HP-2827 in pts with advanced solid tumors harboring FGFR2 alterations. Pts failed to standard therapy with/without prior pan-FGFR inhibitor (FGFRi) are eligible for enrollment. Bayesian Optimal Interval (BOIN) and back filling design were employed in the dose-escalation stage of phase I, followed with the expansion stage. Treatment-related adverse events (TRAEs), PK, and anti-tumor activity (RECIST v1.1) were assessed. **Results:** As of Jan 8, 2026, a total of 52 pts (46 with CCA, 6 with others) were enrolled from 12 centers, received 3HP-2827 at doses of 60-180 mg once daily (QD), including 42 with FGFR2 fusion/rearrangement (f/r), 6 with FGFR2 mutation. 19 pts (36.5%) had prior FGFRi. No dose-limiting toxicities (DLTs) were observed at the dose levels of 60 mg, 120 mg, 180 mg QD. 3HP-2827 had favorable PK with doses≥120 mg QD providing FGFR2 occupancy > 90%. The most common TRAEs were FGFR2 on-target toxicities including dry mouth (69.2%, G3 1.9%), nail toxicity (67.3%, G3 3.8%), stomatitis (50%, G3 3.8%), dry eyes (26.9%, G3 1.9%), PPE (19.2%, G3 3.8%). 12 pts (23.1%) experienced at least one G3/G4 TRAE and no G5 TRAEs occurred. 7 pts (13.5%) experienced at least one serious adverse event, 4 (7.7%) of them were considered related to 3HP-2827. No discontinued treatment or death due to TRAEs. Anti-tumor activities were observed from 60 mg QD. Among 15 CCA pts (FGFR2 f/r, FGFRi-naive) who had at least one post-treatment tumor assessment, objective response rate (ORR) was 80% (95% CI: 51.9, 95.7), and disease control rate (DCR) was 100% (95% CI: 78.2, 100). The ORR and DCR in 15 CCA pts (FGFR2 f/r, FGFRi-refractory) was 26.7% (95% CI: 7.8, 55.1) and 86.7% (95% CI: 59.5, 98.3). The ORR and DCR in 4 advanced solid tumor pts (FGFR2 mutation, FGFRi-naive) was 75% (95% CI: 19.4, 99.4) and 100% (95% CI: 39.8, 100). **Conclusions:** 3HP-2827 was found to be safe and tolerable, with encouraging anti-tumor activity observed in pts with FGFR2 alterations. Further clinical efficacy will be explored in the expansion stage and phase II stage. Clinical trial information: NCT06378593. Research Sponsor: None.

A first-in-human phase I/II study evaluating CTS3497, an MTA-cooperative PRMT5 inhibitor, in advanced or metastatic *MTAP*-deficient solid tumors.

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Background: Protein arginine methyltransferase 5 (PRMT5) methylates multiple protein substrates with a variety of biological functions known to be dysregulated in cancer. CTS3497 is an orally available, brain-penetrable, MTA (methylthioadenosine) -cooperative PRMT5 inhibitor that preferentially targets the MTA-bound PRMT5 in MTAP (MTA phosphorylase) -deficient tumors and potently inhibits tumor growth in various preclinical models. Here we present clinical data from an ongoing Phase I/II study of CTS3497 in solid tumors (NCT06971523). **Methods:** Eligible pts with homozygous MTAP deletion (by next generation sequencing), or MTAP protein loss (by immunohistochemistry [IHC]) and advanced solid tumors in the dose-escalation stage received 50, 200, 300, 400 mg BID of CTS3497 orally, while pts in the dose-expansion stage were treated with 200, 300 or 400 mg BID until disease progression or intolerable toxicity. Efficacy, safety, PK, PD and biomarker profiles were evaluated. **Results:** As of 22 Jan 2026, 41 patients received ≥1 dose of CTS3497 treatment. No DLT was observed, and MTD was not reached; CTS3497 was well-tolerated. Most common (≥20%) treatment-related adverse events (TRAEs) were anemia (34%), white blood cell count decreased (32%), platelet count decreased (27%) and neutrophil count decreased (22%). The most common Grade ≥3 TRAE (occurring in ≥5% of patients) was platelet count decreased. No central nervous system (CNS) effects were reported. Among 21 centrally-confirmed MTAP-deficient, efficacy-evaluable patients, including 9 gastrointestinal (GI) cancers (ampullary cancer, biliary tract carcinoma, esophageal squamous cell carcinoma, gastric cancer and pancreatic ductal adenocarcinoma), 5 non-small cell lung cancer (NSCLC), 1 urothelial carcinoma and 6 rare cancers, the objective response rate (ORR) was 43%, and the disease control rate (DCR) was 91%. In GI cancers, the ORR and DCR were 56% and 89%. In NSCLC, the ORR and DCR were 60% and 80%. The exposures (Cmax, AUC0-24h) of CTS3497 increased in a linear, dose-proportional manner. The pharmacodynamic (PD) marker, plasma symmetric dimethylarginine (SDMA) level, showed a significant decrease. **Conclusions:** CTS3497 demonstrated a favorable safety profile and promising efficacy in heavily pretreated pts with MTAP-deficient advanced solid tumors, including GI cancers, NSCLC. Clinical trial information: NCT06971523. Research Sponsor: Cytosinlab Therapeutics Co., Ltd.

Efficacy of targeting replication stress in neuroblastoma.

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Background: Children with high-risk and relapsed neuroblastoma (NB) need improved therapies, and recurrent cytogenetic abnormalities, such as *MYCN* oncogene amplification, represent candidate therapeutic targets. *MYCN* amplification and increased *MYCN* expression drive deregulated hyper-transcription that leads to development and growth of NB tumors, and *MYCN* amplifications, which can be found both within the linear genome on homogenously staining regions (HSR) and on circular extrachromosomal DNA (ecDNA), are associated with significantly worse survival rates for children with NB. *MYCN* overexpression has been linked to an increase in replication stress (RS), and RS and subsequent genome instability are important drivers of tumor initiation and progression. Flap Endonuclease 1 (FEN1), a non-essential DNA replication enzyme, was identified as a synthetic lethal target in *BRCA1/2*-deficient cancers via induction of RS. Recent success of targeting RS-elevated cancers with replication enzyme inhibitors opens a new avenue to target *MYCN*-amplified NB. **Methods:** Associations of gene expression with patient survival and prognostic features were performed on available neuroblastoma tumor databases using the R2 Genomics Analysis and Visualization Platform. The efficacy of FEN1 inhibition was assessed using live cell imaging and cell viability assays, comparing results in *MYCN*-amplified to -nonamplified NB cells and in NB cells with inducible *MYCN* expression and repression. Mechanisms of cell death and impacts on replication stress in cells treated with FEN1 inhibitors were evaluated by Western blots. **Results:** We have found that *FEN1* expression levels are associated with NB patient outcomes and with features of high-risk disease, including tumor stage and *MYCN* amplification. FEN1 inhibition was effective against NB cells and was significantly more effective in HSR-*MYCN*-amplified NB cells, but not ecDNA-MYCN amplified NB cells, with reduced cell growth and viability. Increased *MYCN* expression also led to increased sensitivity to FEN1 inhibition, and reduced MYCN expression reduced sensitivity. FEN1 inhibition led to the induction of apoptosis but not necroptosis in NB cells and responses to FEN1 inhibition were associated with markers of replication stress, including activation of the ATR-CHK1 and ATM-CHK2 pathways. **Conclusions:** We have discovered that HSR-mediated *MYCN*-amplified NB cells are hypersensitive to FEN1 inhibition, suggesting that FEN1 inhibition may be a promising therapeutic strategy for children with high-risk and relapsed NB. Research Sponsor: None.

MTAP deletions and co-mutational landscape from whole genome sequencing in primary CNS tumors.

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Background: Biallelic deletions of the *MTAP* (methylthioadenosine phosphorylase) gene are frequent in solid tumors and confer synthetic lethality to PRMT5 (protein arginine methyltransferase 5) inhibition. Clinical trials are exploring the safety and efficacy of PRMT5 inhibitors (PRMT5i). Targeting additional co-occurring actionable alterations, such as gain-of-function mutations, with kinase inhibitors in combination with *MTAP*-directed synthetic lethality may potentiate therapeutic efficacy. *MTAP* deletions are present in up to 40% of glioblastomas (GBM) and occur sporadically in other primary central nervous system (CNS) tumors. Identification of actionable targets beyond *MTAP* deletions could enable combination strategies in these diagnoses, with otherwise limited therapeutic options. Whole-genome sequencing (WGS) with exon-level copy number alteration (CNA) analysis allows accurate determination of *MTAP* status, assessment of concordance with copy number variations (CNVs) in the neighboring *CDKN2A* and *CDKN2B* genes, and evaluation of the prevalence of co-occurring actionable alterations (including *IDH1, KRAS, PIK3CA, FGFR,* and *NTRK* alterations).
Methods: A total of 145 consecutive patients with primary WHO grade 4 gliomas or other primary CNS tumors underwent WGS at the time of diagnosis as part of the prospective Neurogenome Study at Copenhagen University Hospital between January 2023 and October 2025. 57 patients (39%) were female, and the median age was 59 years (range, 26–78). *MGMT* promoter methylation was detected in 59 patients (40.4%); 6 tumors were not evaluable for *MGMT* status. 130 cases (GBM, n=118; astrocytoma, *IDH*-mutant, n=12) had reliable *MTAP* copy number analysis, samples with e.g. high fraction of normal tissue where excluded from analysis.
Results: Among the 130 evaluable cases, 52 (40%) harbored biallelic *MTAP* deletions, 37 (28%) had monoallelic deletions, and 39 (30%) had no *MTAP* deletions. 2 cases (1.5%) had deletion of one *MTAP* allele with partial deletion of the second allele (exon-level deletions). Concordance between *MTAP* CNVs and *CDKN2A/B* CNVs—defined as either biallelic deletion or non-biallelic deletion of both *MTAP* and *CDKN2A/B* genes—was observed in 113 of 130 cases (87%). 31 cases harbored additional potentially actionable alterations. In tumors with biallelic *MTAP* deletions, 9 cases contained co-occurring actionable targets (*FGFR* fusion 1; *KRAS* mutation 1; *NTRK* fusion 1; *PIK3CA* mutation 4; *IDH1* + *PIKCA3* mutations 1; *IDH1* mutation + *PTPRZ1-MET* fusion 1).
Conclusions: *MTAP* biallelic deletions were frequent at diagnosis in this primary CNS tumor population, whereas partial deletions of the *MTAP* gene (exon deletions) were rare. High concordance with *CDKN2A/B* status on WGS was observed. A subset of cases with biallelic *MTAP* deletions harbored other actionable targets underscoring the potential for combining PRMT5i with other targeted agents. Research Sponsor: None.

Virtual AI-informed immunocyte profiling (VAIP) from H&E as a predictor of multi-cancer prognosis.

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Background: Improved risk stratification is critically needed across multiple cancers to guide treatment decisions. This includes reducing overtreatment in Ductal Carcinoma in Situ (DCIS), addressing late recurrence risk in estrogen receptor-positive/lymph node-negative (ER+/LN-) breast cancer (BC), and refining prognosis in head & neck squamous cell carcinomas (HNSCC), and high-grade serous ovarian carcinoma (HGSOC). Tumor-infiltrating lymphocytes (TILs) reflect anti-tumor immunity, whereas tumor-associated macrophages (TAMs) polarize toward anti-tumor M1-like (CD68+) or immunosuppressive M2-like (CD163+) phenotypes. Integrating TILs with TAM polarization markers may better capture inflammatory balance and improve outcome prediction. We developed a hematoxylin and eosin (H&E)-only AI method (VAIP) to quantify TILs and virtual CD68/CD163 TAMs to develop multi-cancer based potential prognostic models. **Methods:** TILs were detected on H&E with HoVer-UNet, and virtual CD68 and CD163 macrophages were inferred with VISTA. In cancer regions, we computed cell densities and immune-balance ratios and trained cancer-specific Cox models with compact feature sets (DCIS 6; HGSOC 7; ER+ 4; HNSCC 4). Prognostic stratification used disease-free survival (DFS) for DCIS (N=273), HGSOC (training N=165, independent test N=220), and ER+ BC (training N=144, test N=622), and overall survival (OS) for HNSCC (N=77), reflecting clinical endpoints. Evaluation used cross-validation for cohorts without an external test set (DCIS, HNSCC) and independent training and testing when independent cohort was available (HGSOC, ER+). **Results:** Risk stratification performance across cancer types is in Table 1. The DCIS model used 6 features, largely TIL-macrophage contrast ratios (TIL/M2, TIL/M1). HGSOC used 7 features with a similar ratio-heavy immune-balance signature, plus macrophage-normalized density and polarization metrics (e.g., M1/N, M/N). In contrast, ER+ BC and HNSCC achieved best performance with 4 features dominated by macrophage measures, particularly M2 density and the M1/M2 ratio. Across sites, CD163-related macrophage metrics and immune-balance ratios were consistently informative. **Conclusions:** Integrating H&E-visible TILs with virtual CD68/CD163 TAMs enables fully automated, H&E-only prognostic biomarkers that stratify OS and DFS across multiple cancers, demonstrating consistent prognostic value in DCIS, ER+ BC, HGSOC, and HNSCC. These findings support further study of this histomorphometric risk classifier through broader external and prospective validation. Research Sponsor: None.

Performance across cancer types.

Cancer Type	Cohort	C-index	HR [95% CI]	p-value
DCIS	All	0.616	1.76 [1.20-2.59]	**<0.001**
DCIS	RT/No-treatment	0.624	1.94 [1.15-3.26]	**0.003**
HGSOC	Test	0.553	1.38 [1.02-1.87]	**0.030**
ER+ BC	Test	0.577	1.51 [1.00-2.28]	**0.004**
HNSCC	All	0.603	1.92 [1.03-3.36]	**0.012**

Spatial transcriptomic profiling of the tumor microenvironment associated with sunitinib response in metastatic renal cell carcinoma.

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Background: Metastatic clear cell renal cell carcinoma (ccRCC) exhibits heterogeneous clinical outcomes, and limited biomarkers are available to predict response to targeted therapies. This study evaluated cell compartment-specific transcriptional biomarkers predicting clinical response to the tyrosine kinase inhibitor (TKI) sunitinib. **Methods:** In this phase 2 single-arm clinical trial (NCT00715442), 46 patients with metastatic ccRCC received sunitinib pre- and post-cytoreductive nephrectomy. The primary endpoint was time-to-progression (TTP) and secondary endpoints included overall survival (OS) and sunitinib toxicity. To investigate spatial dynamics of therapeutic response to sunitinib, we applied whole-transcriptome digital spatial profiling (DSP) to tumor tissue to identify myeloid, endothelial, CD8+ T-cell and tumor compartment-specific transcriptional differences between responders (complete or partial response) and non-responders (stable or progressive disease). **Results:** For the 46 trial patients, the median duration of follow-up was 9.8 years (95% CI: 9.4 – NA). The median TTP was 8.2 months (95% CI: 6.1-19.3) and OS 36.3 months (95% CI: 19.7-70.5). Sunitinib-related adverse events occurred in 20% of patients, with grade 3 and 4 toxicities including hand-foot syndrome, fatigue, and hematologic abnormalities (thrombocytopenia, neutropenia). DSP analyses demonstrated that sunitinib responders display a tumor microenvironment enriched in pro-inflammatory and immunostimulatory programs. By contrast, non-responders displayed enrichment of immunosuppressive programs with elevated PD-L1 expression in myeloid cells and exhausted CD8+ T-cell signatures. Sunitinib resistance mechanisms involving pro-angiogenic VEGF-dependent and independent pathways were identified in non-responders, revealing potential therapeutic targets in combination with TKIs. Moreover, gene signatures developed based on DSP analysis of sunitinib response accurately predicted sunitinib response in an external patient cohort. **Conclusions:** Our findings underscore the relevance of spatial omics approaches to inform patient stratification and guide precision and combination treatment strategies aimed at mitigating TKI resistance in metastatic ccRCC. Clinical trial information: NCT00715442. Research Sponsor: The Ohio State University Comprehensive Cancer Center (Pelotonia Institute for Immuno-Oncology) Startup Funds; Society for Immunotherapy of Cancer - NanoString Technologies Single Cell Biology Award; Kidney Cancer Association Young Investigator Award; Pfizer.

Developing harmonized tumor microenvironment subtypes for patient stratification in clinical trials.

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Background: Accurate patient stratification by tumor microenvironment (TME) is critical for optimizing immunotherapy and targeted therapy outcomes. Existing transcriptome-based classification methods often focus on limited TME aspects and tumor types, restricting their clinical utility. Here, we developed a harmonized (H) TME classification by integrating findings from published pan-cancer TME profiling with reported immune evasion mechanisms. **Methods:** We used agglomerative clustering of gene signature scores (ssGSEA) and pathway activities (PROGENy) encompassing immune cells, fibrosis, vascularization, hypoxia, and other signals to acquire 9 transcriptomic HTME subtypes (Table 1) independently on TCGA (n=7,362) and internal (n=5,186) pan-cancer cohorts with high reproducibility (Spearman r=0.94). Next, we validated the subtypes on 29,875 solid cancer samples from open-source transcriptomic datasets by applying the K-Nearest Neighbors classifier. Differential expression analysis followed by Spearman correlation and PCA were used for comparison among classifications. Adjusted Cox models for survival and logistic regressions for response were applied. **Results:** Correlative analysis between existing classifications and HTME subtypes revealed patient stratification along 3 principal biological axes: adaptive immune response vs. tumor cell activity, fibrosis vs. antigen-presenting activity, and proliferation vs. vascularization, with, HTME uniquely covering all three axes. When applied to the selected clinical cohorts, HTME effectively distinguished patients by response (logOR) or progression-free survival (logHR) in a diagnosis- and therapy-specific manner (Table 1; showing values with p≤0.05). **Conclusions:** The proposed HTME patient stratification framework, publicly available and applicable to any RNA-seq sample, constitutes a practical tool for biomarker discovery and trial design across solid tumors. Research Sponsor: None.

logOR and logHR metrics of HTME subtypes based on diagnosis and treatment type.

	BRCA Basal-like, Luminal, Normal-like; ICI logOR [CI]	BRCA HER2+; anti-HER2 logOR [CI]	ccRCC; TKI PFS logHR [CI]	ccRCC; anti-VEGFR+ anti-PDL1 PFS logHR [CI]	ccRCC; anti-mTOR PFS logHR [CI]	SKCM; ICI logOR [CI]	NSCLC; ICI logOR [CI]
Lymphoid-Cell-Enriched							
B-Cell-Enriched/Angiogenic			-0.9 [-1.5, -0.3]**		-0.7 [-1.4, -0.1]*		1.1 [0.2, 2.0]*
Immune-Enriched/Hypoxic	-1.8 [-3.2, -0.4]*		0.6 [0.1, 1.0]**		1.1 [0.4, 1.8]**	-1.3 [-2.5, -0.1]*	
Highly Immune-Enriched/Inflamed	-2.9 [-5.3, -0.4]*	-1.5 [-2.3, -0.6]***			1.1 [0.2, 1.9]*	-2.1 [-3.6, -0.5]**	-1.1 [-1.9, -0.2]*
Immune-Enriched/Fibrotic			1.0 [0.5, 1.6]***				2.3 [0.6, 4.1]**
Fibrotic/Angiogenic/Myeloid				0.9 [0.4, 1.3]***			
Fibrotic/Hypoxic				1.4 [0.4, 2.5]**			
Immune Desert		0.8 [0.0, 1.5]*				1.2 [0.2, 2.2]*	0.6 [0.1, 1.2]*
Desert/Angiogenic		1.1 [0.1, 2.1]*	-0.6 [-1.1, -0.1]*				1.1 [0.1, 2.1]*

*p≤0.05; **p≤0.01; ***p≤0.001.

Identification of high-grade neuroendocrine carcinoma (HGNEC) biology across tumor types through transcriptomic profiling and validation in lung cancer.

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Background: HGNECs, including small-cell (SC) and large-cell (LCNEC), are aggressive malignancies frequently misclassified due to subtle morphology and inconsistent use of neuroendocrine (NE) immunohistochemistry in routine pathology workflows. It is unclear if tumors with transcriptomic signatures reflecting HGNEC-like biology have inferior outcomes with conventional treatment. Leveraging a large real-world dataset, this study aims to identify transcriptomically defined HGNEC to improve upon morphology-based classification. **Methods:** 49,144 specimens underwent DNA and RNA sequencing at Caris Life Sciences. Using a previously reported framework, we developed a weighted, z-scored based HGNEC activity score (HAS) from 10,137 pathologically defined HG- and LG- NEC specimens and applied it to characterize NSCLC samples (without any pathologist assigned HGNEC diagnosis) further stratified by histology (n=39,007). Overall survival (OS) was obtained from insurance claims data and calculated from specimen biopsy to last contact using Kaplan-Meier and Cox proportional hazards estimates. **Results:** To identify a high-confidence HGNEC-like subpopulation, a HAS threshold (z-score>=3) was applied, classifying 0.2% squamous (sq) and 2.3% non-squamous (nsq) as HGNEC-like; this analysis is focused in nsq. Patient demographics, including age, gender, race, ethnicity, and smoking history, were similar between the HGNEC-like and non-HGNEC-like nsq cohorts. However, biopsies from lymph nodes (26 vs 11%) and brain (9.1 vs 5.6%) were more frequent, and lung (39 vs 56%) less frequent in HGNEC-like tumors (all p-adj<0.05). HGNEC-like tumors were associated with poor OS (HR:1.18, 95% CI:1.07–1.31, p<0.001). HGNEC-like tumors were more frequently PD-L1 negative (64% vs 47%), and were enriched for mutations in *TP53*, *PTEN* and *RB1* (OR: 1.7-14.1), as well as amplifications in *MYC* and *CCNE* (OR: 2.2-3.5), with lower odds of *KRAS* and *EGFR* mutations (OR:0.4-0.5, p-adj<0.05). Consistent with a highly proliferative phenotype, HGNEC-like tumors were enriched for *MKI67* expression (1.4-fold) and higher cell-cycle and replication stress scores (1.5-fold) (all p-adj<0.05) . Gene set enrichment analysis revealed significant activation of neurodevelopmental programs (NES: 2.0-3.0, all p-adj<0.05) and negative enrichment of immune pathways (e.g antigen presentation) (NES: -3.0 to -1.5, all p-adj<0.05). Finally, transcriptomic expression of potentially actionable SCLC-directed targets, including *DLL3* (10-fold), *SEZ6* (3.7-fold), and *SSTR2* (10-fold), were all higher in HGNEC-like tumors (all p-adj<0.05). **Conclusions:** We identify a transcriptomically defined HGNEC-like subset of NSCLC with inferior survival and targetable NEC biology, supporting transcriptomic stratification to inform clinical trial design and selection of SCLC-directed therapies. Research Sponsor: None.

ILF2 as a predictor of cisplatin resistance and clinical outcomes in intrahepatic cholangiocarcinoma.

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Background: Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive biliary tract cancer with increasing global incidence and limited therapeutic options, partly due to the low prevalence of actionable genomic alterations such as *FGFR2* fusions (~10%) and *IDH1* mutations (~13%). Using single-cell transcriptomic analyses, we identified recurrent amplification at chromosome 1q21.3 as a dominant genomic alteration in iCCA tumor cells. Given our prior evidence linking 1q21.3 amplification to DNA damage–response (DDR) processes and chemotherapy resistance in multiple cancer types, we focused on Interleukin enhancer binding Factor 2 (ILF2), a gene within 1q21.3, and systematically evaluated its multi-omic features and clinical relevance in iCCA using multiple independent clinical datasets. **Methods:** Single-cell RNA sequencing datasets were analyzed using Single-Cell Variational Aneuploidy (SCEVAN) to identify recurrent chromosomal alterations. Bulk RNA and DNA sequencing datasets were assessed for *ILF2* copy number variation (CNV) and mRNA expression. Clinical validation was performed using independent iCCA cohorts from Keio University and SJCI (n=67) and a public dataset (GSE89748; n=49). *In vitro* assays validated the functional role of ILF2 in DDR and cisplatin sensitivity of iCCA cell lines (n=3). **Results:** SCEVAN analysis of GSE125449 (n=8) and GSE138709 (n=5) revealed that 1q21.3 was the only common highest amplified region of iCCA tumor cells (29.7% and 31.1%, respectively). TCGA-CHOL dataset (n=32) demonstrated that *ILF2* CNV amplification occurred in 46.7% of cases and was strongly correlated with increased *ILF2* mRNA expression ($r = 0.730$, $p < 0.001$), which was significantly higher in tumor tissue than normal liver tissue in iCCA patients ($p < 0.001$). In the iCCA validation cohort (n=67) and GSE89748 dataset (n=49), *ILF2* mRNA level upregulation was significantly associated with shorter recurrence-free survival (log-rank test; $p < 0.001$ and $p = 0.047$, respectively), and independently predicted recurrence risk (multivariate Cox regression analysis HR = 4.63, 95% CI 1.71 – 12.6, $p = 0.003$ and HR = 2.73, 95% CI 1.10 – 6.80, $p = 0.031$, respectively). Consistently, ILF2 protein expression as assessed by multiplex immunofluorescence was significantly lower in FFPE tumor tissues from cisplatin responders than non-responders of iCCA patients ($p < 0.001$, n=16). Across iCCA cell lines, ILF2 interacted with DDR–related factors to suppress R-loop and γH2AX activities; both events are involved in promoting cisplatin resistance. **Conclusions:** *ILF2* is a frequent novel functional gene strongly associated with adverse clinical outcomes and cisplatin resistance of iCCA. This supports its role as a clinically relevant and theranostic biomarker related to DDR in iCCA patients. Research Sponsor: None.

Target-specific therapy for actionable and approved tumor-agnostic biomarkers: Influence on survival in rare cancers.

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Background: Rare cancers - defined as an incidence rate of less than 6 per 100,000 diagnoses per year - collectively account for close to 25% of cancer burden and represent a critical unmet clinical need. The emergence of regulatory approvals for tumor-agnostic therapies based on genomic biomarkers has expanded treatment options for these patients (pts) but clinical sequencing is not yet broadly adopted for rare cancers. Here, we assess the incidence and clinical utility of FDA-approved tumor-agnostic biomarkers in a large real-world rare cancers cohort. **Methods:** The Tempus Lens Platform used to query the de-identified Tempus multimodal database to analyze a cohort of 45,085 real-world pts with 615 rare cancer diagnoses. All pts had DNA (Tempus xT) and/or RNA sequencing (Tempus xR). Pts were screened for FDA-approved tumor-agnostic biomarkers, including high tumor mutational burden (TMB-H, $\geq$ 10 mut/Mb), high microsatellite instability (MSI-H), NTRK and/or RET fusions, BRAFV600E mutations and HER2 overexpression (IHC-3+). Pts were classified based on their reported biomarker status and treatment start of the approved targeted therapy relative to the FDA-approval date. Real-world overall survival (rwOS) was defined as the time from sample collection to death or loss to follow-up. Hazard ratios (HR) from Cox-proportional hazards models were adjusted for age, sex, race, ethnicity, and stage at $p<0.05$ (Wald test). **Results:** The median age of pts was 64 years old, 59% were female, 50% of those with documented race were white and 36% had metastatic disease. The most common diagnoses were within the genital system (25%), digestive system (23%), soft tissue (12%), brain (11%) and lung (6.5%). Of the total cohort, 13% (5,881) were positive for at least one tumor-agnostic biomarker. TMB-H was the most prevalent (10.3%), followed by HER2+ (5.5%), BRAFV600E (2.6%), MSI-H (1.9%), NTRK (0.5%) and RET (0.2%) fusions. Of 59% (3,480) of pts with recorded treatments, 33% (1,138) received the approved treatment following the approval date (tumor-agnostic biomarker-positive matched) while 64% (2,227) received other treatments (tumor-agnostic biomarker-positive unmatched). Pts with tumor-agnostic biomarker-positive matched treatments had significantly improved rwOS compared to tumor-agnostic biomarker-positive unmatched pts (HR=0.8, p=0.024) and to tumor-agnostic biomarker-negative individuals (HR=0.68, $p<0.001$). **Conclusions:** A large percent (13%) of pts with rare cancer diagnoses were found to harbor an actionable biomarker associated with an FDA-approved tumor-agnostic therapy. Pts who received therapies for approved tumor-agnostic biomarkers versus those pts with the biomarker who did not receive the matched treatment demonstrated a significant survival benefit, underscoring the importance of NGS testing to optimize treatment selection for rare cancer pts. Research Sponsor: None.

Pan-cancer computational analysis of adaptive immune and vascular changes in primary versus metastatic tumors.

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Background: Metastasis drives cancer mortality, yet tumor microenvironment (TME) evolution during systemic spread remains poorly understood. Current paradigms often assume uniform immunosuppression at metastatic sites or seek a universal pro-metastatic signature. We investigated whether a conserved immune signature exists across metastatic sites or if remodeling follows tissue-specific trajectories that could inform precision therapeutic strategies. **Methods:** We performed computational meta-analysis from TCGA using xCell enrichment scores across >20,000 transcriptomic samples from primary tumors and distant metastases in five solid tumor types: Lung (n=1,622), Breast (n=1,543), Kidney (n=1,541), Brain (n=1,243), and Thyroid (n=1,016). Mann-Whitney U testing with Bonferroni correction identified cell populations with differential enrichment (padj$<$0.05). Cohorts were balanced for age, gender, and race (all p$>$0.05). **Results:** We identified two convergent metastatic trajectories with opposite directional changes in a four-cell plasticity module: B-cells, class-switched memory B-cells, CD4+ effector memory T-cells, and platelets. The Immune-Vascular Acquisition Trajectory (Breast, Brain, Thyroid) showed metastatic enrichment of all four cell types (Mean Difference [Primary-Metastatic]: -0.62; padj$<$0.001). The Immune-Vascular Depletion Trajectory (Lung, Kidney) showed significant depletion of all four populations at metastatic sites (Mean Difference [Primary-Metastatic]: +0.74; padj$<$0.001). Platelet dynamics consistently mirrored adaptive immune trajectories across all cancer types. **Conclusions:** These findings challenge two prevailing assumptions: uniform immunosuppression at metastatic sites and a single universal pro-metastatic immune signature. Instead, metastatic immune remodeling follows organ-specific convergent trajectories driven by adaptive and vascular plasticity. The identification of shared trajectories among biologically distinct cancers suggests that metastatic site microenvironment dictates TME evolution. The de novo acquisition of immune signatures in brain metastases challenges the "immunologically cold metastasis" paradigm, while depletion in naturally immunogenic tumors (Lung, Kidney) indicates TME "cooling" for immune evasion. The invariant coupling of platelet and adaptive immune dynamics highlights vascular remodeling as critical to metastatic niche establishment. These distinct trajectories may explain differential responses to immunotherapy and anti-angiogenic agents across metastatic sites, supporting the need for organ-specific therapeutic strategies. Future studies are needed to investigate whether primary tumors harbor early signatures of this module predictive of metastatic trajectory, enabling stratified surveillance and intervention. Research Sponsor: None.

Pan-cancer prevalence, molecular landscape, and prognostic impact of *CCNE1* amplification across 76,046 malignancies.

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Background: *CCNE1* amplification (*CCNE1*amp) is an oncogenic driver that confers synthetic-lethal vulnerability to agents targeting cell cycle and replication stress. While *CCNE1*amp is a poor prognostic marker in some solid tumor types, pan-tumor data are limited. We used the MSK Clinical Sequencing Cohort to characterize its pan-tumor prevalence, molecular landscape, and prognostic impact. **Methods:** We analyzed data from consented patients with solid tumors sequenced by MSK-IMPACT between July 2014 and August 2025. *CCNE1*amp was defined as an amplification or gain per clinical report. Tumor-level prevalence was calculated and reported for histologies with ≥10 CCNE1amp tumors. Co-occurring alterations were evaluated using the first *CCNE1*amp sample per tumor type in each patient, with Fisher's exact test and Benjamini-Hochberg correction. Overall survival was measured from the date of first sequencing to death or last contact. **Results:** Among 76,046 tumors, the prevalence of CCNE1amp was 2.7% (n = 2,036). Our *CCNE1*amp cohort comprised predominantly ovarian (21%, n=435), uterine (15%, n=301), non-small cell lung (11%, n=231), esophagogastric (10%, n=206), and breast cancers (8%, n=168). Prevalence rates were highest in uterine carcinosarcoma (25.6%); ovarian carcinosarcoma (20%); uterine serous carcinoma (16.2%); high-grade serous ovarian carcinoma (15.4%); osteosarcoma (11.9%); gallbladder adenocarcinoma (9.7%); and esophageal adenocarcinoma (9.1%). Prevalence rates in breast cancer were 2.1% and in non-small cell lung cancer 2.6%. Among 67 patients with paired pre- and post-treatment samples of purity ≥30%, *CCNE1*amp was reported in all samples in 42% of patients. The most frequently co-mutated genes were *TP53* (87%), *PIK3CA* (12%), *KRAS* (8%), and *RB1* (7%). Most common amplifications included the 19q neighbors *CEBPA* (31%), *KMT2B* (22%), and *AKT2* (22%); as well as *MYC* (14%); and *ERBB2* (13%). The most significant co-occurrences ($q<0.05$) were *TP53* mutations (OR 11.5) and *MYC* amplifications (OR 3.5); CCNE1amp was mutually exclusive with *PTEN* (OR 0.37) and *KRAS* mutations (OR 0.55). CCNE1amp samples had a higher median fraction of genome altered (median 0.35 vs. 0.12; $p<0.001$). *CCNE1*amp was associated with worsened overall survival in a multivariate Cox model stratified by cancer type and adjusted for age, stage and *TP53* status (adjusted HR 1.25; 95% CI 1.17-1.33). Its adverse prognostic impact was more pronounced in *TP53*wt (HR 1.62; 95% CI 1.38-1.91) vs. *TP53*mut tumors (HR 1.19; 95% CI 1.11-1.27; p for interaction <0.001). **Conclusions:** *CCNE1* amplification defines a pan-cancer genomic subset associated with poor prognosis, genomic instability, and few co-occurring actionable alterations, supporting its relevance as a therapeutic target. Discordance between paired samples suggests that a single negative biopsy may not rule out CCNE1amp. Research Sponsor: Memorial Sloan Kettering Cancer Center NCI Support Grant (P30 CA008748).

Early-onset cancer signature (EOCS): Pan-cancer molecular alterations with prognostic significance in early-onset (EOC) and late-onset (LOC) cancer.

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Background: Early-onset cancer (EOC) is an emerging global epidemic with biological and molecular features distinct from late-onset cancer (LOC). Improved delineation of genomic pathway aberrations in EOC is essential to inform risk stratification and therapeutic decision-making. However, large-scale, unbiased analyses of biological drivers across tumour types remain limited. To address this gap, we developed a pan-cancer Early-Onset Cancer Signature (EOCS) to advance understanding of the genomic architecture underpinning EOC. **Methods:** The AACR GENIE v16 dataset comprising 241,551 tumour samples was analysed, including 22,408 early-onset cases (≤40 years) and 219,143 late-onset cases (≥41 years) from multiple international repositories. Differentially enriched genomic alterations and pathways between EOC and LOC were identified to define the EOCS. The EOCS was subsequently evaluated across TCGA pan-cancer datasets and validated in independent cohorts, including METABRIC (breast cancer), MSKCC colorectal cancer, and MSKCC prostate cancer datasets. **Results:** Analysis of the AACR GENIE cohort revealed that the most significantly enriched alterations in EOC compared with LOC were CCDC6 (20% vs 10%), SYNE1 (8% vs 6%), BRAF (9% vs 6%), FLI1 (19% vs 0.5%), and EML4 (8% vs 4%). In contrast, alterations significantly enriched in LOC included KRAS (15% vs 5%), TP53 (38% vs 29%), EGFR(15% vs 5%), STK11 (3% vs 1%), and CDKN2A (10% vs 6%). Gene set enrichment analysis of EOCS-associated genes identified DNA recombination, regulation of histone H3K9 trimethylation, and homologous recombination–mediated double-strand break repair as the top three enriched Gene Ontology pathways. The EOCS was altered in 30% (3,736/10,967) of TCGA pan-cancer samples, with the highest prevalence observed in endometrial, skin, carcinosarcoma, and gastric cancers. The most frequently altered genes included SYNE1(12%), CTNNB1 (4%), PPMD1 (3%), BCR (3%), ETV6 (3%), RAD52 (3%), and H3-3A (3%). Across TCGA pan-cancer and tumour-specific cohorts, EOCS alterations were consistently associated with inferior overall survival irrespective of age at diagnosis, including pan-cancer (68 vs 83 months; $p = 9.1 \times 10^{-3}$), breast cancer (142 vs 164 months; $p < 0.04$), colorectal cancer (45 vs 56 months; $p = 1.75 \times 10^{-4}$), and prostate cancer (56 vs 77 months; $p = 2.0 \times 10^{-4}$). **Conclusions:** This pan-cancer Early-Onset Cancer Signature identifies distinct genomic pathways driving tumourigenesis in EOC. The findings provide novel biological insights into disease pathogenesis and highlight potential diagnostic and therapeutic targets, supporting the clinical relevance of EOCS across multiple cancer types. Research Sponsor: None.

Clinical utility of whole transcriptome sequencing for fusion detection in advanced solid tumors: SCRUM-Japan MONSTAR-SCREEN-2.

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Background: Fusion variants represent established therapeutic targets in precision oncology yet are incompletely captured by conventional targeted DNA panel sequencing. Recent studies have reported that RNA sequencing enables detection of oncogenic fusions and structural variants that escape conventional DNA panel sequencing, particularly complex rearrangements occurring in intergenic regions. Herein, we evaluated the landscape of fusion variant detection by whole transcriptome sequencing (WTS) in advanced solid tumors from the SCRUM-Japan MONSTAR-SCREEN-2, a nationwide molecular profiling project. **Methods:** Patients with advanced solid tumors were enrolled; tumor tissues were profiled using whole exome/transcriptome sequencing (MI CancerSeek, Caris Life Sciences, Phoenix, AZ, USA). For fusion detection comparison, we performed an in silico analysis cross-referencing each fusion detected by WTS against publicly available information from conventional DNA panels including both target gene lists and breakpoint information where available, to evaluate theoretical detectability. **Results:** Among 2,768 patients enrolled as of March 2024, WTS data from baseline tissue samples were available in 2,253 pts across 33 cancer subtypes: the most common subtypes were colorectal adenocarcinoma (n=520), gastric adenocarcinoma (n=306), breast cancer (n = 198), prostate cancer (n=177) and pancreatic cancer (n=156). Pathogenic gene fusions and structural variants were detected by WTS in 122 of the 2,253 patients (5.4%), with a total of 126 pathogenic fusions identified. Among 126 pathogenic fusions, 75 (59.5%) represented variants that would theoretically have escaped detection by targeted panel DNA sequencing methodologies, including druggable kinase fusions (FGFR2, FGFR3, and BRAF). Among 18 patients treated with kinase fusion-targeted therapy with evaluable response data, 1 (5.6%) showed complete response, 3 (16.7%) showed partial response and 11 (61.1%) showed stable disease. WTS identified a MYO5A-BRAF fusion in a patient with melanoma that was undetectable by conventional DNA panel sequencing. Based on this finding, the patient received combination BRAF and MEK inhibitor therapy, achieving stable disease for four months, demonstrating the therapeutic relevance of WTS-guided treatment selection. **Conclusions:** WTS detected fusion variants at a high frequency, highlighting the importance of WTS in precision oncology. Clinical trial information: UMIN000043899. Research Sponsor: SCRUM-Japan Fund.

Pan-cancer *KRAS* atlas of 9,056 Chinese patients: Subtype-specific immuno-genomic profiling to guide G12C, G12D, and pan-*KRAS* strategies.

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Background: *KRAS* therapy is shifting from allele-specific inhibitors to pan-*KRAS* strategies. However, pivotal trials are largely Western, and Asian subtype-specific immunogenicity and co-mutation benchmarks remain limited. We present the largest pan-cancer Asian *KRAS* clinogenomic atlas to define these benchmarks and inform treatment selection and trial stratification for the pan-*KRAS* inhibitor era. **Methods:** We analyzed 9,056 Chinese patients with *KRAS* mutations across over 30 tumor types, including pancreatic 27.4%, colorectal 25.1%, NSCLC 20.8%, and biliary tract 10.0%. All underwent ~600 gene next generation sequencing profiling in a CAP/CLIA certified laboratory including all classes of genomic alterations with integrated analysis of clinical variables, treatment history, co-mutations, TMB, MSI, and PD-L1. **Results:** *KRAS* mutations clustered at four hotspot codons: G12 (80%), G13 (9%), Q61 (6%), and A146 (3%). Alleles were dominated by G12D (33.3%), G12V (22.8%), and G12C (11.8%), followed by G13D (7.8%) and G12R (4.6%), together covering 80.3% of patients. Overall, 55% carried non-G12C/D variants. More than one *KRAS* point mutations occurred in 1.8% of the patients and *KRAS* amplification in 2.5%. Co-mutations were common, led by *TP53* (61.7%), *APC* (22.2%), *SMAD4* (17.9%), *CDKN2A* (17.1%), *PIK3CA* (12.5%), *ARID1A* (11.9%), and *STK11* (7.7%). TMB in 98.5% (median 4.0 mut/Mb) with 19.2% TMB-high (≥10 mut/Mb), MSI in 97.4% with 3.5% MSI-H, and PD-L1 in 58.0% with 49.5% positive expression. Subtype patterns were distinct. G12C had the highest TMB-high rate (42.4%) with rare MSI-H (0.8%), supporting targeted inhibition with rational IO combination evaluation. In contrast, G13D showed an Asian-enriched immunogenic phenotype with MSI-H 16.1%, higher than Western benchmarks (7.9%, $P<0.001$), and elevated TMB-high (30.8%). Clinically relevant stratification emerged in NSCLC G12C, with 82.5% male predominance versus about 40% in Western populations ($P<0.0001$) and an age gradient consistent with smoking (67% male <50 years rising to 89% at ≥70 years). Adverse co-mutations were enriched in G12C, including *STK11* (14.4%) and *KEAP1* (9.1%). Multi-*KRAS* mutations were strongly associated with MSI-H (OR 5.48, $P<0.0001$). Conversely, G12R showed an immune-cold profile (TMB-high 3.2%, MSI-H 0.2%), supporting reliance on targeted inhibition rather than IO-based approaches. Nineteen percent of patients were treatment-naive at profiling, most commonly in NSCLC (30%). Versus post-treatment cases, treatment-naive patients were enriched for G12C (15.9% vs 10.4%, $P<0.0001$) and showed higher TMB and PD-L1positives. **Conclusions:** This largest Asian *KRAS* atlas defines actionable benchmarks for precision therapy and provides a molecular rationale for region-specific stratification in global pan-*KRAS* trials. Research Sponsor: None.

3129 Poster Session

Tumor and immune microenvironment remodeling with neoadjuvant trastuzumab deruxtecan in HER2-positive gastric cancer: Exploratory analyses from the phase 2 EPOC2003 study.

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Background: We previously reported the efficacy and safety of neoadjuvant trastuzumab deruxtecan (T-DXd) for HER2-positive gastric and gastroesophageal junction adenocarcinoma (EPOC2003) (Takahari et al., ASCO GI 2024). This exploratory analysis aimed to investigate the associations of baseline molecular features of the tumor, the immune landscape, and their longitudinal changes with the therapeutic efficacy of T-DXd. **Methods:** Tumor samples were collected at baseline, pre-cycle 2, post-cycle 3 (before surgery), and at surgery. We performed bulk/single-cell RNA sequencing (scRNA-seq) and multiplex immunohistochemistry to identify correlates of pathological response. Responders were defined as patients achieving a major pathological response according to the Becker criteria. Blood samples were collected at baseline and post-cycle 3 for circulating tumor DNA (ctDNA) analysis using a clinically validated, tumor-informed, personalized assay (Signatera, Natera, Inc.). **Results:** Baseline HER2 expression did not differ between responders (n= 4) and non-responders (n= 22). In the post-treatment sample analysis, a decreasing trend in proliferation index was observed in responders, whereas this trend was not observed in non-responders, suggesting preferential elimination of proliferative tumor cells by T-DXd. Early on-treatment samples (pre-cycle 2 or post cycle 3) tended to demonstrate upregulation of cytokine signaling, inflammatory, immune response signatures, and CD8+ T cell density in both tumor and stroma regardless of response. Notably, scRNA-seq revealed an expansion of neutrophils, which was more pronounced in responders with a stronger baseline interferon signature. These post-treatment neutrophils displayed upregulated migration, phagocytosis, and degranulation signatures, indicative of enhanced neutrophil mediated anti-tumor activity following T-DXd. ctDNA testing was performed in 18 patients, with a baseline positivity rate of 94.4% (17/18). All responders (3/3) achieved ctDNA clearance after cycle 3, compared with only 35.7% (5/14) of non-responders. **Conclusions:** Neoadjuvant T-DXd therapy induced biological remodeling of the tumor and immune microenvironment. Together with on-treatment ctDNA kinetics, these findings suggest distinct response-associated biological patterns and may help guide future treatment optimization for HER2-positive gastric and gastroesophageal junction adenocarcinoma. Clinical trial information: NCT05034887. Research Sponsor: Daiichi Sankyo.

APOBEC mutational signatures to predict immune checkpoint inhibitor benefit in TMB-low metastatic NSCLC independent of PD-L1 status.

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Background: Most metastatic non-small cell lung cancer (NSCLC) patients are tumor mutational burden (TMB)-low (<10 mut/Mb) and lack validated biomarkers to guide immune checkpoint inhibitor (ICI) use beyond PD-L1 expression. APOBEC mutagenesis, characterized by distinct mutational signatures, has been linked to ICI response in urothelial and head and neck cancers – but primarily in TMB-high tumors. Whether APOBEC activity predicts ICI benefit specifically in TMB-low NSCLC, independent of PD-L1 status, remains unclear. **Methods:** We analyzed a discovery cohort of 857 metastatic TMB-low NSCLC patients treated with ICI from the MSK-CHORD cohort. To distinguish predictive from prognostic effects, we examined 1,328 ICI-untreated TMB-low metastatic NSCLC patients as controls. Findings were validated in an independent cohort of 82 TMB-low, ICI-treated stage IV NSCLC patients using whole exome sequencing (WES). APOBEC positivity was determined using MESiCA, a validated machine-learning algorithm designed to detect mutational signatures from targeted gene panels with low mutation counts (≥4 mutations). Primary endpoints were overall survival (OS) and disease control rate (DCR) in the discovery cohort, and progression-free survival (PFS) and objective response rate (ORR) in the validation cohort. Multivariate Cox regression adjusted for PD-L1 status and age. **Results:** In the discovery cohort, APOBEC-positive (n=52, 6.1%) and APOBEC-negative (n=805) patients were balanced for sex (44% vs 46% male), histology (83% vs 79% adenocarcinoma), and PD-L1 status (40% vs 40%; all p>0.05); APOBEC-positive patients were younger (median 64 vs 69 years, p=0.002). The APOBEC-positive group demonstrated significantly improved OS (median 33.7 vs 17.4 months; HR=0.60; 95% CI, 0.42–0.85; p=0.004). The survival benefit was absent in ICI-untreated patients (HR=0.98; 95% CI, 0.76–1.26; p=0.85). Formal interaction testing confirmed that the APOBEC benefit was specific to ICI-treated patients (interaction HR=0.62; p=0.032). APOBEC-positive tumors demonstrated higher DCR at 180 days (21.4% vs 7.6%; OR=3.32; p=0.006). In multivariate analysis adjusting for PD-L1 and age, APOBEC remained independently predictive (HR=0.57; 95% CI, 0.40–0.81; p=0.002). In the validation cohort, APOBEC independently predicted superior PFS (HR=0.23; 95% CI, 0.05–0.94; p=0.020) after adjusting for PD-L1, with numerically higher ORR (55.6% vs 25.4%, p=0.068). **Conclusions:** APOBEC mutational signatures represent a robust, independently validated predictive biomarker for ICI response in TMB-low metastatic NSCLC. Unlike prior studies linking APOBEC predominantly to TMB-high tumors, we demonstrate clinical utility specifically in the TMB-low population, where predictive biomarkers are most needed. This biomarker could expand immunotherapy access for NSCLC patients. Research Sponsor: None.

Dynamics of nectin-4 (N4) expression in urothelial carcinoma (UC): Across disease states.

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Background: Enfortumab vedotin (EV), which targets N4, has revolutionized advanced UC management. Despite high prevalence of N4 in UC, the temporal stability of N4 is poorly characterized. Conflicting reports describe both decreased and increased expression in metastatic (met) UC compared to primary tumors raising uncertainty as to whether changes reflect antigen loss or quantitative modulation—an issue central to resistance to EV. **Methods:** This single-center retrospective study identified pts with met UC who received treatment (trt) with EV. Demographic, clinicopathologic, trt and survival data (from time of met diagnosis) were recorded. N4 expression was evaluated via immunohistochemistry (IHC) (N4 Clone EPR15163-68) H-Score in available primary (TURBT, cystectomy/nephroureterectomy) and met tissue. H-Score was assessed as N4 positive (+) vs negative (neg,-) (>0 vs 0) and ordinally (neg, low <100, medium 100-200, high >200). Concordance between specimen pairs was assessed using percent agreement, McNemar's test, and weighted Cohen's kappa. Overall survival (OS) was evaluated via Kaplan–Meier methods and exploratory Cox regression. **Results:** We identified 141 pts (median age 70; 71% male; primary: bladder (83%), upper tract (15%), synchronous (2.1%), unknown (0.7%). 93% of primary tumors were N4+ (n=44). In matched TURBT-Cystectomy pairs (n=21), binary status was stable (95% agreement), but ordinal concordance was poor (27% agreement, $\kappa = -0.05$) and significant antigenic dampening was observed: High N4 expression decreased from 90% at TURBT to 29% at cystectomy, with a reciprocal increase in medium-level expression from 10% to 48% ($p<0.001$). 89% of met sites (n=27) were N4+. There were no differences in receipt of prior neoadjuvant chemotherapy (NAC) or 1st line trt between met N4+ and N4- groups. In matched cystectomy and metastases pairs (n=11), binary N4 concordance remained high (82% agreement) with poor ordinal concordance (27% agreement, p=0.12). Neither binary nor ordinal metastatic expression, nor changes in H-score over time, were associated with OS. There were no differences in OS in binary met N4+ vs N4- (p=0.82) nor ordinally classified groups (p=0.43). **Conclusions:** N4 is a stable binary target in UC, maintaining positivity across primary and metastatic sites despite significant quantitative dampening in expression intensity. These findings, although exploratory suggest that tumor evolution and therapeutic resistance may be characterized by dynamic antigen density modulation rather than categorical loss, an interpretation that may help reconcile prior discordant reports of expression changes in metastatic disease. Future studies should evaluate whether the degree of H-score shift (rather than absolute value) correlates with the durability of response to EV as well as the impact of neoadjuvant and subsequent sequential treatments on N4 expression intensity. Research Sponsor: None.

Implementing clinical-scale multiscale spatial transcriptomics: Tumor architecture profiling in SCRUM-Japan MONSTAR-SCREEN-3.

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Background: Spatial interactions between tumor cells and the tumor microenvironment (TME) influence disease progression, yet current diagnostic profiling lacks spatial resolution. A clinically implementable framework enabling cross-cancer spatial characterization using pretreatment clinical specimens is needed. SCRUM-Japan MONSTAR-SCREEN-3 (MONSTAR3) is an ongoing prospective clinical screening platform enrolling over 3,200 patients with solid tumors, integrating clinical annotation with multi-omic. We report an intermediate analysis validating the feasibility of extracting reproducible spatial phenotypes from pretreatment specimens at clinical scale. **Methods:** Spatial transcriptomics (Xenium 5K) was performed on 331 pretreatment FFPE tumor specimens from 309 patients representing ≥15 solid cancer types enrolled in MONSTAR3. Specimens obtained at diagnosis or prior to systemic therapy included unresectable advanced and curative-intent settings. Analyses examined spatial organization of tumor–immune interactions at the TME level, cancer cell functional states, neighborhoods, and tertiary lymphoid structures. Spatial features were systematically compared across cancer types and disease settings without treatment outcomes. **Results:** We generated a spatial atlas comprising approximately 20 million cells with high-confidence annotation across over 15 cancer types, representing one of the largest clinically annotated pan-cancer spatial transcriptomic resources to date. The atlas captures tumor-microenvironment organization, cancer-intrinsic functional heterogeneity, conserved cellular niches, and specialized immune structures including tertiary lymphoid structures with defined maturation states. Spatial tumor architecture varies substantially across cancer types despite similar cellular composition, underscoring value of spatially-resolved profiling beyond conventional cell-type quantification. Analysis across disease stages revealed that advanced tumors exhibit higher spatial compartmentalization of cancer functional states, with immunogenic and proliferative cancer populations showing consistent spatial separation across cancer types. Pan-cancer niche analysis identified conserved cellular neighborhoods, a subset of which showed stage-specific enrichment or prognostic associations. We also performed detailed spatial characterization of tertiary lymphoid structures, which demonstrated association with immunotherapy response in an independent cohort. **Conclusions:** We present a large-scale pan-cancer spatial atlas integrated within a nationwide precision oncology framework. This resource enables systematic investigation of spatial tumor biology and nominates spatially-defined features as candidate biomarkers for patient stratification and therapeutic response studies. Research Sponsor: None.

AACR GENIE analysis of 211,526 patients to evaluate hormone receptor alterations across solid tumors: Rationale for tissue-agnostic basket trials.

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Background: Steroid Hormone receptors (HR) that include estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) were oncology's first predictive biomarkers, yet HR-directed therapies remain largely confined to breast, prostate, and endometrial cancers. Emerging data suggest broader HR relevance across tumor types. The development of oral SERDs (selective ER degraders) and next-generation AR degraders/antagonists creates new opportunities to target HR alterations across tumor types. We performed pan-cancer genomic profiling to define the landscape of ESR1/AR alterations and resistance co-alterations, providing rationale for biomarker-enriched basket trial designs. **Methods:** We analyzed the AACR Project GENIE v18 public dataset, comprising 250,018 tumor samples from 211,526 patients across multiple solid tumor types. Genomic alterations in ESR1 and AR were assessed, including mutations, copy-number alterations, and structural variants. Co-alterations with selected genes involved in resistance and cell-cycle regulation (PIK3CA, PTEN, AKT1, TP53, RB1, CDKN2A) were evaluated using pairwise co-occurrence analyses. **Results:** Across 250,018 solid tumor samples, ESR1 alterations were identified in 2.0% of cases, with highest prevalence in breast (8.4%) and endometrial cancers (4.6%), and lower frequencies in uterine sarcoma (2.7%) and melanoma (3.6%). Most ESR1 alterations were missense mutations localized to the ligand-binding domain, with recurrent hotspots at codons Y537 and D538. AR alterations were present in 2.4% of samples overall, most frequently in prostate cancer (7.6%), and were also detected in endometrial cancer (5.5%), lung cancer (~5%), and melanoma (4.9%). AR alterations consisted predominantly of copy-number amplifications, with additional ligand-binding domain mutations observed. Co-alteration analyses demonstrated frequent co-occurrence of ESR1 with PIK3CA, PTEN, and AKT1, and AR with TP53, RB1, and CDKN2A, whereas ESR1 and KRAS alterations did not significantly co-occur. **Conclusions:** Recurrent ESR1 and AR alterations occur in 2-5% of diverse solid tumors beyond breast, prostate, and endometrial cancers, with co-enrichment of PI3K-AKT and cell-cycle pathway alterations mirroring resistance patterns in canonical HR-driven malignancies. These findings support systematic evaluation of selective ER and AR degraders in biomarker-selected basket trials, expanding precision oncology beyond anatomically-defined indications. Research Sponsor: None.

Impact of first-line comprehensive genomic profiling on survival outcomes for patients with advanced solid tumors who received molecularly-matched therapies: 3-year follow-up of the prospective FIRST-Dx study.

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Background: Comprehensive genomic profiling (CGP) by next-generation sequencing has been reimbursed in Japan since 2019. However, only 8.2% of patients (pts) had received molecularly-matched treatments. One major reason for this limited drug accessibility is that CGP is covered only after progression with standard of care (SoC). We previously reported that first-line CGP using FoundationOne CDx in advanced solid tumors (FIRST-Dx study) could identify molecular-based recommended therapy (MBRT) for 61% of pts (105/172), and 22.7% (39/172) could be treated by MBRT (JAMA Netw Open 2023, Cancer Sci 2025). To evaluate the impact of the first-line CGP test on survival outcomes, a 3-year follow-up analysis was conducted. **Methods:** The FIRST-Dx study was a multi-institutional prospective study in Japan. A total of 172 chemotherapy-naïve adult pts with advanced solid tumors (GI, Lung, Breast, GYN, Melanoma) and ECOG performance status of 0-1 were registered. This follow-up study was planned for 3 years after the final patient enrollment. The primary endpoint was overall survival (OS). Secondary endpoints were the proportion of pts receiving MBRT, overall response rate, progression-free survival (PFS), and PFS ratio (PFS on MBRT/PFS on prior therapy). **Results:** Median follow-up period was 25.0 months (0.5–45.2). Forty-six pts (26.7%) received MBRT. The number of pts treated with MBRT was 21 in the 1st-line, 22 in the 2nd-line, 6 in the 3rd-line, and 6 in the 4th-line or later setting. Median OS was significantly longer in pts treated with MBRT (not reached) than in those who did not receive MBRT (26.2 months, HR 0.62 [95% CI: 0.39–0.99], log-rank p=0.047). PFS and response rates were shown in Table. Among pts who received 2nd-line MBRT (N=15), the median PFS ratio (PFS on MBRT in 2nd-line/PFS on 1st-line therapy), was 1.2 (range: 0.4–14.6), and 7 pts (47%) achieved a PFS ratio of >1.3, indicating a clinically meaningful benefit of the first-line CGP based MBRT. In an exploratory analysis, propensity score matching (age, sex, cancer type) was performed between pts registered in this study and concurrent real-world pts who did not undergo the first-line CGP, resulting in 67 pts per group. Median OS was significantly longer in the FIRST-Dx group than in the real-world group (23.5 months vs 13.4 months, HR 0.61 [95% CI: 0.40–0.94], log-rank p=0.02). **Conclusions:** MBRT identified by CGP in the first-line setting improved access to targeted therapies and was associated with superior survival outcomes than SoC in advanced solid tumors. Our data suggest that CGP in Japan should be available prior to SoC initiation. Clinical trial information: jRCT1050220041. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

Median progression-free survival and response rate.

	MBRT	SoC	p-value
Median PFS (months)			
1st-line	13.7	11.3	0.04
2nd-line	11.0	5.6	<0.01
Response Rate (%)			
1st-line	52.4	37.8	0.24
2nd-line	45.5	13.2	<0.01

3135 Poster Session

Carcinomas of unknown primary treated with molecularly guided therapies and immune checkpoint inhibitors: A subset from the I-PREDICT N-of-1 Precision Oncology study.

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Background: Carcinoma of unknown primary (CUP) is a heterogenous group of aggressive malignancies lacking a detectable primary site and collectively comprises 3–5% of cancer diagnoses. Current treatments rely upon empiric chemotherapeutic regimens with high toxicity, limited efficacy, and historic median overall survival times of 3-11 months. There is emerging evidence to support a precision medicine approach using molecularly guided therapies and tumor-agnostic biomarkers. **Methods:** We performed a subset analysis of patients previously enrolled in the I-PREDICT (NCT02534675) study who had a CUP that was treated with a combination of targeted therapies and biomarker-driven immune checkpoint inhibitors (ICI), based upon comprehensive genomic profiling and recommendations by a Molecular Tumor Board. **Results:** Among the 210 evaluable patients, 10 (4.8%) had a CUP from which 9 were molecularly matched to one or more targeted therapies and an ICI based on biomarkers for both types of agents. Baseline characteristics include median age of 67 years (range: 59 – 82), with the majority of patients being male (5/9, 56%), non-Hispanic white (7/9, 78%) and treatment naïve (8/9, 89%). Histological subtypes of CUP included poorly differentiated or unspecified (5/9), adenocarcinoma (3/9) and squamous cell carcinoma (1/9). Administered targeted therapies included bevacizumab (4/9), trametinib (4/9), palbociclib (1/9), crizotinib (1/9), everolimus (1/9), and lenvatinib (1/9), while ICI included nivolumab (6/9), pembrolizumab (2/9) and atezolizumab (1/9). ICI were matched based on positive PD-L1 immunohistochemistry (IHC) (6/9), TMB ≥10 mutations/megabase (4/9), SWI/SNF chromatin remodeling gene alterations (3/9), PD-L1 amplification (1/9), mismatch repair gene alterations (1/9) and microsatellite instability-high (1/9). Most patients were matched to >1 ICI biomarker (5/9). Most patients received treatment doublets (6/9, 67%) while the remaining received triplet regimens (3/9, 33%). The best overall response rate was 44% based on RECIST 1.1. This included partial response (4/9), stable disease (3/9), progressive disease (1/9) and not restaged (1/9). Median progression free survival (PFS) was 10.4 months (95% confidence interval [CI] 4.2 - not estimable [NE]) and median overall survival was 16.9 months (95% CI 6.9 - NE). One patient in particular achieved 36-months of PFS on trametinib + nivolumab as matched to NF1 R440* and PD-L1 IHC 5%. Grade ≥3 treatment related serious adverse events occurred in only one patient. **Conclusions:** As compared to historic chemotherapy treated cohorts, these results support the safety and efficacy of administering molecularly guided combination therapies including a targeted agent plus an ICI in CUP patients. Larger prospective trials of biomarker-matched N-of-1 combinations in CUP are warranted. Clinical trial information: NCT02534675. Research Sponsor: None.

Association of treatment-induced decrease of tumor chromosome Y and prognosis.

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Background: Loss of chromosome Y (LOY) in cancer has been linked to increased mortality. Since tumors that are not completely eradicated often harbor additional molecular changes which may alter biological behavior, here we sought to examine if therapy has any impact on tumor chromosome Y content and if so, the relevance this has on patient outcome. Changes in chromosome Y content with therapy would impact clinical decision making in patients with persistent or recurrent tumors since tumors with LOY have also been shown to be more responsive to specific therapies. **Methods:** Male patients with >=2 sequential tumor samples profiled at Caris Life Sciences (Phoenix, AZ) who received systemic therapy between collections were included. RNASeq was performed using NovaSeq platform. Chromosome Y score (YChr score) was calculated using ssGSEA (log-rank normalization) based on a previously published 9-gene signature (*Nature* 2025). Change in YChr score between pre and post treatment paired samples (ΔYChr) was computed per patient. A decrease in YChr score in post sample compared to pre sample was defined as ΔYChr ≥0.029 (cohort mean) and called progressive LOY (pLOY) while the remainder were called no-pLOY. Real-world clinical data were obtained from insurance claims. Overall survival (OS) was defined from first sample collection to last contact. Hazard ratios (HRs) were estimated using Cox proportional hazards models, with log-rank p values reported. **Results:** Among 1,343 patients with paired samples, pLOY was associated with shorter OS compared with no-pLOY (median OS [mOS]: 33.2 vs. 36.0 months; HR 1.168, 95% CI 1.028–1.326; p=0.0167). Tumor-specific analyses demonstrated significantly worse OS in pLOY versus no-pLOY for colorectal cancer (CRC; N=124 vs. 157; mOS 38.9 vs. 50.6 months; HR 1.535, p=0.0038), bladder cancer (N=26 vs. 41; mOS 25.7 vs. 37.7 months; HR 1.992, p=0.0204), NSCLC (N=100 vs. 134; mOS 27.6 vs. 32.7 months; HR 1.379, p=0.0379), and gastric cancer (N=13 vs. 16; mOS 17.6 vs. 28.5 months; HR 2.603, p=0.0223), with a trend observed in melanoma (N=17 vs. 27; mOS: 31.4m vs. inf, HR: 2.231 [0.922-5.4], p=0.075). No association was observed in other tumor types. Treatment distributions for mentioned cancer types did not differ between pLOY and no-pLOY groups (p>0.05). Among CRC patients with primary-to-metastatic paired samples (57%), pLOY remained significantly associated with worse OS (mOS 39.5 vs. 56.3 months; HR 1.647; p=0.0112). pLOY was not associated with specific therapies or combinations across the full cohort. **Conclusions:** In a large real-world clinico-genomic cohort, longitudinal decrease in Chromosome Y score is independently associated with poor prognosis across multiple cancer types supporting further investigation into the biological and clinical relevance of Y chromosome loss and providing insights on novel treatment selection strategies. Research Sponsor: None.

Detection of mutational signatures in advanced cancer patients using clinical-grade specimens.

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Background: The underlying extrinsic and/or intrinsic mutational processes underlying tumor development lead to genome-wide "passenger" alterations that can be identified as mutational signatures. Mutational signatures are known to be both prognostic and predictive in certain clinical contexts. Whole genome sequencing (WGS) based approaches are optimal for detection of mutational signatures but to date studies using formalin fixed paraffin embedded (FFPE) clinical grade specimens are limited. **Methods:** Archival DNA specimens from tumors of United States Veterans that underwent clinical sequencing in the VA National Precision Oncology Program were subjected to 30X WGS. Somatic alterations were identified by a tumor-only variant calling method employing filtering of variants found in the dataset at >10% frequency and putative germline variants found in multiple databases and germline WGS from the Million Veteran Program (MVP). Mutational signatures were identified using deconstructSigs. **Results:** WGS was performed on 134 tumor samples with matched germline WGS from MVP; variants were called using the tumor-only variant calling pipeline in addition to tumor-normal calling. Tumor-only WGS derived tumor mutational burden (TMB) was highly correlated with TMB from clinical targeted sequencing (White, R2=0.48; Black, R2=0.63; Other, R2=0.85) and with TMB from tumor-normal variant calling (White, R2=0.96; Black, R2=0.63; Other, R2=0.85). We used our tumor-only variant calling pipeline on WGS from 397 tumors. The median (+SD) number of mutations per tumor varied per tumor type, with the lowest number in head and neck squamous cell carcinomas (12445+4186 mutations) and highest in melanoma (119089+259854 mutations). Overall, 66 single base substitution (SBS) mutational signatures were identified. The SBS1 clock signature was found in 339 of 397 tumors. The SBS4 smoking mutational signature was found in 100% of small cell lung cancers (n=5), 76% of lung squamous cell cancers (n=38), 50% of lung adenocarcinomas (n=50), 36% of cancers of unknown primary (n=14), 29% of bladder cancers (n=7), and 14% of HNSC (n=36), but was not found in any other cancer type. The SBS7a UV mutational signature was found in 80% of melanomas (n=10) and 7% of cancers of unknown primary, but not in any other cancer type. Finally, the SBS6 and SBS15 mismatch repair mutational signatures were found in 10 and 12 of 16 MSI-high tumors, respectively. **Conclusions:** We have established a pipeline for evaluation of mutational signatures from tumor-only WGS of clinical grade FFPE tumors. Preliminary analysis shows identification of expected mutational signatures. Work is ongoing to determine whether ancestry matched panel of normals improves signature identification and to determine the prognostic and/or predictive ability of mutational signatures in a variety of clinical contexts which could greatly expand the clinical utility of WGS in advanced cancers. Research Sponsor: Veterans Affairs Office of Research and Development; 1I01CX002709.

Validation of SNHG11 as a prognostic and predictive biomarker for anti-EGFR benefit in colorectal cancer using real-world data.

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Background: Long non-coding RNAs (lncRNAs) regulate colorectal cancer (CRC) initiation, progression, and therapeutic response through interactions with oncogenic and microenvironmental pathways. *SNHG11* has been implicated in CRC through epigenetic and c-Myc–driven transcriptional programs. In CALGB/SWOG 80405, higher tumor *SNHG11* expression correlated with improved outcomes, particularly anti-EGFR therapy (Bartolini 2025, ASCO 43; 16_suppl). We comprehensively evaluated molecular correlates with *SNHG11* and validated the prognostic and predictive value in an independent real-world CRC cohort. **Methods:** In total, 15,456 CRC underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences. Tumors were stratified by *SNHG11* expression quartiles, comparing low (Q1) vs high (Q4). CMS classification was assessed using RNAseq. Associations were assessed using X^2/Fisher's exact with p-values adjusted for multiple comparisons ($q<0.05$). Clinical outcome was obtained from insurance claims. Overall survival (OS) was calculated from tissue collection to last contact and time-on-treatment (ToT) from treatment start to end. Cox proportional hazards model generated hazard ratio (HR) and log-rank p-values. **Results:** *SNHG11* Q1 tumors were associated with higher right-sided prevalence (28% vs 18%, $p<0.001$), lower left-sided prevalence (50% vs 62%, $p<0.001$), and older age than Q4 (64 vs 62, $p<0.001$). Consistent with the findings in CALGB/SWOG 80405, Q4 were associated with CMS2 (53% vs 19%, $p<0.001$) while Q1 with CMS4 (49% vs 21%, $p<0.001$). Q1 tumors showed increased MSI-H/dMMR, TMB-H and PD-L1 expression (10% vs 3%, 15% vs 5% and 5% vs 2%, respectively, all $p<0.001$). *TP53* and *APC* mutations were enriched in Q4 vs Q1 (84% vs 69% and 85% vs 72%, $p<0.001$) whereas *KRAS* (49% vs 41%), *BRAF* (13% vs 7%), *ARID1A* (12% vs 8%), *RNF43* (6% vs 2%) and *CTNNB1* (3% vs 2%) mutations were higher in Q1 vs Q4 ($p<0.001$). Q4 was associated with longer OS vs Q1 (mOS 30.8 vs 27.8 months; HR 0.93; 95% CI 0.89–0.97, $p<0.001$). After adjusting for MSI status, tumor sidedness, age, race, and anti-EGFR therapy, Q4 remained a significant independent predictor of improved OS compared to Q1 (adjusted HR=0.93; 95% CI: 0.89-0.96; $p<0.001$). Q4 was significantly associated with longer ToT in patients receiving anti-EGFR therapy vs Q1 (7.4 vs 5.8 months, HR 0.86; 95% CI 0.79–0.93, $p<0.001$) with no association observed with bevacizumab ToT. **Conclusions:** In this large independent real-world cohort, we provided additional molecular insight into a key lncRNA *SNHG11* in CRC. Consistent with previous findings in a large randomized controlled trial, we confirm that elevated *SNHG11* expression was associated with CMS2, left-sided tumors, longer OS and longer TOT of anti-EGFR therapy, supporting *SNHG11* as a promising prognostic biomarker and a candidate predictive biomarker for anti-EGFR benefit in CRC. Research Sponsor: None.

Sensitivity of portal vein ctDNA versus peripheral blood in predicting postoperative liver metastasis adjuvant therapy in colorectal cancer.

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Background: The detection of minimal residual disease (MRD) in colorectal cancer (CRC) is crucial for predicting postoperative recurrence, particularly liver metastasis. While peripheral blood (PB) liquid biopsy is widely used, portal vein blood (PVB) may offer higher sensitivity due to direct drainage of the hepatic circulation. **Methods:** We prospectively enrolled 297 CRC patients undergoing curative surgery. Intraoperative portal vein blood (PVB) and matched preoperative peripheral blood (PB) samples were collected simultaneously. Cell-free DNA was sequenced using a targeted 689-gene panel (1.5 Mb). Variants were filtered to retain only those with increased allele frequency (AF) in PVB relative to PB or exclusive detection in PVB (AF $\geq$1%), followed by stringent germline and noise removal. Binary mutation matrices were constructed for both blood sources. Machine learning (random forest, SVM, logistic regression, gradient boosting) was used to identify predictive gene signatures separately for PVB and PB. Model performance was compared using five-fold cross-validation. **Results:** PVB-derived ctDNA detected a significantly higher number of tumor-specific mutations compared to PB (mean 3.2 vs. 1.4 mutations per patient, $p<0.001$). PVB contained significantly higher ctDNA concentration (median 8.4 ng/mL vs 2.1 ng/mL in PB, $p<0.001$). A 20-gene panel selected from PVB data demonstrated superior predictive accuracy for liver metastasis compared to PB-derived markers. When validated in the same cohort, the PVB panel achieved an AUC of 0.849 (95% CI: 0.802–0.891) versus 0.714 (95% CI: 0.653–0.771) for PB-based prediction ($p=0.003$). Sensitivity for predicting liver metastasis was 70.0% for PVB versus 48.5% for PB. The PVB panel identified 26.6% of mutation carriers as high-risk, with 100% specificity (no recurrence in mutation-negative patients). In contrast, the PB model failed to achieve comparable risk stratification, with lower positive predictive value and higher false-negative rates. **Conclusions:** Portal vein blood ctDNA analysis is significantly more sensitive and accurate than peripheral blood in predicting postoperative liver metastasis in CRC. PVB-based liquid biopsy provides superior risk stratification, which could better inform adjuvant therapy decisions—identifying high-risk patients for intensified surveillance or treatment, while reducing over-treatment in low-risk patients. These findings support the clinical integration of PVB sampling for MRD detection in CRC surgical practice. Research Sponsor: None.

Spatial mapping of human colorectal cancer cell states to identify co-targeting opportunities and determinants of drug response.

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Background: Colorectal cancer (CRC) progression relies on multiple mechanistically distinct proliferative and survival programs differing in lineage dependence, plasticity, and environmental sensitivity. LGR5-driven proliferation represents a stem-like program, whereas non-LGR5 modes—including progenitor, KRAS/MAPK, AP-1, and YAP-driven proliferation—reflect inflammatory and adaptive states that may confer therapeutic resistance. Single-cell studies revealed these programs, but technical barriers have restricted their quantitative and spatial analysis in human tumors, limiting translation to drug development and patient stratification. **Methods:** We integrated single-cell RNA sequencing (81 CRC patients) with spatial transcriptomics (Xenium; 16 matched primary CRC samples) to quantify epithelial cell states and tissue organization. Analyses focused on proliferative programs defined by LGR5, CDX2, ANXA1, and MKI67, stratified by KRAS genotype and intratumoral location, with extended spatial annotation of immune and stromal niches. **Results:** CRC tumors showed high compositional heterogeneity across subgroups (mean normalized Shannon entropy >0.6). On average, 36% of tumor epithelial cells were proliferative; only 50% expressed LGR5, with substantial inter-patient variability and genotype dependence. 14% of proliferating cells expressed ANXA1 alone, corresponding to inflammatory, YAP-high states with potential cytotoxic implications. LGR5-driven proliferation was enriched in KRAS-mutant tumors, contrasting with mouse models suggesting KRAS-mediated suppression and potentially indicating reduced sensitivity to KRAS inhibition. EGFR−LGR5 double-positive cells were abundant, identifying additional targetable niches. Spatial analyses revealed regions with high TGFβ signaling and co-localization with $SPP1^{+}$ macrophages consistent with TGFβ-driven immunosuppressive niches described in complementary studies. These niches associate with reduced PD-1/PD-L1 blockade response, coincide with states responsive to combined TGFβ and PD-1 inhibition, and are not captured by genotype alone. **Conclusions:** Spatial transcriptomics provides quantitative, systems-level resolution of tissue architecture, revealing opportunities for rational co-targeting to disrupt tumor homeostasis and enhance immunotherapy efficacy. Ongoing analyses of neoadjuvant-treated tumors and paired primary–metastatic samples will extend this framework to capture therapy-induced and naturally evolving tumor states. Research Sponsor: None.

3141 Poster Session

Phase 1/2 trial of ATR inhibitor berzosertib plus immune checkpoint inhibitor avelumab in patients with advanced cancers with DNA damage response (DDR) gene alterations: Tumor microenvironment–mediated pathways of resistance from correlative data.

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Background: Herein we present novel correlative data from baseline and on-treatment tumor and blood sampling with associated therapeutic outcomes from a phase 1/2 trial of ATRi (berzosertib) plus ICI (avelumab) in patients (pts) with advanced cancers with pathogenic mutations in select DDR genes. **Methods:** 17 pts enrolled on trial, and they received berzosertib (day 1, 8, 15, 22) plus avelumab (day 1 and 15, q28 days). Paired tumor biopsies were collected at baseline and on Day 12 of treatment, with spatial gene expression profiling (Visium) performed on the tumor tissues. Spot-level bioinformatics and manual annotations were performed to identify regions enriched for tumor cells and key TME components. Blood was collected at baseline and longitudinally for high-dimensional CyTOF profiling for immune cell populations and Luminex for circulating cytokines. **Results:** The ATRi + ICI combination was safe and well tolerated as previously reported, with ORR of 12.5% in this heavily pre-treated study population, with 2 durable RECISTv1.1 partial responses observed in advanced HPV+ vaginal cancer pt with pathogenic somatic *RAD51* mutation lasting 23 months and an advanced colorectal cancer with *MSH2* mutation lasting >24 months. In liquid sampling (N=16 pts), CyTOF analysis revealed a common baseline monocyte "stress-brake" state marked by elevated MRE11 and impaired antigen presentation. Treatment resulted in relief of innate DNA stress and induction of a myeloid-to-lymphoid immune shift, with subsequent expansion of adaptive T-cell effectors (EM1 CD4 T cells), with the durable responses characterized by an early proliferative CD8 T-cell burst (D12–D28) followed by sustained lymphoid dominance. Luminex assay revealed substantial cytokine remodeling at D12–D28 relative to baseline, with multiple analytes exceeding the predefined effect-size threshold ($|\log2FC| \geq 0.58$; ~1.5-fold), suggesting an acute inflammatory response and myeloid infiltration. Spatial profiling in non-responders showed high baseline levels of cancer associated fibroblasts (CAFs) and intra-tumoral CNV heterogeneity, with treatment resulting in upregulation of immunosuppressive, pro-survival pathways (SPP1, MIF, MYC, and Annexin). In contrast, the available on-treatment pt tissue from the vaginal cancer responding tumor displayed higher lymphoid infiltrate and lower immune suppression genes. **Conclusions:** Despite universal acute immune activation in circulation following ATRi + ICI, resistant tumors displayed high CNV heterogeneity, CAFs, and increased immunosuppressive pathways, in contrast to responder tissue. Co-clinical studies will further elucidate targetable mechanisms of resistance and guide further DDRi and ICI combinations. Clinical trial information: NCT04266912. Research Sponsor: None.

Genomic and transcriptomic correlates of HER3 expression in prostate cancer.

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Background: HER3 (*ERBB3*) is a key receptor in prostate cancer (PC) that signals via HER3 heterodimerization to promote PI3K-AKT-mediated survival and adaptive resistance in castration-sensitive (CSPC) and castration-resistant prostate cancer (CRPC). Despite its biological relevance, the clinical and genomic significance of HER3 RNA expression remains poorly defined. We therefore performed a comprehensive multi-omic analysis to evaluate the prognostic relevance of HER3 RNA in PC. **Methods:** DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing were performed on prostate tumor samples (n=19,238) submitted to Caris Life Sciences. HER3 expression was quantified as transcripts per million (TPM) and stratified into high (HER3-H) and low (HER3-L) groups defined by the top and bottom quartiles, respectively. CRPC was defined as ≥3 months of androgen deprivation therapy before tissue collection. Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from biopsy to last contact. Tumor microenvironment (TME) cell fractions were estimated by RNA deconvolution using quanTIseq. Group comparisons were conducted using Mann–Whitney U and chi-square tests as appropriate. Survival outcomes were evaluated using Cox proportional hazards models and log-rank testing, with false discovery rate correction for multiple comparisons. **Results:** Across genitourinary malignancies, PC demonstrated highest median HER3 RNA expression (107.04 TPM). Within PC, HER3 expression varied by tumor site and race, with higher median levels in primary tumors compared to metastatic sites (116.5 vs 86.22 T PM, $p<0.0001$), and in tumors from Black patients compared with White patients (115.3 TPM v 103.3 TPM, $p<0.0001$). Prognostic associations differed by tumor source and castrate status: HER3-H expression was associated with improved rwOS in metastatic tumors (32.0 vs. 23.3 months, HR 0.72, $p < 0.00001$), and in CRPC (29.3 vs. 21.3 months; HR 0.84; $p < 0.001$), but not in primary tumors or CSPC. Immune profiling revealed that HER3-high tumors exhibited significantly reduced inferred infiltration of Tregs, neutrophils, macrophages, and NK cells ($q < 0.05$), while PD-L1 positivity and TMB-high status were not significantly associated with HER3 expression. Genomic analysis revealed enrichment of *FOXA1* and *SPOP* alterations ($q<0.05$) in HER3-H tumors, whereas HER3-L tumors were enriched for *TP53*, *RB1*, *AR*, *CDK12*, and *APC* ($q<0.05$). On multivariable analysis, HER3-H status remained independently associated with improved rwOS in CRPC. **Conclusions:** HER3 RNA expression defines biologically and clinically distinct subsets of PC, with HER3-high tumors exhibiting luminal, androgen receptor–dependent biology, an immune-cold phenotype, and improved survival in metastatic disease and CRPC, supporting HER3 as a tumor-intrinsic therapeutic target and rationale for HER3-directed therapy. Research Sponsor: None.

Can GLP-1 receptor agonists mitigate cancer progression? A propensity-matched analysis across seven solid tumors.

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Background: GLP-1 receptor agonists (GLP-1RAs) are pleiotropic medications, initially developed for diabetes, yet with beneficial effects on obesity and cardiovascular disease. Given the rapidly expanding therapeutic use of these agents and emerging preclinical data suggesting immunomodulatory effects, we examined whether GLP-1RA exposure following cancer diagnosis was associated with altered risk of progression to metastatic disease. **Methods:** Utilizing the TriNetX Global Health Research Network, we identified 10,225 patients with stage I-III cancer who initiated GLP-1RA therapy after diagnosis. GLP-1RA-exposed patients were propensity-matched 1:1 to DPP-4 inhibitor controls across seven cancers: breast adenocarcinoma, prostate adenocarcinoma, NSCLC, colorectal adenocarcinoma (CRC), hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), and pancreatic adenocarcinoma. Matching included demographics, BMI, glycemic factors, smoking, comorbidities, screening frequency, oncologic treatments, and concurrent medications. Primary outcome was progression to stage IV disease. Additionally, we used The Cancer Genome Atlas (TCGA) data to assess whether GLP-1R expression correlated with overall survival. **Results:** GLP-1RA exposure demonstrated reduced metastatic progression across 6/7 malignancies, with statistically significant reductions in four cancer types: NSCLC, breast, CRC, and HCC (Table 1). No significant safety signals or increased adverse events were observed in GLP-1RA-exposed patients compared to controls. Additionally, high tumor GLP-1R expression correlated with improved survival across the seven tumors (HR=0.67, 95% CI 0.54-0.83, $p<0.001$), most notably in breast cancer (HR=0.55, 95% CI 0.35-0.87, p=0.011). **Conclusions:** In this large propensity-matched cohort, GLP-1RA initiation after cancer diagnosis was associated with dramatically reduced metastatic progression across multiple solid tumors. Corroborating these clinical findings, elevated GLP-1R expression independently predicted improved overall survival. These findings warrant validation in prospective randomized controlled trials and mechanistic investigation of potential antineoplastic pathways driven by GLP-1RAs. Research Sponsor: None.

Effect of GLP1-1RA exposure compared to DPP-4i exposure on progression of stage I-III cancer to stage IV cancer.

Cancer Type	Matched Pairs (n)	Events GLP-1RA/DPP-4i	Cumulative Incidence (%)	Hazard Ratio (95% CI)	P-value
NSCLC	2,157	215/482	10.0 vs 22.3	0.50 (0.43-0.59)	<0.001
Breast	1,187	121/239	10.2 vs 20.1	0.57 (0.46-0.71)	<0.001
Colorectal	784	105/174	13.4 vs 22.2	0.69 (0.54-0.88)	0.003
HCC	275	52/78	18.9 vs 28.4	0.62 (0.44-0.89)	0.009
Prostate	1,010	83/137	8.2 vs 13.6	0.79 (0.60-1.04)	0.09
RCC	523	75/99	14.3 vs 18.9	0.95 (0.71-1.29)	0.76
Pancreatic	120	28/37	23.3 vs 30.8	0.69 (0.42-1.13)	0.14

Efficacy and safety of pralsetinib in *RET* fusion–positive solid tumors: Data from the TAPISTRY trial.

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Background: Pralsetinib is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusion and mutation proteins, present in multiple tumor types. We report results from the phase 2 TAPISTRY study (NCT04589845), a global, open-label, multicohort study evaluating the efficacy and safety of pralsetinib in a cohort of patients with *RET* fusion-positive solid tumors. **Methods:** Eligible patients ≥12 years old with unresectable, locally advanced or metastatic *RET* fusion-positive solid tumors received 400 mg pralsetinib QD until disease progression, loss of clinical benefit, or unacceptable toxicity. Independent review committee (IRC)-assessed objective response rate (ORR) was the primary end point. Key secondary end points included IRC-assessed duration of response (DOR) and progression-free survival (PFS), and overall survival (OS). **Results:** Forty-six patients were enrolled and received ≥1 pralsetinib dose; 78% had ≤1 prior line of therapy in the metastatic setting. Median age was 56 y (range: 12-79); 61% were male. Median treatment duration was 14.3 mo (range: 0.7-31.5). Cancers included thyroid (n=18, 39%); colorectal (n=9, 20%); head and neck (n=4, 9%); pancreatic (n=4, 9%); hepatobiliary (n=3, 7%); CNS, sarcoma, and neuroendocrine and adrenal (n=2, 4% each); gastroesophageal (n=1, 2%); and unknown primary origin (n=1, 2%). ORR for the efficacy evaluable population (n=39) was 67% (95% CI: 50, 81; Table), with 5 (13%) CRs and 21 (54%) PRs. Intracranial response was observed in 1/2 (50%) patients with baseline CNS metastases. All patients experienced treatment-related adverse events (TRAEs); 33/46 (72%) reported TRAEs grade ≥3. The most common TRAEs included anemia (n=18; 39%), increased AST (n=16; 35%), and decreased neutrophil count (n=13; 28%). Hypertension was reported in 11 (24%) patients, with 3 (7%) reporting grade ≥3. Safety results were consistent with the known pralsetinib profile, with no new signals. **Conclusions:** Pralsetinib demonstrated robust and durable activity against *RET* fusion-positive solid tumors, with an ORR of 67%. These data validate RET fusions as a tissue-agnostic target with sensitivity to RET inhibition, suggesting therapeutic utility of pralsetinib. Clinical trial information: NCT04589845. Research Sponsor: Rigel Pharmaceuticals, Inc.

Efficacy summary by tumor type.

	Overall (N=39)	Thyroid (n=16)	Pancreatic (n=3)	Colorectal (n=8)	Hepatobiliary (n=3)	Head and Neck (n=3)
ORR, % (95% CI)	67 (50, 81)	81 (54, 96)	67 (9, 99)	38 (9, 76)	33 (1, 91)	100 (29, 100)
DOR, median, mo (95% CI)	26.7 (14.7, NE)	26.7 (26.7, NE)	3.9 (3.7, NE)	12.2 (5.7, NE)	14.9 (NE)	NE
PFS, median, mo (95% CI)	16.5 (7.2, NE)	30.3 (16.3, NE)	5.6 (1.9, NE)	6.5 (1.6, 12.9)	8.3 (1.4, NE)	NE
OS, median, mo (95% CI)	30.8 (16.3, NE)	NE (NE)	21.7 (12.7, NE)	10.2 (5.7, NE)	13.8 (8.3, NE)	NE
Follow-up, median, mo (range)	14.5 (2, 32)	19.4 (10, 32)	12.6 (2, 31)	9.2 (2, 19)	8.3 (2, 19)	14.3 (14, 27)

NE, not evaluable.

Efficacy and safety of larotrectinib in patients with non-primary central nervous system *TRK* fusion cancer: An updated analysis.

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Background: Larotrectinib (laro) is the first-in-class, highly selective TRK inhibitor approved for tumor-agnostic use in patients (pts) with TRK fusion cancer based on a robust and durable objective response rate in pts with various cancers. Here, we report updated long-term efficacy and safety in adult and pediatric pts treated with laro with non-primary central nervous system (CNS) TRK fusion cancer. **Methods:** Pts from 3 clinical trials (NCT02637687 [SCOUT], NCT02576431 [NAVIGATE], NCT02122913) were included. Laro was administered at 100 mg twice daily (BID) and 100 mg/m^2 (max 100 mg) BID in most adult and pediatric pts, respectively. Responses were independent review committee-assessed (RECIST v1.1). Pts enrolled in SCOUT could stop laro in the absence of on-treatment progression ("wait-and-see") and remain on trial. If pts were re-treated due to progression, response was assessed by investigators. Data cutoff: July 20, 2025. **Results:** In total, 304 pts were treated; 25 had baseline CNS metastases. There were 28 tumor types, including soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung (11%), and thyroid (10%). *NTRK* gene fusions were detected by next-generation sequencing (NGS) in 266 (88%) pts. Overall response rate was 65% (95% confidence interval [CI] 59–70) with 61 (20%) complete responses (CR), 18 (6%) pathological CR, 118 (39%) partial responses (PR), 55 (18%) stable disease (SD), 32 (11%) progressive disease (PD), and 20 (7%) not evaluable/undefined. Median duration of treatment was 19 months ([mo] range 0–111). At data cutoff, 52 pts (17%) remained on trial (either on treatment or in "wait-and-see"). Median time to response was 1.8 mo (range 0.9–80.3). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 42 mo (95% CI 31–59), 26 mo (95% CI 19–35), and not reached (95% CI 89–not estimable), respectively, at median follow-ups of 54, 52, and 65 mo. The 5-year rates for DoR, PFS, and OS were 41% (95% CI 33–49), 33% (95% CI 27–40), and 61% (95% CI 55–67), respectively. Fifty-seven pediatric pts entered a first "wait-and-see" period (median duration 24 mo [range 0–75+]). Of these, 38 exited the "wait-and-see" period. By investigator assessment, 20 pts had PD and resumed treatment (with 6 CR, 5 PR [including 2 pending confirmation], 7 SD, 2 unevaluable/undefined). The other 18 pts discontinued laro permanently but were all alive at data cutoff. Treatment-related adverse events (TRAEs) were mainly worst Grade 1/2 (n=189; 62%). Worst Grade 3/4 TRAEs occurred in 72 (24%) pts. Five (2%) pts discontinued due to TRAEs. **Conclusions:** Laro continues to demonstrate rapid and durable responses, extended survival, clinical benefit, and a favorable safety profile in pts with TRK fusion cancer. These data support the wider adoption of NGS panels that include *NTRK* gene fusions to identify pts who may benefit from TRK inhibitor therapy. Clinical trial information: NCT02637687, NCT02576431, NCT02122913. Research Sponsor: Healthcare and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company.; was supported by the National Cancer Institute/National Institutes of Health P30CA008748, 1R01CA226864-01A1 grants, and Nonna's Garden.

BMS-986504 in patients (pts) with advanced solid tumors with homozygous *MTAP* deletion (*MTAP*-del): Exploratory pharmacodynamic (PD) and biomarker analyses from CA240-0007.

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Background: The MTA-cooperative PRMT5 inhibitor BMS-986504 selectively binds to the PRMT5-MTA complex, a synthetic lethal target in *MTAP*-del cancer cells, while sparing *MTAP*–wild-type normal cells. In the phase 1 CA240-0007 study, BMS-986504 was well tolerated and had antitumor activity in pts with *MTAP*-del advanced solid tumors (ORR, 23%; median DOR, 10.5 mo). BMS-986504 also demonstrated dose-dependent reductions in plasma symmetric dimethylarginine (SDMA) levels, a PD biomarker of PRMT5 inhibition. Here, we report expanded PD and genomic analyses and initial results of exploratory proteomic analyses from CA240-0007. **Methods:** Pts with advanced, unresectable, or metastatic solid tumors with homozygous *MTAP*-del received BMS-986504 (50–800 mg) in 3-wk cycles. Analyses of SDMA levels and proteomic profiles from paired plasma samples (baseline and C2D1) were performed using mass spectrometry and SomaScan 11K, respectively. Tumor genomic information was extracted from local pathology reports. ORR was assessed per RECIST v1.1. **Results:** Among 78 pts with paired samples at data cutoff (22 Sept 2025; median f/u, 15.9 mo), dose-dependent reductions were seen in plasma SDMA levels, with the greatest reductions at 400 mg QD (median, 60.3%; n = 31) and 600 mg QD (median, 60.3%; n = 23). Proteomic pathway enrichment analysis demonstrated downregulation of PI3K/Akt/mTOR, Myc target, cell cycle, and DNA damage repair (DDR) pathways with BMS-986504 on C2D1 (n = 87), consistent with the expected effect of PRMT5 inhibition; a trend toward deeper modulation of PRMT5-regulated pathways was observed at higher doses. No proteins at baseline (n = 94) were found to be significantly associated with ORR (false discovery rate $>$ 0.05). Responses in clinically evaluable pts with NSCLC (n = 33) or PDAC (n = 35) were observed regardless of *EGFR*, *KRAS*, or *TP53* status. In pts with NSCLC, *STK11* and *SMARCA4* alterations were numerically higher in nonresponders. No gene alterations were associated with response in PDAC, except *GABRA6* alterations (n = 2, both responders). A trend toward higher ORRs was seen in pts with alterations in DDR genes (*CHEK2*, *FANCD2*, *XRCC4*, and/or *MSH2*), consistent with the role of PRMT5 in DDR via regulation of mRNA splicing. ctDNA analysis will be presented. **Conclusions:** BMS-986504 demonstrated robust dose-dependent PD effects in pts with advanced solid tumors in plasma SDMA and proteomic analyses. Downregulation of PRMT5-regulated pathways was observed with BMS-986504 treatment. Response was seen regardless of *EGFR*, *KRAS*, and *TP53* alterations in NSCLC or PDAC, and DDR gene alterations were associated with improved response. These findings further support the MOA of BMS-986504 and its ongoing investigation in the phase 2/3 MountainTAP-9, -29, and -30 studies as a potential treatment option in pts with *MTAP*-del advanced solid tumors. Clinical trial information: NCT05245500. Research Sponsor: Bristol Myers Squibb.

Fast-TRACKing precision oncology for rare cancers: A national decentralized trial offering comprehensive genomic profiling and a molecular tumor board.

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Background: The TargetCancer Foundation TCF-001 TRACK study (Target RAre Cancer Knowledge, NCT04504604) initiated on Oct 01, 2020, is a fully remote, advocacy-driven decentralized precision trial seeking to evaluate the clinical impact of utilizing comprehensive genomic profiling (CGP) reviewed by a molecular tumor board (MTB) for patients (pts) with rare cancers. **Methods:** Pts were remotely enrolled/consented. Blood samples were collected via mobile phlebotomy and tested with FoundationOne Liquid CDx; tissue biopsies (TBx) were tested using FoundationOne CDx ± laboratory developed (LD) FoundationOne RNA or LD FoundationOne Heme. Liquid biopsy testing (LBx) included algorithmic predictions for clonal hematopoiesis (CH). MTB reviewed results and provided recommendations. **Results:** As of Oct 01, 2025, 230 pts from 46 US states were enrolled with evaluable results; 76% (175/230) had TBx and LBx, 22% LBx, and 2% TBx biopsies. MTB review was completed for 226 pts. Median age was 57 years (interquartile range [IQR]: 47,66); > 60 tumor types were represented: cholangiocarcinoma (35%), gastrointestinal (19%), soft tissue-related sarcomas (17%), brain (14%), and others (15%). First on-study TBx CGP (n=173) showed microsatellite instability high in 2%, homologous repair deficiency-signature in 2%, and median tumor mutational burden (TMB) of 1.3 mut/Mb (IQR: 0.8,3.6; 5 pts ≥ 10 mut/Mb). In LBx (n=57), ctDNA tumor fraction (TF) was ≥1% in 28% of pts; median blood TMB was 1.3 (IQR: 0,2.5; 1 pt ≥ 10 mut/Mb). Overall, 95% (219/230) of tumors had >1 pathogenic alteration; TBx CGP detected alterations in 96% (172/179), most frequently *TP53* (35%), *CDKN2A* (29%), *CDKN2B*(21%), *KRAS* (19%), *MTAP* (17%), and *TERT* (14%). LBx CGP detected alterations in 85% (192/225), with tumor-derived (TD) variants in *KRAS* (11%), *IDH1* (7%), and *CDKN2A* (6%). *TP53* (31%) included both TD and CH variants, while *DNM3TA* (30%), *ATM* (10%), *TET2* (10%), and *CHEK2* (8%) were mostly CH. In brain tumors, 52 variants from 28 pts with LBx identified 45 CH, 4 germline, and 3 TD. Across all tumor types, 9% (20/230) had biomarkers for FDA-approved tissue-agnostic therapies. This includes *ERBB2* amplification (2% overall), which is often correlated with *HER2* immunohistochemistry positivity. LBx sensitivity for DNA tissue-detected clonal SVs and rearrangements was 85% (95% CI: 0.74,0.92) when ctDNA TF≥1%; 24% (95% CI: 0.19,0.29) when <1%. Pathogenic fusions detected by RNA sequencing were not detected by DNA in 33% of cases (9/27). **Conclusions:** CGP identified pathogenic alterations in nearly all rare cancer patients, with tissue-agnostic biomarkers in 9%. RNA sequencing adds diagnostic yield. CH in liquid biopsies underscores need for expert MTB interpretation. TRACK, a first-of-its-kind national decentralized trial, provides a scalable framework for equitable precision oncology access. Clinical trial information: NCT04504604. Research Sponsor: TargetCancer Foundation; Foundation Medicine.

Multi-modal molecular profiling of CDH1 and CLDN18.2 to identify predictive biomarkers for zolbetuximab efficacy in patients with advanced gastric adenocarcinoma: The ZOL-C3 study.

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Background: Zolbetuximab is a chimeric monoclonal antibody designed to bind to claudin 18.2 (CLDN18.2) and induce antibody-dependent cell-mediated cytotoxicity (ADCC). Although phase 3 trials established its efficacy in CLDN18.2-positive advanced gastric adenocarcinoma (GAC), robust predictive biomarkers beyond protein expression remain an unmet need. We investigated how epithelial-mesenchymal transition (EMT), mediated by CDH1 alterations and the tumor mutational burden (TMB), modulates the therapeutic target and affects zolbetuximab-mediated ADCC efficacy. **Methods:** This study employed a multi-layered integrative framework across four independent datasets to cross-validate genomic, transcriptomic, and phenotypic findings: (1) mechanistic characterization using the TCGA-STAD cohort (n=375); (2) the genomic screening of 2,483 patients with GAC in the Japanese national database (C-CAT), which identified 49 treated with zolbetuximab-containing regimens; (3) a spatial transcriptomic evaluation (10× Genomics Visium platform, GSE251950); and (4) immunohistochemical (IHC) validation of CLDN18.2 in 36 institutional GAC patients. The trial is registered at UMIN-CTR (UMIN000060223), a WHO ICTRP primary registry. **Results:** In the TCGA cohort, CDH1 low-expression was significantly associated with 3.2-fold lower CLDN18 mRNA levels than in the high-expression group ($p < 0.001$). CDH1 expression was strictly regulated by promoter methylation ($p < 0.001$), whereas CLDN18 down-regulation in CDH1-low tumors appeared to be driven by non-epigenetic EMT pathways. Spatial transcriptomics revealed a spatial correlation between CDH1 and CLDN18 mRNAs within the malignant epithelial compartment ($p < 0.001$). The objective response rate within the zolbetuximab-treated C-CAT subset was 22.2%. TMB was markedly lower in responders than in non-responders (median 1.82 vs. 4.0 mut/Mb; $p = 0.050$). Furthermore, patients without CDH1 single nucleotide variants had higher ORR ($p = 0.086$). Institutional IHC validation revealed a superior response in cases that retained membranous CDH1 expression to that in cases with the loss of epithelial integrity (100% vs 50% ORR; p=0.088). **Conclusions:** These results demonstrate that CDH1/E-cadherin integrity and low TMB are critical co-determinants of CLDN18.2 expression and zolbetuximab efficacy. Maintenance of the epithelial phenotype appears to be essential for optimal zolbetuximab-mediated ADCC. The integration of comprehensive molecular profiling, including the CDH1 status and TMB, may significantly refine patient selection, with a shift from simple target positivity to a more biological enrichment strategy for zolbetuximab therapy. Research Sponsor: None.

Clinical outcomes of patients with cell cycle alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study.

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Background: Cell cycle pathway alterations are a hallmark of cancer. Disruption of cell cycle checkpoints results in genomic instability, uncontrolled proliferation and tumor progression to aggressive and treatment-resistant phenotypes. We report the clinical outcomes of patients with cell cycle pathway alterations treated in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. Cell cycle pathway alterations were defined as those involving the *CCND1*, *CCND2*, *CCNE1*, *CDK4*, *CDK6*, *CDKN2A*, *CDKN2B*, and *RB1* genes. Cases were discussed at Molecular Tumor Board meetings. Patients were treated on clinical trials with investigational agents that included matched targeted therapies (MTTs) when available. We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (complete response + partial response), clinical benefit rate (CBR; ORR + stable disease≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 157 (32.0%) had cell cycle pathway alterations (median age, 61 years [range, 21-82]; female, 46.5%; ECOG performance status 1, 85.4%; median number of prior therapies, 3 [range, 0-9]; liver metastases, 40.8%; >2 metastatic sites, 36.3%; high LDH, 33.1%; low albumin, 10.8%). The most common cancers were sarcoma (19.7%), other gastrointestinal (17.2%), head and neck (14.0%), lung (9.6%), and breast (8.3%). Other tumor characteristics included PD-L1 ≥1%, 45.6% (41/90); MSI-H, 2.0% (2/102); and TMB-H, 13.0% (13/100). Concomitant pathway alterations were TP53 (67.5%), PI3K (29.9%), and RTK-RAS (47.1%). MTT targeted CDK4/6, n=9; BET, n=2; ATR, n=1; PKMYT1, n=1; and ACAT, n=1. Clinical outcomes are shown in the Table. **Conclusions:** Very few investigational therapies that target the cell cycle pathway were available. No differences were noted in tumor response, PFS, or OS by type of therapy, likely owing to the limited antitumor activity of the MTTs and the complexity of targeting this pathway. Novel and effective MTTs are needed for tumors with cell cycle dysregulation. Clinical trial information: NCT02152254. Research Sponsor: National Cancer Institute; P30 CA016672; Mr. and Mrs. Steven Mckenzie's Endowment; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Ritter; Foundation Medicine; TEMPUS AI.

	All patients N=157	MTT N=14	NTT N=143	*P*	IO N=40	Non-IO N=117	*P*
ORR (%)	7/135 (5.2)	0/12 (0)	7/123 (5.7)	1.00	4/33 (12.1)	3/102 (2.9)	0.14
CBR (%)	76/135 (56.3)	6/12 (50.0)	70/123 (56.9)	0.76	19/33 (57.6)	57/102 (55.9)	1.00
Median PFS, months (95% CI)	3.75 (2.66, 5.49)	3.75 (1.81, NA)	3.58 (2.66, 5.52)	0.81	2.96 (1.81, 8.98)	3.75 (2.66, 5.59)	0.98
Median OS, months (95% CI)	8.48 (7.1, 11.21)	6.66 (5.56, NA)	8.61 (7.17, 11.57)	0.40	7.46 (5.19, 17.42)	8.48 (7.1, 11.57)	0.72

Clinical outcomes of patients with PI3K pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study.

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Background: The phosphatidylinositol 3-kinase (PI3K) pathway regulates cell growth, metabolism, and survival and is involved in immune modulation. Alterations in PI3K signaling drive tumor progression and drug resistance in advanced cancers and are associated with poorer prognosis. Herein, we report the clinical outcomes of patients with PI3K pathway alterations treated in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. PI3K pathway alterations were defined as those involving the *PI3K*, *AKT1*, *AKT2*, *AKT3*, *MTOR*, *PIK3CA*, *PIK3CB*, *PIK3R1*, *PTEN*, *TSC1*, and *TSC2* genes. Cases were discussed at Molecular Tumor Board meetings. Patients were treated on clinical trials with investigational agents that included matched targeted therapies (MTTs) when available. We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (ORR; complete response + partial response), clinical benefit rate (CBR; ORR + stable disease ≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 133 (27.1%) had PI3K pathway alterations (median age, 60.3 years [range, 20.5-79.8]; female, 60.9%; ECOG performance status 1, 85.7%; median number of prior therapies, 3 [range, 0-14]; liver metastases, 42.9%; >2 metastatic sites, 44.3%; high lactate dehydrogenase levels, 42.1%; low albumin level, 9%). The most common tumor types were breast cancer (18%), colorectal cancer (15%), and sarcoma (12%). Concomitant pathway alterations were TP53 (49.6% of patients), RTK/RAS (43.6%), and cell cycle (35.3%). Other tumor characteristics included PD-L1≥1%, 40.5% (32/79); MSI-H, 2.2% (2/89); and TMB-H, 10.3% (9/87). MTT included mTOR inhibitors, n=17; AKT inhibitors, n=5, and PI3K inhibitors, n=4. Clinical outcomes are shown in the Table. **Conclusions:** Taking into consideration the relatively limited use of AKT and PI3K inhibitors compared with mTOR inhibitors, no differences were noted in tumor response, PFS, or OS, by type of treatment. Other contributing factors may include the biological complexity of targeting this pathway, the small number of patients and/or the limited availability and antitumor activity of MTTs. Clinical trial information: NCT02152254. Research Sponsor: Foundation Medicine; Tempus AI; Mr. and Mrs. Steven Mckenzie's Endowment; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Ritter; National Cancer Institute; P30 CA016672.

	All patients N = 133	MTT N=26	NTT N=107	*P*	IO N=35	Non-IO N=98	*P*
ORR (%)	9/112 (8.0)	1/23 (4.3)	8/89 (9.0)	0.68	4/32 (12.5)	5/80 (6.3)	0.51
CBR (%)	63/112 (56.3)	15/23 (65.2)	48/89 (53.9)	0.36	18/32 (56.3)	45/80 (56.3)	1.00
Median PFS, months (95% CI)	2.96 (2.27, 4.57)	4.08 (2.17, NA)	2.66 (2.1, 4.37)	0.36	4.14 (1.84, 9.86)	2.96 (2.24, 4.37)	0.31
Median OS, months (95% CI)	7.79 (6.54, 10.92)	9.04 (6.64, 14.99)	7.3 (5.59, 11.21)	0.64	8.75 (5.36, 25.55)	7.17 (6.18, 0.78)	0.40

Clinical outcomes of patients with RTK-RAS pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study.

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Background: The receptor tyrosine kinase (RTK)-RAS signaling axis comprises distinct membrane receptors and downstream effectors that regulate cell proliferation and survival. Alterations in this pathway drive carcinogenesis and are associated with poor prognosis. We analyzed the outcomes of patients with RTK-RAS pathway alterations enrolled in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. RTK-RAS pathway alterations were defined as those involving *EGFR, ERBB2, ALK, MET, KRAS, NRAS, BRAF*, and *MAP2K1/2* genes. Cases were discussed at Molecular Tumor Board meetings. Patients were treated in clinical trials with investigational agents, including matched targeted therapies (MTTs) when available. We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (ORR; complete response + partial response), clinical benefit rate (CBR; ORR + stable disease≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 216 (44%) had RTK-RAS pathway alterations (median age, 62.3 years [range, 21-80]; female, 54.1%; ECOG performance status 1, 90.3%; median number of prior therapies, 3 [range, 0-10]; liver metastases, 46.3%; > 2 metastatic sites, 34.7%; high LDH, 37.0%; low albumin level, 11.1%). The most common cancers were gastrointestinal (40.3%), head/neck (10.2%), and lung (10.2%). Other tumor characteristics included PD-L1≥1%, 43.6% (58/133); MSI-H, 1.3% (2/153); and TMB-H, 10.7% (16/150). Concomitant pathway alterations were TP53 (62.5%), PI3K (26.9%), and cell cycle (34.3%) pathways. MTT targeted EGFR, n = 8; FGFR, n = 10; HER2, n = 6; BRAF+MEK, n = 3; ALK, n = 1; and MEK, n = 4 among others (n = 24). Clinical outcomes are shown in the Table. **Conclusions:** The ORR was 14.6% in IO-treated patients vs. 5% in the non-IO-treated group (p = 0.049), although the difference was not significant. No differences in PFS or OS were observed by therapy type in patients with RTK-RAS pathway alterations. Novel MTTs (i.e., KRAS inhibitors) that were unavailable during the study period may improve the outcomes of these patients. Identification of molecular subsets benefiting from MTT is needed. Clinical trial information: NCT02152254. Research Sponsor: National Cancer Institute; Foundation medicine; TEMPUS AI; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Bitter.

	All patients N=216	MTT N=56	NTT N=160	*P* value	IO N=57	Non-IO N=159	*P* value
ORR (%)	14/189 (7.4)	5/50 (10)	9/139 (6.5)	0.53	7/48 (14.6)	7/141 (5)	0.049
CBR (%)	110/189 (58.2)	31/50 (62)	79/139 (56.8)	0.62	27/48 (56.3)	83/141 (58.9)	0.87
Median PFS, months (95% CI)	2.96 (2.3, 3.81)	3.09 (2.66, 8.02)	2.89 (1.97, 4.08)	0.5	2.3 (1.61, 5.42)	3.19 (2.66, 4.08)	0.72
Median OS, months (95% CI)	7.36 (5.69, 9.21)	5.88 (4.7, 18.28)	7.79 (5.69, 9.44)	0.10	6.61 (4.6, 12.76)	7.46 (5.69, 9.21)	0.85

Clinical outcomes of patients with TP53 pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study.

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Background: TP53 pathway alterations are found in over 50% of human cancers, with variable frequency across tumor types. They are associated with aggressive tumor biology, increased metastatic potential, and poor prognosis. Herein, we report the clinical outcomes of patients with TP53 pathway alterations treated in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. TP53 pathway alterations were defined as those involving the *TP53*, *ATM*, *CHEK1*, *CHEK2*, *MDM2*, and *MDM4* genes. Patients were treated on clinical trials with investigational agents that included matched targeted therapies (MTTs) when available. MTT included anti-vascular endothelial growth factor (VEGF) targeted therapy, as previously published (PMID: 27466356). We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (ORR; complete response + partial response), clinical benefit rate (CBR; ORR + stable disease≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 278 (56.6%) had p53 pathway alterations (median age, 60.1 years [range, 20.5-81.7]; female, 51.4%; ECOG performance status 1, 86.0%; median number of prior therapies, 3 [range, 0-11]; liver metastases, 42.2%; >2 metastatic sites, 36.0%; high lactate dehydrogenase level, 41.0%; low albumin level, 9%). The most common tumors were colorectal (21.2%), sarcoma (13.7%), other gastrointestinal (12.2%), and breast (8.6%). Immune markers included PD-L1≥1%, 47.3% (78/165); MSI-H, 1% (2/199); and TMB-H, 10.5% (19/181). Concomitant pathway alterations were RTK-RAS (48.6%), PI3K (24.8%), and cell cycle (38.1%) pathways. MTT included VEGF/VEGFR inhibitors, N=57; MDM2 inhibitors, N=4; and TP53 activator, N=1. Clinical outcomes are shown in the Table. **Conclusions:** Median OS was significantly longer in patients with TP53 pathway alterations treated with IO compared with non-IO regimens. Considering the limited availability of TP53-targeted agents, no differences in clinical outcomes were noted for MTT compared with NTT. Further analyses are warranted to elucidate the molecular substrates underlying immunotherapy benefit. Clinical trial information: NCT02152254. Research Sponsor: National Cancer Institute; P30 CA016672; Foundation Medicine; Tempus AI; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Ritter.

	All patients N=278	MTT N=62	NTT N=216	*P*	IO N=69	Non-IO N=209	*P*
ORR	18/247	4/59	14/188	1.00	9/64	9/183	0.024*
%	7.3	6.8	7.4		14.1	4.9	
CBR	142/247	37/59	105/188	0.37	43/64	99/183	0.87
%	57.5	62.7	55.9		67.2	54.1	
Median PFS, months	3.75	5.52	2.93	0.11	4.37	3.19	0.46
95% CI	2.89, 4.8	4.67, 8.19	2.5, 4.14		2.73, 5.56	2.66, 4.08	
Median OS, months	7.99	9.01	7.3	0.96	10.85	6.9	0.024
95% CI	6.18, 9.3	7.17,12.36	5.69, 9.24		7.86, 17.42	5.65, 8.65	

*Not significant after multiple testing correction (threshold α = 0.0125).

Impact of dual inhibition of iNOS and COX2 on antitumor immunity and response to immune checkpoint blockade in hepatocellular carcinoma.

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Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide. Although immune checkpoint blockade (ICB) benefits a subset of patients, efficacy is often limited by an immunosuppressive tumor microenvironment. Inducible nitric oxide synthase (iNOS/NOS2) and cyclooxygenase-2 (COX2) are inflammation-associated enzymes implicated in immune regulation. We hypothesized that inhibition of these pathways enhances antitumor immunity and improves responsiveness to immune checkpoint therapy in HCC. **Methods:** Tumor tissues from 75 patients with resected hepatocellular carcinoma (HCC) were analyzed by immunohistochemistry for NOS2, COX2, and CD8 to assess expression levels and spatial correlations. In parallel, an orthotopic murine HCC model was established by intrahepatic injection of 7.5×10^5 RIL-175 cells (n = 6–10 mice per group). Mice were treated with vehicle control, selective NOS2 inhibition (1400W), COX2 inhibition (celecoxib), anti–PD-L1, or combination regimens including triple therapy. After two weeks of treatment, tumors were harvested for immune profiling, including flow cytometry, spatial imaging, plasma cytokine analysis, and CITE-seq. In vitro, splenocytes isolated from B6 mice were treated with prostaglandin E2 (PGE2) or the nitric oxide donor DETA-NONOate, and expression of CD226 and TIGIT was quantified by flow cytometry. **Results:** High intratumoral NOS2 expression was associated with inferior overall survival in resected HCC patients (HR 3.65, p=0.0011), with further worsening observed in tumors co-expressing NOS2 and COX2 (HR 9.31, $p<0.0001$). In murine HCC, combined iNOS and COX2 inhibition significantly reduced tumor burden and promoted intratumoral accumulation of $CD8^+$ and $CD4^+$ T cells, accompanied by increased B-cell recruitment and elevated circulating IL-2 and IFN-γ. Triple therapy with dual enzyme inhibition plus anti–PD-L1 resulted in superior tumor control and prolonged survival. Single-cell transcriptomic analysis comparing control, dual inhibition, and triple-treatment groups revealed a progressive enhancement of $CD8^+$ T-cell activation states, characterized by increased expression of activation-associated markers and reduced expression of inhibitory receptors. Dual and triple therapy induced upregulation of CD226 and downregulation of TIGIT in $CD8^+$ T cells, reflecting enhanced antitumor effector function. In vitro, nitric oxide and prostaglandin E2 directly impaired $CD8^+$ T-cell function, as evidenced by reduced CD226 and increased TIGIT expression. **Conclusions:** iNOS and COX2 cooperatively establish an immunosuppressive inflammatory program in HCC that limits $CD8^+$ T-cell–mediated antitumor immunity and response to checkpoint blockade. Dual targeting of these pathways represents a promising strategy to enhance immunotherapy efficacy in HCC. Research Sponsor: UPMC enterprise.

Safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activities of FL115, a novel IL-15 superagonist, from the first-in-human study in patients with locally advanced/metastatic solid tumors.

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Background: FL115 is an engineered IL-15/IL15Rα-Fbody fusion protein, in which Fbody is a single-chain Fc designed to eliminate classical Fc effects including ADCC/CDC/ADCP while retaining FcRn engagement. It aims to enhance anti-tumor immunity via IL-15-mediated signaling on NK and CD8+ T cells while minimizing complexity from Fc. **Methods:** The first-in-human, dose-escalation study of FL115 (NCT06130722) evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of FL115 in adult patients with advanced solid tumors. FL115 monotherapy was administered intravenously once weekly. **Results:** 11 patients (7F, 4M) were enrolled, median age 64, who had progressed on prior systemic therapies across four dose cohorts (3–60 μg/kg). MTD was not reached. No SAEs related to FL115 or DLT were observed. Most TRAEs were Grade 1–2 and aligned with the known safety profile of cytokine-based therapies and underlying conditions of patients. Only three reversible TRAEs occurred, including transient Grade 3 alanine aminotransferase elevation, Grade 3 headache, and Grade 4 neutropenia. PK was dose-dependent, with half-life at 2.1-3.1 hours. Four patients had Stable Disease per imaging (DCR 36.3%). Dose-dependent expansion of lymphocytes was observed, with average absolute lymphocyte count (ALC) of 1257 cells/μl at baseline, and peak ALC count of 2371 cells/μl post treatment, mainly from increase in NK cells and CD8+T cells. One patient (Cervical Cancer) had Stable Disease from 1st dose at July 2024 (ALC of 1100 cells/μl) to study completion (ALC of 1900 cells/μl in August 2025). FL115 treatment led to significant transient cytokine release in peripheral blood: at 3 μg/kg, peak interferon-γ level reached 3730 pg/ml with IL-6 at 0.8 pg/ml, suggesting specific targeting of NK and T cells. An essentially identical Phase 1 study of FL115 was conducted in China, in which similar trends were observed; two patients remained on treatment with confirmed partial responses lasting 32 and 24 weeks, respectively. **Conclusions:** FL115 is the first IL-15 superagonist as monotherapy has shown a favorable safety profile and promising signs of durable antitumor activities in heavily pretreated patients, along with significant and sustained expansion of NK and T cell population and unique robust transient induction of interferon-γ. A Phase II study of FL115 with Bacillus Calmette-Guérin in patients with nonmuscle invasive bladder cancer (NCT07122414) and a Phase Ib study of FL115 (IV) in combination with an anti-PD-1 antibody in solid tumor patients (NCT07131202) are ongoing, and a Phase I study of FL115 subcutaneous injection will be initiated soon (IND submitted). Clinical trial information: NCT # 06130722. Research Sponsor: Furlong.

TPS3155 Poster Session

A phase 1/2, first-in-human, open-label, dose-escalation and -expansion study of TAK-188, a novel antibody-drug conjugate (ADC) targeting CCR8$^+$ regulatory T cells, in adult patients with locally advanced or metastatic solid tumors.

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Background: Regulatory T cells (Tregs) are key contributors to an immunosuppressive tumor microenvironment (TME). Their abundance in solid tumors is often linked to poor patient prognosis, decreased overall survival, and resistance to immunotherapy. Tumor-infiltrating Tregs express high levels of chemokine receptor CCR8, making CCR8 an attractive target for immunotherapy. TAK-188 is a first-in-class anti-CCR8 ADC that aims to enhance patients' own antitumor activity by selectively eliminating CCR8-positive Tregs within the TME. It uses a novel amanitin payload capable of killing both actively dividing and non-dividing cells and is linked to the antibody via a cleavable linker. The nonclinical toxicology profile demonstrated monitorable and partially-to-completely reversible toxicities at doses exceeding projected clinically efficacious exposures. Preclinical evaluation of TAK-188 showed robust and deep depletion of CCR8$^+$ cells *in vitro* and *in vivo*, and demonstrated anti-tumor activity as a single agent in non-clinical models (Casson et al. AACR 2026). **Methods:** This phase 1/2 study (NCT07205718) is enrolling adult patients with locally advanced or metastatic solid tumors known to express high levels of CCR8 on Tregs in the TME (gastroesophageal adenocarcinoma [GC] and esophageal squamous cell carcinoma [ESCC], pancreatic ductal adenocarcinoma, non-squamous and squamous non-small cell lung cancer [NSCLC], head & neck SCC [SCCHN], or colorectal cancer), and whose disease has progressed on, or are intolerant to, all standard therapies. Eligible patients must have Eastern Cooperative Oncology Group performance status $\leq$1 and radiographically measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. In phase 1, TAK-188 is intravenously administered weekly at escalating dose levels following a Bayesian Optimal Interval design, to determine the recommended phase 2 dose (RP2D) and dosing schedules for the cohort-expansion phase. The primary objective is to determine the safety and tolerability of TAK-188 in phase 1 and to assess the preliminary efficacy in phase 2 in NSCLC, SCCHN and GC. Secondary objectives include characterization of the RP2D and pharmacokinetic parameters for TAK-188, changes in T cell populations (abundance and ratio of Tregs and effector T cells) within the tumor post-treatment, and preliminary efficacy in select cancer types. Exploratory objectives include the impact of TAK-188 on CCR8$^+$ Tregs, molecular response determined by circulating tumor DNA (ctDNA) analysis, and changes in cytokines and chemokines in peripheral blood. The study plans to enroll up to 223 patients in the USA (47 patients across 15 sites for dose-escalation; 62–176 patients across ~35 sites in cohort-expansion). Clinical trial information: NCT07205718. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA), Cambridge, MA, USA.

TPS3156 Poster Session

A phase 1 study of HWK-007, a next-generation, protein tyrosine kinase 7 (PTK7)–targeted antibody-drug conjugate (ADC), in patients with advanced solid tumors.

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Background: PTK7 is a pseudokinase expressed during embryogenesis and downregulated in normal adult tissue. Aberrant overexpression of PTK7 has been reported in up to 70% of solid tumors and is associated with tumor progression, metastasis, chemoresistance, and poor prognosis. A previous analysis demonstrated particularly high *PTK7* expression in non-small cell lung cancer (NSCLC), endometrial carcinoma (EC), and ovarian cancer (OC), across histologic subtypes and disease stages, making PTK7 an attractive therapeutic target with cross-indication applicability (Matulonis et al. AACR-NCI-EORTC 2025, Poster C040). Results from early clinical trials of cofetuzumab pelidotin, a PTK7-targeted, auristatin-based ADC, showed promising clinical activity. HWK-007 is a next-generation, PTK7-targeted ADC comprising an Fc effector-attenuated IgG1 antibody conjugated to the DNA topoisomerase I inhibitor (TOP1i) CPT116. It was designed using novel bioconjugation and advanced linker–payload technologies that enhance intracellular delivery and minimize systemic release of unconjugated TOP1i. This first-in-human, phase 1 trial evaluates HWK-007 in patients with advanced or metastatic solid tumors. **Methods:** This multicenter, open-label, single-arm, phase 1 dose-escalation (a)/expansion (b) trial is enrolling patients aged ≥18 years with advanced or metastatic NSCLC (non-squamous, epidermal growth factor receptor–wild-type [*EGFR*wt]), EC (all histologies), or epithelial OC (all histologies). Patients with NSCLC or EC must have prior treatment with platinum-based chemotherapy and a PD-(L)1 inhibitor, if eligible. Patients with OC must have platinum-resistant disease and prior treatment with standard-of-care therapy. All patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (except in the OC dose-escalation cohorts in which patients with non-target lesions per RECIST and CA125 ≥2 times ULN are permitted), Eastern Cooperative Oncology Group performance status 0 or 1, and no prior treatment with a TOP1i-containing ADC. Patients with clinically active brain metastases or a history of pneumonitis/interstitial lung disease are ineligible. In phase 1a, patients are sequentially assigned to HWK-007 dose levels (DLs; administered intravenously, once every three weeks) using a Bayesian Optimal Interval design (toxicity threshold, 25%), with potential backfill. Backfill cohorts are enriched for patients with *EGFR*wt NSCLC. Primary endpoints are safety, maximum tolerated dose, and recommended dose for expansion cohorts (phase 1a); and safety and objective response rate (phase 1b). Secondary endpoints include pharmacokinetics and preliminary efficacy outcomes. Recruitment is underway; planned enrollment is up to 226 patients. Clinical trial information: NCT07444814. Research Sponsor: None.

TPS3157 **Poster Session**

A phase 2 study of telisotuzumab adizutecan (ABBV-400; Temab-A) in patients with advanced solid tumors harboring *MET* amplification.

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Background: *MET* amplification is a rare alteration occurring at a rate of 0.06%–4.2%, in different solid tumor types across genomic databases. It is associated with poor prognosis and has limited treatment options. Currently, there are no therapies approved specifically to target *MET*-amplified tumors. Temab-A is an antibody-drug conjugate targeting c-Met and conjugated to a topoisomerase 1 inhibitor payload. In a first-in-human study (NCT05029882), Temab-A demonstrated encouraging activity (objective response rate 46%) and a manageable safety profile in *MET*-amplified solid tumors (Murciano-Goroff et al. ESMO 2025), supporting the continued investigation of Temab-A. The present phase 2 study evaluates Temab-A in adults and adolescents (12–17 years) with relapsed/refractory advanced solid tumors harboring *MET* amplification. **Methods:** This is an open-label, single-arm, global, multicenter phase 2 study (NCT07196644) enrolling approximately 125 patients (100 global; 25 China cohort) with locally advanced or metastatic solid tumors harboring *MET* amplification. Patients must have received ≥1 prior systemic therapy appropriate for their tumor type in the advanced/metastatic setting and have no satisfactory alternative treatment options. Patients must be ≥12 years old, have ECOG PS 0–1, measurable disease per RECIST v1.1 or RANO, and documented *MET* amplification by local next-generation sequencing or central FoundationOne CDx. Patients are treated with Temab-A 2.4 mg/kg IV every 3 weeks until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Trial objectives are listed in the table. Enrollment began in November 2025; as of December 2025, 1 patient has enrolled. Clinical trial information: EU CT: 2024-518871-74-00. Research Sponsor: AbbVie.

Objectives.	
Primary	Evaluate efficacy (ORR per ICR, RECIST v1.1/RANO) and safety of Temab-A (AEs, vital signs, ECG, clinical laboratory testing)
Secondary	Further assess efficacy (DOR, PFS, OS, disease control) and characterize PK and immunogenicity (PK parameters, ADAs, nADAs)
Exploratory	Biomarker analyses (eg, c-Met expression) and PROs evaluation

ADAs, antidrug antibodies; AEs, adverse events; DOR, duration of response; ECG, electrocardiogram; ICR, independent central review; nADAs, neutralizing antidrug antibodies; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROs, patient-reported outcomes; RANO, Response Assessment in Neuro-Oncology; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

TPS3158 Poster Session

A phase I, multi-center study of KIVU-107, a novel PTK7-targeting antibody-drug conjugate (ADC), in participants with advanced solid tumors.

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Background: Protein tyrosine kinase 7 (PTK7) is a transmembrane pseudokinase involved in normal embryonic development and has been associated with tumor initiation, metastasis and therapeutic resistance in cancer. PTK7 is over-expressed in multiple solid tumors, including lung, head and neck, breast, ovarian and endometrial cancers. KIVU-107 is an antibody-drug conjugate (ADC) comprised of a PTK7-targeting antibody conjugated to the SYNtecan E linker-payload via the GlycoConnect/Hydraspace (GC/HS) site-specific conjugation technology with a drug-to-antibody ratio of 4.[1,2] The GC/HS platform abolishes Fcγ receptor-mediated effector activity and utilizes a highly polar spacer to reduce hydrophobicity and aggregation of the ADC, translating into improved safety and pharmacokinetic profiles.[1,2] KIVU-107 has demonstrated potent anti-tumor efficacy as a single agent and in combination across multiple preclinical tumor models, including regression in tumors refractory to chemotherapy or ADCs.[1,2] Moreover, KIVU-107 is highly stable and well tolerated in non-human primates.[1,2] **Methods:** This Phase 1, multi-center, open-label, dose-finding and dose-expansion study is designed to investigate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of KIVU-107 in patients with select advanced solid tumors. The Dose Finding stage will employ Backfill Bayesian Optimal Interval (BF-BOIN) design to establish the maximum tolerated dose (MTD) and recommended dose for expansion (RDE). Eligible participants for the Dose Finding stage include those with advanced solid tumors known to be enriched for PTK7 overexpression and that have exhausted available standard-of-care (SOC) treatments including non-small cell lung, small cell lung, head and neck squamous cell carcinoma, breast, endometrial, ovarian and others. The Dose Expansion stage will further explore the safety, tolerability and preliminary efficacy in disease-specific cohorts relapsed or refractory to SOC therapies. The primary endpoints include safety, tolerability, and determination of MTD and RDE for KIVU-107. Secondary and exploratory endpoints include PK, immunogenicity, preliminary clinical activity and biomarker assessments. Enrollment for Dose Finding has initiated. Clinical trial information: NCT07229313. 1) Trikha M. Striving for Kinder and Gentler ADCs: Spotlight on Solid Tumor Target and Preclinical Development of KIVU-107. Presented at: 16th World ADC San Diego; November 4, 2025; San Diego, CA. 2) Viller V, Zhang L, Jiang X, et al. Preclinical Efficacy and Safety of KIVU-107, a Novel PTK7-Targeting Antibody-Drug Conjugate (ADC). Poster presented at: 16th World ADC San Diego; November 5, 2025; San Diego, CA. Clinical trial information: NCT07229313. Research Sponsor: Kivu Bioscience.

TPS3159 **Poster Session**

A phase 1, first-in-human study of DS3610, a stimulator of interferon genes (STING) agonist antibody-drug conjugate (ADC), in patients with advanced/metastatic solid tumors.

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Background: While immunotherapies have improved treatment for patients with advanced/metastatic solid tumors, there remains a need for novel therapies that can overcome resistance to existing therapies, enhance antitumor activity, and delay disease progression. Promoting the innate immune response through activation of the endoplasmic reticulum adaptor protein stimulator of interferon genes (STING) has been associated with antitumor activity. DS3610 is an antibody–drug conjugate (ADC) comprising an anti-epidermal growth factor receptor (EGFR) monoclonal antibody attached to an immunomodulatory payload that acts as an agonist of STING. EGFR is a transmembrane receptor tyrosine kinase that is overexpressed in a broad range of solid tumors. DS3610 is designed to deliver the STING agonist payload directly to the tumor microenvironment, activating immune cells such as antigen-presenting cells and T cells, and inducing immune targeting of cancer cells. The antibody component has novel Fc modifications designed to reduce the risk of class-specific adverse events, such as systemic cytokine release. **Methods:** DS3610-071 (NCT07159126) is a Phase 1, first-in-human, open-label, global, dose-escalation study of DS3610 (N≈70). Patients must be adults with advanced or metastatic solid tumors and be intolerant to standard-of-care therapies or have disease that has relapsed after or is refractory to such therapies. Eligible tumor types include non-small cell lung cancer, head and neck cancer, renal cell carcinoma, urothelial carcinoma, colorectal cancer, gastric cancer, pancreatic cancer, esophageal cancer, biliary tract cancer, and uterine cancer. Patients must have measurable disease per RECIST 1.1; an ECOG performance status of 0, 1, or 2; and be willing and able to provide a pretreatment or archival tumor tissue sample. Patients will receive DS3610 at escalating doses. The primary objectives are to assess the safety and tolerability of DS3610 and to determine the recommended dose(s) for expansion for further evaluation of DS3610. Safety endpoints include identifying dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints include the assessment of DS3610 immunogenicity, based on the prevalence and incidence of antidrug antibodies, and the evaluation of DS3610 pharmacokinetics. Exploratory endpoints include evaluating the efficacy of DS3610 and identifying biomarkers that may be associated with clinical benefit. Enrollment is ongoing. Clinical trial information: NCT07159126. Research Sponsor: Daiichi Sankyo.

TPS3160 **Poster Session**

BNT326-01: A Phase 1b/2 trial of BNT326/YL202 (HER3 ADC) as monotherapy and in combination with pumitamig (anti-PD-L1 × VEGF bsAb) in patients with advanced solid tumors.

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Background: BNT326/YL202 is an investigational ADC composed of an anti-HER3 IgG1 monoclonal antibody conjugated to ~8 molecules of a novel topoisomerase I inhibitor payload via a tripeptide linker. HER3 is frequently overexpressed in various solid tumors, particularly in relapsed or refractory tumors, making it an attractive therapeutic target. Increasing evidence suggests that ADCs may enhance the efficacy of immunotherapeutic agents. It is hypothesized that combining BNT326 with immunotherapy including pumitamig, an investigational anti-PD-L1 x VEGF-A bispecific antibody, could lead to better patient outcomes than administering either drug alone. Targeting angiogenesis may facilitate ADC penetration, which in turn could stimulate tumor immunity and increase sensitivity to PD-L1 inhibition. Preclinical in vivo models testing the combination of pumitamig with BNT326 showed superior tumor growth inhibition compared to each treatment alone (Hamilton E, AACR 2025, #648). **Methods:** This global Phase 1b/2, open-label, adaptive two-part multicohort trial (NCT07070232) will evaluate safety, efficacy, optimal dose and pharmacokinetics of BNT326 in selected indications, both as monotherapy (Part 1) and in combination with pumitamig (Part 2) in patients (≥18y, ECOG PS 0 or 1) with histologically or cytologically confirmed solid tumors that are advanced and/or have relapsed/progressed after prior therapy. Both parts will start enrolling patients independently of each other. In Part 1, patients in Cohorts 1A-C will be randomized to one of two dose levels of BNT326 based on doses derived from the ongoing monotherapy trials (YL202-INT-101-01 [NCT05653752] and YL202-CN-201-01 [NCT06107686], whereas Cohorts 1D, 1E, and 1G receive dose level 2 of BNT326. 1A: cutaneous melanoma 2L+; 1B: NSCLC 2L+, negative for actionable oncogenic alterations; 1C: EGFRm NSCLC 2L+; 1D: rare melanoma; 1E: other advanced solid tumors; 1F: drug-drug interaction cohort, dose defined in randomization cohorts 1A - 1C; and 1G: cervical cancer 2L+. In Part 2, patients in Cohorts 2A and 2B will receive two dose levels of BNT326 in combination with pumitamig. Patients in Cohorts 2D and 2E will receive two dose levels of BNT326 with pumitamig and dose level 2 of BNT326 as monotherapy. Patients in Cohort 2F receive one combination dose level. 2A: cutaneous melanoma 2L+; 2B: HER2-negative breast cancer 2L+/1L; 2C (optional, not open): cutaneous melanoma 1L+; 2D: gastric/gastroesophageal junction cancer 2L+; 2E: colorectal cancer 2L+; and 2F: cervical cancer 2L+. Primary endpoints are safety, overall response rate, and pharmacokinetics for cohort 1F. Enrollment for all cohorts is ongoing globally. Clinical trial information: NCT07070232. Research Sponsor: BioNTech SE.

A phase 1, multicenter, open-label, dose-escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of SBO-154 in subjects with advanced solid tumors.

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Background: Mucin 1 (MUC1) is a transmembrane glycoprotein overexpressed in advanced epithelial malignancies, where it promotes tumor progression and correlates with poor clinical outcomes. The membrane-proximal SEA domain of MUC1 is exposed on tumor cells and undergoes rapid internalization, enabling targeted intracellular delivery of cytotoxic payloads. SBO-154 is a MUC1 SEA–directed antibody–drug conjugate (ADC) conjugated to the clinically validated cytotoxic payload monomethyl auristatin E (MMAE) via a protease-cleavable linker. Unlike the shed MUC1-VNTR that creates an antigen sink limiting efficacy of prior ADCs, the negligibly shed MUC1-SEA epitope enables more effective SBO-154 tumor targeting. Nonclinical studies of SBO-154 showed MUC1-dependent cytotoxicity, dose-dependent tumor inhibition in vivo, and a favorable safety for clinical evaluation. This first-in-human study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary antitumor activity of SBO-154 in subjects with locally recurrent or metastatic solid tumors who have exhausted or are intolerant to available therapies. **Methods:** This phase 1, open-label, multicenter study comprises two parts: dose escalation (Part 1) and dose expansion (Part 2). Eligible adults (≥18 years) must have RECIST v1.1–measurable, locally recurrent or metastatic solid tumors (excluding sarcoma), documented progression after or intolerance to standard therapy, ECOG performance status 0–1, adequate organ function, and tumor tissue for immunohistochemistry (IHC) analysis. SBO-154 will be administered as an intravenous infusion on Day 1 of each 21-day treatment cycle (Q3W) over 30 minutes. Part 1 will use an mTPI-2 design with intra-patient dose escalation from 0.3 mg/kg to 2.5 mg/kg. Approximately 75 subjects will be enrolled in Part 1 (~50 in dose escalation and ~25 in backfill cohorts), and up to 102 subjects in Part 2. After determining the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE), Part 2 will be initiated with a Simon's two-stage design. Planned expansion cohorts will include NSCLC, ER+ breast cancer, and ovarian cancer, with enrolment to be restricted to tumors with high MUC1-SEA expression. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal from the study. Primary endpoints: include dose-limiting toxicities (DLTs), treatment-related serious adverse events, dose modifications, and clinical/laboratory safety findings. Secondary endpoints: include PK, immunogenicity and efficacy. Enrollment Status: The study initiated enrolment in August 2025. Cohorts 1 and 2 have been completed without any DLTs, and enrolment in Cohort 3 is ongoing as of December 2025. Clinical trial information: NCT07042100. Research Sponsor: None.

TPS3162 **Poster Session**

Phase 1/2 study of CLIO-8221, a HER2-targeted, dual-payload exatecan and ATR inhibitor antibody-drug conjugate (ADC) in patients with advanced HER2-expressing solid tumors.

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Background: CLIO-8221 is a novel anti-HER2 ADC designed to overcome topoisomerase 1 inhibitor (Topo1i) resistance by incorporating both Topo1i (exatecan) and ataxia telangiectasia and rad3-related protein inhibitor (ATRi; berzosertib) payloads. Enabled by proprietary dual-payload ADC linker technology, CLIO-8221 uses an Fc-engineered trastuzumab, site-specifically conjugated with a stable protease-cleavable linker designed for optimal efficacy and tolerability. Trastuzumab deruxtecan (T-DXd) has redefined the treatment paradigm for HER2-expressing breast cancer and is emerging as a frontline treatment option. However, most patients develop resistance and disease progression. Topo1i-induced replication stress triggers activation of the DNA damage response pathway, which is an important driver of Topo1i resistance. Studies show that ATRi synergizes with Topo1i to enhance DNA damage and increase antitumor activity. In preclinical studies, CLIO-8221 binds with high affinity and specificity to HER2-expressing tumor cells and is rapidly internalized to release the Topo1i and ATRi payloads to drive direct tumor cell killing with a strong bystander effect. CLIO-8221 shows superior *in vivo* efficacy across tumor models with a range of T-DXd sensitivity, inducing tumor regression after a single dose in T-DXd resistant and refractory xenograft models. Additionally, CLIO-8221 is designed to minimize off-target uptake through Fc engineering for abrogated FcγR binding, and a proprietary hydrophilic linker for reduced macropinocytosis. CLIO-8221 is well tolerated in nonclinical toxicity studies in non-human primates. **Methods:** CLIO-8221-001 is a Phase 1/2, first in human dose-escalation and -expansion study. Eligible patients are adults with metastatic or unresectable HER2-expressing solid tumors, including those who previously received T-DXd. Patients must have measurable disease per RECISTv1.1 and have previously received therapies known to confer clinical benefit unless ineligible, refused by the patient, or not available in the region. CLIO-8221 will initially be given by intravenous infusion on Day 1 of a 21-day cycle; treatment may continue until disease progression, unacceptable toxicity, or other reason for discontinuation. The primary objectives are to assess the safety and tolerability of CLIO-8221 and to identify the maximum tolerated dose, if reached, and recommended Phase 2 dose. Phase 1 of the study utilizes a BOIN dose-escalation design with an expansion phase, while Phase 2 comprises tumor-specific expansion cohorts treated at the doses recommended from Phase 1. Antitumor activity, PK, immunogenicity, and biomarkers including HER2 status and ctDNA dynamics will also be evaluated. Enrollment is planned at sites in Australia, US, and China (NCT07300943). Clinical trial information: NCT07300943. Research Sponsor: Callio Therapeutics.

TPS3163 **Poster Session**

Phase 1, first-in-human, open-label study evaluating the safety, tolerability, pharmacokinetics, and preliminary efficacy of TGW101 in patients with advanced solid tumors.

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Background: Tumor-associated glycoprotein 72 (TAG-72) is a non-internalizing glycoepitope that is aberrantly expressed in a broad range of epithelial cancers, predominantly adenocarcinomas. TGW101 is an antibody-drug conjugate (ADC) therapy that utilizes a novel, bioorthogonal click chemistry-based linker technology that enables the targeting of non-internalizing cancer antigens and controlled payload release. The first component of TGW101 is a chemically cleavable ADC (TGW101-ADC) that consists of a diabody targeting TAG-72 and a highly stable *trans*-cyclooctene (TCO) linker conjugated to a monomethyl auristatin E (MMAE) payload. Once the TGW101-ADC binds to intratumoral TAG-72 and is largely cleared from the systemic circulation, the second drug component, a tetrazine trigger (TRG001), is administered, leading to rapid MMAE release from TGW101-ADC via a selective cleavage reaction with the TCO linker. Upon release of MMAE into the tumor microenvironment, it readily diffuses into surrounding tumor cells, binds to microtubules, inhibits cell cycle progression, and activates local immune cells. In preclinical studies, TGW101 treatment led to tumor regressions in the OVCAR3 (ovarian) cell line and GXF214 (gastric) patient-derived xenograft model, and improved survival in LS174T (colon) tumor bearing mice. **Methods:** This first-in-human, open-label Phase 1 study evaluates the safety and tolerability of TGW101 and defines a maximum tolerated dose (MTD). A Bayesian Optimal Interval (BOIN) design is used to determine the recommended dosing regimen(s) for expansion. Secondary objectives include assessing the pharmacokinetic (PK) profile, intratumoral pharmacodynamics, preliminary anti-tumor activity, and immunogenicity of TGW101. Exploratory analysis will investigate the relationship between TAG-72 expression and tumor response, as well as the effect of TGW101 exposure on tumor biomarkers. Up to 50 participants with advanced solid tumors, including breast, NSCLC, prostate, cervical, endometrial, ovarian, gastroesophageal, and non-squamous cell carcinoma of the head and neck are planned for enrollment. During dose escalation, increasing doses of TGW101-ADC, administered intravenously on Day 1 followed 7 days later by a fixed-dose infusion of TRG001, will be explored in cohorts of 3-4 participants treated in 3-week cycles. Once pharmacologically active dose levels are identified, specific cohorts may enroll additional participants to further explore safety, PK, tumor biomarker changes, and efficacy. Adverse events are assessed according to CTCAE v5 and tumor response is determined by RECIST 1.1 or PCWG3 criteria every 6 weeks for the first 2 cycles, then every 9 weeks. The trial began in May 2025 and 7 sites, all within the United States, are open for enrollment. Clinical trial information: NCT06959706. Research Sponsor: None.

TPS3164 **Poster Session**

First-in-human clinical evaluation of ST-01156, an optimized and selective degrader of RNA-binding motif 39 (RBM39): A phase 1 study in advanced solid malignancies with a focus on RBM39-dependent cancers.

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Background: ST-01156 is an orally administered agent developed to degrade RBM39, a protein target that is principally involved with splicing RNA into messenger RNA and is commonly upregulated in cancer. ST-01156 has entered phase 1 clinical trials for the treatment of several cancer types supported by its novel mechanism of action and data from preclinical testing. The lead optimization process for ST-01156 maximized degradation selectivity, anticancer potency, metabolic stability (including deuteration), and other drug-like properties. The ability of ST-01156 to achieve functionally meaningful and selective effects is exemplified by complete degradation of RBM39 within hours following treatment *in vitro*, accompanied by downstream mis-splicing of pathogenic transcripts, most notably the *EWSR1-FLl1* fusion transcript driving Ewing sarcoma (ES). Adding to this effect, ST-01156 depleted proteins involved in DNA damage repair (DDR), supporting the potential for synthetic lethality with cancer cells that depend on proficient DDR. RBM39 is also involved in the splicing of KRAS isoforms thought to be essential for the proliferation and survival of oncogenic KRAS cancer stem cells, providing an anticancer mechanism distinct from the mechanisms of current KRAS inhibitory agents. In advanced hepatocellular carcinoma (aHCC), RBM39 is substantially overexpressed and likely impedes essential arginine sensor activities. In addition to demonstrating robust activity in these malignancies, ST-01156 is highly active in patient-derived xenograft models of neuroblastoma, biliary tract carcinoma (BTC), and endometrial carcinoma (EC). In animal toxicology studies, hematologic and gastrointestinal tissues were most susceptible to RBM39 inhibition. **Methods:** In the first-in-human study, ST-01156 doses will be adaptively escalated based on the rate and severity of adverse events in trial participants with advanced solid malignancies. ST-01156 will be administered orally for 5 consecutive days every 7 days with an option of adapting a continuous dosing schedule, if tolerable. Backfilling of safe dose levels with participants with high priority malignancies will be allowed. In addition to traditional safety and tolerability endpoints, dose escalation and Phase 2 dose derivation will be based on pharmacokinetic (PK) endpoints and real-time RBM39 targeting measurements in peripheral mononuclear cells. The optimal dose of ST-01156 derived from safety tolerability, PK and pharmacodynamic data will be evaluated in trial participants in the following expansion cohorts: A, ES; B, aHCC; C, *KRAS*-mutant cancers; and D, an adaptive cohort of cancers projected to be susceptible to RBM39 inhibition including BTC, EC, and cancers with DDR aberrations. Clinical trial information: NCT07197554. Research Sponsor: SEED Therapeutics Inc.

TPS3165 **Poster Session**

A phase 1/2 first-in-human study of TH9619 in patients with advanced refractory solid tumors (ODIN).

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Background: TH9619 is a first-in-class, potent, small-molecule, and dual inhibitor of methylene-tetrahydrofolate dehydrogenase (MTHFD)1 and MTHFD2, both highly overexpressed in solid tumors and cancer-specific key enzymes within the one-carbon metabolic pathway. TH9619 kills cancer cells via a dual mechanism of action (1) inhibition of MTHFD1 traps folate leading to thymidine depletion, and (2) inhibition of nuclear MTHFD2 disrupts DNA damage response and repair pathways. With its unique characteristics, in preclinical models, TH9619 kills tumour cells, while sparing healthy tissues. The results from pre-clinical models, the novel mechanism of action, and the high unmet medical need in advanced refractory solid tumours support this investigation. **Methods:** ODIN (NCT07151040; EudraCT No. 2024-519639-40-00) is a first-in-human, multicentre, open-label, Phase 1/2 study. Eligible patients include adults with histologically confirmed advanced colorectal cancer, non–small cell lung cancer, head and neck squamous cell carcinoma, gastric cancer, or gastroesophageal junction cancer who have exhausted the institutional standard of care and have progressive and measurable disease per RECIST 1.1. Patients will receive TH9619 monotherapy via an intravenous infusion, weekly for 3 weeks, followed by one week without infusion, of a 28-day cycle, for up to 2 years. The Phase 1a dose-escalation, planning to recruit up to 80 patients, will assess the overall safety and tolerability profile and determine the maximum tolerated dose (MTD) and recommended Phase 2 dose(s) (RP2D(s)). Phase 1b is cohort expansion and plans to recruit up to 60 patients. Assessments include adverse events, pharmacokinetic (PK) and pharmacodynamic (PD) parameters, and preliminary anti-tumor activity per RECIST v1.1. Additionally, predictive biomarkers and metabolites related to the one-carbon metabolism and potential correlation with efficacy of TH9619 will be explored. The Phase 2 will further characterize safety, PK, PD, and efficacy at the RP2D(s). The ODIN phase 1/2 study is actively enrolling across leading academic and clinical research centres in the United Kingdom, France, and Spain, with expansion planned across additional European sites in the coming months. As of this submission, dose escalation is ongoing. Clinical trial information: NCT07151040. Research Sponsor: None.

TPS3166 **Poster Session**

TAGNOT: A phase 1b/2 tumor-agnostic study of the selective anti-FGFR1 monoclonal antibody OM-RCA-01 in FGFR1-expressing advanced solid tumors.

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Background: Fibroblast growth factor receptor 1 (FGFR1) plays a key role in the pathogenesis of multiple malignancies; however, no highly selective FGFR1-targeted therapies for solid tumors are currently approved. OM-RCA-01 is a humanized monoclonal antibody that selectively binds extracellular domains II–IIIc of FGFR1 with high affinity (Kd = 1.59 nM) and has demonstrated promising antitumor activity in preclinical models. In the first-in-human, tumor-agnostic (TAGNOT) study, patients with FGFR1-expressing advanced cancers are being treated with OM-RCA-01. **Methods:** TAGNOT is a phase 1b/2, multicenter, multicohort, prospective study designed according to the FDA-recommended OPTIMUS approach. Key eligibility criteria include FGFR1 expression by immunohistochemistry (IHC 2+ or 3+ in ≥10% of tumor cells) and metastatic disease progressing after ≥2 prior systemic treatment lines. The primary objective of the phase 1b component is to determine the recommended phase 2 dose (RP2D). Two dose levels of OM-RCA-01 (50 mg and 100 mg administered intravenously every 2 weeks) will be compared for safety (CTCAE v5.0), preliminary efficacy (objective response rate [ORR] per RECIST v1.1), pharmacokinetics, neutralizing antibody formation, and circulating tumor DNA dynamics. The primary endpoint of the phase 2 component is ORR in the ITT population. Five tumor-specific cohorts are planned: clear-cell renal cell carcinoma (n = 11), castration-resistant prostate cancer (n = 11), non-small cell lung cancer without EGFR or ALK alterations (n = 11), breast adenocarcinoma with known receptor status (n = 11), and head and neck squamous cell or salivary gland carcinomas (n = 11). Using Simon's two-stage design, a total of 55 patients will be enrolled. The null hypothesis of a true ORR of 10% will be tested against a one-sided alternative of 25%. The study will be terminated after the first stage if ≤3 responses are observed among 31 patients. Otherwise, 24 additional patients will be enrolled. The null hypothesis will be rejected if ≥10 responses are observed in 55 patients, yielding a one-sided type I error rate of 0.05 and 90% power. Clinical trial information: NCT07292168. Research Sponsor: Bureau for Cancer Research - BUCARE.

TPS3167 **Poster Session**

A first-in-human study of ATX-295, an oral inhibitor of KIF18A, in patients with advanced or metastatic solid tumors, including ovarian cancer.

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Background: ATX-295 is an oral inhibitor of KIF18A, an adenosine triphosphate (ATP)-dependent, plus end-directed mitotic kinesin. KIF18A facilitates chromosomal alignment and spindle microtubule dynamics during mitosis in certain advanced solid tumors with chromosomal instability (CIN). In preclinical studies, ATX-295 demonstrated robust antiproliferative activity in chromosomally instable solid tumor models, including in high grade serous ovarian cancer. In vivo, oral administration of ATX-295 induced dose-dependent tumor growth inhibition in CIN platinum-resistant ovarian and squamous non-small cell lung cancer cell-line derived xenograft (CDX) and patient derived xenograft (PDX) models. **Methods:** NCT06799065 is a multi-center, first-in-human, Phase 1/2, open-label, single-arm, dose-escalation and expansion study to evaluate the safety profile of ATX-295 and determine the recommended phase 2 dose (RP2D) in subjects with locally advanced or metastatic solid tumors. The study in progress will be conducted in two parts: dose escalation, followed by dose expansion. Participant enrollment and continuous safety assessment will be guided by a mTPI-2 design (Guo, 2017) to identify an optimal dose. To assess evidence of preliminary antitumor activity, a Simon 2-stage design (Simon, 1989) will be used during dose expansion. Key eligibility criteria: patients with histologically confirmed solid tumors who have locally recurrent or metastatic disease, including high grade serous ovarian cancer (HGSOC) and squamous non-small cell lung cancer (sqNSCLC); refractory to or relapsed after all standard therapies with proven clinical benefit. For the expansion cohorts, participants must have histological confirmation of HGSOC and be determined to be platinum-resistant, platinum-refractory, or platinum-intolerant; have measurable disease; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Primary endpoints will evaluate safety and tolerability of ATX-295 at pharmacologically active dose(s) and/or schedule(s) and determine the recommended phase 2 dose (RP2D). Secondary endpoints will evaluate pharmacokinetics (PK) of ATX-295 in plasma and evaluate pharmacodynamic (PD) effects of ATX-295 to assess preliminary evidence of anti-tumor activity. The study is actively recruiting. Clinical trial information: NCT06799065. Research Sponsor: Accent Therapeutics.

TPS3168 **Poster Session**

First-in-human phase 1 dose escalation and expansion study of PIN-5018, a CK1α-selective molecular glue degrader, in patients with advanced solid tumors.

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Background: Casein kinase 1 alpha (CK1α) is a serine/threonine kinase involved in multiple oncogenic signaling pathways regulating cell proliferation, differentiation, and survival. Dysregulation of CK1α has been implicated across several solid tumor types, supporting its evaluation as a therapeutic target. PIN-5018 is an orally administered, CK1α-selective molecular glue degrader designed to induce targeted proteasomal degradation of CK1α via cereblon-mediated ubiquitination. Previously presented preclinical studies have demonstrated selective CK1α degradation and antitumor activity in multiple solid tumor models, providing the scientific rationale for first-in-human clinical evaluation. In addition to safety and dose optimization, the study incorporates tumor- and blood-based correlative analyses to characterize CK1α degradation and downstream pathway modulation. **Methods:** PIN-5018-001 is an ongoing, first-in-human, open-label, multicenter phase 1 study evaluating PIN-5018 in patients with progressive, locally advanced (unresectable), or metastatic solid tumors who have exhausted standard treatment options. The study consists of a dose escalation phase followed by dose expansion at selected dose levels based on safety, pharmacokinetics, and preliminary antitumor activity. PIN-5018 is administered orally once daily in 21-day cycles (14 days on treatment followed by 7 days off). Dose escalation evaluates six planned dose levels (10–100 mg) using a Bayesian Optimal Interval (BOIN) design with a target dose-limiting toxicity rate of 25%. Dose-limiting toxicities are assessed during Cycle 1. Up to 36 patients may be enrolled in dose escalation, with plan to add dose optimization and dose expansion cohorts. Eligible patients are adults (≥18 years) with ECOG performance status 0–1 and at least one measurable lesion per RECIST v1.1. Mandatory pre-treatment and on-treatment tumor biopsies are required when medically feasible to support correlative biomarker analyses. Enrollment has begun. Cohort 1 has been completed without DLT, and enrollment to subsequent cohorts is ongoing. Clinical trial information: KCT0011322. Research Sponsor: Pin Therapeutics, Inc.

TPS3169 **Poster Session**

An open-label, multicenter study of DPTX3186 to evaluate safety, tolerability, and pharmacokinetics in subjects with known Wnt pathway–activated solid tumors where no other treatments exist.

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Background: Constitutive activation of the Wnt/β-catenin pathway drives malignancy in a wide range of cancers, where β-catenin has been notoriously difficult to drug due to its disordered nature, lack of defined drug-binding pockets, and associated toxicities. Biomolecular condensates are membraneless organelles that orchestrate cellular processes, biological pathways, and protein activity by compartmentalizing biomolecules. DPTX-3186 is a small molecule condensate modulator (c-mod) that acts via a novel mechanism of action, sequestering β-catenin into inactive condensate depots. This sequestration selectively inhibits β-catenin-driven transcription and induces robust cancer cell death. DPTX3186 is an orally bioavailable small molecule c-mod that demonstrates strong anti-tumor activity across multiple tumor types driven by various defects along the Wnt/β-catenin pathway. Studies in xenographs show that DPTX-3186 modulates Wnt pathway activity as evidenced by formation of inactive β-catenin condensates and modulation of β-catenin-driven gene transcription. Profound pharmacological efficacy, including regressions and complete responses, has been observed in murine models of gastric cancer as monotherapy. The molecule has been granted Fast Track and Orphan Drug Designations by the FDA. **Methods:** This first-in-human, phase 1/2, multicenter, open-label, dose-escalation (phase 1) and dose-expansion (phase 2) study evaluates the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor effects of DPTX3186 monotherapy in patients with known Wnt pathway activated solid tumors. Eligible patients must have no other approved treatment options available. In Phase 1, DPTX3186 is administered orally in a 4 days on / three days off schedule, at escalating dose levels, evaluated sequentially in a BOIN design. Phase 2 dose expansion will utilize a TOP-BOIN design and will evaluate DPTX3186 monotherapy in patients with histologically or cytologically confirmed non-resectable gastric adenocarcinoma who are refractory to prior treatment. Primary endpoints are safety and tolerability of DPTX-3186, including dose-limiting toxicities (DLT) and the determination of the MTD and recommended dose for expansion. Secondary endpoints are PK, PD, and preliminary anti-tumor activity (e.g. overall response rate, duration of response, progression-free survival, disease control rate, and overall survival). 40 patients are planned to be enrolled in Part 1, which is currently enrolling in the USA. Clinical trial information: NCT07312903. Research Sponsor: Dewpoint Therapeutics.

TPS3170 **Poster Session**

Phase 1/2 study of the novel Werner helicase inhibitor EIK1005 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors, including MSI-H or dMMR tumors.

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Background: Cancers with deficient mismatch repair (dMMR) have high microsatellite instability (MSI-H) and are reported to be sensitive to inhibition of the Werner syndrome helicase (WRN) via synthetic lethality. WRN inhibition in MSI-H cells leads to loss of genomic integrity and ultimately cell death while not affecting microsatellite stable (MSS) and healthy cells. Standard of care for patients (pts) with MSI-H tumors includes surgery and immunotherapy (checkpoint inhibitors [CPIs] like pembrolizumab [pembro]). While these are viable treatment options, depending on the indication, ~30 to 50% do not respond to first-line immune CPIs, or acquire resistance. A critical unmet medical need exists for new therapies for such patients (pts). EIK1005 is a novel, potent, high-affinity and selective WRN inhibitor (WRNi) with the potential for targeted antitumor activity in MSI-H or dMMR solid tumors. In vitro studies demonstrated sustained target engagement leading to cell death in MSI-H cells while sparing MSS and healthy cells. In a Phase 1 single ascending dose study in healthy participants, EIK1005 was well tolerated at the doses evaluated. **Methods:** EIK1005-002 (NCT#07262619) is a multicenter, multi-part, Phase 1/2 study of EIK1005 monotherapy and combination with pembro, in participants with advanced solid tumors including MSI-H and dMMR tumors. The study has three parts; Part 1A (monotherapy dose escalation [DE]): EIK1005 will be evaluated at ~ three dose levels (DL) in participants without alternative therapeutic options (n~40). Preference is given to pts with MSI-H or dMMR cancer for whom prior CPI therapy has failed, or with MSS cancer who progressed after ≥1 regimen of platinum, alkylating or topoisomerase chemotherapy as evidence suggests MMR alterations and MSI induction in previously MSS cancer. Part 1B (combination DE): participants with MSI-H or dMMR tumors (n~40) will receive EIK1005 + pembro (Q3W). Part 2 (dose optimization [DO]): participants (n~80) with MSI-H and dMMR tumors and slowly progressive disease are randomized 1:1 to receive EIK1005 at one of two doses from Part 1A. Key eligibility criteria: participants ≥18 years, life expectancy ≥3 months, unresectable and/or metastatic solid tumor, measurable disease at baseline (RECIST v1.1), progression after or intolerance to ≥ 1 advanced-setting standard treatment regimen (Part 1A), has MSI-H or dMMR tumor (Parts 1B and 2) and slowly progressive disease (Part 2). Primary objectives: safety and tolerability of EIK1005 monotherapy and + pembro to determine the MTD (Part 1) and to inform DO (Part 2). Secondary objectives: preliminary antitumor activity, characterize plasma PK profile of EIK1005 monotherapy and + pembro. This study began in December 2025. Clinical trial information: NCT07262619. Research Sponsor: None.

TPS3171 Poster Session

Phase 1, multi-center clinical trial evaluating the safety, pharmacokinetics, pharmacodynamics and anti-cancer activity of PQ203, a first-in-class peptide drug conjugate targeting SORT1 in patients with advanced solid tumor malignancies (NCT07190469).

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Background: Antibody–drug conjugates (ADCs) have improved outcomes in several refractory cancers by enabling the targeted delivery of potent cytotoxins but their use is limited by suboptimal payload release, off-target and immune-related toxicities, poor tumor penetration and complex manufacturing. Peptide drug conjugates (PDCs) offer potential advantages over ADCs including smaller size, increased tumor penetration, more rapid systemic clearance and decreased immunogenicity. PQ203 is a first in class, AI-designed PDC comprised of a 17 amino acid peptide targeting sortilin (SORT1) conjugated to the cytotoxin monomethyl auristatin E (MMAE) via a para-amino-benzyl-valine-citrulline (PAB-VC) cleavable linker. SORT1, a receptor of the Vps10p family involved in protein trafficking, is overexpressed across multiple tumor types and associated with tumor invasiveness. Preclinical breast cancer models, including patient-derived xenografts, show that PQ203 can overcome resistance to commonly used TOP1-based ADCs. **Methods:** This first-in-human, multi-country Phase 1A/B dose-escalation, expansion and optimization clinical trial is designed to assess the safety, pharmacokinetics, pharmacodynamics, immunogenicity and preliminary anti-tumor activity of PQ203. Treatment consists of once weekly IV infusion $\times$ 4 weeks (Q1Wx4) and continues until the occurrence of disease progression or dose-limiting toxicity. In Part 1 of the study, up to 7 dose cohorts are anticipated (commencing at 0.02 mg/kg) in a backfill Bayesian optimization (BF-BOIN) dose escalation design with a target toxicity rate of 27.5%. Upon satisfaction of pre-defined safety criteria for particular dosing cohorts, up to 9 additional patients (pts.) in pre-defined settings of biologic and clinical interest may be enrolled to backfill expansion of that dose level. Upon identification of one or more recommended doses for expansion, up to 50 pts. across 1-3 tumor types of particular clinical interest, including pts. with triple negative breast cancer, will be enrolled in the expansion and dose optimization phases of the study. Alternative dosing schedule(s) with reduced frequency may additionally be explored based on emerging PK and safety data. At the time of submission, cohorts 1 and 2 were completed without DLTs and enrollment of Cohort 3 was initiated in January, 2026. Clinical trial information: NCT07190469. Research Sponsor: None.

TPS3172 Poster Session

A phase 1 first-in-human study of BGM-2121 in patients with advanced solid tumors.

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Background: Parathyroid hormone-related protein (PTHrP) is a hormone frequently overexpressed in tumors such as pancreatic ductal adenocarcinoma (PDAC), lung, and head and neck cancers. In some cases, this overexpression can lead to hypercalcemia in patients with malignancies. PTHrP is a ligand of G-protein–coupled receptor (GPCR) known as parathyroid hormone type 1 receptor (PTH1R), thereby activating multiple downstream signaling pathways. Despite the significant role of GPCRs in cancer biology, therapeutic options targeting these receptors in oncology remain limited. BGM-2121 is a potent, first-in-class, humanized IgG1 monoclonal antibody targeting the N-terminal region of PTHrP, aiming to inhibit the PTHrP/PTH1R pathway. Preclinical studies exhibit high affinity and specificity for PTHrP, demonstrating robust antitumor activity in pancreatic cancer xenograft models, and significantly prolonging survival. In lung squamous cell carcinoma models, BGM-2121 was found to prevent and reverse hypercalcemia and cancer-associated weight loss, which are the key features of humoral hypercalcemia of malignancy and cachexia. **Methods:** BGM-2121-001 (NCT07346846) is a first-in-human, open-label, phase 1 trial designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary antitumor, anti-cachexia, and anti-hypercalcemia activity in adults with advanced solid tumors. Eligible participants are adults with histologically or radiographically confirmed advanced solid tumors who are refractory to, intolerant of, or without available standard therapies. Tumor types of primary interest include pancreatic, esophageal, head and neck, and non–small cell lung cancers, particularly sub-type of squamous cell carcinoma. Participants must have ECOG performance status ≤2 and adequate organ function. Key exclusions include active central nervous system metastases, significant cardiovascular disease, uncontrolled infections, recent anticancer therapy, prior allogeneic transplantation, active viral hepatitis or HIV infection. BGM-2121 is administered intravenously every 2 weeks in sequential dose-escalation cohorts (160, 320, 480, 800, and 1200 mg) using a standard 3+3 design. Dose-limiting toxicities are assessed during the first 28 days, and the maximum tolerated dose is defined as the highest dose at which ≤1 of 6 patients experiences a dose-limiting toxicity. Dose modifications are determined by the Safety Review Committee. Treatment continues until disease progression, unacceptable toxicity, or loss of clinical benefit. Clinical trial information: NCT07346846. Research Sponsor: Biogate Precision Medicine Corporation.

TPS3173 **Poster Session**

A multicenter phase 1/1b study of AMG 436 as monotherapy and combination therapy in patients with advanced MSI-H/dMMR solid tumors.

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Background: Microsatellite instability-high (MSI-H)/mismatch repair deficiency (dMMR) tumors are characterized by high mutational burden and replication stress. These tumors rely on Werner syndrome protein (WRN), a DNA helicase required for DNA replication and repair, to sustain tumor cell survival. As a result, this reliance on WRN creates a synthetic lethal vulnerability, making WRN inhibition a promising therapeutic strategy. AMG 436 is a selective, covalent WRN inhibitor that is designed to exploit this dependency in MSI-H/dMMR tumors. AMG 436 represents a tumor-intrinsic approach that is mechanistically distinct from immune checkpoint inhibitors (ICIs), the current standard of care. This first-in-human Phase 1/1b trial evaluates AMG 436 as monotherapy and in combination with immune checkpoint inhibitors and/or chemotherapy in adults with MSI-H/dMMR solid tumors, including ICI-naïve and post-ICI populations. **Methods:** This study is a Phase 1/1b, open-label, multicenter trial enrolling approximately 464 adult participants with metastatic or locally advanced MSI-H/dMMR solid tumors. The study consists of 4 parts: Part 1 involves monotherapy dose exploration; Part 2 explores combination doses with chemotherapy or an immune checkpoint inhibitor; Part 3 focuses on monotherapy dose expansion and randomized dose optimization; and Part 4 involves combination dose expansion with chemotherapy and/or ICIs. The primary objectives are to assess safety and determine the maximum tolerated dose or recommended dose for expansion, with primary endpoints being the incidence of dose-limiting toxicities (DLTs) during the DLT evaluation period and the incidence of treatment-emergent adverse events and serious adverse events. Secondary objectives include pharmacokinetics and preliminary antitumor activity per RECIST v1.1. Descriptive statistics will be used to summarize safety, pharmacokinetic, and efficacy data. Key eligibility criteria are adults with MSI-H/dMMR status, ECOG 0–1, and adequate organ function. Enrollment is ongoing globally across North America, South America, Europe, and Asia-Pacific. Participants may remain on treatment for up to 2 years, with total trial duration including follow-up extending up to 5 years. Clinical trial information: 177459. Research Sponsor: Amgen Inc.

TPS3174 **Poster Session**

Phase I study of [^{225}Ac]Ac-ETN029, a DLL3-targeted radioligand therapy, in patients with advanced DLL3-expressing solid tumors.

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Background: Delta-like ligand 3 (DLL3) is an atypical Notch ligand that is highly expressed in small cell lung cancer (SCLC) and other neuroendocrine carcinomas, with minimal expression in normal adult tissues. [^{225}Ac]Ac-ETN029 (^{225}Ac-ETN029) is a novel, DLL3-targeted, macrocyclic peptide-based radioligand therapy (RLT) demonstrating potent antitumor activity in DLL3-positive, SCLC cell line–derived, xenograft mouse models. Here, we describe CESP359A12101 (NCT07006727), a global first-in-human phase 1 study evaluating ^{225}Ac-ETN029 in patients with selected advanced DLL3-expressing solid tumors. **Methods:** The primary objectives of the study are to assess the safety and tolerability of ^{225}Ac-ETN029 and to identify the recommended radioactive dose(s) of ^{225}Ac-ETN029 for further clinical evaluation. Secondary objectives are to assess the preliminary antitumor activity of ^{225}Ac-ETN029, characterize the pharmacokinetics (PK) and dosimetry of ^{225}Ac-ETN029, and characterize the safety, PK, dosimetry, and imaging properties of [^{111}In]In-ETN029 (^{111}In-ETN029). Study participants are expected to receive 4 cycles of ^{225}Ac-ETN029 at 6-week intervals, although a lower or higher number of cycles may be explored if deemed beneficial and safe. The study includes dose escalation and dose expansion parts. During dose escalation, increasing levels of administered activity per cycle will be assessed across cohorts. Dose escalation decisions will be based on a review of all available data, including safety, tolerability, dosimetry, PK, pharmacodynamics, and preliminary efficacy, and guided by the Bayesian logistic regression model using the escalation with overdose control principle. Dose expansion will begin once recommended radioactive dose(s) of ^{225}Ac-ETN029 for further clinical investigation have been determined. Eligible patients must be ≥18 years old; have locally advanced, unresectable, or metastatic disease measurable per RECIST v1.1; and be diagnosed with one of the following: (1) SCLC, (2) large cell neuroendocrine carcinoma (LCNEC) of the lung (escalation only), (3) de novo or castration-resistant, treatment-emergent, neuroendocrine prostate cancer (NEPC; expansion only), or (4) gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC; expansion only). Patients with SCLC, LCNEC, and GEP-NEC must have disease progression following, or intolerance of, ≥1 prior line of systemic therapy. Patients with NEPC and GEP-NEC must have ≥1 measurable lesion (per RECIST 1.1) demonstrating ^{111}In-ETN029 uptake higher than surrounding tissues on SPECT/CT as assessed by the investigator. Patients with prior DLL3-targeted therapy (except for SCLC) or prior RLT (except for NEPC) will be excluded. Patient enrollment began in October 2025. Clinical trial information: NCT07006727. Research Sponsor: None.

TPS3175 Poster Session

Alpha-emitting radionuclide or beta-emitting radionuclide combined with metastasis-directed stereotactic body radiotherapy for oligorecurrent prostate adenocarcinoma (ANDROMEDA): A phase II trial.

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Background: The recent LUNAR study (NCT05496959) found that adding beta-emitting ^{177}Lutetium-PNT2002 (^{177}Lu-PSMA) to stereotactic body radiation therapy (SBRT) more than doubled median progression-free survival (PFS) compared to SBRT alone in oligorecurrent hormone-sensitive prostate cancer (orHSPC), hazard ratio (HR)=0.37. However, the relative efficacy compared to novel alpha-emitting ^{225}Actinium-PSMA-617 (^{225}Ac-PSMA) is unknown. The hypothesis is that ^{225}Ac-PSMA will improve PFS by treating more micrometastases, given its higher radiobiologic effectiveness. We aim to compare the relative benefit of 2 cycles of ^{177}Lu-PSMA versus 1 cycle of ^{225}Ac-PSMA followed by SBRT metastasis-directed therapy (MDT). **Methods:** ANDROMEDA (NCT07150715) is a phase II, non-blinded, single-center randomized trial for individuals with orHSPC and 1-5 PSMA-avid metastases outside the prostate/prostate bed (N1 and/or M1). Eligibility criteria include testosterone >150 ng/dL, ≥18 years, and ECOG performance status ≤2. Exclusion criteria include *de novo* metastatic disease, castrate-resistance (testosterone <50 ng/mL with rising PSA), ADT/chemotherapy within 6 months of enrollment, and neuroendocrine histology. Participants are randomized 1:1 to 2 cycles ^{177}Lu-PSMA (7.4 GBq/cycle, 6 weeks apart) or 1 cycle of ^{225}Ac-PSMA (8 MBq, once), followed by SBRT to all lesions 1-2 weeks after radioligand therapy infusion. The primary endpoint of PFS is defined as the time from randomization to either 1) a new PSMA-avid lesion or 2) PSMA-PET local progression (>30% SUV increase or >20% increase in the sum of the longest lesion diameters) with a PSA rise. For those alive without progression, PFS will be censored at the time of the last scan. All randomized subjects will be analyzed based on intent-to-treat. Secondary endpoints include 24-month disease burden by PSMA-PET, physician-scored toxicity, patient-reported quality of life, ADT-free survival, local control of SBRT lesions at 24 months after last radionuclide infusion, and time-to-progression (locoregional, distant, new metastasis). We hypothesize that the 24-month post-SBRT PSA-based recurrence rate of ^{177}Lu-PSMA will be ~50%, which will be reduced with ^{225}Ac-PSMA to ~30% (PFS HR~0.51). We anticipate an accrual time of 1.5 years and a median follow-up time of 24-months. A sample size of 96 patients (48 per arm) would provide 80% power to detect the expected difference in PFS at a 0.1 alpha level. Assuming a 10% drop-out/screen failure rate, the target trial accrual is 107 patients. Early stopping guidelines include monitoring site-specific grade 4-5 toxicity with a safety threshold of 20% from the time of the first enrolled patient, which would trigger halting the trial and safety consultation. ANDROMEDA is currently open for enrollment. Clinical trial information: NCT07150715. Research Sponsor: None.

TPS3176 **Poster Session**

[^{212}Pb] Pb-MP0712 in patients with small cell lung cancer and other Delta-like ligand 3–expressing solid tumors: A phase 1/2a study to assess safety, tolerability, and efficacy.

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Background: [^{212}Pb]Pb-MP0712 is a novel radiopharmaceutical comprising a Designed Ankyrin Repeat Protein (DARPin) that binds with high affinity to DLL3 and carries the alpha-emitting isotope lead-212 (^{212}Pb) for targeted delivery of high linear energy transfer radiation. DLL3 is highly expressed in SCLC, large cell neuroendocrine carcinoma (LC-NEC) of the lung, and extrapulmonary NEC (epNEC), while its expression in healthy tissue is virtually absent. In preclinical studies, [^{212}Pb]Pb-MP0712 selectively accumulates in DLL3-positive tumors, exhibits an adequate biodistribution profile, and induces complete and durable tumor regression with prolonged survival and a favorable safety profile (Croset et al. AACR 2025). Initial human imaging data from a patient who received [^{203}Pb]Pb-MP0712 in a Named Patient Access Program under the legal framework for compassionate care in South Africa indicate its specific uptake in tumor (Steiner et al. TRP EU 2025). **Methods:** This first-in-human Phase 1/2a study evaluates the safety, biodistribution, dosimetry, and preliminary antitumor efficacy of [^{212}Pb]Pb-MP0712 (NCT07278479). Key inclusion criteria are SCLC and progression or recurrence following ≥2 prior lines of systemic therapy, or lung LC-NEC or epNEC with progression or recurrence following ≥1 prior line of systemic therapy, and measurable disease by RECIST v1.1. Patients with clinically stable central nervous system metastasis or prior DLL3-targeted therapy are eligible. Key exclusion criteria are Merkel cell carcinoma, neuroendocrine prostate cancer, interstitial lung disease, and active non-infectious pneumonitis. This study has two parts, a dose escalation (Part 1) and an expansion (Part 2). Primary objectives of Part 1 are to evaluate safety and tolerability of [^{212}Pb]Pb-MP0712, and to determine the maximum tolerated dose and recommended phase 2 dose (RP2D). Primary objective of Part 2 is to assess preliminary antitumor activity of [^{212}Pb]Pb-MP0712. All patients will receive a single dose of [^{203}Pb]Pb-MP0712 as intravenous (IV) injection at 185 MBq to evaluate DLL3-expressing tumor lesions, pharmacokinetics, biodistribution and dosimetry using single-photon emission computerized tomography (SPECT)/CT, followed by [^{212}Pb]Pb-MP0712 treatment. In study Part 1, for SCLC/lung LC-NEC cohorts, treatment proceeds regardless of imaging results; for epNEC cohorts, a DLL3-positive SPECT/CT is required. Patients will be enrolled in sequential cohorts to receive escalating doses of [^{212}Pb]Pb-MP0712 as IV injection on Day 1 of each 28-day cycle for up to six cycles. The dose escalation will be guided by an adaptive Bayesian Logistic Regression Model. Upon completion of Part 1, Part 2 will enroll two groups of patients with DLL3-positive SCLC/lung LC-NEC or epNEC at the RP2D. Clinical trial information: NCT07278479. Research Sponsor: Molecular Partners AG, Zuerich-Schlieren, Switzerland; Orano Med SAS.

TPS3177 Poster Session

Beamion BCGC-1: Four new phase Ib/II cohorts to evaluate oral zongertinib with other agents in HER2-positive metastatic breast cancer (mBC) and metastatic colorectal cancer (mCRC).

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Background: Zongertinib, an oral, irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Beamion BCGC-1 (NCT06324357) is an ongoing Phase (Ph) Ib/II trial evaluating zongertinib in HER2-positive tumors. Trial details for Cohorts A–K, evaluating zongertinib as monotherapy or combined with T-DM1, T-DXd, or trastuzumab ± capecitabine in patients (pts) with HER2-positive mBC, and with T-DXd in pts with HER2-positive metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma (mGEAC), have recently been published (Hurvitz et al, *Future Oncol* 2025). In addition to BC and GEAC, early-phase data indicate zongertinib is also active in mCRC (Yoh et al, *Ann Oncol* 2025, abstr 491P). Here, we report 4 new cohorts (L–O) to evaluate the efficacy and safety of zongertinib plus zanidatamab in HER2-positive mBC, or plus trastuzumab or mFOLFOX6 ± trastuzumab in HER2-positive mCRC. **Methods:** For the 4 new cohorts, pts must have histologically/cytologically confirmed, unresectable HER2-positive mBC or mCRC, and documented HER2-positive disease (overexpression/amplification). Pts with mBC must have disease progression following ≥1 prior HER2-targeted treatment; pts with mCRC must have disease progression/recurrence during or following their latest treatment. Pts with brain metastases are allowed. There are 3 new Ph Ib cohorts (M, N, and O; each ~20 pts). Cohorts M and N will assess zongertinib in mCRC: pts will receive once-daily zongertinib across escalating dose levels plus mFOLFOX6 every 14 days (Cohort M), or mFOLFOX6 every 14 days + trastuzumab every 21 days (Cohort N; Table). In Cohort O, pts with mBC will receive once-daily zongertinib across escalating dose levels plus zanidatamab every 21 days. Dose escalation will be guided by a BLRM with overdose control. In Ph II, Cohort L, a new dose justification cohort (~40 pts with mCRC), will receive zongertinib 120 mg once daily plus trastuzumab every 21 days. In Ph Ib, the primary endpoint is DLTs during the MTD evaluation period; secondary endpoints include objective response (OR) by RECIST v1.1, DLTs in the on-treatment period, and pharmacokinetics (PK). In Ph II, the primary endpoint is OR by RECIST v1.1; secondary endpoints include PFS, disease control, AEs leading to dose reduction, PK, and pt-reported outcomes. Pts will remain on treatment until any protocol-defined stopping criterion occurs. Clinical trial information: NCT06324357. Research Sponsor: Boehringer Ingelheim.

Cohort	Indication	Zongertinib Regimen
Ph Ib dose escalation		
M	mCRC	+ mFOLFOX6: oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), 5-FU (2400 mg/m^2)
N	mCRC	+ mFOLFOX6: oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), 5-FU (2400 mg/m^2) + trastuzumab (8 mg/kg loading; 6 mg/kg maintenance)
O	mBC	+ zanidatamab (1800 mg <70 kg; 2400 mg ≥70 kg)
Ph II dose justification		
L	mCRC	+ trastuzumab (8 mg/kg loading; 6 mg/kg maintenance)

TPS3178 **Poster Session**

A study of MT-4561 in patients with various advanced solid tumors (NCT06943521).

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Background: MT-4561 is a bromodomain-containing protein 4 (BRD4) protein degrader, which is a bi-functional molecule having both a binder moiety that binds to BRD4 and a degron moiety that binds to damage-specific deoxyribonucleic acid (DNA) binding protein 1 (DDB1) and cullin 4 (CUL4) associated factor 16 (DCAF16), which is responsible for the ubiquitination of BRD4. MT-4561 degrades BRD4, a bromodomain protein that stimulates oncogene transcription, using the ubiquitin-proteasome system. Tanabe Pharma has demonstrated that this novel BRD4 degrader, MT-4561, exerts continuous anti-tumor effects in various cancer xenograft models (Ooike, 2024). **Methods:** This trial is a FIH, Phase I/II study to evaluate safety, tolerability, PK, PD, and efficacy of MT-4561 in patients with advanced solid tumors. Part 1 is evaluating safety, tolerability, PK, MTD, and the doses to be investigated in Part 2 (dose optimization) using the BOIN design. Part 2 evaluates the safety and efficacy of MT-4561 in patients with pre-specified tumor types based on data from Part 1, and to determine the RP2D. Part 2 can begin enrollment after the MTD and/or the doses to be investigated in Part 2 have been determined based on data from Part 1. Part 3 of the study is the open-label drug-drug interaction (DDI) cohort to evaluate the effect of MT-4561 on the PK established in Part 1. A retrospective analysis will also be conducted to assess the correlation between efficacy and expression of BRD4/its downstream gene products in patient samples to explore predictive biomarkers. MT-4561 is administered as an intravenous (IV) infusion over 30 minutes once every week in 28-day cycles, until disease progression or discontinuation criteria are met. Parts 1 and 3 of the study will enroll patients 18 years and older with who have failed at least 1 therapy , who have $\geq$ 1 measurable lesion by RECIST v1.1 and with confirmed histologic or cytologic diagnosis of one of the following tumors: HNSCC, NSCLC, esophageal cancer, gastric cancer, biliary tract cancer, PDAC, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, prostate cancer, urothelial carcinoma, NET or NEC, soft tissue sarcoma, and NUT carcinoma. Part 2 will enroll only pre-specified tumors for dose optimization to determine the RP2D. Key exclusion criteria include patients with unresolved $\geq$ Grade 2 toxicities from previous treatment and those with QTc prolongation $>$ 470 msec at screening. Also, patients who received drugs with a known risk of QT interval prolongation or torsade de pointes, before the start of IMP administration. Enrollment in Part 1 of the study began May 2025 and continues to enroll patients in the US and Japan with 10 patients enrolled through Dose Level 2 as of Jan 2026. The safety data along with DLT continues to be reviewed in Part 1. Ooike S, et al. PB069, Poster Session, 36th EORTC-NCI-AACR Symposium, 2024. Clinical trial information: NCT06943521. Research Sponsor: None.

TPS3179 **Poster Session**

A phase 1, first-in-human study of DS9051, a novel targeted protein degradation molecule, in patients with advanced/metastatic adrenocortical carcinoma (ACC) or metastatic castration-resistant prostate cancer (mCRPC).

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Background: ACC and mCRPC are difficult-to-treat malignancies. mCRPC typically progresses despite androgen deprivation and androgen receptor pathway inhibitor (ARPI) therapy, with or without taxanes. Similarly, treatment options for ACC are limited and prognosis is generally unfavorable. DS9051 is a targeted protein degradation molecule that has been designed to selectively degrade a key protein involved in the development and progression of both ACC and mCRPC via a novel mechanism. It leverages the ubiquitin-proteasome system, where DS9051 acts as a bridge to link the target protein and E3 ligase, initiating ubiquitination and degradation of the target protein. **Methods:** DS9051-079 (NCT07189403) is a Phase 1, first-in-human, open-label, multicenter study of DS9051 (N≈40). Patients must be adults with histologically confirmed advanced or metastatic ACC (Stage III–IV) or mCRPC and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with ACC must have measurable disease per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1) that is not amenable to radical surgical resection or definitive radiotherapy. Further inclusion criteria for patients with mCRPC include prior treatment with ≥1 line of ARPI therapy for castration-sensitive or -resistant prostate cancer for ≥12 weeks and with ≥1 line of chemotherapy (or not amenable to chemotherapy). These patients must also have ≥1 of the following criteria: prostate-specific antigen (PSA) progression per Prostate Cancer Working Group 3 (PCWG3) criteria, bone disease progression per PCWG3 criteria, or soft tissue disease progression per RECIST 1.1. Patients will receive DS9051 orally at escalating doses. The primary objective is to assess the safety and tolerability of DS9051 and to determine the maximum tolerated dose and/or recommended dose for expansion. Safety endpoints include dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints for both tumor types include objective response rate, disease control rate, clinical benefit rate, and duration of response (all assessed by the investigator, per RECIST 1.1 for ACC and per PCWG3 criteria for mCRPC); for ACC, progression-free survival (PFS) will be assessed by the investigator per RECIST 1.1, and for mCRPC, radiographic PFS and PSA decline will be assessed by the investigator per PCWG3 criteria. Enrollment is ongoing. Clinical trial information: NCT07189403. Research Sponsor: Daiichi Sankyo.

TPS3180 **Poster Session**

A phase 1, first-in-human, open-label, dose-escalation and -expansion study of gamitrinib, a first-in-class, mitochondria-directed inhibitor of the molecular chaperone heat shock protein-90 (Hsp90) in patients with advanced cancer.

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Background: Mitochondria are subcellular organelles whose signaling and bioenergetics functions are exploited in cancer. This requires tight control of intra-organelle protein folding, which is made possible by the accumulation of molecular chaperones of the Heat Shock Protein-90 (Hsp90) family in mitochondria of tumors, but not normal tissues. This provides a unique therapeutic opportunity to disable multiple tumor pathways at once, but previously developed Hsp90 inhibitors do not accumulate in mitochondria, and systemic inhibition of chaperone activity is toxic in humans. Gamitrinib is a first-in-class anticancer agent specifically designed to disrupt protein folding in mitochondria, combining the Hsp90 inhibitory backbone of 17-allylamino-geldanamycin (17-AAG) to the mitochondria-targeting moiety, triphenylphosphonium. Gamitrinib selectively accumulates in mitochondria, does not affect the function of cytosolic Hsp90, and irreversibly disrupts organelle protein folding with activation of multiple cell death pathways. In preclinical studies, Gamitrinib shows potent, cytotoxic activity against multiple cancer cell types (IC_{50} 0.16–29 μM), inhibits primary and metastatic tumor growth in xenograft and genetic mouse models, has slower clearance (85.6 $\pm$ 5.8 mL/min/kg) and longer half-life (12.2 $\pm$ 1.55 h) than unconjugated 17-AAG, and is well-tolerated with no alterations in clinical-chemistry parameters, organ function, or tissue histology at dose levels of up to 5 (rats)- and 12 (dogs)-fold higher than therapeutically effective doses in mice (Cancer Biol Ther 23:117). **Methods:** Based on preclinical activity, favorable safety, and unique mechanism of anticancer activity, a first-in-human, open-label, dose-escalation phase 1 trial of Gamitrinib in sequential cohorts of adult patients with advanced solid tumors or lymphoma, for whom no standard therapy is available, was initiated (NCT04827810). Per study protocol, Gamitrinib is administered as a 1-h weekly intravenous (IV) injection on a 28 day-cycle with a 3+3 dose-escalation design and dosing continuing until disease progression, unacceptable toxicity, or patient discontinuation for any other reason. Trial objectives include determination of MTD and/or RP2D, overall safety, PK profile, correlative studies of target engagement in paired pre- and post-treatment biopsies in a 6-patient expansion cohort at MTD and documentation of anti-tumor activity by RECIST 1.1 and RECIL 2017 criteria. As of 2026, 18 evaluable patients have been accrued over 5 escalating Gamitrinib dose levels (10-85 mg) with no DLTs as assessed by NCI CTCAE v5.0 grading. 336 plasma samples have been collected for PK analysis. The study is currently open and enrollment is ongoing. Clinical trial information: NCT04827810. Research Sponsor: Gateway Foundation.

TPS3181 **Poster Session**

Phase Ib study of POLQ inhibitor SYN818 combined with olaparib in advanced solid tumors.

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Background: SYN818 is a selective, potent oral POLQ helicase inhibitor. POLQ is essential for microhomology-mediated end-joining and fills single-stranded DNA (ssDNA) gaps during replication. In tumors with homologous recombination repair (HRR) deficiencies (e.g., BRCA1/2 mutations), inhibition of PARP creates a dependency on POLQ for ssDNA gap filling, providing a synthetic lethal therapeutic strategy. Preclinically, SYN818 significantly enhanced the antitumor activity of Olaparib in breast and ovarian cancer models. Phase 1a monotherapy data demonstrate that SYN818 has a favorable pharmacokinetic profile and is well tolerated, supporting further evaluation of SYN818 in combination with Olaparib in HRR-deficient metastatic solid tumors. **Methods:** This phase 1b, open-label, multicenter study (NCT07156253; CTR20253189) evaluates SYN818 in combination with Olaparib in adults with locally advanced or metastatic solid tumors harboring BRCA mutations and/or homologous recombination repair (HRR) deficiency. During dose escalation (Part 1), patients receive escalating doses of SYN818 in combination with Olaparib (300 mg BID) administered in 21-day cycles to determine the recommended Phase 2 dose (RP2D), guided by a Bayesian dose-finding model. In the dose-expansion phase (Part 2), tumor-specific cohorts, including ovarian cancer and HER2-negative breast cancer, will further assess safety and preliminary antitumor activity at the RP2D. The primary objectives are to evaluate safety, tolerability, and determine the RP2D. Secondary objectives include characterization of pharmacokinetics, pharmacodynamics, and preliminary antitumor activity per RECIST v1.1. Key eligibility criteria include age ≥18 years, ECOG performance status 0–1, documented BRCA mutation and/or HRR deficiency, and adequate organ function. Prior PARP inhibitor therapy is permitted. Enrollment initiated in September 2025. Clinical trial information: NCT07156253. Research Sponsor: None.

TPS3182 **Poster Session**

IDE892 as monotherapy and in combination with IDE397 in patients with 5-methylthioadenosine phosphorylase-deleted (*MTAP*-Del) advanced solid tumors (IDE892001): Phase 1 trial.

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Background: MTAP deletion in solid tumors causes intracellular accumulation of methylthioadenosine (MTA) which partially inhibits activity of the key methylating enzyme, protein arginine methyltransferase 5 (PRMT5) and creates synthetic lethal dependencies on PRMT5 and methionine adenosyltransferase 2A (MAT2A), the rate limiting step in the synthesis of PRMT5 substrate, S-adenosyl methionine. PRMT5 and MAT2A are essential to transcription modulation, gene splicing, and DNA damage response. IDE892 is an MTA-cooperative PRMT5 inhibitor designed to exploit this vulnerability in MTAPdel tumors. Preclinical studies report robust antitumor activity with IDE892 monotherapy in MTAPdel xenograft models and an enhanced response when combined with IDE397 (an allosteric MAT2A inhibitor). IDE892-001 is a Phase 1 study evaluating safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of IDE892 alone and in combination with IDE397. **Methods:** IDE892-001 is an ongoing, open-label, multicenter four-part study: IDE892 monotherapy dose escalation (Part 1), monotherapy dose expansion in MTAPdel NSCLC (Part 2), IDE892 + IDE397 dose escalation (Part 3), and combination expansion in MTAPdel NSCLC (Part 4). Adults with advanced or metastatic MTAPdel solid tumors including lung, urothelial, gastrointestinal cancers (including pancreatic and biliary tract cancers) and mesothelioma are eligible following disease progression on standard therapies. Key exclusion criteria include symptomatic brain metastases, cardiac disease, active severe infection, and prior treatment with a PRMT5 or MAT2A inhibitor. Part 1 uses a Bayesian optimal interval design to determine maximum tolerated dose (MTD) and recommended doses for expansion (RDE). Part 3 uses a modified toxicity probability interval design to evaluate escalating combinations of IDE892 and IDE397. Oral treatment is given QD in 21-day cycles until progression or unacceptable toxicity. Serial blood samples are collected for PD analyses. Imaging will be performed every 6 weeks through week 24, then every 9–12 weeks. Efficacy endpoints will be assessed by RECIST v1.1. Primary objectives for dose-escalation cohorts (Parts 1 and 3) are safety and tolerability, including determination of MTD/RDE. In expansion cohorts (Parts 2 and 4), co-primary objectives include safety and preliminary antitumor activity (objective response rate and duration of response). Secondary endpoints for all parts include PK of IDE892 alone and in combination with IDE397. Exploratory assessments include progression free survival, changes in circulating and tumor-based markers of PRMT5 pathway modulation, molecular predictors of response, exposure–response relationships, and metabolite characterization. Clinical trial information: NCT07277413. Research Sponsor: IDEAYA Biosciences.

TPS3183 **Poster Session**

Study design of OMAHA-015: A phase 2 basket study of steroidogenesis inhibitor opevesostat in participants with selected solid tumors.

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Background: Opevesostat (MK-5684; ODM-208), an oral steroidogenesis inhibitor, selectively inhibits CYP11A1, blocking synthesis of all steroid hormones and their precursors, and may suppress steroid-driven tumor growth. The randomized, open-label, phase 2 OMAHA-015 trial (NCT06979596) is designed to evaluate the efficacy and safety of opevesostat compared with standard of care in breast, ovarian, and endometrial cancers. **Methods:** Cohort A will enroll participants (pts) with locally advanced unresectable or metastatic hormone receptor–positive (estrogen receptor and/or progesterone receptor ≥1% expression)/HER2-negative breast cancer (IHC 0, 1+ or 2+/ISH-) and disease progression on or after ≥1 prior endocrine-based therapy in the metastatic setting. Exclusion criteria include any line of cytotoxic chemotherapy (chemo) or PARP inhibitor in the inoperable or noncurative advanced/metastatic setting and prior treatment with both fulvestrant and exemestane in the metastatic setting. Cohort B will enroll pts with platinum-sensitive, histologically confirmed high-grade epithelial ovarian (including high-grade serous or predominantly serous, high-grade endometrioid, clear cell, or malignant mixed Müllerian tumors [carcinosarcoma]), fallopian tube, or primary peritoneal carcinomas. Pts must have received 4-8 cycles of platinum-based doublet chemo in a third-line setting for ovarian cancer with ≤9 weeks between the last dose of third-line chemo and randomization. Cohort C will enroll pts with histologically confirmed primary advanced or recurrent low-grade endometrioid carcinoma (FIGO grade 1/2, or well/moderately differentiated), with known pMMR status, and wild type p53 expression. Pts must either be treatment naive or have received 1 prior line of platinum-based therapy in the advanced/metastatic or adjuvant/neoadjuvant setting. In cohort A, ~80 pts will be randomized 1:1 to arm 1: opevesostat 5 mg PO twice daily (BID) + daily corticosteroids or arm 2: physician's decision of fulvestrant 500 mg IM (D1 and D15 of cycle 1 and D1 of each cycle thereafter) or exemestane 25 mg PO daily. Randomization will be stratified by 1 line versus ≥2 lines of prior endocrine therapy. In cohort B, ~90 pts will be randomized 1:1 to arm 3: opevesostat 5 mg PO BID + daily corticosteroids; or arm 4: observation. In cohort C, ~80 pts will be randomized 1:1 to arm 5: opevesostat 5 mg PO BID + daily corticosteroids; or arm 6: physician's choice of megestrol acetate 80 mg PO BID, alternating megestrol + tamoxifen 20 mg PO BID, or letrozole 2.5 mg PO daily. The primary end point is progression-free survival per RECIST v1.1 assessed by blinded independent central review (BICR). Secondary end points include overall survival, clinical benefit rate (cohort A only), objective response rate, and duration of response per RECIST v1.1 assessed by BICR, and safety. The study is currently enrolling. Clinical trial information: NCT06979596. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS3184 **Poster Session**

STELLA: A dose expansion of the ATR kinase inhibitor alnodesertib (ART0380) administered orally in combination with low-dose irinotecan to patients with advanced or metastatic CRC and PDAC.

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Background: Replication stress (RS) creates cancer cell vulnerability to which the critical DNA damage response kinase, ATR (Ataxia-Telangiectasia and Rad3-related) responds. ATR senses the stress, halts the cell cycle, and promotes DNA repair to allow proliferation. Alnodesertib is an ATR inhibitor developed to prevent cancer cells from successfully repairing RS and proliferating further. In earlier stages of alnodesertib development, preclinical and translational research demonstrated that tumor cells experience three combined biological insults: irinotecan-induced RS, endogenous RS via ataxia-telangiectasia mutated (ATM) loss, and RS rescue prevention by ATR inhibition. Data from the dose escalation and initial dose expansion cohorts of this trial in a tumor agnostic population showed encouraging results in ATM-negative cancers (confirmed Overall Response Rate of 50% in 20 patients with ATM negative cancers and responses across 8 cancer types including complete responses, Ulahannan et al, AACR 2025). Tumor-specific dose expansion cohorts are now enrolling, including colorectal cancer (CRC) and pancreas ductal adenocarcinoma (PDAC). **Methods:** Two tumor-specific cohorts are now open, each enrolling approximately 50 patients (pts): ATM-negative CRC and ATM-negative PDAC. Pts will receive the recommended dose of alnodesertib 200mg orally on days 1-3 and 8-10 combined with low-dose irinotecan 60mg/m^2 IV on days 1 and 8, of each 21-day cycle. Tumor tissue is prescreened by immunohistochemistry for ATM protein loss (H score 0) for enrollment eligibility. Pts with CRC must have received a maximum of 2 prior chemotherapies excluding prior trifluridine/tipiracil, fruquintinib, or regorafenib, and pts with PDAC must have received a maximum of 1 prior chemotherapy for advanced disease. Prior targeted agents are allowed and do not count as prior lines of therapy. Key objectives include safety, tolerability, and preliminary efficacy. Clinical trial information: NCT04657068. Research Sponsor: Artios Pharma.

TPS3185 **Poster Session**

KANDLELIT-014: A phase 2 study of MK-1084 as monotherapy and in combination with cetuximab in *KRAS* G12C-mutant advanced solid tumors.

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Background: *KRAS* is one of the most frequently mutated oncogenes in human cancers, with the G12C mutant isoform accounting for ~15% of all *KRAS* mutations. Despite their promising antitumor activity and manageable safety profile in advanced solid tumors, first-generation KRAS G12C inhibitors are often limited by acquired resistance in the monotherapy setting. MK-1084 is a next-generation, highly potent and selective KRAS G12C–GDP covalent inhibitor that exerts downstream regulation of the MAPK pathway. EGFR-mediated reactivation of RAS-MAPK signaling is proposed as a key driver of resistance to KRAS G12C inhibitors, particularly in colorectal cancer (CRC). The combination of KRAS G12C inhibitors and EGFR-targeted monoclonal antibodies has demonstrated clinical benefit in *KRAS* G12C-mutated CRC and non-small cell lung cancer (NSCLC), supporting the potential of this mutation as a clinically-relevant target across tumor types. KANDLELIT-014 (NCT07209111) is a phase 2, randomized, open-label, multicenter, tumor-agnostic study of MK-1084 as monotherapy and in combination with EGFR inhibitor cetuximab in participants with previously treated advanced solid tumors harboring a *KRAS* G12C mutation. **Methods:** Eligible participants are aged ≥18 years with histological or blood-based *KRAS* G12C-mutated locally advanced unresectable or metastatic solid tumors (other than CRC) that have progressed on or following standard-of-care systemic treatment, or for whom no satisfactory alternative treatment options are available. Additional eligibility criteria include an ECOG PS score of 0 or 1 and measurable disease per RECIST v1.1. Participants were excluded if they had uncontrolled, significant cardiovascular or cerebrovascular diseases; an additional progressive active malignancy that required treatment within the past 3 years; or active CNS metastases, carcinomatous meningitis, or primary brain tumors. Participants will be randomly assigned 1:1 to receive MK-1084 100 mg orally once daily as monotherapy (Arm 1) or in combination with cetuximab 500 mg/m^2 intravenously every 2 weeks (Arm 2) until discontinuation criteria are met. Randomization will be stratified according to the following tumor groups: NSCLC, pancreatic ductal adenocarcinoma, endometrial cancer, biliary tract cancer, and other solid tumors. The primary end points are ORR per RECIST v1.1 as assessed by blinded independent central review (BICR), safety, and tolerability. Key secondary end points include OS, DOR per RECIST v1.1 by BICR, and PFS per RECIST v1.1 by BICR. Imaging will be performed every 6 weeks until Week 18, every 8 weeks until Week 50, and every 12 weeks thereafter until disease progression or discontinuation. AEs will be evaluated from randomization to 30 days after the last dose of study treatment per NCI CTCAE v5.0. This global study is actively enrolling. Clinical trial information: NCT07209111. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.