3000 Oral Abstract Session

DB-1310, a HER3-targeted ADC, in pts with advanced solid tumors: Preliminary results from the phase 1/2a trial.

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Background: DB-1310 is a novel ADC comprised of a humanized anti-HER3 IgG1 monoclonal antibody, cleavable peptide linker, and DNA topoisomerase I inhibitor. Here, we report the preliminary results of the FIH trial. **Methods:** This global, multi-center, open-label Ph 1/2a trial includes dose escalation and expansion. Pts with advanced solid tumors who had failed standard therapy were enrolled. In Ph1, DB-1310 was planned to be administered at doses from 1.5 mg/kg to 6.5 mg/kg, Q3W, iv, using a 3+3 design, with additional pts enrolled to determine the RP2D. Ph 2a will include approximately 30-40 pts per cohort to optimize the RP2D and assess efficacy. **Results:** As of Jan 17, 2025, 123 pts were enrolled and treated with DB-1310 monotherapy in Ph1 (ECOG PS 1, 80.5%; White, 39.0%, Asian, 52.8%; NSCLC, 65.0%, EGFRm NSCLC, 37.4%; brain metastasis, 17.1%), median prior lines of systemic therapy was 3 (range, 1-11). Of the 42 efficacy-evaluable pts with EGFRm NSCLC, 92.9% had previously received 3rd generation EGFR TKI, 92.9% had received platinum-based chemotherapy. The unconfirmed ORR was 25.5% (95% CI, 17.63, 34.65) across all tumor types and 35.7% (95% CI, 21.55, 51.97) in EGFRm NSCLC. Median PFS was 5.4 months overall and 7.0 months for EGFRm NSCLC. 38 (30.9%) pts experienced ≥ G3 TRAEs, while 7 (5.7%) had drug-related SAEs. TRAEs led to dose reduction in 14 (11.4%) pts and discontinuation in 5 (4.1%) pts. No TRAE leading to death was reported. Most common TRAE (> 20%, any grade/≥G3) were nausea (36.6%/0.8%), anemia (35.8%/4.1%), neutrophil count decreased (34.1%/17.9%), platelet count decreased (31.7%/9.8%), white blood cell count decreased (29.3%/8.9%), decreased appetite (23.6%/0.8%), and vomiting (21.1%/0%). Interstitial lung disease occurred in 7 pts (5.7%, 6 G1 and 1 G2). PK exposure was increased through dose escalation, with low systemic payload exposure and no accumulation of DB-1310 upon repeated administration. **Conclusions:** DB-1310 showed a manageable safety profile and encouraging antitumor activity in pts with heavily pretreated advanced solid tumors, particularly EGFRm NSCLC. Clinical trial information: NCT05785741. Research Sponsor: None.

Tumor response by dose (efficacy-evaluable).

Dose (mg/kg)	1.5	3	4.5	5.0	5.5	6	Total
All tumors, n	3	10	25	53	16	3	110
uORR, n (%) (95% CI)	0 (0) (0.00, 70.76)	1(10.0) (0.25, 44.50)	8 (32.0) (14.95, 53.50)	13 (24.5) (13.76, 38.28)	6 (37.5) (15.20, 64.57)	0 (0) (0.00, 70.76)	28 (25.5) (17.63, 34.65)
DCR, n (%) (95% CI)	3 (100.0) (29.24, 100.00)	8 (80.0) (44.39, 97.48)	23 (92.0) (73.97, 99.02)	42 (79.2) (65.89, 89.16)	11 (68.8) (41.34, 88.98)	2 (66.7) (9.43, 99.16)	89 (80.9) (72.31, 87.78%)
EGFRm NSCLC, n	0	7	9	16	8	2	42
uORR, n (%) (95% CI)	-	1 (14.3) (0.36, 57.87)	4 (44.4) (13.70, 78.80)	5 (31.3) (11.02, 58.66)	5 (62.5) (24.49, 91.48)	0 (0) (0.00, 84.19)	15 (35.7) (21.55, 51.97)
DCR, n (%) (95% CI)	-	6 (85.7) (42.13, 99.64)	9 (100.0) (66.37, 100.00)	14 (87.5) (61.65, 98.45)	7 (87.5) (47.35, 99.68)	2 (100.0) (15.81, 100.00)	38 (90.5) (77.38, 97.34)

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with driver genomic alterations (GA) outside of classic EGFR mutations.

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Background: iza-bren is a first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topo-I inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker. Safety/efficacy data from the phase Ib study are presented, focusing on NSCLC patients (pts) with driver mutations outside of classic TKI-sensitizing EGFR mutations. **Methods:** Phase Ib part of this study included the expansion cohorts, each defined by a prespecified GA, including EGFR exon 20 insertions, non-classical EGFR mutations, mutations in HER2, ALK, ROS1, BRAF (V600E and others), KRAS (G12C and others), SMARCA4, MET (Exon 14), RET, and NTRK. Pts with these GA who progressed on standard targeted therapies (if available) and no more than one prior line of chemotherapy were enrolled. iza-bren was given at 2.5 mg/kg D1D8 Q3W. **Results:** As of Dec 5, 2024, a total of 73 NSCLC pts with listed GA were enrolled. Five pts were still on treatment, but were excluded from the analysis due to insufficient follow-up for the first post-baseline scan (see table below). Among 7 pts with EGFR exon 20 insertions, 85.7% (6 out of 7) achieved cPR. Among 8 pts with KRAS G12C mutations, 3 cPR and 1 PR pending confirmation were observed. Efficacy for subgroups will be presented. The most frequent hematologic TRAEs (all grades) were anemia (87.7%), leukopenia (74.0%), thrombocytopenia (74.0%), and neutropenia (72.6%); the most frequent non-hematologic TRAEs were asthenia (42.5%), nausea (41.1%), stomatitis (37.0%), diarrhea (32.9%), and alopecia (31.5%). 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 2.7%. Only 1 case of G2 ILD was observed. Notably, no iza-bren related death was reported. No new safety signals were observed. **Conclusions:** In NSCLC pts with these GAs, iza-bren showed promising activity with a manageable safety profile, supporting further evaluation of iza-bren in these populations. Clinical trial information: NCT05194982. Research Sponsor: None.

	Total (N = 68)	EGFR mut exon20ins/ non-classical (N=12)	HER2 mut (N=13)	ALK/ROS1/ RET fusion (N=19)	KRAS/ BRAF/ MET mut (N=22)	SMARCA4 (N=2)
Prior lines of therapy, median (range)	1 (1-5)	1 (1-2)	1 (1-3)	3 (1-5)	1 (1-2)	1 (1-1)
BOR, n						
PR	31	9	8	5	9	0
cPR	24	8	7	3	6	0
PR pending confirmation	6	1	1	2	2	0
SD	25	3	5	10	7	0
PD	9	0	0	3	5	1
NE[1]	3	0	0	1	1	1
ORR, %	45.6	75.0	61.5	26.3	40.9	0
cORR, %	35.3	66.7	53.8	15.8	27.3	0
DCR, %	82.4	100.0	100.0	78.9	72.7	0
mDOR (mo) (95% CI)	7.0 (5.6, NR)	NR (5.6, NR)	5.7 (4.2, NR)	4.5 (2.7, NR)	NR (NR, NR)	/
mPFS (mo) (95% CI)	6.7 (4.1, 11.2)	NR (6.9, NR)	8.4 (2.1, NR)	2.8 (1.3, 4.1)	6.7 (1.5, NR)	1.4 (1.3, NR)

Note:
[1]Including pts w/o post-baseline scan.

Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic small cell lung cancer (SCLC).

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Background: iza-bren is a first-in-class ADC comprised of an EGFR x HER3 bispecific antibody conjugated to a novel topo-I inhibitor payload (Ed-04) via a stable tetrapeptide-based cleavable linker. Unlike existing ADCs targeting general tumor antigens, iza-bren uniquely targets the EGFR and HER3 pathways, which are implicated in the aggressive biology of SCLC. It has shown promising clinical activity and a manageable safety profile in patients (pts) with advanced or metastatic solid tumors. Results for safety/efficacy from this phase I study in SCLC pts are presented. **Methods:** Pts with locally advanced or metastatic SCLC who had progressed on prior systemic therapies were enrolled and treated at 2.0, 2.5 mg/kg D1D8 Q3W, or 4.5, 5.0 mg/kg D1 Q3W. Tumor scans were done every 6 weeks. Efficacy was evaluated in the overall cohort and specific subgroups, with a particular focus on pts with limited prior treatment exposure. **Results:** As of Dec 5, 2024, a total of 58 SCLC pts were enrolled. All pts who received at least one dose of iza-bren are included in the analysis. The median follow-up was 16.4 mo, ORR was 55.2%, confirmed ORR was 44.8%, median PFS was 4.0 mo, and median OS was 12.0 mo. Among the 52 pts at 2.5 mg/kg, 20 pts received only 1 prior line of PD(L)-1 and PBC combination treatment. In this subgroup, ORR was 80.0%, confirmed ORR was 75.0%, median DOR was 5.6 mo, median PFS was 6.9 mo, and median OS was 15.1 mo. The most frequent hematologic TRAEs (all grades) were anemia (84.5%), leukopenia (74.1%), thrombocytopenia (72.4%), and neutropenia (70.7%); the most frequent non-hematologic TRAEs were asthenia (41.4%), hypoalbuminemia (39.7%), stomatitis (34.5%), nausea (31.0%), and vomiting (31.0%). 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 12.1%. Two infection-related deaths (1 respiratory failure, 1 gastrointestinal infection) associated with iza-bren were reported. No ILD was observed. No new safety signals were identified. **Conclusions:** In SCLC pts, iza-bren has demonstrated an encouraging efficacy with a manageable safety profile. Notably, the high confirmed response rate of 75% in pts with limited prior treatment underscores its potential as a novel therapeutic option for SCLC, a disease with limited therapeutic advancements over decades. The phase III study of iza-bren in SCLC pts who received 1 prior line of PD(L)-1 and PBC combination treatment is ongoing (NCT06500026). Clinical trial information: NCT05194982. Research Sponsor: None.

3003 Oral Abstract Session

Safety and efficacy of TQB2102, a novel bispecific anti-HER2 antibody–drug conjugate, in patients with advanced solid tumors: Preliminary data from the first-in-human phase 1 trial.

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Background: TQB2102 is an antibody-drug conjugate (ADC) comprised of a recombinant, humanized anti-human epidermal growth factor receptor 2 (HER2) bispecific antibody conjugated to a topoisomerase I inhibitor via an enzyme-cleavable linker. The bispecific antibody component can target both extra-cellular domains II (pertuzumab binding site) and IV (trastuzumab binding site) of HER2. We conducted a multicenter, dose escalation and expansion first-in human (FIH) phase 1 study of TQB2102 in advanced solid tumors. **Methods:** In the dose escalation phase, eligible patients (pts) with advanced solid tumors whose disease had progressed after standard systemic treatments, were enrolled in a 3+3 dose escalation study of TQB2102(1.5, 3, 4.5, 6, 7.5 or 9 mg/kg) IV, every 3wks (Q3W). In the dose expansion phase, pts with HER2 positive cancers and HER2 low (HER2 1+ or HER2 2+ and FISH negative) metastatic breast cancer (MBC) received the selected recommended phase 2 dose (RP2D). The primary objectives were to evaluate the safety and tolerability, dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of TQB2102. **Results:** As of October 1, 2024, 181pts (41 pts in dose escalation phase and 140 pts in dose expansion phase) were enrolled from 12 centers. Most common tumor types included MBC (N = 80), Colorectal cancer (N = 37) and Gastric cancer (N = 23).Twenty-five (31%) MBC received prior anti-HER2 ADCs, including 21 pts received T-DM1, 8 pts received DS-8201.The median duration of follow-up was 8.15 months. TQB2102 was well-tolerated with no DLTs occurred and MTD was not reached. The most common (occurring in ≥5%) grade ≥3 AEs were neutrophil count decrease (21.7%), WBC count decreased (10.6%), anemia (8.9%), platelet count decreased (6.1%), diarrhea (5.0%). Only one patient had grade 2 interstitial lung disease (ILD) until the cutoff date. 6 or 7.5mg/kg was selected for dose expansion. Objective response rate (ORR) per RECIST v1.1 was 41.2% (68 partial responses [PR]) in 165 responses evaluable pts who had ≥1 response assessment. Surprisingly, 7 pts reached PR in 10 HER2+ MBC pts with brain metastases, one of whom the brain metastatic lesions reached complete response after 4 cycles of treatment. This trial is ongoing now. **Conclusions:** TQB2102 is well tolerated with promising anti-tumor activity in pts with HER2-expressing cancer. These early signs of activity support a phase 3 trial in patients with HER2-low MBC that has been initiated (NCT06561607). Clinical trial information: NCT05735496. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

6mg/kg and above	ORR(%)	DCR(%)	6-months PFS rate, (%)
HER2 positive MBC (N=39)	51.3	84.7	87.0
HER2 low MBC (N=33)	51.5	87.9	63.0
HER2 3+ colorectal cancer (N=23)	34.8	87.0	88.4
HER2 positive gastric cancer (N=10)	70.0	90.0	90.0
HER2 positive Other (N=5)	60.0	100.0	NE

Efficacy and safety of the DLL3/CD3 T-cell engager obrixtamig in patients with extrapulmonary neuroendocrine carcinomas with high or low DLL3 expression: Results from an ongoing phase I trial.

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Background: Delta-like ligand 3 (DLL3) is highly expressed in neuroendocrine carcinomas (NEC). Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that targets DLL3-positive (DLL3+) tumors. NCT04429087 is an ongoing, Phase (Ph) I dose-escalation trial of obrixtamig in patients (pts) with DLL3+ pulmonary and extrapulmonary NEC (epNEC), who had failed to respond to standard treatment (Tx). This analysis examined the efficacy and safety of obrixtamig in pts with epNEC with high vs low DLL3 expression. **Methods:** Obrixtamig was given IV in 4 dose-escalation regimens (R): RA (fixed dose q3w); RB1 (fixed dose qw); RB2 (step-up dose, then qw) and RB3 (step-up dose, then qw for 3 weeks, then q3w), until disease progression or unacceptable toxicity. Efficacy was assessed through objective response rate (ORR) and disease control rate (DCR) using RECIST v1.1. Results are reported for pts who received obrixtamig RB2 or RB3, categorized as having high vs low DLL3, using a threshold of ≥50% of tumor cells stained with an investigational antibody for DLL3 (SP347, Roche Diagnostics). **Results:** As of June 21, 2024, 60 pts with epNEC were included (gastroenteropancreatic [GEP]: 45.0%, genitourinary [GU]: 30.0%, other/unknown primary site: 25.0%); 30 each DLL3-high and DLL3-low. Mean age: 63.9 years in DLL3-high; 59.1 in DLL3-low pts. Baseline characteristics were well-balanced across DLL3 groups. All pts had received prior systemic therapy; 30.0% of DLL3-high and 50.0% of DLL3-low pts had received > 2 lines of prior Tx. Efficacy data are shown in the Table. After obrixtamig Tx, pts with high DLL3 expression had greater ORR, DCR, and duration of response (DoR) than DLL3-low pts. Responses were seen most frequently amongst pts with DLL3-high GEP (50.0%) or GU (60.0%) epNECs. Seven DLL3-high pts are still receiving Tx. Most treatment-related AEs (TRAEs) were mild to moderate for both groups (Table). **Conclusions:** Analyses from this ongoing Ph I study show greater obrixtamig efficacy in patients with epNEC with high DLL3 expression compared with low DLL3 expression, with a manageable safety profile that is comparable across both groups. The ORR of 40.0% and median DoR of 7.9 months in heavily pretreated epNEC tumors with DLL3 high expression are encouraging, and support further development of obrixtamig for this subgroup. Clinical trial information: NCT04429087. Research Sponsor: Boehringer Ingelheim.

Efficacy/safety parameter	DLL3-high (n=30)	DLL3-low (n=30)
ORR, % (95% CI)	40.0 (24.6–57.7)	3.3 (0.6–16.7)
DCR, % (95% CI)	66.7 (48.8–80.8)	26.7 (14.2–44.4)
Median DoR (95% CI), months	7.9 (6.2–NC)	2.8 (NC–NC)
TRAEs, all G/G ≥3, (%)	100.0/23.3	90.0/20.0
Cytokine release syndrome, all G/G ≥3, (%)	70.0/3.3	60.0/3.3
Neurotoxicity, including immune effector cell-associated neurotoxicity syndrome*, all G/G ≥3, (%)	16.7/6.7	10.0/3.3

*Evaluated with a customised MedDRA query.
CI, confidence interval; NC, not calculable.

3005 Oral Abstract Session

[^{212}Pb]VMT-α-NET therapy in somatostatin receptor 2 (SSTR2) expressing neuroendocrine tumors (NETs): Dose-limiting toxicity (DLT) observation participants after 1 year follow-up and preliminary report for expansion participants.

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Background: [^{212}Pb]VMT-α-NET, a next generation ^{212}Pb-based, SSTR2-targeted alpha-particle radiopharmaceutical therapy (RPT), was designed to achieve superior biodistribution via optimized tumor uptake and retention and rapid renal clearance. Results reported here are from the Phase 1/2a first-in-human study [NCT05636618]. **Methods:** Safety, pharmacokinetics, dosimetry and efficacy using RECIST v1.1 were investigated in the treatment of participants with [^{212}Pb]VMT-α-NET who had SSTR2-expressing, well-differentiated adult NETs of any grade. Participants received ≥1 prior therapy. No prior peptide receptor radionuclide therapy was allowed. The trial has multiple dose cohorts including 92.5 MBq (2.5 mCi, cohort 1) and 185 MBq (5 mCi, cohort 2) of administered activity based on a Bayesian modified toxicity probability interval (mTPI-2) design. Up to 8 participants per cohort were treated with 4 doses of [^{212}Pb]VMT-α-NET for DLT observation. Cohort 2 enrollment was expanded to further define the safety and efficacy profile at this dose level. **Results:** Nine (9) gastroenteropancreatic NET participants were enrolled into cohorts 1 and 2 for DLT observation. The ninth of these participants was enrolled more than 1 year prior to presentation of these data. Among these participants at the time of abstract submission, no DLTs were observed, and there were no grade 4, 5 or serious adverse events (SAEs). Specifically, no renal insufficiency or dysphagia were observed. Hematologic AEs were low grade and few in number. No treatment discontinuations due to AE occurred. Three (3) of the 7 cohort 2 participants enrolled for DLT observation achieved investigator-assessed partial responses (PRs). Two PRs were unconfirmed at the time of abstract submission. Durable progression-free survival (PFS) was consistently observed. More than 15 additional participants were enrolled in the cohort 2 expansion. Preliminary data for these patients will be reported at the congress. **Conclusions:** [^{212}Pb]VMT-α-NET is a well-tolerated, next generation RPT showing signs of clinical activity at early dose-levels in this phase 1/2a study. Based on these clinical data, further dose-escalation and development of this promising therapy are warranted. Clinical trial information: NCT05636618. Research Sponsor: Perspective Therapeutics, Inc.

Comprehensive genomic profiling of matched ctDNA and tissue from patients with less common cancers enrolled in but not eligible for a treatment arm of the NCI-MATCH trial.

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Background: During NCI-MATCH (NCT02465060) clinical trial screening, 5961 advanced cancer patients underwent next-generation sequencing to assess eligibility. About 60% of these patients had less common tumors (i.e., cancers other than colon, rectal, breast, non-small cell lung, or prostate). Most patients lacked a study eligible mutation of interest (MOI) and thus didn't receive a trial therapy. Analysis of plasma samples from these patients may illuminate circulating tumor DNA (ctDNA) profiles, potentially guiding ctDNA testing for clinically relevant mutations in less common cancer types. Here we report the molecular profiles of ctDNA and matched tumor from a subset of the NCI-MATCH screened patients. **Methods:** Comprehensive genomic profiling of ctDNA (from blood collected at enrollment) was performed using the TSO500 ctDNA v2 assay (523-genes) and sequenced on the Illumina NovaSeq 6000. Matched tumor was sequenced with the Oncomine Comprehensive Assay v2, a 143-gene panel. Positive percent agreement (PPA) between mutations of interest (MOI) identified in plasma ctDNA and tissue-based screening was calculated with tumor tissue as referent (PPA_{ref_tumor}). **Results:** We tested 2253 patients from the less common tumor cohort. 2194 samples were evaluable with 98.6% pass and 1.4% failure rates. A subset of five tumor histologies with larger representation ($n > 35$) in sample size were further analyzed: cholangiocarcinoma (CCA, n = 90), small cell lung cancer (SCLC, n = 59), adenocarcinoma of the esophagus (EAC, n = 37), adenocarcinoma of the pancreas (PDAC, n = 232), and salivary gland cancer (SGC, n = 47). Overall, $PPA_{ref\ tumor}$ was 83.4% (range: 76.5%-97.9%) in these five histologies. In patients with concordance $< 75\%$, median tumor fraction (as determined by maximum somatic allele frequency) was much lower (0.37%) than for specimens with concordance $> = 75\%$ (6.49%). The most frequently mutated genes identified in CCA were *TP53*, *KRAS*, and *IDH1*; in SCLC were *TP53* and *RB1* loss; in EAC were *TP53*, *KRAS, and ERRB2* amplification; in PDAC were *TP53* and *KRAS*; and in SGC was *TP53*. Additionally, there were several clinically relevant mutations detected only in ctDNA such as *IDH1* for CCA; and *BRAF*, *TP53*, and *PIK3CA* in several histologies. Microsatellite instability, as measured only in ctDNA, was most prevalent in SCLC, followed by CCA. **Conclusions:** Concordance of rare tumors in the NCI-MATCH trial is 83.4% in the representative histologies analyzed, which is similar to concordance of clinically relevant MOIs in common cancer studies. Liquid biopsy may be a viable screening option for matching targeted therapies in clinical trials, especially when a tumor biopsy is not practical or evaluable. The detection of some mutations in ctDNA only may suggest the presence of tumor heterogeneity in multiple lesions in patients with less common cancers. Research Sponsor: National Cancer Institute, National Institutes of Health; Illumina Inc.

3007 Oral Abstract Session

Ultra-sensitive pan-cancer molecular residual disease assessment using whole-genome sequencing-based personalized ctDNA panel: Initial results from the MONSTAR-SCREEN-3 project.

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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. We are evaluating an ultra-sensitive whole-genome sequencing (WGS)-based MRD assay in the MONSTAR-SCREEN-3 study to establish a comprehensive pan-cancer MRD platform inclusive of traditionally low-shedding tumors. **Methods:** MONSTAR-SCREEN-3, a prospective multicenter study targeting 1,100 patients with solid tumors undergoing curative-intent treatment in the definitive cohort, utilizes personalized panels constructed via Precise MRD (Myriad Genetics). These panels incorporate up to 1,000 tumor-specific alterations identified through WGS of matched tumor tissue, including both short variants and insertion-deletions. Serial plasma samples were collected at baseline, post-neoadjuvant chemotherapy (when applicable), 1-month post-surgery, quarterly in year 1, and biannually thereafter up to 2 years. The assay performance was evaluated across multiple cancer types for ctDNA detection and recurrence monitoring. **Results:** As of December 2024, 114 patients across 15 cancer types were enrolled, including colorectal (n = 33), gastric (n = 22), head and neck (n = 13), renal cell (n = 10), esophageal (n = 8), and pancreatic (n = 7) cancers. Treatment strategies included upfront surgery (n = 76) and neoadjuvant chemotherapy (n = 38). The median follow-up time was 2.4 months (range, 0.5–7.7). WGS analysis identified a median of 6,089 panel-eligible alterations per patient (range: 214-14,112), with high variants counts observed in a deficient mismatch-repair colorectal cancer, enabling comprehensive personalized panel design. Customized panel creation was successful in 69/71 patients (97.2%) across 8 cancer types, with two pancreatic cancer cases deferred to surgical specimens due to insufficient variants in FNA samples. The assay demonstrated 100% baseline sensitivity (41/41), detecting tumor fractions ranging from $< 0.001\%$ to 45.2% across all cancer types, including traditionally low-shedding tumors. Post-operative 1-month MRD assessment revealed 35.7% positivity (10/28), with tumor fractions ranging from $< 0.001\%$ to 0.27%. Two MRD-positive patients developed radiological recurrence with lead times of 2.5 and 3 months before conventional imaging detection. **Conclusions:** These interim results demonstrate successful pan-cancer implementation of WGS-based personalized ctDNA detection, achieving universal baseline sensitivity and ultra-sensitive MRD detection across tumor types, including those traditionally challenging to assess. Updated molecular and clinical outcome data will be presented. Clinical trial information: UMIN000053975. Research Sponsor: SCRUM-Japan Funds (http:// www. scrum -japan. ncc. go. jp/ index. html); Myriad Genetics.

Circulating tumor DNA (ctDNA) in patients with stage 2/3 HR+HER2-negative breast cancer (BC) treated with neoadjuvant endocrine therapy (NET) in the I-SPY2 endocrine optimization pilot (EOP) trial.

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Background: Numerous studies have demonstrated the prognostic value of ctDNA analysis after neoadjuvant chemotherapy for early-stage high-risk breast cancer. Few studies have characterized ctDNA in pts receiving NET for early-stage hormone receptor positive (HR+)/HER2- BC that is predicted to benefit less from chemotherapy. **Methods:** Cell-free DNA (cfDNA) was isolated from 432 plasma samples from 108 pts enrolled in the I-SPY2 EOP trial. Pts had Stage 2/3 HR+/HER2-, MammaPrint low or high risk 1 BC. Pts were randomized to one of 7 neoadjuvant-based treatment arms including arms containing AI, Z-endoxifen, Lasofoxifene, vepdegestrant (ARV-471), and Abemaciclib. Pts were treated for 6 months prior to surgery. Blood was collected at baseline (T0), 3 weeks (T1), 12 weeks (T2), and 6 months (T3). A personalized ctDNA test (Signatera) was designed to detect up to 16 patient-specific mutations (from whole-exome sequencing of pretreatment tumor) in cfDNA by ultra-deep sequencing. The chi-square test was used to assess associations between categorical variables, and the Wilcoxon rank-sum test was used to evaluate differences in medians. **Results:** ctDNA information was available for 101 patients at baseline (T0) (Table 1). At T0, 36 (35.6%) patients were ctDNA-positive. 23/36 (63.9%) became ctDNA-negative and 13/36 (36.1%) remained ctDNA-positive. At T0, 65/101 patients (64.4%) were ctDNA-negative. Of these, 57 (87.7%) remained negative, while 8 (12.3%) became ctDNA-positive at T1 before reverting to ctDNA-negative. A higher percentage of ctDNA-positive patients at T0 were cN+ compared to ctDNA-negative pts ($p = 0.036$, 64% vs. 40%). Additionally, ctDNA-positivity at T0 was strongly associated with higher Ki67 ($p = 0.03$) and larger functional tumor volume by MRI at baseline ($p = 0.03$). T3/T4 and high-grade tumors at baseline were also associated with having ctDNA positivity at baseline, though this was not statistically significant ($p = 0.34$ and 0.058, respectively). **Conclusions:** In this study of pts with Stage 2/3 HR+ HER2- BC with largely MammaPrint low risk signatures, over one-third of pts had detectable ctDNA at baseline. Detectable ctDNA at baseline was associated with cN+ disease, larger FTV, and high baseline Ki67. The majority of pts with positive ctDNA at baseline cleared the ctDNA on NET. Clinical trial information: NCT01042379. Research Sponsor: NIH/NCI ctDNA/MR; Breast Cancer Research Foundation; Give Breast Cancer the Boot; Quantum Leap Healthcare Collaborative.

Clinicopathologic characteristics of EOP patients.

	All Patients (N=101)
Age at screening	55 (27-80) years*
Clinical N Stage	
Node+ (cN+)	49 (48.5%)
Node- (cN-)	52 (51.5%)
SET status	
High	84 (83.2%)
Low	14 (13.9%)
Missing	3 (2.97%)
MammaPrint (MP) risk**	
High risk 1 (H1)	15 (14.9%)
Low risk	86 (85.1%)

*Mean(min-max).
**H1: MP score between 0 and -0.57; low: MP score between 0 and 0.355.

3009 Rapid Oral Abstract Session

Initial phase 1 dose escalation data for emiltatug ledadotin (Emi-Le), a novel B7-H4-directed dolasynthen antibody-drug conjugate.

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Background: B7-H4 is a transmembrane protein over-expressed in breast (BC), ovarian (OC), endometrial (EC), and adenoid cystic carcinoma type 1 (ACC-1) cancers, with limited expression in healthy tissues. Emi-Le (XMT-1660) is a B7-H4-directed Dolasynthen ADC designed with a proprietary auristatin F-HPA microtubule inhibitor payload with controlled bystander effect. **Methods:** The Phase 1 trial is investigating Emi-Le monotherapy in adult patients (pts) with advanced/metastatic TNBC, HR+/HER2- BC, OC, EC and ACC-1. In dose escalation, eligible pts received Emi-Le at doses of 7.2-115 mg/m2 per cycle, with all collected data informing the recommended doses for the expansion (EXP) portion of the trial. Tumors were evaluated retrospectively for B7-H4 expression by IHC, with the preliminary high cutoff set at TPS≥70. **Results:** As of December 13, 2024, 130 pts were dosed. Across all tumor types, median age of pts was 55; median 4.5 prior lines of therapy (range 0-15). B7-H4 status was evaluated for 103 pts, with 44% determined to be B7-H4 TPS high. Overall, Emi-Le was generally well tolerated. The most common TRAEs were transient AST increase (38%, G3 14%), proteinuria (31%, G3 9%), nausea (29%, G3 1%) and fatigue (28%, G3 0%). The only G3 TRAEs in ≥5% of pts were AST increase and proteinuria. No G4 or 5 TRAEs were reported. No observed dose-limiting treatment-related neutropenia, neuropathy, ocular toxicity, interstitial lung disease or thrombocytopenia. TRAEs leading to discontinuation were observed in 2.3% of pts. Clinical activity was correlated with both dose and B7-H4 expression. For pts treated with doses ranging from 38.1–67.4 mg/m2 per cycle (intermediate dose range), the confirmed ORR in evaluable pts with high B7-H4 expression was 23% (6/26), including a 23% (3/13) confirmed ORR in evaluable pts with TNBC, with all 13 pts having previously received at least one topoisomerase-1 inhibitor (topo-1) ADC. At doses ≥76.2 mg/m2 per cycle (high dose range), the confirmed ORR in evaluable pts with high B7-H4 expression was 22% (2/9), with 78% (7/9) having ≥30% reduction in target lesions. Of the 8 pts with confirmed responses at doses ≥38.1 mg/m2, 5 had reduction in target lesions > 60%, including 1 CR. All 4 pts with high B7-H4 expression treated at the initial EXP dose of 67.4mg/m2 Q4W had tumor reductions and were on treatment with durations of ≥16 weeks as of data cutoff. **Conclusions:** Based on the initial reported data, Emi-Le appears to have encouraging clinical activity and tolerability in a heavily pretreated population. Further clinical development is ongoing in the EXP portion of the trial at a dose of 67.4 mg/m2 Q4W in pts with advanced/metastatic TNBC who have received 1-4 prior lines of systemic therapy, including at least one topo-1 ADC. Dose exploration is ongoing to identify a potential second higher EXP dose. Clinical trial information: NCT05377996. Research Sponsor: Mersana Therapeutics.

Sigvotatug vedotin (SV), an investigational integrin beta-6 (IB6)–directed antibody–drug conjugate (ADC), and pembrolizumab combination therapy: Initial results from an ongoing phase 1 study (SGNB6A-001).

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Background: IB6, a tumor-associated membrane protein, is overexpressed in many solid tumors, including non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). SV, an IB6-directed ADC, demonstrated encouraging antitumor activity and manageable safety as a monotherapy in patients (pts) with advanced NSCLC in SGNB6A-001, an ongoing phase 1 study (Peters, ASCO 2024). Due to immunogenic cell death induction and innate immune system activation, SV activity may be enhanced when combined with pembrolizumab (P; SV+P). We report initial results of SV+P in pts with advanced solid tumors. **Methods:** SGNB6A-001 (NCT04389632) is an open-label, multicenter, dose-escalation and dose-expansion phase 1 study evaluating the safety, pharmacokinetics (PK), and antitumor activity of SV. Part C is evaluating safety of SV+P in pts with advanced solid tumors; part D is currently enrolling to evaluate SV+P in treatment-naive pts with locally advanced, unresectable, or metastatic NSCLC and HNSCC. Pts receive SV 1.8 mg/kg by adjusted ideal body weight IV Q2W and P 400 mg IV Q6W. Primary endpoint is safety; secondary endpoints include efficacy and PK. Results reported here are from parts C and D. **Results:** As of Nov 26, 2024, 31 pts received ≥1 dose of SV+P in parts C and D (19 NSCLC, 11 HNSCC, and 1 esophageal); median (95% CI) follow-up was 2.9 (1.6-5.0) months, and 26 pts remain on treatment. Median (range) age was 65 (34-80) years, 61% were male, and 52% had ECOG PS 0. Of pts with NSCLC, 12 (63%) had non-squamous tumors and 11 (58%) had tumors with PD-L1 TPS ≥1. All pts with HNSCC had tumors with PD-L1 CPS ≥1. Any-grade (Gr) and Gr ≥3 treatment-emergent adverse events (TEAEs) occurred in 87% and 35% of pts, respectively. Most common TEAEs are shown in the Table. Any-Gr and Gr ≥3 immune-mediated TEAEs occurred in 61% and 10% of pts, respectively. Pneumonitis/interstitial lung disease occurred in 3 pts (9.7%), with no Gr ≥3 events. Renal TEAEs led to discontinuation of both SV and P in 2 pts (6%); 3 other pts discontinued treatment (1 progressive disease, 2 consent withdrawal). There were no treatment-related deaths. In 7 efficacy-evaluable pts with TPS≥1 NSCLC, 1 confirmed (c) complete response (CR), 1 c partial response (PR), and 2 PRs pending confirmation were observed (ORR 57%; cORR 29%). In 8 efficacy-evaluable pts with 1L HNSCC, 2 cCR and 1 cPR were observed (cORR 37.5%). **Conclusions:** SV+P demonstrated manageable safety and encouraging preliminary efficacy. These data support the ongoing phase 3 Be6A-Lung-02 study (NCT06758401) comparing SV+P vs P as first-line treatment for pts with PD-L1 high (TPS≥50) advanced NSCLC. Clinical trial information: NCT04389632. Research Sponsor: Seagen, which was acquired by Pfizer in December 2023.

	All Treated Pts (n=31)	
TEAEs	Any Gr (>25%) n (%)	Gr ≥3 n (%)
Fatigue	13 (42)	1 (3)
Decreased appetite	13 (42)	3 (10)
Nausea	12 (39)	0
Alopecia	11 (35)	0
Asthenia	9 (29)	2 (6)
Decreased weight	8 (26)	0
Dysgeusia	8 (26)	0

BMS-986504 in patients (pts) with advanced solid tumors with homozygous *MTAP* deletion (*MTAP*-del): Clinical update and first report of pharmacokinetics (PK) and pharmacodynamic (PD) analyses from CA240-0007.

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Background: BMS-986504 selectively binds to the PRMT5-MTA complex, which represents a synthetic lethal target in *MTAP*-del cancer cells, while sparing *MTAP*–wild-type cells. In the first-in-human phase 1/2 CA240-0007 study in advanced, unresectable or metastatic solid tumors with homozygous *MTAP*-del, BMS-986504 was found to be well tolerated and demonstrated antitumor activity in multiple tumors. Here, we report clinical results and the first PK and PD analyses of BMS-986504 from the dose escalation and expansion phases of CA240-0007. **Methods:** Pts with measurable/evaluable disease and no available treatment (Tx) with curative intent were enrolled; 7 doses were evaluated (50 to 800 mg) in dose escalation. Objective response rate (ORR), disease control rate (DCR), duration of response (DOR), time to response (TTR), safety, PK, PD, including plasma SDMA were assessed. **Results:** As of 2 Dec 24, 152 heavily pretreated pts were enrolled across all doses: NSCLC (n = 34), PDAC (n = 41), cholangiocarcinoma (n = 12), and mesothelioma (n = 12) were the most common tumor types. With a median f/u of 9.0 mo (95% CI 7.6–9.9), continued durable antitumor activity and deepening tumor regression were seen across tumor types and doses (ORR = 23%, DCR = 70%, median DOR = 10.5 mo, TTR = 4.6 mo). No new safety signals were identified. Most Tx-related adverse events (TRAEs) were grade (Gr) 1 or 2; 13% had Gr ≥ 3 TRAEs (Gr 3 = 12%, Gr 4 = < 1%, Gr 5 = 0). Doses from 50 to 600 mg QD were assessed for PK/PD. The $AUC_{(0-24)}$ after multiple doses was approximately dose proportional at 200 to 600 mg, and the terminal $t_{1/2}$ after a single dose was approximately 24 h (table). There were dose-dependent reductions in predicted plasma SDMA, with the 400 and 600 mg doses approaching the plateau. **Conclusions:** With longer f/u, BMS-986504 continued to show increasingly durable antitumor activity. BMS-986504 demonstrated a favorable PK/PD profile, supporting QD dosing at 400 and 600 mg. These results support further investigation of BMS-986504 at 400 and 600 mg QD as a potential first-in-class synthetic lethal Tx option in pts with advanced solid tumors with *MTAP*-del. Clinical trial information: NCT05245500. Research Sponsor: Bristol Myers Squibb.

PK and PD.

	50 mg QD	100 mg QD	200 mg QD	400 mg QD	600 mg QD
PK after multiple doses					
t_{max}[a] (min–max), h	2.0 (2.0–4.0)	2.0 (1.0–2.0)	2.0 (0.5–6.0)	2.0 (0.5–4.0)	2.0 (1.0–6.0)
	n = 3	n = 3	n = 8	n = 10	n = 10
C_{max},[b] ng/mL	107	377	685	1240	2110
	n = 3	n = 3	n = 8	n = 10	n = 10
$AUC_{(0-24)}$,[b] h•ng/mL	948	3060	7150	11,800	26,700
	n = 3	n = 3	n = 7	n = 10	n = 9
$AUC_{(0-24)}$,[b,c] h•ng/mL/mg	19.0	30.6	35.8	29.5	44.6
	n = 3	n = 3	n = 7	n = 10	n = 9
Terminal $t_{1/2}$ after single dose,[d] h	21.7	80.7	21.5	21.7	24.1
	n = 1	n = 1	n = 14	n = 14	n = 1
PD					
Translational exposure targets (C_{avgss}), X	0.08	0.21	0.5	1.1	1.7
Predicted plasma SDMA reduction,[a] % (90% PI)	30.0 (23.2–37.8)	38.8 (27.1–47.5)	48.3 (42.0–53.0)	55.0 (50.7–57.6)	57.4 (54.3–59.0)

[a]Median. [b]Geometric mean. [c]Dose-normalized. [d]Arithmetic mean.

Preliminary results from a first-in-human, phase I/II study of VLS-1488, an oral KIF18A inhibitor, in patients with advanced solid tumors.

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Background: VLS-1488 is an oral small molecule inhibitor of KIF18A, a mitotic kinesin protein important for successful division of cancer cells with chromosomal instability (CIN) but not required for mitosis in normal cells. Preclinical studies of VLS-1488 showed dose-dependent inhibition of tumor growth in CIN models. **Methods:** VLS-1488-2201 is a phase I/II study of patients (pts) with advanced solid tumors consisting of two parts, Dose Escalation and Dose Expansion. During Dose Escalation, a Bayesian Optimal Interval design was utilized to enroll pts to dose escalation cohorts with additional pts enrolled to backfill cohorts at dose levels (DLs) that did not meet de-escalation/elimination rules. Primary objective was to assess safety/tolerability of VLS-1488 at various DLs to determine the Maximum Tolerated Dose (MTD). Secondary objectives included evaluating preliminary efficacy and pharmacokinetics (PK). Eligible pts had exhausted standard of care treatments and had measurable disease per RECIST v1.1. Pts received VLS-1488 once daily, orally for 28-day cycles until disease progression, unacceptable toxicity or other stopping criteria. **Results:** 52 pts (ITT) were enrolled across 5 DLs including 50mg (n = 4), 100mg (n = 12), 200mg (n = 14), 400mg (n = 12) and 800mg (n = 10). Tumor types were high grade serous ovarian (HGSOC; n = 20), colorectal (n = 14), triple negative breast (n = 7), squamous lung (n = 3), endometrial (n = 3), ovarian carcinosarcoma (n = 2), esophageal (n = 2) and bladder (n = 1). The median number of prior lines was 4 (range 1-8). As of data cutoff, 52 pts (100%) received >1 dose of VLS-1488. No dose-limiting toxicities (as assessed during the first 28 days) were observed and MTD was not reached. Treatment-related AEs (TRAEs) occurred in 22 pts (42%), with fatigue (17.3%; G1 13.5%, G2 3.8%), aspartate aminotransferase increased (13.5%; G1 7.7%, G2 1.9%, G3 3.8%) and rash (11.5%; G1 3.8%, G2 1.9%, G3 5.8%) observed in >10% of pts. 6 pts (12%) experienced G3 TRAEs and no > G3 TRAEs were observed. Drug exposures exceeded preclinically defined efficacious thresholds and were approximately dose proportional at analyzed DLs. 41 pts (79%) were evaluable for response per RECIST v1.1. In the 16 HGSOC pts evaluable for response (where the median number of prior lines was 4.5; range 2-8), 3 partial responses (PRs; including 2 pts with sustained PR >24 weeks) and 6 with stable disease (SD; including 4 pts with tumor reductions) were observed across multiple DLs, with 5 pts continuing with study treatment. **Conclusions:** VLS-1488 was found to be safe and tolerable, with encouraging anti-tumor activity observed in heavily treated HGSOC pts. VLS-1488 will be evaluated further in the Dose Expansion phase of the study. Clinical trial information: NCT05902988. Research Sponsor: Volastra Therapeutics, Inc.

A first-in-human phase I/II study of GFH375, a highly selective and potent oral KRAS G12D inhibitor in patients with KRAS G12D mutant advanced solid tumors.

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Background: Kirsten rat sarcoma (KRAS) G12D is one of the most prevalent RAS mutations in human cancers and suggests poor survival. GFH375 is an orally bioavailable, highly selective and potent KRAS G12D inhibitor targeting both "ON" (GTP-bound) and "OFF" (GDP-bound) states. Here we report the preliminary results of GFH375 in patients (pts) with advanced KRAS G12D mutant solid tumors. **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 mutation. Pts with locally advanced or metastatic solid tumor failed to prior standard therapies are eligible for enrollment. Accelerated titration, plus Bayesian Optimal Interval (BOIN) and back filling design are employed in the phase I part with safety and tolerability as the primary objective, and pharmacokinetics and anti-tumor activity as the secondary objectives. **Results:** As of 03Jan2025, thirty-two pts were treated, including 11 pancreatic ductal adenocarcinoma (PDAC), 11 non-small cell lung cancer (NSCLC), 5 colorectal cancer (CRC) and 5 others (median age: 59.5 yrs; 62.5% female). No dose-limiting toxicities (DLTs) were observed at the tested dose levels of 100 mg, 200 mg, 400 mg, 600 mg, 750 mg, 900 mg once daily (QD) and 300 mg twice daily (BID). Eight pts (25%) experienced at least one G3/G4 treatment related adverse event (TRAE) and no G5 TRAEs. Five pts (15.6%) experienced at least one serious adverse event. Eight pts (25%) had treatment interruptions, and 2 (6.3%) discontinued treatment due to treatment emergent adverse events (TEAEs). No dose reduction occurred. The most common TRAEs were gastrointestinal events including diarrhea (71.9%), vomiting (71.9%) and nausea (62.5%); all were grade 1 or 2. Anti-tumor activities were observed starting from 100 mg QD. Among 22 pts who had at least one post-treatment tumor assessment, objective response rate (ORR) was 27.3% (6/22), and disease control rate (DCR) was 86.4% (19/22). Nine out of 13 pts with stable disease (SD) had tumor shrinkage. Among the 7 pts with PDAC, all exhibited tumor shrinkage with 3 partial response (PR) and 4 SD. Among the 9 pts with NSCLC, 3 achieved PR, 5 SD, and 1 progression disease (PD). GFH375 demonstrated good oral bioavailability with a T_{max} of 2~4 h and a terminal half-life of 18.5-21.6 h. **Conclusions:** According to the preliminary data from ongoing FIH study, GFH375 monotherapy has demonstrated good tolerability and promising anti-tumor activities in pts with advanced solid tumor supporting further clinical development. Clinical trial information: NCT06500676. Research Sponsor: GenFleet Therapeutics (Shanghai) Inc.

Efficacy and safety of selumetinib in adults with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN): Primary analysis of KOMET (NCT04924608), a phase 3, international, randomized, placebo-controlled study.

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Background: No globally approved therapies exist for adults with NF1 and symptomatic, inoperable PN.KOMET is evaluating the efficacy and safety of selumetinib (SELU; ARRY-142886, AZD6244) in adults. **Methods:** KOMET is an ongoingPhase 3, randomized, double-blind, placebo-controlled trial. Adults (≥18 yrs) with NF1 and symptomatic, inoperable PN were randomized 1:1 to 28-day cycles of oral SELU 25 mg/m^2 BID or placebo (PBO) with crossover to SELU at progression or the end of Cycle (C) 12. Among others, baseline (BL) PAINS-pNF target PN chronic pain intensity score (< 3 or ≥3) was a stratification factor; 70% of patients (pts) were required to have a score ≥3. Primary analyses were conducted after the last pt completed C16 (data cutoff: Aug 5, 2024). The primary endpoint was objective response rate (ORR; confirmed partial/complete response) per ICR REiNS by the end of C16. Key secondary endpoints were change from BL to C12 in PAINS-pNF chronic pain score in pts with a BL score ≥3 and PlexiQoL total score in all randomized pts (SELU vs PBO). 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%. Key secondary endpoints were analyzed with a mixed model for repeated measures. **Results:** Of 145 randomized pts (SELU: 71; PBO: 74), 51.7% were male; median age was 29 yrs (range 18–60). SELU led to a rapid onset of response (median 3.7 mos), with an ORR of 19.7% (95% CI 11.2, 30.9) by C16 vs 5.4% (95% CI 1.5, 13.3) with PBO (p = 0.011). At C12, pts with a BL chronic pain score ≥3 had a greater reduction in pain score with SELU (LS mean −2.0; 95% CI −2.6, −1.4) vs PBO (LS mean −1.3; 95% CI −1.8, −0.7); and clinically meaningful improvement (meaningful score difference −2 points) vs BL, but this was not statistically significant vs PBO (p = 0.070). Reduction in chronic pain intensity was observed with SELU vs PBO in the full analysis set (all pts regardless of BL chronic pain intensity, nominal p = 0.024). Change from BL to C12 in PlexiQoL total score between treatment arms was not statistically significant (LS mean difference −0.1; 95% CI −1.2, 1.1). Adverse events (AEs) in the randomized period were consistent with the known safety profile of SELU. The most common AEs (≥10% of pts) were dermatitis acneiform (59%), increased blood creatine phosphokinase (45%), and diarrhea (42%) with SELU, and COVID-19 (20%), nausea (16%), and fatigue (14%) with PBO. Fourteen pts on SELU and 1 pt on PBO reported CTCAE Grade ≥3 treatment-related AEs; 9 SELU and 5 PBO pts discontinued due to AEs. **Conclusions:** In the first international, randomized, placebo-controlled trial in adults with NF1-PN, SELU achieved a significant ORR vs PBO (C16), meeting the primary endpoint, and a clinically meaningful reduction in PN-associated chronic pain (C12). Clinical trial information: NCT04924608. Research Sponsor: Alexion, AstraZeneca Rare Disease and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

3015 Rapid Oral Abstract Session

Phase 2 evaluation of the nilotinib-paclitaxel combination in patients with rare solid tumors: Rapid analysis and response evaluation of combination anti-neoplastic agents in rare tumors trial 1 (RARE CANCER 1).

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Background: Rare tumors constitute a heterogeneous group of cancers with limited treatment options and poor outcomes. To address the need for novel therapeutic options in this challenging population, patient-derived xenograft models of rare cancers were developed to screen combinations of anticancer agents. Based on these preclinical data, the NCI Developmental Therapeutics Clinic designed a series of phase 2 clinical trials to assess promising novel combination therapies in patients (pts) with rare tumors. RARE1—the first trial in this series—evaluates the nilotinib-paclitaxel combination, for which a preceding phase 1 study (NCT02379416) recently identified the recommended phase 2 dose (RP2D) and promising clinical activity, including confirmed partial responses (PR) in 3 pts (2 adult granulosa cell ovarian tumors [AGCOT], 1 endometrial cancer) and 1 unconfirmed PR (anal cancer). Given this clinical experience and preclinical activity in rare tumor models, RARE1 (NCT04449549) aims to evaluate the response and mechanism of action of the nilotinib and paclitaxel combination in rare, refractory solid tumors. **Methods:** Pts with rare tumors meeting the RARECARE definition were treated at the RP2D: nilotinib 300 mg orally twice a day and paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 in 28-day cycles. Response was assessed by RECIST v1.1. Tissue biopsies and research blood were collected at multiple timepoints for pharmacodynamic and genomic analyses. **Results:** This study enrolled 31 pts of diverse rare cancers as of the data cut-off. Of the 30 evaluable pts, 2 (7%) had confirmed PRs: 1 Ewing sarcoma and 1 ovarian clear cell cancer, completing 12 and 11 cycles (C) on study, respectively. Stable disease (SD) was the best response in 15 pts (50%), of which 5 pts (17%) had prolonged SD: 1 AGCOT (23+ C), 1 testicular embryonal rhabdomyosarcoma (22 C), 1 non-uterine leiomyosarcoma (21 C), 1 salivary gland (12 C), and 1 ampullary adenocarcinoma (6 C). Overall, the median number of cycles completed is 2 (range 0 - 23) and the median progression free survival is 3.8 months. No unexpected treatment-related adverse events have occurred. No grade 3-4 peripheral neuropathy has been observed. **Conclusions:** Preliminary clinical outcomes for the nilotinib-paclitaxel combination in patients with rare tumors showed encouraging signals of activity. To facilitate further evaluation of response and the underlying mechanism of action for this combination, enrollment now focuses on the 4 tumor types that have previously demonstrated response: Ewing sarcoma, ovarian clear cell carcinoma, AGCOT, and anal cancers. Pharmacodynamic and genomic analyses are also ongoing. This project has been funded in whole or in part with federal funds from the NCI, NIH, under contract HHSN261201500003I. Clinical trial information: NCT04449549. Research Sponsor: U.S. National Institutes of Health.

Clinical utility of circulating tumor RNA (ctRNA) in a combined circulating tumor DNA (ctDNA) and ctRNA next-generation sequencing (NGS) pan-cancer liquid biopsy assay.

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Background: Liquid biopsies are increasingly used in the real world for cancer therapy selection, disease monitoring, and early detection. Combining RNA with DNA sequencing for the detection of FDA-actionable gene fusions is already recommended as standard of care in guidelines as fusions are inherently challenging to detect by DNA-only methods. However, the clinical utility of profiling plasma ctRNA in addition to ctDNA has not yet been quantified in large studies. Here we report results from the first large real-world study establishing the clinical utility of combining ctRNA and ctDNA in a single liquid biopsy assay. **Methods:** A total of 1,007 consecutive plasma samples from 979 cancer patients across the USA and Asia underwent real-world liquid biopsy testing with a combined ctDNA and ctRNA assay (LiquidHALLMARK) in two CAP-accredited CLIA-certified laboratories from Jun 2021 to Dec 2024. The combined amplicon-based assay profiles genomic alterations in 80 genes on ctDNA and up to 37 genes on ctRNA. Only gene fusions (including *MET* exon 14 skipping) were included in this analysis. The limit of detection for gene fusions of the ctDNA and ctRNA panel were validated as 0.5% and 10 copies. **Results:** Plasma ctRNA was successfully analyzed in 99.6% (1003/1007) of samples across 30 cancer types. The top 5 cancer types (lung, prostate, breast, colorectal, and pancreas) comprised 84.2% of the clinical volume. Gene fusions were detected across 11 genes (*ALK*, *RET*, *ROS1*, *MET*, *NRG1*, *NTRK1*, *FGFR2*, *FGFR3*, *ESR1*, *ERG*, *ETV4*) in 7.8% (78/1003) of cases, primarily in prostate and lung, but also in breast, bile duct, thyroid, liver, and bladder cancers. A total of 80 fusions were detected, of which 25 were detected by both ctDNA and ctRNA, while ctDNA and ctRNA each exclusively detected 27 and 28 fusions. Among the 28 ctRNA-only fusions, 5 were not covered by the ctDNA panel (1 *ATP1B1-NRG1*, 1 *ESR1-CCDC170*, 1 *ESR1-AKAP12*, and 2 *SLC45A3-ERG* fusions). Eleven (11/28) ctRNA-only fusions were actionable; all 11 were found in lung cancer. Two of these co-occurred with another lung driver mutation, highlighting potential resistance mechanisms to targeted therapy. Of the remaining 9, 3 were treated with fusion-matched targeted therapy. Two patients had real-world response rates available; both exhibited partial response to treatment. Overall, inclusion of ctRNA analysis increased the diagnostic yield of all fusions by 53.8% and actionable fusions by 36.7%. **Conclusions:** This is the first large study showing that adding ctRNA to ctDNA liquid biopsy increases total actionable diagnostic yield by 36.7%, highlights potential resistance mechanisms, and can broaden panel coverage to include gene fusions not amenable to detection by conventional DNA-based methods. These findings support recommendations for combined DNA/RNA testing of fusions in both tissue and liquid samples. Research Sponsor: None.

Enhancing prognostic precision in bladder cancer: AI-driven tumor microenvironment analysis from H&E images.

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Background: Bladder cancer (BC) represents a significant healthcare burden. Despite advancements in diagnostics and treatment, the survival rate remains low, underscoring the need for improved prognostic tools. The current UICC staging system often lacks precision in patient stratification. Moreover, there is a paucity of scalable methods that explore and quantify tumor microenvironment (TME) features and their influence on patient outcome. Here, we present an artificial intelligence (AI) framework that operates on routine hematoxylin & eosin-stained (H&E) slides to enable systematic TME characterization and improve prognostic accuracy. **Methods:** In a bicentric cohort of over 700 resected BC patients, we developed and validated a deep learning approach for TME analysis. The model was trained using multiplex immunofluorescence-validated annotations but operates solely on H&E-stained images, maximizing clinical applicability. Key features included tissue compartment segmentation, cell classification, and spatially resolved cell patterns. We evaluated the model's performance and integrated TME features with clinicopathological variables to improve prognostic stratification beyond UICC staging. **Results:** The model demonstrated robust tissue compartment segmentation (F1-score = 0.91) and accurately identified key immune cell populations in tissue regions. When integrating the spatially resolved cellular features with clinicopathological variables, we observed significant improvements in prognostic capabilities for overall survival. The integrated approach demonstrated a 22% relative improvement over the conventional UICC staging system alone (C-index increased from 0.59 to 0.61, $p < 0.01$), measured against the random baseline C-index of 0.5. Our integrated model displayed a hazard ratio of 1.859 (95% CI: 1.530-2.259, p = 4.390e-10), markedly stronger than traditional risk stratification which showed a hazard ratio of 1.477 for high versus low risk groups (95% CI: 1.219-1.791, p = 7.117e-05). These findings demonstrate that AI-driven analysis of the tumor microenvironment provides valuable prognostic information beyond current clinical staging methods, suggesting promising opportunities for enhancing patient risk stratification. **Conclusions:** We show that a combination of AI with UICC staging shows improved patient stratification compared to stratifying by UICC alone. This study demonstrates the feasibility of automated TME characterization from routine H&E slides in BC and suggests that incorporating TME features into prognostic models enhances accuracy and could support personalized patient management in individualized oncology. While further validation in larger, multicentric-datasets is required, our approach shows potential for facilitating systematic biomarker development and improving clinical decision-making in BC care. Research Sponsor: BMBF.

Preliminary results from a first-in-human phase 1 dose escalation trial of ADRX-0706, a next generation Nectin-4 ADC, in subjects with advanced solid tumors.

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Background: ADRX-0706 is a Nectin-4 targeting ADC designed to provide an increased therapeutic window through stable conjugation of a novel microtubule inhibitor payload (AP052) to an IgG1 monoclonal antibody at a drug-to-antibody ratio of 8. Preliminary safety, anti-tumor activity, pharmacokinetic (PK) and Nectin-4 expression results are presented from the dose escalation part of the ongoing Phase 1 trial (NCT06036121). **Methods:** Eligible subjects with select advanced solid tumors (urothelial [UC], cervical [CC], breast [BC], head and neck [HNSCC], ovarian [OC], non-small cell lung [NSCLC], and pancreatic [PC]) were enrolled in cohorts of escalating dose levels (1-16 mg/kg, Q3W, IV) using a BOIN design with backfill. Nectin-4 expression was evaluated retrospectively. Primary and secondary endpoints included dose-limiting toxicities [DLTs], adverse events [AEs], laboratory value changes, PK, immunogenicity, and response per RECIST v1.1. **Results:** As of the 13Dec24 data cutoff, 53 subjects with a median age of 59 years and median of 4 (1-14) prior therapies were enrolled. One DLT (G3 stomatitis) occurred at the highest dose of 16 mg/kg. The most common treatment related AEs (TRAE ≥15%) were arthralgia (32%), fatigue (21%), rash (19%), anemia (17%), and nausea (15%). The majority of TRAEs were G1-2 in severity and manageable, including only 3 (5.7%) subjects with peripheral neuropathy and 2 (3.8%) with liver enzyme increase. The most common ≥G3 TRAE was neutropenia (11%). ADC exposure increased in a dose-proportional manner with minimal deconjugation and the ADC half-life was 15 days. There were 5 subjects who achieved objective response across different tumor types (UC, NSCLC, CC) and 9 with stable disease per RECIST among 30 response-evaluable subjects treated at doses ≥8 mg/kg (ORR 16.7%, DCR 46.7%), including 2 triple negative BC (TNBC) subjects with 27% and 29% decrease in tumor size who remain on treatment. ADRX-0706 demonstrated Nectin-4 expression-dependent anti-tumor activity with all responses observed in tumors with H-score ≥100, including a confirmed complete response (CR) in a CC subject (H-score 250). Two responses were observed after prior progression on other Nectin-4 targeting MMAE drugs and three responses remain ongoing with subjects on treatment for 9+ to 23+ weeks. Based on these data, 10 mg/kg Q3W was selected as the Phase 1b dose. **Conclusions:** ADRX-0706 demonstrated a preliminary safety profile differentiated from MMAE-conjugates and with manageable toxicities. The antibody-like PK profile together with minimal deconjugation supports Q3W dosing. Encouraging anti-tumor activity was observed in multiple heavily pretreated tumors with moderate-high Nectin-4 expression. Enrollment in Phase 1b cohorts of UC, CC, and TNBC is ongoing. Clinical trial information: NCT06036121. Research Sponsor: Adcentrx Therapeutics.

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

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Background: Cadherin-3 (CDH3), a calcium-dependent cell-cell adhesion glycoprotein, is overexpressed on lung, breast, head and neck and other malignancies, and associated with cancer invasiveness and poor prognosis. BC3195 is known as the only antibody drug conjugate (ADC) in clinical stage, targeting CDH3 with cleavable linker and payload of monomethyl auristatin E (MMAE). **Methods:** A phase I, open-label, first in human study whose objectives were to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of BC3195 is being performed in patients (pts) with advanced solid malignancies. BC3195 is administered as 1-hr IV infusion every 3 weeks (Q3W) or every week (QW). An evaluation of seven dose levels (DLs) is planned: 0.3, 0.6, 1.2, 1.8, 2.1, 2.4 mg/kg Q3W and 1.2 mg/kg QW with a BOIN design guiding dose escalation. **Results:** As of the data cut-off-date (Dec 26th, 2024), 56 pts have been enrolled. The number of pts in each DL is shown in the table. Twenty-five (44.6%) pts had received ≥3 prior lines of treatment. Stomatitis (71.4%), rash (60.7%) and anemia (53.6%) were the main adverse events (AEs). Stomatitis and rash typically occurred in the first cycle and were manageable. Twenty-one pts (37.5%) experienced Grade≥3 treatment related adverse events (TRAEs). Among the 50 pts who were evaluable for tumor response, 5 pts in 2.4 mg/kg Q3W had partial response (PR). Of the 20 NSCLC pts treated in 2.4 mg/kg, 4 pts had confirmed PR (cPR), and 14 pts had stable disease (SD) as their best response; the objective response rate (ORR) was 50% (4/8) in previously-treated EGFR-mutant NSCLC pts, and mPFS was 168 days (Table). PK results demonstrated that exposure of the ADC, total antibody (TA) and MMAE increased in a non-linear manner at dose up to 2.4 mg/kg. Median T_{max} values for ADC and TA were 1 h, and median T_{max} for free MMAE was 25-169 h. In addition, elimination $t_{1/2}$ values averaged 54 h, 78 h and 63 h for the ADC, TA, and MMAE at 2.4 mg/kg, respectively. **Conclusions:** BC3195 has a manageable safety profile and favorable PK characteristics and demonstrated impressive preliminary antitumor activity in heavily-pretreated pts with NSCLC, of which most had EGFR-mutations (ORR=50%). Dose optimization and expansion are ongoing. Clinical trial information: NCT05957471. Research Sponsor: Biocity Biopharmaceutics Co. Ltd.

Safety and efficacy data of study BC3195-101 (safety analysis set).

Efficacy and Safety	0.3 mg/kg Q3W (N = 3)	0.6 mg/kg Q3W (N = 3)	1.2 mg/kg Q3W (N = 3)	1.8 mg/kg Q3W (N = 9)	2.1 mg/kg Q3W (N = 6)	2.4 mg/kg Q3W (N =31)		All* (N=56)
All tumor types (N = 31)	EGFR-mut NSCLC (N = 8)							
ORR, n (%)	0	0	0	0	0	5 (16.1)	4 (50.0)	5 (8.9)
DCR, n (%)	1 (33.3)	2 (66.7)	1 (33.3)	3 (33.3)	2 (33.3)	22 (71.0)	7 (87.5)	32 (57.1)
mPFS, days	40	82	40	40	39	130	168	91
Grade≥3 TRAE n (%)	0	0	0	2 (22.2)	1 (16.7)	17 (54.8)	3 (37.5)	21 (37.5)

*The subject in 1.2 mg/kg QW dose level is not presented in a dedicated column in this table.

A phase 2 basket trial of ado-trastuzumab emtansine for patients with *HER2* amplified cancers.

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Background: The *HER2* gene is commonly amplified (amp) across a variety of tumor types. Ado-trastuzumab emtansine (TDM1) is a potent antibody-drug conjugate targeting HER2 that is approved in HER2+ breast cancer. The efficacy of TDM1 in other *HER2*-amp solid tumors is unknown. **Methods:** We conducted a single-arm, phase 2 basket trial of TDM1 in which patients (pts) were enrolled in one of 5 *HER2*-amp cohorts: non-small cell lung cancer (NSCLC), colorectal cancer, endometrial cancer, salivary gland cancer, or other solid tumor. *HER2* amp was identified through next generation sequencing by MSK-IMPACT, defined as two-fold change, or by in-situ hybridization (ISH) with *HER2/CEP17* ratio $\geq$2.0 in a CLIA-certified laboratory. In tumors sequenced by MSK-IMPACT, precise level of the ERBB2 amplification (i.e. integer copy number) was assessed and correlated with clinical response. All pts received TDM1 3.6mg/kg IV every 21 days. The primary endpoint was overall response rate (ORR). For each cohort, a Simon two-stage optimal design was used. In the first stage, 7 pts were accrued in each cohort; if 0/7 responses, the cohort was closed. Otherwise, up to 11 additional pts were accrued. Cohorts 1, 3, and 4 were expanded by up to 5 pts (max 23 pts) due to durable responses seen early on. Response and progression of disease was evaluated using RECIST version 1.1. Modified PERCIST was allowed if pts did not have RECIST measurable disease. Toxicity was graded as per CTCAE v4.1. Circulating tumor DNA was collected pre-, post-, and on-treatment for all pts when feasible. **Results:** 88 pts were accrued between 2016 and 2023. The ORR by cohort is listed in Table 1. The most common toxicities were decreased platelet count and elevated ALT. There was one incident of grade 5 pneumonitis in a patient in cohort 1. Median time on treatment was 2.5 months (range 0.03 – 53.7 months); in pts with salivary gland tumors, median time on treatment was 17.6 months (0.3 – 53.7). **Conclusions:** TDM1 demonstrated efficacy in multiple *HER2*-amp tumor types. The highest ORR was seen in salivary gland tumors, with a median time on treatment of about 1.5 years. More work is needed to understand the enhanced efficacy of TDM1 in these tumors. Clinical trial information: NCT02675829. Research Sponsor: Genentech.

Response rate by cohort and disease site.

Cohort	RECIST-only ORR	Combined* ORR
1: *HER2*-amp lung	4/18 (22.2%)	4/19 (21.1%)
2: *HER2*-amp colorectal	0/7 (0.0%)	0/7 (0.0%)
3: *HER2*-amp endometrial	5/23 (21.7%)	5/23 (21.7%)
4: *HER2*-amp salivary	8/10 (80.0%)	14/16 (87.5%)
5: Other *HER2*-amp solid tumors	2/23 (8.7%)	2/23 (8.7%)
Biliary	1/8 (12.5%)	1/8 (12.5%)
Bladder & urinary tract	0/5 (0.0%)	0/5 (0.0%)
Cervical	0/2 (0.0%)	0/2 (0.0%)
Ovarian	1/7 (14.3%)	1/7 (14.3%)
Pancreatic	0/1 (0.0%)	0/1 (0.0%)
TOTAL	**19/81 (23.5%)**	**25/88 (28.4%)**

ORR=overall response rate. *Combined: RECIST when available, PERCIST if non-RECIST-evaluable.

The safety, tolerability, and efficacy of BRY812 in patients with advanced solid tumors: Preliminary results from the phase I clinical study.

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Background: Antibody-conjugated drugs (ADCs) have demonstrated outstanding clinical efficacy in treating a wide range of solid tumors as well as hematological tumors currently. An ongoing multicenter, open-label, phase I clinical study assessed the safety, tolerability and preliminary efficacy of BRY812, the ADC targeting transmembrane protein LIV-1 with MMAE as cytotoxic payload, in advanced solid tumors. Here we report the interim analysis results. **Methods:** In Phase Ia (dose escalation), the eligible patients with advanced solid tumors were enrolled in each of 7 dose groups (0.25, 0.5, 1.0, 2.0, 2.8, 3.6 and 4.4 mg/kg) for evaluation to determine the MTD of BRY812. An "accelerated titration" method (0.25, 0.5 mg/kg) as well as a modified toxicity probability interval-2 method (subsequent doses) was applied. Subsequently dose expansion was conducted for dose levels of 2.0, 2.8 and 3.6 mg/kg that demonstrated tolerability and relative efficacy. The patients received treatment every 3 weeks until intolerable toxicity or disease progression. The primary endpoint was to evaluate DLT and MTD to determine RP2D, other endpoints included ORR. **Results:** Overall, as data cut-off date (Dec 13, 2024), 36 patients (including 30 patients with breast cancer) with advanced solid tumors were enrolled, including 20 patients in dose escalation phase and 16 patients in dose expansion respectively. Treatment is still ongoing for 19 patients. No DLT was observed up to 3.6 mg/kg. 4.4 mg/kg was not tolerated due to DLTs (2 of 4 patients experienced DLT events). The most common grade ≥3 TEAE was neutropenia, and grade 4 neutropenia was observed in 3.6 mg/kg (2/12) and 4.4 mg/kg (4/4). 4 patients discontinued treatment due to AE including 2 injury corneal (each of 3.6 & 4.4 mg/kg), 1 peripheral neuropathy (2.8 mg/kg) and 1 hepatic enzyme increase (3.6 mg/kg). Among 34 patients in efficacy analysis, 8 (23.5%) patients and 7 (20.6%) patients had PR and SD, respectively, and 17 (50%) patients had PD, leading to ORR of 23.5% (95% CI: 10.7, 41.1) and DCR of 44.1% (95% CI: 27.2, 62.1). The patients with higher LIV-1 expression showed better efficacy, as among 14 patients with PS2+ enriched, ORR was 43% (6/14 in breast cancer). In addition, ADC and Total antibody clearance were similar. BRY812 showed dose-dependent decrease of clearance in the dose range of 0.25 to 2.0 mg/kg, while approximately linear clearance in the dose range of 2.0 to 4.4 mg/kg, and the half-life were ~7 days. No accumulation was observed after multiple dosing. ADA positive rate was 11.43% (4/35). **Conclusions:** BRY812 demonstrated favorable safety and tolerability profile, with promising clinical efficacy in patients with advanced solid tumors. Further dose optimization and clinical efficacy will be explored in Phase Ib. Clinical trial information: NCT06038058. Research Sponsor: BioRay Pharmaceutical (Hangzhou) Co., Ltd.

A pooled analysis of JSKN003, a biparatopic anti-HER2 antibody conjugate (ADC), in patients with advanced HER2-overexpressing (IHC 3+) gastrointestinal tumors.

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Background: JSKN003 is a biparatopic HER2-targeting ADC conjugated with a topoisomerase I inhibitor (TOP1i) payload via a dibenzocylooctyne tetrapeptide linker. The efficacy and safety of JSKN003 in several solid tumors have been highlighted in previous reports. **Methods:** JSKN003-101 and JSKN003-102 are dose escalation and expansion studies involving Australian and Chinese patients (pts) with metastatic solid tumors. This pooled analysis of two studies was performed to assess the efficacy and safety in advanced HER2-overexpressing (IHC 3+) gastric or gastroesophageal cancer (GC/GEJC) and colorectal cancer (CRC) pts. **Results:** As of data cutoff (18 Dec 2024), 40 patients with HER2-overexpressing (IHC 3+ by local lab) gastrointestinal tumor (23 in GC/GEJC and 17 in CRC) were enrolled across 7 dose levels: 2.1 mg/kg (n = 1), 4.2 mg/kg (n = 1), 5.2 mg/kg (n = 1), 6.3 mg/kg (n = 33), 7.3 mg/kg (n = 1), 8.4 mg/kg (n = 2), 10.5 mg/kg (n = 1). The median follow-up time of two studies was 7.16 months. Most pts were heavily pretreated (37.5% had ≥3 lines of prior treatment; 45.0% received irinotecan; 67.5% received anti-HER2 therapy; 42.5% received IO therapy). Four of the 17 CRC pts were RAF/RAS mutations (n = 2 RAS-mut, n = 2 RAF-mut). Thirty-nine patients had at least one tumor assessment after baseline. The overall response rate (ORR) per RECIST v1.1 in HER2-overexpressing gastrointestinal tumor was 66.7% and the disease control rate (DCR) was 94.7%. Among 22 GC/GEJC pts, the ORR was 68.2% and DCR was 95.5%. The median progression-free survival (PFS) was 9.59 months (95% CI: 2.96, NE) with 66.3% (95% CI: 29.4, 87.1) PFS rate at 6 months. Among 17 CRC pts, the ORR was 64.7% (66.7% in RAF-wild pts, n = 15) and DCR was 94.1%. The mPFS was 13.77m (95% CI: 7.1, NE) with 94.1% (95% CI: 65, 99.2) PFS rate at 6 months. The median overall survival (OS) was not yet mature. Notably, one BRAF-mut patient achieved PR at first tumor assessment after baseline, two RAS-mut pts achieved PR and duration was over 48 weeks. The most common treatment-related adverse events (TRAEs) included nausea, diarrhea, neutropenia, decreased appetite, vomiting, rash, anemia and fatigue. Grade 3/4 neutropenia was observed in 2 (5.0%) pts, Grade 3/4 anemia was observed in 1 (3.0%) pts. No TEAEs led to death or treatment discontinuation. Interstitial lung disease (ILD) occurred in 3 (7.5%; n = 2 G1; n = 1 G2) pts. **Conclusions:** JSKN003 demonstrated promising efficacy in heavily pretreated pts with advanced HER2-overexpressing gastrointestinal tumors, with a manageable and predictable safety profile. Clinical trial information: NCT05494918, NCT05744427. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

Initial results from a first-in-human phase 1 study of LY4170156, an ADC targeting folate receptor alpha (FRα), in advanced ovarian cancer and other solid tumors.

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Background: Folate receptor alpha (FRα) is overexpressed in several solid tumors. LY4170156 is an Fc-silent, FRα specific humanized IgG1 ADC linked to exatecan, a topo-I inhibitor, via a novel cleavable polysarcosine linker at a homogenous DAR of 8. LY4170156 demonstrated *in vivo* preclinical efficacy in tumor models, across all FRα expression levels. **Methods:** This is a multicenter, open-label, first-in-human phase 1a/b study of LY4170156 in patients (pts) with advanced FRα-expressing ovarian, endometrial, cervical, and other solid tumors. Pts with prior ADCs targeting FRα with payloads other than topo-I (including mirvetuximab soravtansine-gynx [mirv]) were allowed. Dose escalation followed the mTPI-2 method. LY4170156 was administered Q3W IV (dose range of 2-6 mg/kg); dose limiting toxicity (DLT) evaluation period was 21 days. Dose escalation included a randomized dose optimization cohort in PROC. Key endpoints were safety, PK, and antitumor activity per RECIST v1.1. Efficacy evaluable pts were those who had a post baseline response assessment or discontinued treatment prior to the response assessment. **Results:** As of 27 Nov 2024, 45 pts were treated with LY4170156. Median age was 63 yrs (range, 24-85), 100% had ECOG PS 0-1, and 32 (71%) had high-grade serous ovarian cancer (HGSOC). Among the HGSOC pts (32), median lines of prior therapy was 5 (range, 1-10), 19% had received prior mirv, and 44% had FRα expression $< 75\%$ by local or central testing. PK of LY4170156, total antibody, and exatecan were linear and dose-proportional within the tested dose range. Unconjugated payload release from ADC at C_{max} was $< 4\%$ at 4 mg/kg; median half-life of LY4170156 was 5.7-7.0 days and exatecan was 7.2-8.6 days. Main toxicities were myelosuppression and GI-related, as expected from an exatecan payload. Across all doses, the most common treatment-emergent adverse events (TEAEs; ≥15%) were nausea (58%, 2% gr 3), fatigue (44%, 0% gr 3-4), anemia (33%, 24% gr 3), vomiting (27%, no gr 3-4), diarrhea (22%, 4% gr 3), and neutropenia (20%, 11% gr 3-4). Febrile neutropenia (FN) was observed in 3 pts (7%). To date, no pulmonary or ocular toxicity were noted. Two DLTs were observed (1 gr 3 FN [6 mg/kg]; 1 gr 3 anemia [2 mg/kg]); no MTD has been established to date. Among 13 efficacy evaluable HGSOC pts (6 FRα ≥75%; 6 $< 75\%$; 1 pending data), 9 showed reduction in target lesions; preliminary ORR was 38% (n = 5) with 1 CR, 4 PR, and 4 SD across all dose levels. Combined ORR for 4 and 6 mg/kg dose levels was 55%. All responses were unconfirmed and ongoing at the time of data cutoff. Three of 5 responders had FRa expression $< 75\%$ and two ≥75% including 1 who was mirv refractory. **Conclusions:** LY4170156 was well-tolerated with encouraging clinical activity among HGSOC pts, including those with FRα expression $< 75\%$ and those with prior mirv. Randomized dose optimization is ongoing and updated data will be presented. Clinical trial information: NCT06400472. Research Sponsor: Eli Lilly and Company.

BAT8008, a TROP-2 antibody-drug conjugate (ADC), in patients with advanced solid tumor: Results from a phase 1 study.

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Background: BAT8008 is a monoclonal ADC that delivers exatecan to cells expressing TROP-2. TROP-2 is a cell surface glycoprotein that can be expressed in certain normal tissue but is frequently overexpressed in multiple carcinomas including cervical cancer (CC) and esophageal cancer (EC). Here we report the safety and efficacy data of BAT8008. **Methods:** BAT8008 was administered by intravenous infusion at doses of 0.8-2.7mg/kg on days 1 of each14-day cycle(the first cycle is 21-day). The study included dose escalation, dose expansion and cohort expansion which included CC, EC and other solid tumors that progressed after $>$ l systemic treatments (Tx). Primary objectives were assessment of safety and preliminary efficacy. **Results:** As of Jan 15, 2025, 170 patients (pts) were enrolled with doses ranging from 0.8 to 2.7mg/kg. 2 out of 6 pts in 2.7mg/kg group had dose limiting toxicity (1 with G3 increased lipase, 1 with G4 thrombocytopenia and G4 febrile neutropenia). The maximum tolerated dose and the RP2D was selected as 2.4mg/kg. 147 pts were enrolled at dose of 2.4mg/kg. The most common TRAEs of 2.4mg/kg dose group ($\geq$20%, all grade/$\geq$5%, $\geq$G3) were anemia (78.8%,13.7%), white blood cell count decreased (62.3%, 18.5%), nausea (59.6%,0%), stomatitis(59.6%,19.2%), neutrophil count decreased (52.7%,19.2%), platelet count decreased (38.4%,8.2%), vomiting (38.4%,0.7%), lymphocyte count decreased (35.6%,5.5%), fatigue (34.9%, 0%), body weight loss (29.5%, 0.6%), constipation (26.7%,0%), anorexia (23.3%,2.7%). 22 CC pts and 13 EC pts were enrolled at 2.4mg/kg and evaluable for tumor assessment. The obiective response rate (ORR) was 36.4% and 23.1%, respectively. Median prior lines of Tx were 2(range, 1-5). 50% CC and 93% EC pts progressed after platinum-based chemotherapy and immune checkpoint inhibitors, respectively. 23% EC had previously used topoisomerase I inhibitors. Objective responses were also observed in pts with other solid tumor types. **Conclusions:** The data indicated encouraging efficacy of BAT8008 in advanced CC and EC. The safety profile showed adequate tolerability. Clinical trial information: NCT05620017. Research Sponsor: Bio-Thera Solutions, Ltd.

Tumor Type	CC	EC
n	22	13
CR	1	1
PR	7	2
ORR,%	36.4	23.1
cORR,%	31.8	15.4
DCR,%	77.3	100
PFS, months	6.8	5.3
(95% CI)	(3.4-10.2)	(3.1-7.4)

A phase I clinical study to evaluate the safety, tolerability, and pharmacokinetic characteristics of HLX43 (anti-PD-L1 ADC) in patients with advanced/metastatic solid tumors.

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Background: Antigens highly expressed in tumors such as HER2 and TROP2 have been widely investigated as antibody-drug conjugate (ADC) targets, leading to their approval for various cancers due to their promising efficacies. However, limited targets for approved ADCs and resistance to the cytotoxic agents render the imperative need for new ADCs. This study aimed to evaluate the safety, tolerability, and preliminary efficacy of HLX43, a novel anti-PD-L1 ADC in patients with advanced/metastatic solid tumors. **Methods:** This phase 1 study consisted of 2 parts. Parts 1 and 2 were dose escalation and dose expansion phases, respectively, to explore different doses of HLX43. In Part 1, patients with histologically or cytologically confirmed advanced/metastatic malignant solid tumors refractory to or not amenable to standard therapies received intravenous HLX43 at 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, or 4 mg/kg, Q3W. In Part 2, patients with advanced/metastatic non-small cell lung cancer (NSCLC) refractory to standard treatment received HLX43 at 2 mg/kg, 2.5 mg/kg, or 3 mg/kg, Q3W. The primary endpoints for Part 1 were the proportion of subjects experiencing dose-limiting toxicity (DLT) in each dose group within three weeks after the first drug administration and the maximum tolerable dose (MTD) while that for Part 2 were the recommended Phase 2 dose and IRRC-assessed objective response rate (ORR). **Results:** As of 27 June 2023, 18 patients with non-small cell lung cancer (n = 12, 66.7%), head and neck squamous carcinoma, cervical squamous carcinoma, thymic squamous cell carcinoma, nasopharyngeal cancer, uterine carcinosarcoma, or small cell lung cancer (n = 1, 5.6% for each) were enrolled in Part 1 and received HLX43 at 0.5 mg/kg (n = 3), 1 mg/kg (n = 3), 2 mg/kg (n = 3), 3 mg/kg (n = 3), or 4 mg/kg (n = 6). All the patients experienced treatment-emergent adverse events (TEAEs) that were mostly grades 1-2. One patient in the 4 mg/kg dose group experienced DLTs of febrile neutropenia and decreased white blood cell count. Investigator-assessed ORR was 31.3% (95% CI 11.0-58.7). In Part 2, only data from 21 patients enrolled to receive HLX43 at 2 mg/kg is available and presented here. Among these patients, 15 (71.4%) had squamous NSCLC and 6 (28.6%) had nonsquamous NSCLC. Investigator-assessed ORR and disease control rate were 38.1% (95% CI 18.1-61.6) and 81.0% (95% CI 58.1-94.6); no complete response was achieved, and 8 patients (6 sqNSCLC and 2 nsqNSCLC) had partial response. All the patients experienced TEAEs, most of which were grades 1-2; grade ≥3 TEAEs occurred in 7 (33.3%) patients. **Conclusions:** HLX43 was well tolerated with no new safety signals across different dose and exhibited encouraging preliminary efficacy in patients with advanced solid tumors, including those with NSCLC, who had failed standard therapies, which warrants further investigation. Clinical trial information: NCT06115642. Research Sponsor: Shanghai Henlius Biotech, Inc.

First in human phase I study of TQB2103, a Claudin18.2 (CLDN18.2) targeted antibody-drug conjugate (ADC), in patients with advanced solid tumors.

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Background: Claudin18.2 is a promising target for CLDN18.2-expressing cancers such as gastric and pancreatic cancers. TQB2103 is a novel ADC comprised of a humanized anti-CLDN18.2 IgG1 monoclonal antibody, a cleavable linker and topoisomerase I inhibitor, with a drug-to-antibody-ratio (DAR) of 8. **Methods:** This is a multicenter, first-in-human study of TQB2103 in patients (pts) with previously treated advanced solid tumors. This study comprised of a dose escalation part in patients regardless of Claudin18.2 expression level and a dose expansion part in patients specified by CLDN18.2 positive expression. The primary objectives were to assess safety and tolerability and determine the recommended phase 2 dose. Secondary objectives were to assess the pharmacokinetics and preliminary anti-tumor activity. **Results:** As of December 16 2024, 59 pts were enrolled to receive TQB2103 intravenously every 3 weeks at 7 dose level (range from 0.5 to 6.0mg/kg). One patient experienced dose-limiting toxicity (DLT) of grade 3 transaminase elevation at 0.5mg/kg which might also be related to the comorbidity of choledocholithiasis. Fifty-six (94.9%) patients experienced at least one treatment-related adverse event (TRAE). The most frequent TRAEs were nausea (72.9%), vomiting (64.4%), appetite decreased (57.6%), hypoalbuminemia (49.2%), anemia (49.2%), white blood cell decreased (44.1%), and asthenia (44.1%). The most frequent grade ≥3 TRAEs were anemia (11.9%) and neutrophil count decreased (10.2%). Most of AEs were grade 1 or grade 2 and manageable. Among the 30 response evaluable pts with CLDN18.2 expression, the ORR and DCR were 20% and 76.7%, respectively. Shrinkage of the target lesions occurred in 17(56.7%) patients. In patients with CLDN18.2 moderate to high expression, the ORR was 42.9% of gastric cancer at 5mg/kg. Surprisingly, all of 3 response-evaluable biliary tract cancer had shrinkage of the target lesions at the first assessment, and 1/3 achieved partial response. **Conclusions:** TQB2103 demonstrated encouraging anti-tumor activity in CLDN18.2 positive solid tumors, with a favorable safety profile. The findings support further development of TQB2103 mono-therapy or in combination with other anti-cancer therapies. Clinical trial information: NCT05867563. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Association of genomic alterations in circulating tumor DNA (ctDNA) with clinical response to telisotuzumab vedotin (Teliso-V) in 2L+ *EGFR* wildtype (*EGFR*wt) non-squamous non-small cell lung cancer (NSCLC) patients (pts) with c-Met over-expression (OE).

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Background: Teliso-V is an antibody-drug conjugate comprising the c-Met–targeting antibody telisotuzumab linked to the microtubule inhibitor monomethyl auristatin E. In the LUMINOSITY trial (NCT03539536), Teliso-V monotherapy demonstrated efficacy in *EGFR*wt pts with c-Met OE (≥25% tumor cells at 3+ intensity by IHC) (Camidge et al. JCO 2024;42:3000-11). We used ctDNA molecular profiling to investigate baseline (BSL) and longitudinal changes in pts' tumor mutational spectrum, and to identify potential mechanisms of tumor response and drug resistance to Teliso-V. **Methods:** Pts received 1.9 mg/kg Teliso-V intravenously Q2W. In total, 83 pts with ctDNA data and evaluable tumor assessments in Stage 2 were included in the analysis. Plasma ctDNA was collected at multiple timepoints and analyzed for genomic alterations using the PGDx elio Complete NGS assay (521 genes). Variants with allele frequency (VAF) < 0.3% or from putative clonal hematopoiesis of indeterminate potential genes were removed. High ctDNA levels were defined as having a mean (m)VAF ≥median (2.05%), and low ctDNA levels as mVAF < median. Molecular response (MR) was defined as having ≥50% reduction in the mVAF vs BSL levels without gene amplification. Mutational profiles and their association with RECIST-defined tumor response and/or drug resistance were assessed. **Results:** Overall, pts with high BSL ctDNA levels had an ORR (28.6%, 12/42) similar to all *EGFR*wt pts with c-Met OE (28.6%, 46/161) and were not statistically different vs pts with low BSL levels. However, pts with low BSL ctDNA had longer median OS (16.3 vs 8.5 mo) and mPFS (8.1 vs 5.4 mo) vs those with high BSL levels. Although the total pts with genomic alterations (GA) in this analysis was limited, *KRAS* GA were one of the most common mutations detected at BSL (24%, 20/83 pts). ORR to Teliso-V among pts with the actionable GA (AGA) of *KRAS* G12C was 100% (5/5). Conversely, among pts with non-AGA *KRAS* G12V/D/A and Q61H/L, the ORR was 23% (3/13). Additional AGAs were found in BSL ctDNA, including 1 *BRAF* V600E, 3 *MET* ex14del, 1 *EGFR* G719C, and 2 *RET1-KIF5B* translocations; none had response to Teliso-V. Pts with a MR at week 6 had higher ORR (35% vs 23%), longer median OS (15.5 vs 12.2 mo), and median PFS (8.5 vs 5.7 mo) vs those who did not. One pt with stable disease had several new AGAs detected in circulation at week 6, including activating *EGFR* ex20ins. At week 24, clinical progression was accompanied by gene amplifications of *ERBB2*, *FGF4*, *FGFR4*, and *FGFR3*. Other types of pharmacodynamic changes in ctDNA that could predict clinical response or drug resistance will be presented. **Conclusions:** ctDNA is a promising biomarker in predicting Teliso-V activity. Confirmatory research is planned in larger pt cohorts and/or with tissue-based NGS analyses. Clinical trial information: NCT03539536. Research Sponsor: AbbVie, Inc.; n/a.

First-in-human phase 1 dose escalation trial of OMTX705, a novel anti-fibroblast activation protein (FAP) antibody drug conjugate (ADC), in monotherapy and in combination with pembrolizumab in patients with solid tumors.

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Background: Cancer Associated Fibroblasts (CAFs) are key components of tumor microenvironment and have immunosuppressive functions. FAP is expressed in a restricted fashion on CAFs. OMTX705 is a first-in-class ADC targeting FAP with a novel tubulysin payload. OMTX705 demonstrated a good safety profile in relevant toxicology models and high linker stability in plasma. We report the dose escalation phase 1 trial of OMTX705 in monotherapy and in combination with pembrolizumab (PEM). **Methods:** Patients (pts) with advanced carcinomas or sarcomas received 1-18 mg/kg of OMTX705 monotherapy and 2-10 mg/kg with standard PEM. Escalation used a classical 3+3 design with backfilling. OMTX705 schedule is Day 1, 8 every 21 days. The primary endpoint is safety and key secondary are efficacy, pharmacokinetics and biomarkers. Biopsy and blood samples were collected for biomarker analysis. **Results:** A total of 78 pts have been dosed: 31 pts in monotherapy in 9 dose cohorts and 47 in combination in 7 cohorts of 3 pts each plus 2 backfilling cohorts at 4 and 7.5 mg/kg in pancreatic adenocarcinoma (PDAC) and microsatellite stable (MSS) colorectal cancer (CRC). Median age was 60, 43% male and ECOG PS 0 in 44%. Main histologies were PDAC 33% and MSS CRC 21% with median of 2 (1 to 5) and 3 (1 to 5) prior lines of therapy, respectively. Median treatment exposure was 44 days (range 8 to 113) in monotherapy and 92 days (1 to 422) in combination. OMTX705 relative dose intensity was ~100% in all dose levels. No DLT has been observed. The most frequent related TEAEs were asthenia 35%, AST increased 14%, diarrhea 8%, anemia 8%, and nausea 8%. Grade 3 related TEAEs (pts): anemia (2), immune-mediated hepatitis (2), GGT increased (1), neutropenia (1) and asthenia (1). In monotherapy, best response was SD in 26%. In combination, PR was achieved in 4% (1 MSS CRC and 1 PDAC; DOR 11+ and 8 months, respectively), SD in 33%, PD in 51%, and NE in 13%. In 13 pts there was target lesion reduction: median -17% (-46 to -1%). Median PFS was 1.4 months (0 to 14+). In combination, 20% PDAC (4/20) and 21% CRC (3/14) pts showed PFS $>$ 4 months. 2/3 NSCLC with previous checkpoint inhibitor treatment, 2 PDAC, and 2 MSS CRC showed PFS $>$ 7 months. High FAP expression (H-score $>$ 30) was observed in 86% PDAC, 64% CRC and 50% other carcinomas. CD8+ and CD56+ immune-cell infiltration in tumor biopsies and downregulation of immunosuppressive cytokines in plasma samples were observed in PDAC and CRC best responders. OMTX705 tubulysin payload was detected in both CAFs and tumor epithelial apoptotic regions. **Conclusions:** OMTX705 is a novel anti-FAP ADC with excellent safety profile. The combination with PEM showed disease control in some heavily pretreated PDAC, MSS CRC and NSCLC. Changes in immune infiltrates and cytokines suggest that OMTX705 may revert CAF-mediated immunosuppression. Clinical trial information: NCT05547321. Research Sponsor: Oncomatryx Biopharma.

A first-in-human clinical study of 9MW2921, a novel TROP-2 antibody-drug conjugate (ADC), in patients with advanced solid tumors.

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Background: TROP-2 (trophoblast cell surface antigen 2) is commonly overexpressed in multiple solid tumors and associated with poor prognosis. 9MW2921 is a novel TROP-2 ADC developed with a site-specific linker to conjugate the class of novel camptothecin-based payload Mtoxin, with a drug-to-antibody-ratio (DAR) of 4. Here we report the safety and efficacy data of 9MW2921 in patients with advanced solid tumors in a phase 1 study. **Methods:** 9MW2921 was administered by intravenous infusion at doses of 1.0-6.0 mg/kg once every 3 weeks. Primary objectives were assessment of dose-limiting toxicity, safety and the recommended phase 2 dose/maximum dose. **Results:** As of 12 November, 2024, thirty-nine patients (pts) were enrolled and treated at dose levels of 1.0 (N = 1), 2.0 (N = 3), 2.5 (N = 12), 3.0 (N = 20) and 4.5 (N = 3) mg/kg. The average age of all patients was 55.6 (range: 37-72) years with 20.5% male and 79.5% female. The median prior therapy lines were 2 (range: 1~11); 48.7% pts treated after immunotherapy. Three patients at 4.5mg/kg experienced at least one dose limiting toxicity (DLT), and this dose level was considered intolerable. No other pts was observed DLTs at the 1.0~3.0 mg/kg groups. The most common ≥grade 3 (≥5% pts)TRAEs were stomatitis, anemia, white blood cell (WBC) count decreased, neutropenia, lymphocyte count decreased, rash, vomiting and platelet count decreased. There were no TRAEs leading to death. 38 pts were evaluable for efficacy with at least one post-baseline tumor assessment, 12 pts achieved partial response and 16 pts maintained stable disease. The ORR of 3.0 mg/kg was 42.1% (8/19) and DCR was 84.2% (16/19). The ORR, DCR of 3.0 mg/kg in patients diagnosed with endometrial cancer (4 pts), HR+/HER2- breast cancer (4 pts), HER2- gastric cancer (4 pts) and Non-squamous non-small cell lung cancer (4 pts) were 75%, 100%; 50%, 75%; 50%, 100%; 25%, 100%, respectively. **Conclusions:** The data indicated that 9MW2921 has acceptable tolerability and promising anti-tumor activity in patients with advanced EC, HR+/HER2- BC, HER2- GC and nsq-NSCLC. Clinical trial information: NCT05990452. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

Efficacy and safety results of a multi-center phase I study of utidelone capsule, a novel oral microtubule inhibitor, in advanced solid tumor patients.

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Background: Utidelone is a novel microtubule inhibitor, whose injectable formulation (UTD1) has been approved for advanced breast cancer in China since 2021. Attempts to develop oral microtubule inhibitor have not made significant progress; no oral microtubule inhibitors have been approved in the United States to date. Utidelone is insusceptible to P-glycoprotein-mediated efflux, thereby optimizing it for oral administration on an intermittent schedule. Utidelone capsule (UTD2) can significantly improve medication compliance and the convenience of clinical application. This is the first-in-human study of UTD2, and the trial has been completed with final results presented here. **Methods:** Eligible patients were aged ≥18, with an ECOG PS of 0-1, life expectancy ≥12weeks, pathologically confirmed advanced solid tumor refractory to prior standard therapies. Patients were treated with UTD2 monotherapy. The starting dose was 5-day 25 mg/m^2/d for 2 patients, with planned escalation to 5-day 50, 75, 100 mg/m^2/d and 7-day 70 mg/m^2/d for 2, 6, 3 and 2 patients, repectively in a 21-day cycle. The primary objective was to determine DLT and the MTD. Secondary objectives included efficacy, PK profile and RP2D. **Results:** 18 advanced solid tumor patients were enrolled (3 didn't complete DLT observation) with median age of 60.8 years (range 29.0-81.0), 9 females and 9 males. All patients had received prior treatment in advanced settings with maximal 9 lines. Two DLTs of Grade 3 and Grade 4 diarrhea occurred, one at 5-day 100 mg/m^2/d and one at 7-day 70 mg/m^2/d. Considering the total dose per cycle for both cohorts were similar, the MTD was determined to be 5-day 75 mg/m^2/d via SMC. 11 patients were evaluated for efficacy with an outcome of 1 CR (ovarian cancer), 1 PR (ovarian cancer), 7 SD (testicular Sertoli cell tumor, NSCLC*2, pancreatic adenocarcinoma*2, appendiceal adenocarcinoma and soft tissue sarcoma), with the longest DoT of 12 cycles. The ORR was 18.2% and the CBR was 81.8%. PK results showed that the characteristics of utidelone were consistent with a two-compartment model. Compared to single-dose administration, there was no accumulation of utidelone in plasma upon multi-dose. The most frequent TEAEs were Grade 1/2, including diarrhea, fatigue, nausea, peripheral sensory neuropathy, vomiting, and decreased appetite (≥20% incidence rate), which recovered with supportive treatments. The ≥Grade 3 TRAE included diarrhea (27.8%) and fatigue (5.6%). **Conclusions:** This completed study demonstrates encouraging anti-tumor activity with manageable safety of UTD2 in patients with heavily pre-treated advanced solid tumors. The results support continuing development of UTD2 for the upcoming phase II/III studies for gastric and ovarian cancers. Clinical trial information: NCT05681000. Research Sponsor: Biostar Pharma, Inc.

RC48-ADC combined with radiotherapy and immunotherapy as salvage therapy for advanced solid tumors with HER2 expression: A multicenter, phase II trial.

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Background: Antibody-drug conjugates (ADC) have demonstrated efficacy in treating tumors with HER2 over expression. However, the clinical benefits of ADCs are limited in tumors with lower HER2 expression. The combination of ADCs, radiotherapy, and immunotherapy has shown promising feasibility with HER2-expressing tumors across various cancer types. This approach can enhance spatial and physicochemical synergistic effects, resulting in a more diverse and increased release of tumor antigens. Subsequently, PD-1 inhibitors activate effector T cells, generating a robust immune response that targets and eliminates tumor cells. A single-arm, multicenter phase II trial was initiated to evaluate the clinical efficacy of RC48-ADC combined with radiotherapy and immunotherapy, in HER2-expressing advanced solid tumors. The findings from this trial may establish a new salvage treatment strategy for tumors with low HER2 expression. **Methods:** This study enrolled patients with advanced, HER2-expressing (IHC 1+, 2+, or 3+) solid tumors that had progressed following standard therapies or due to intolerance. Participants received RC48 (disitamab vedotin, 2.0 mg/kg on day 1), followed by radiotherapy every other day (2-3 fractions of 5-8 Gy), GM-CSF 200 μg on days 3-7), sequential IL-2 (2 million IU on days 8-12), and a PD-1 inhibitor administered within one week after completing radiotherapy. This regimen was repeated every three weeks. The primary endpoint was the objective response rate (ORR). **Results:** As of the cutoff date (December 31, 2024), 52 patients were enrolled, including 10 with gynecological cancers, 10 with pancreatic cancer, and 32 with various other tumor types (including breast, gastric and colorectal cancers). All participants had evaluable data. According to RECIST 1.1, the overall ORR was 36.5%, with two patients achieving a complete response (CR) that lasted nearly two years, maintaining minimal residual disease negative status. The ORRs for patients with HER2 expression of 1+, 2+, and 3+ were 29.0%, 43.4%, and 60.0%, respectively. The median progression-free survival (PFS) for all patients was 5.9 months (95% CI: 4.1–9.7 months). The median overall survival (OS) for all patients was 14.3 months (95% CI: 8.6–15.7 months).Treatment-related adverse events were predominantly mild (grade 2 or lower), including fatigue, hair loss, nausea, fever, and rash. Only three patients (5.8%) experienced grade 3 adverse events. **Conclusions:** The results indicate promising efficacy and manageable safety, with a favorable short-term tumor response rate. This suggests that the combination of RC48-ADC, radiotherapy, and immunotherapy could serve as an effective salvage therapy option for patients with HER2-expressing advanced solid tumors. The combination therapy appears to enhance the synergistic effects of radiotherapy and immunotherapy. Clinical trial information: NCT0511550. Research Sponsor: None.

First-in-human study of BG-C9074, a B7-H4-targeting ADC in patients with advanced solid tumors: Preliminary results of the dose-escalation phase.

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Background: B7-H4 is a transmembrane glycoprotein in the B7 superfamily with limited expression in normal tissue but is upregulated in solid tumors including cholangiocarcinoma, breast, ovarian, and endometrial cancers. BG-C9074 is an investigational topoisomerase I inhibitor antibody-drug conjugate. This abstract presents the initial results of monotherapy dose escalation from the ongoing phase 1 study. **Methods:** BG-C9074-101 (NCT06233942) is a first-in-human, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary antitumor activity (per RECIST v1.1) of BG-C9074 as monotherapy and in combination with tislelizumab in patients with advanced solid tumors. Patients with histologically or cytologically confirmed locally advanced, unresectable, or metastatic solid tumors, irrespective of B7-H4 expression, received BG-C9074 intravenously every 3 weeks in sequentially escalating dose cohorts ranging from 1 to 7 mg/kg. **Results:** As of January 22, 2025, 55 patients with advanced tumors (n = 25, ovarian cancer; n = 16, breast cancer; n = 10, cholangiocarcinoma; n = 4, other tumor types) received BG-C9074 monotherapy. Three patients experienced dose-limiting toxicities including fatigue (6 mg/kg), and febrile neutropenia and thrombocytopenia (7 mg/kg). Treatment-emergent adverse events (TEAEs) were reported in 48 patients (87.3%) with grade ≥3 TEAEs occurring in 27.3% of patients. The most common TEAEs were nausea (45.5%), fatigue (38.2%), and neutropenia (32.7%), with neutropenia being the most frequent grade ≥3 TEAE (16.4%). Among 39 efficacy-evaluable patients, eight (20.5%) partial responses (n = 4, confirmed; n = 4, unconfirmed) were observed. **Conclusions:** BG-C9074 showed a manageable safety/tolerability profile in patients with B7-H4 advanced solid tumors. Preliminary clinical responses were observed at multiple dose levels across various tumor types without selection for B7H4 expression. Dose-escalation and dose-level expansion are ongoing and updated clinical data will be presented at the conference. Clinical trial information: NCT06233942. Research Sponsor: BeOne Medicines Ltd.

Efficacy and safety of XNW27011, a Claudin 18.2 targeting antibody drug conjugate with topoisomerase 1 inhibitor payload, in patients with Claudin 18.2 positive gastric/gastroesophageal junction cancer: Results from ongoing phase I/II study.

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Background: CLDN18.2 is a clinically validated target for cancer treatment. XNW27011 is a CLDN18.2 targeted ADC conjugated with a novel topoisomerase 1inhibitor (topo1i). Dose-escalation study of XNW27011 demonstrated favorable safety, pharmacokinetics, and promising preliminary efficacy in advanced solid tumors. Here we report the results of XNW27011 in CLDN18.2+ GC/GEJC pts from ongoing expansion cohorts. **Methods:** Pts with CLDN18.2+ (TC≥5%, IHC ≥ 2+), advanced/metastatic solid tumors progressed on standard therapy and an ECOG PS of 0-2 are eligible to be enrolled in dose expansion cohorts. Pts received XNW27011 iv infusion Q3W at doses of 2.4, 3.0 and 3.6 mg/kg. 1st endpoint is ORR, 2nd endpoints include safety, other efficacy parameters, PK, ADA, and correlation between CLDN18.2 expression and efficacy. **Results:** As of Dec 28th, 2024, a total of 116 pts with CLDN18.2+ solid tumors including 84 GC/GEJC pts were enrolled in expansion cohorts at doses of 2.4 mg/kg, 3.0 mg/kg and 3.6 mg/kg, with median age of 59 years, median lines of prior treatment 2, 80.2% received checkpoint inhibitors and 18.6% topo1i-containing therapies. The most common any grade TEAE (≥ 20%) in all patients were nausea, vomiting, anemia, appetite ↓, WBC ↓, neutrophil ↓, asthenia, hypoalbuminemia, platelet ↓, body weight ↓, and hypokalemia. The most common ≥ G3 TEAEs (≥5%) were neutrophil ↓, WBC ↓, anemia, lymphocyte ↓, and asthenia. TEAEs leading to dose interruption at 2.4, 3.0 and 3.6 mg/kg were 15.2%, 26% and 60%, dose reduction 10.9%, 26%, and 65%, and dose discontinuation 10.9%, 8%, and 0%. 1 pt at 3.0 mg/kg experienced TEAE leading to death (pneumonia). Safety profile was consistent with that of dose escalation part. In the 84 GC/GEJC pts enrolled in dose expansion, 75 pts were evaluable with at least one post baseline scan. The BOR and DCR across dose groups were 46.7% and 88.0%, respectively. Efficacy in each dose group was summarized in the table below. The median follow up was 4.3M, 4.0M and 7.0M for 2.4, 3.0, and 3.6 mg/kg. Preliminary anti-tumor activity was also observed in pts who had prior CPI and topo 1i containing treatments, as well as in other CLDN18.2+ solid tumor pts. **Conclusions:** In the expansion cohorts,XNW27011 demonstrated promising anti-tumor activity and favorable safety profile in GC/GEJC pts with wide expression level of CLDN18.2.The results support further development of XNW27011 in CLDN18.2+ GC/GEJC. Clinical trial information: CTR20231735. Research Sponsor: Evopoint Biosciences, Co. Ltd.

	2.4 mg/kg N=27	3.0 mg/kg N=30	3.6 mg/kg N=18
BOR, n (%)	7 (25.9%)	16 (53.3%)	12 (66.7%)
PR (confirmed)	4 (14.8%)	9 (30%)	6 (33.3%)
cPR Pending	2 (7.4%)	5 (16.6%)	3 (16.7%)
DCR, n (%)	23 (85.2%)	27 (90.0%)	16 (88.9%)

Results from a phase 1/2 study of 7MW3711: A novel B7-H3 antibody-drug conjugate (ADC) incorporating a topoisomerase I inhibitor in patients with advanced solid tumors.

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Background: 7MW3711 is a B7-H3 targeting ADC comprised of a recombinant humanized monoclonal anti-human B7-H3 antibody conjugated to the topoisomerase I inhibitor via a protease cleavable linker. B7-H3 is upregulated in several malignant cancers, such as lung, ovarian, breast, prostate and esophageal cancer, which plays an important role in multiple processes such as tumor occurrence, development, and immune escape. Here we present the safety and efficacy data of 7MW3711 from a first-in-human phase 1/2 study. **Methods:** The study enrolled patients (pts) with advanced solid tumor across three segments: dose-escalation (D-esc), dose-expansion (D-exp) and cohort-expansion. In the D-esc and D-exp phase, 7MW3711 was administered intravenously at doses of 1.5, 3.0, 4.5, 6.0 mg/kg every three weeks (Q3W); 4.0 mg/kg every two weeks (Q2W). **Results:** As of the data cutoff on Jan 2, 2025, 43 pts were enrolled and received at least one dose of 7MW3711 (D-esc, n = 15; D-exp, n = 28). At baseline, the median of prior lines of therapy for all pts was 2 (range, 1-9). No dose-limiting toxicities (DLTs) were observed in the D-esc phase. The maximum tolerated dose (MTD) has not yet been reached. The most common Grade ≥3 TRAEs (≥5% of pts) were decreased white blood cell count, anemia, decreased neutrophil count, decreased lymphocyte count, decreased platelet count, diarrhea, and hypokalemia. Among 33 pts treated with 7MW3711 at 4.0 mg/kg or above and reaching tumor assessment, 8 partial responses (PRs) were observed. The objective response rate (ORR) and disease control rate (DCR) were 24.2% and 84.8%, respectively. 15 pts diagnosed with esophageal cancer (EC), ovarian cancer (OC) and prostate cancer (PC) were enrolled at 4.5 mg/kg or above and were evaluable for tumor assessment. All EC pts had previously progressed after receiving platinum-based chemotherapy and immune checkpoint inhibitors. All OC pts were platinum-resistant. All PC pts had previously progressed after receiving docetaxel and endocrine therapy. The ORR of EC, OC and PC was 33.3%, 60.0% and 50.0%, respectively. The DCR of EC, OC and PC was 100.0%. Objective responses were also observed in pts with other solid tumor types, such as lung adenocarcinoma and breast cancer. **Conclusions:** The data indicated encouraging efficacy of 7MW3711 in advanced EC, OC and PC. The safety profile showed adequate tolerability. The dose optimization and expansion study is continuing to establish the RP2D for 7MW3711. Clinical trial information: NCT06008366. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

Results from a phase 1/2 study of 7MW3711: A novel B7-H3 antibody-drug conjugate (ADC) incorporating a topoisomerase I inhibitor in patients with lung cancer.

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Background: 7MW3711 is a B7-H3 targeting ADC comprised of a recombinant humanized monoclonal anti-human B7-H3 antibody conjugated to the topoisomerase I inhibitor via a protease cleavable linker. B7-H3 is upregulated in several malignant cancers, such as lung, ovarian, breast, prostate and esophageal cancer, which plays an important role in multiple processes such as tumor occurrence, development, and immune escape. Here we present the safety and efficacy data of 7MW3711 from a first-in-human phase 1/2 study. **Methods:** The study enrolled patients (pts) with advanced solid tumor across three segments: dose-escalation (D-esc), dose-expansion (D-exp) and cohort-expansion. In the D-esc and D-exp phase, 7MW3711 was administered intravenously at doses of 1.5, 3.0, 4.5, 5.0, 6.0 mg/kg every three weeks (Q3W). **Results:** As of the data cutoff on Jan 8, 2025, 37 pts with lung cancer were enrolled and received at least one dose of 7MW3711 (D-esc, n = 25; D-exp, n = 12), which included 16 pts with small cell lung cancer (SCLC) and 21 pts with non-small cell lung cancer (NSCLC). At baseline, the median of prior lines of therapy for all pts was one (range, 1-5). Five pts experienced dose-limiting toxicities (2 pts at 5.0 mg/kg; 3 pts at 6.0 mg/kg), including decreased platelet count, decreased neutrophil count, myelosuppression and decreased appetite. The maximum tolerated dose (MTD) has not yet been determined. The most common Grade $\geq$3 TRAEs ($\geq$5% of pts) were decreased neutrophil count, decreased white blood cell count, anemia, decreased lymphocyte count, decreased platelet count, hyponatremia, hypokalemia, and myelosuppression. Among 25 pts treated with 7MW3711 at 4.5 mg/kg or above and reaching tumor assessment, 9 partial responses (PRs) were observed. The overall objective response rate (ORR) and disease control rate (DCR) were 36.0% and 96.0%, respectively. 8 pts diagnosed with SCLC were enrolled at 4.5 mg/kg and were evaluable for tumor assessment. All 8 SCLC pts had previously progressed after receiving platinum-based chemotherapy and immune checkpoint inhibitors. The ORR and DCR of them were 62.5% and 100.0%, respectively. Among pts with B7-H3 H-score $>$ 5, the ORR and DCR of lung squamous cell carcinoma (Sq-NSCLC) at 4.5 mg/kg or above were 37.5% (3/8) and 87.5% (7/8), respectively. **Conclusions:** The data indicated encouraging efficacy of 7MW3711 in SCLC and Sq-NSCLC. The safety profile showed adequate tolerability. The dose optimization and expansion study is continuing to establish the RP2D for 7MW3711. Clinical trial information: NCT06008379. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

First-in-human trial of SYS6010 combined with SYH2051 in patients with advanced gastrointestinal tumors.

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Background: SYS6010 is an antibody-drug conjugate (ADC) composed of an EGFR-specific antibody, a cleavable linker, and JS-1, a topoisomerase I inhibitor, as its cytotoxic payload. It targets EGFR, a transmembrane receptor tyrosine kinase overexpressed in malignancies such as lung, breast, gastric, and colorectal cancers. SYS6010 induces DNA damage leading to apoptosis, while resistance may occur through ATM-mediated DNA repair. SYH2051, an ATM inhibitor, disrupts DNA repair, enhancing SYS6010-induced apoptosis. This combination is hypothesized to exert synergistic anti-tumor effects. **Methods:** This first-in-human clinical trial employed a single-center, open-label, non-randomized design to evaluate the safety, tolerability, and preliminary efficacy of SYS6010 combined with SYH2051. Patients with advanced gastrointestinal tumors expressing EGFR who had progressed on at least one prior line of standard therapy were enrolled. SYS6010 was administered intravenously at a dose of 3.2 mg/kg on day 1 of each 14-day cycle, while SYH2051 was given orally at doses of 40 mg or 80 mg, once daily, for five consecutive days within the same cycle. Safety was assessed using CTCAE v5.0, and efficacy was evaluated according to RECIST v1.1 criteria. **Results:** As of December 31, 2024, 25 patients were enrolled, including 18 with colorectal cancer and 7 with gastric cancer. Twelve patients had received ≥3 prior lines of therapy. Among 6 evaluable gastric cancer patients, 3 achieved partial response (PR) and 3 stable disease (SD), resulting in an objective response rate (ORR) of 50% and a disease control rate (DCR) of 100%. The median progression-free survival (PFS) was approximately 5.8 months (data not mature), and 3 patients remained on treatment. Among 18 colorectal cancer patients (9 with KRAS mutations and 9 wild-type), preliminary analysis showed a median PFS of approximately 4.2 months in wild-type KRAS patients (data not mature). Common treatment-related adverse events (TRAEs) included hematologic toxicity, gastrointestinal symptoms, and fatigue. Frequently observed TRAEs were fatigue (60%), decreased appetite (56%), leukopenia (56%), anemia (48%), neutropenia (48%), nausea (48%), thrombocytopenia (36%), and hypoalbuminemia (32%). Grade ≥3 TRAEs occurred in 12 patients (48%), including neutropenia (7 patients), anemia (6 patients), thrombocytopenia (3 patients), vomiting (3 patients), leukopenia (2 patients), interstitial lung disease (1 patient), infection (1 patient), and elevated bilirubin (1 patient). No treatment-related deaths were reported. **Conclusions:** SYS6010 combined with SYH2051 was well tolerated and demonstrated preliminary antitumor activity in advanced gastrointestinal tumors, particularly in gastric cancer. Further evaluation is ongoing. Research Sponsor: CSPC Pharmaceutical Group Limited.

Precemtabart tocentecan (M9140), an anti-CEACAM5 ADC with exatecan payload, in patients with metastatic colorectal cancer (mCRC): Results from the dose optimization of the phase 1 PROCEADE CRC-01 study.

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Background: CEACAM5 is overexpressed in ~90% of CRCs, with limited expression on healthy cells. Precemtabart tocentecan (M9140), the first anti-CEACAM5 ADC with an exatecan payload (topoisomerase 1 inhibitor), showed a predictable, manageable safety profile and promising early clinical activity in the dose escalation of the Phase 1 PROCEADE-CRC-01 study (NCT05464030) in heavily pretreated patients with mCRC. **Methods:** This global Phase 1 study in 3L adult patients with locally advanced/mCRC (ECOG PS ≤1; previous irinotecan therapy) evaluates clinical activity, safety, and tolerability of precemtabart tocentecan. Here, we report on dose optimization of precemtabart tocentecan tested at 2.8 mg/kg Q3W (Arm A1) or 2.4 mg/kg Q3W (A2; 1:1 randomization) to select the recommended phase 2 dose (RP2D). **Results:** As of Jan 2025, 60 patients (recruited Apr–Oct 2024) had been treated (A1, n = 29; A2, n = 31). Median age was 60.0 years, and 51.7% were male. In A1, 18 (62.1%) patients remained on treatment and 16 (51.6%) in A2. Treatment-emergent AEs (TEAEs) were reported in all patients; grade ≥3 in 38 (63.3%) patients (A1: n = 19 [65.5%]; A2: n = 19 [61.3%]); anemia and neutropenia (any grade; grade ≥3) were most common. Serious TEAEs were reported in 18 (30.0%) patients (A1: n = 8 [27.6%]; A2: n = 10 [32.3%]). Grade ≥3 hematologic AEs were reported in 32 (53.3%) patients: anemia (A1, n = 9; A2, n = 10), neutropenia (A1, n = 14; A2, n = 12), thrombocytopenia (n = 6 both), leukopenia (A1, n = 7; A2, n = 6), lymphopenia (A1, n = 1; A2, n = 2), febrile neutropenia (n = 3 both), and pancytopenia (A1, n = 0; A2, n = 1). Treatment was discontinued in 26 (43.3%) patients (A1: progressive disease (PD), n = 9, patient withdrawal, n = 1, other, n = 1; A2: PD, n = 14, death, n = 1). No treatment-related deaths were reported. Overall, PK profiles were consistent with previous data, with overlap attributed to high between-subject variability. Partial responses were reported in 7 (24.1%; n = 4 [13.8%] confirmed) patients in A1 and 3 (9.7%; n = 1 [3.2%] confirmed) in A2 (all responders remain on treatment), stable disease in 15 (51.7%) and 21 (67.7%), and PD in 5 (17.2%) and 6 (19.4%) patients, respectively. DCR at 12 weeks was 72.4% in A1 and 67.7% in A2. **Conclusions:** These preliminary results corroborate the encouraging efficacy and safety data from the dose escalation part of the PROCEADE CRC-01 study, with no new relevant safety findings. ORR was higher at 2.8 mg/kg, with similar tolerability at both doses. The ORR of 24.1% (13.8% confirmed) at 2.8 mg/kg compares favorably with current monotherapy SoCs (ORRs 1-2%) and recent phase 3 data with trifluridine–tipiracil + bevacizumab (ORR 6.1%) in 3L+ mCRC. These results suggest 2.8 mg/kg as the RP2D for further development in CRC, and other solid tumors (NCT06710132). More mature data, including PFS, will be presented at the congress. Clinical trial information: NCT05464030. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Rinatabart sesutecan (Rina-S) for patients with advanced endometrial cancer: First disclosure from dose expansion cohort B2 of the GTC1184-01 study.

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Background: Rina-S is an investigational antibody-drug conjugate targeting folate receptor alpha with a novel hydrophilic protease-cleavable linker and a topoisomerase I inhibitor, exatecan payload. Patients (pts) with advanced endometrial cancer (EC) who progress after programmed death-ligand 1 [PD-(L)1] inhibitor plus chemotherapy have very poor prognoses and limited, ineffective treatment options (objective response rate [ORR] $<$ 16% and median progression-free survival $<$ 5 months with single-agent chemotherapy); thus, there is urgent need for novel therapies. In the dose escalation cohort, single-agent Rina-S showed preliminary anti-tumor activity in pts with heavily pretreated EC. Here we first report results for single-agent Rina-S in pts with heavily pretreated EC from dose expansion cohort B2 of the phase 1/2 GCT1184-01 study (NCT05579366). **Methods:** Pts with metastatic or unresectable EC who received prior platinum-based chemotherapy and a PD-(L)1 inhibitor received either Rina-S 100 mg/m^2 or 120 mg/m^2 every 3 weeks after initial enrollment with 120 mg/m^2 only. The primary endpoint was safety and tolerability of Rina-S. Secondary endpoints included ORR and disease control rate (DCR). **Results:** As of data cutoff November 22, 2024, 64 pts with heavily pretreated EC (median 3 prior lines [range 1-8]) received Rina-S 100 mg/m^2 (n = 22) or 120 mg/m^2 (n = 42) for a median treatment duration of 15.9 weeks. Most pts had ECOG PS 1 (64.1%), approximately half (46.9%) were aged $\geq$70 years, and 48.4% had received prior radiotherapy. Pts primarily had endometrioid carcinoma (45.3%) followed by serous carcinoma (26.6%). The most common ($>$ 25%) treatment-emergent adverse events (TEAEs) were similar across doses and were primarily cytopenias and grade 1-2 gastrointestinal events (nausea, vomiting, decreased appetite). Grade 3-4 cytopenia included neutropenia (48.4%), anemia (35.9%) and thrombocytopenia (21.9%). TEAEs led to Rina-S dose reductions in 15.6% of pts and discontinuation of Rina-S in 3.1% of pts; 37.5% of pts had serious TEAEs. There was 1 related (assessed by investigator) grade 5 TEAE at 120 mg/m^2 confounded by comorbidities; no fatal TEAEs occurred at 100 mg/m^2. No signals of ocular toxicity, neuropathy, or interstitial lung disease were observed. In efficacy-evaluable pts (median follow-up: 18.7 weeks), the unconfirmed ORR was 50%, including 2 complete responses, with Rina-S 100 mg/m^2 (n = 22) and 45.5% with 120 mg/m^2 (n = 33). DCR was 100% and 81.8% with 100 mg/m^2 and 120 mg/m^2, respectively. Responses were ongoing for 9 of 11 (81.8%) and 12 of 15 (80.0%) responders with 100 mg/m^2 and 120 mg/m^2, respectively. **Conclusions:** Rina-S showed encouraging anti-tumor activity in pts with heavily pretreated EC and had a manageable safety profile consistent with previous reports. Further evaluation of single-agent Rina-S in pts with advanced EC is ongoing. Clinical trial information: NCT05579366. Research Sponsor: Genmab A/S.

EVEREST-2: Initial data of the logic-gated Tmod chimeric antigen receptor T-cell (CAR T) therapy A2B694 for patients with solid tumors associated with mesothelin (MSLN) expression and with human leukocyte antigen (HLA) loss of heterozygosity (LOH).

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Background: EVEREST-2 is a first-in-human, phase 1/2 trial to assess the safety and efficacy of A2B694, an autologous, logic-gated Tmod CAR T therapy targeted to MSLN, which is normally expressed in the mesothelium and can be upregulated in many solid tumors. A2B694 is designed to overcome challenges of on-target, off-tumor toxicity that have limited other MSLN-targeted approaches by combining a CAR-activating receptor targeting MSLN with a blocker CAR that recognizes HLA-A*02, to distinguish between normal and tumor cells (Tokatlian, et al. *J Immunother Cancer.* 2022). **Methods:** Adults with recurrent unresectable, locally advanced, or metastatic cancers with MSLN expression who have progressed after standard-of-care therapy are eligible for EVEREST-2. Enrollment to EVEREST-2 and collection of T-cells occurs through the ongoing prescreening study BASECAMP-1 (NCT04981119). When clinically appropriate, A2B694 is manufactured from cryopreserved T cells, and patients undergo lymphodepletion before A2B694 infusion. The dose-escalation phase is evaluating the safety and tolerability of A2B694 to identify the recommended phase 2 dose (RP2D). Dose escalation was started at $1x10^8$ Tmod positive cells (dose level [DL] 1) and will increase up to $14x10^8$ in combination with low-dose IL-2 (DL 5). The dose-expansion phase will confirm RP2D and collect biomarker data to further characterize A2B694. **Results:** As of January 15, 2025, 5 participants (median age: 60 years; range, 50-84) have enrolled on EVEREST-2 and received A2B694 at DLs 1-2; participants had ovarian cancer (n = 3), pancreatic cancer (n = 1), and non-small cell lung cancer (n = 1) and had received a median of 4 prior lines of therapy (range, 1-7). Lymphodepleting chemotherapy was well tolerated with no significant cytopenias observed. The most common adverse events were lymphopenia (7 [14.6%]) and decreased appetite (6 [12.5%]). There were no dose-limiting toxicities, cytokine release syndrome, nor related neurotoxicity. One participant was admitted to the hospital for decreased appetite. No long-term toxicities have been noted up to 7.5 months post-infusion. Of the participants who have received A2B694, 5 were efficacy evaluable at DLs 1-2. A2B694 was detected post-infusion in the peripheral blood in all patients. Additionally, A2B694 was detected in an abdominal tumor biopsy from a patient with pancreatic cancer 42 days post-infusion. **Conclusions:** The logic-gated approach was successful at reducing toxicity seen with prior MSLN-targeted CAR T therapies, and A2B694 showed successful CAR T expansion and tumor infiltration. The maximum tolerated dose has not been reached, and results from the dose-escalation phase continue to determine the RP2D. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

ZL-1310, a DLL3 ADC, in patients with extensive stage small cell lung cancer: Ph1 trial update.

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Background: Treatment options are limited for patients (pts) with extensive-stage small cell lung cancer (ES-SCLC) that progress after platinum-based chemotherapy (chemo). ZL-1310, a DLL3-targeted antibody drug conjugate (ADC) with a topoisomerase 1 inhibitor payload and cleavable linker, demonstrated promising preliminary results in pts with relapsed/refractory (r/r) ES-SCLC (Spira et al, ENA 2024). Here, we report updated data with additional pts and follow-up (NCT06179069). **Methods:** This is a two-part Phase I study of ZL-1310 administered intravenously every 3 weeks to pts with r/r SCLC who have progressed after at least one platinum-based chemo regimen. Part 1A is a monotherapy dose escalation; Part 2 is a randomized dose optimization/expansion. Study endpoints include safety parameters, objective response rate (ORR) per RECIST v1.1, duration of response (DOR), disease control rate (DCR) and pharmacokinetics (PK). Exploratory tumor biomarkers, including DLL3 expression (expressed as H-score), are examined. **Results:** As of 28 Jan 2025, 28 pts were enrolled in the dose escalation Part 1A and received ZL-1310 at dose levels ranging from 0.8 mg/kg to 2.8 mg/kg. The median time on study is 5.1 months (range 2.4-10.1+). Median age was 66 years (range 36-79); 43% were female; 75% had an ECOG performance status of 1; 93% progressed after prior anti-PD-L1 therapy; 39% had prior lung irradiation, and 36% had baseline brain metastases. Any-grade treatment-related adverse events (TRAEs) occurred in 89% of pts (Grade≥3 TRAEs, 39%). One pt (2.4 mg/kg) had dose limiting toxicities of neutropenia and thrombocytopenia; 5 pts underwent drug reduction and 5 had drug discontinued due to TRAE. Grade≥3 TRAEs occurring in more than 1 patient include anemia (6 pts), neutropenia (5), thrombocytopenia (3), WBC decreased (2), and interstitial lung disease (2). Objective responses were observed in 19 of 28 pts (68%), including one pt pending response confirmation, and a DCR of 93%. Responses were observed across all dose levels and all levels of DLL3 expression (H-score range: 0-260), including one pt with prior tarlatamab treatment. Pts with baseline brain metastases had an 80% response rate and 100% DCR. Fourteen of 19 (74%) responders remain on study. PK data from 25 pts showed dose-proportional increase of systemic ADC and payload exposure, with relatively low exposure of the payload and no significant accumulation. **Conclusions:** ZL-1310 demonstrated a tolerable safety profile and promising antitumor activity in r/r ES-SCLC, including pts with brain metastases, pt with prior tarlatamab, and in the setting of low DLL3 expression. Updated data, including patients in the randomized Part 2 dose optimization, will be presented. Clinical trial information: NCT06179069. Research Sponsor: None.

First-in-human (FIH) phase 1 study of CUSP06, a cadherin-6 (CDH6)-directed antibody-drug conjugate (ADC), in patients with platinum-refractory/resistant ovarian cancer and other advanced solid tumors.

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Background: CDH6 is a transmembrane glycoprotein involved in cancer metastasis expressed in various tumors including ovarian cancer (OC), renal cell carcinoma (RCC), cholangiocarcinoma (CCA), and uterine cancer. CUSP06 is an ADC composed of a humanized IgG1 mAb against CDH6 conjugated with a cleavable linker to exatecan, a topoisomerase I inhibitor. In preclinical studies, CUSP06 showed CDH6-dependent cell growth inhibition in OC cell lines and tumor regression in CDH6-expressing OC, RCC, and other tumor models including those with low CDH6 expression supporting its use across various indications and CDH6 expression levels. We report here the initial results from a FIH study of CUSP06. **Methods:** CUSP06-1001 is a Phase 1a/1b, open-label, multi-center dose escalation and expansion study to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, recommended Phase 2 dose, and preliminary efficacy of CUSP06 in patients (pts) with platinum-refractory/resistant ovarian cancer (PRROC), advanced RCC and other advanced CDH6-positive solid tumors. Prescreening for CDH6 expression was required for those pts with solid tumors other than OC or RCC. CUSP06 was administered IV every 21 days. Phase 1a followed a standard 3+3 dose escalation design and included dose enrichment cohorts at doses that had demonstrated safety. Phase 1b consists of dose expansion cohorts for pts with OC, RCC, and other CDH6-positive solid tumors to assess the safety, tolerability and efficacy at the RDE. **Results:** As of 03JAN25, 26 pts were dosed with data available for 22 pts in Phase 1a (18 OC, 2 RCC, and 2 CCA) at doses from 1.6 mg/kg to 5.6 mg/kg. The median age was 60.5 yrs and the median prior therapies was 3. Of the 18 pts with OC, all pts received prior platinum and taxane, 67% received bevacizumab, and 22% received mirvetuximab (MIRV). All patients with RCC received an immune checkpoint inhibitor and a TKI. Related TEAEs occurred in 20 pts (91%). The most common related TEAEs ($>$ 20%) were anemia (50%), neutropenia (46%), thrombocytopenia (46%), fatigue (46%), nausea (36%), diarrhea (23%), and vomiting (23%). The most common related Grade $\geq$3 TEAEs were neutropenia, thrombocytopenia, and anemia. AEs led to discontinuation in 3 (14%) pts. Five of 14 GCIG-evaluable OC pts (36%) had a CA-125 response. Among the 20 RECIST-evaluable pts, 5 partial responses (4 confirmed, & 1 unconfirmed) including MIRV-pretreated pts, and 11 stable disease were observed. All PRs were in pts with platinum-resistant high grade serous OC, with an ORR of 36% (5/14). 18 pts were ongoing at the cutoff date. **Conclusions:** The preliminary data from the Phase 1a dose escalation portion of this study showed acceptable tolerability and encouraging efficacy in pts with OC, which support further evaluation of CUSP06 in the Phase 1b expansion cohorts. Clinical trial information: NCT06234423. Research Sponsor: None.

Phase 1 dose-escalation trial of talazoparib in combination with belinostat in select advanced solid tumors.

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Background: Inhibitors of histone deacetylase (HDACi) may synergize with poly (ADP-ribose) polymerase inhibitors (PARPi). This Phase 1 dose escalation trial tested the combination of the PARPi talazoparib and the HDACi belinostat. **Methods:** This open-label study was conducted with a combined dose escalation of talazoparib (0.75 mg-1 mg) and belinostat (500-1000 mg/m2) in subjects with advanced breast, ovarian, prostate and pancreatic cancers. Primary objectives were to identify the safety, tolerability, and recommended phase 2 dose (RP2D) of the combination. A TITE-CRM model was used for dose level assignment and identification of RP2D. **Results:** A total of 25 evaluable subjects were enrolled. Tumor types included breast cancer (10 subjects), ovarian cancer (5), prostate cancer (5), and pancreatic cancer (5). Treatment-related adverse events (AEs) included nausea (n = 8, 32%), fatigue (n = 8, 32%), thromboembolic events (n = 6, 24%), vomiting (n = 5, 25%), and anemia (n = 4, 16%). Treatment-related serious adverse events (SAEs) encompassed thromboembolic events (n = 4) and anemia (n = 1). Dose limiting toxicities (DLTs) occurred in 3 subjects including decreased white blood cell count, fatigue, anemia, and failure to thrive. Seven subjects experienced stable disease (SD), for a clinical benefit rate (CBR) of 28% (7/25); of those with SD, 6 were assigned to the highest dose (dose level 4) and 1 subject was assigned to dose level 3. Duration of enrollment ranged from 18-291 days. **Conclusions:** In subjects with select advanced solid tumors, talazoparib and belinostat combination therapy exhibits a favorable safety profile and manageable toxicity. Nausea and fatigue were the most common adverse events. Further studies are warranted to determine the efficacy of this combination. Clinical trial information: NCT04703920. Research Sponsor: Pfizer; Acrotech.

Impact of stereotactic ablative radiotherapy (SABR) on detection of ctDNA in patients with early-stage lung cancer: Interim findings from the prospective SABR-DETECT trial.

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Background: Stereotactic ablative radiotherapy (SABR) is the preferred curative treatment for inoperable patients with stage I/IIA non–small-cell lung cancer (NSCLC). In cases where the tumor is inaccessible or biopsy carries a high risk of complications, SABR is offered even in the absence of a tissue diagnosis, based on a high likelihood of malignancy as calculated by validated predictive models. In these situations, a blood based liquid biopsy detecting circulating tumor DNA (ctDNA) can serve as an aide to confirm malignancy and allow molecular testing. However, low ctDNA yield in early stage NSCLC presents a challenge for diagnosis. This study hypothesizes that ctDNA detection rates will improve by combining assessment of pre- and post-SABR plasma samples. **Methods:** This is a multi-institutional study including two cohorts: 1) patients with suspected stage I/IIA NSCLC, with a pretreatment likelihood of malignancy of ≥60% on Herder or Brock models, and 2) patients with biopsy-proven NSCLC. SABR was delivered according to standard guidelines. Plasma was collected for ctDNA analysis before and 24-72 hours following the first fraction of SABR. SHIELDING ULTRA MRD panel of hotspot regions in 2365 cancer-related genes with ultra-high sensitivity was used for ctDNA analysis (mutation + fragment profile + CNV). In this pre-planned interim analysis, we report on the secondary objective: to assess the impact of SABR on detection rates of ctDNA. **Results:** Paired plasma samples (pre- and post-SABR) were tested for 69 patients. After quality control analysis, 66 paired samples were analyzed and included in this interim analysis. The median age was 76 years (range, 56-89) and 36 (54%) were male. The median concentration of circulating free DNA (ng/mL) did not increase from pre- (5.5, inter quartile range (IQR): 3.3-8.1) to post-SABR (5.7, IQR: 4.1-7.6) (P=0.82). The ctDNA detection rate in pre-SABR samples was 22.7% versus 27.3% in post-SABR samples (Table). Interestingly, in 10 patients (15.2%), ctDNA became detectable in post-SABR samples and in 7 patients (10.6%) the ctDNA was no longer detectable in the post-SABR samples. The ctDNA remained undetectable in 41 patients (62.1%). 37.9% of patients had detectable ctDNA either before or after SABR. **Conclusions:** The diagnostic yield of ctDNA for confirming malignancy in early stage NSCLC is improved by testing both the pre- and the post-SABR samples, collected within 24-72 hours after the first fraction of SABR. This approach may improve the diagnostic rates of liquid biopsies for patients with presumed NSCLC undergoing SABR, warranting further investigation of ctDNA detection before and shortly after treatment. Clinical trial information: NCT05921474. Research Sponsor: Verspeeten Family Cancer Centre Medical Oncology Research Fund (MORF); Lawson Internal Research Fund; Lung Cancer Canada Geoffrey Ogram Memorial Research Grant; 'Crush it with Bev' fundraiser.

ctDNA detection rates (N=66).

Pre-SABR	Post-SABR	n (%)
detected	detected	8 (12.1%)
not detected	detected	10 (15.2%)
detected	not detected	7 (10.6%)
not detected	not detected	41 (62.1%)

Prognostic significance of preoperational circulating tumor DNA detection in early-stage NSCLC using a tissue-free blood test.

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Background: There is a growing need for risk evaluation and treatment monitoring in cancer care. However, current methods, mainly imaging, can be burdensome for patients over time and prone to variability among readers. Recent research has highlighted the potential of tumor-informed circulating tumor DNA (ctDNA) testing for identifying postoperative minimal residual disease (MRD) due to its high sensitivity by tracking individualized mutations. Nevertheless, its use in early-stage patients prior to surgery is constrained by limited tissue availability and extended turnaround times. MUSETALK-Lung01 (multiomics sequencing technique application kick-start) is a prospective, longitudinal, observational study designed to evaluate the clinical utility of a tumor-naïve ctDNA assay in patients with early-stage non-small cell lung cancer (NSCLC). **Methods:** Pretreatment plasma samples were prospectively collected from participants with stage I-IIIA NSCLC. Cell-free DNA was extracted and analyzed using a blood assay that interrogates both epigenetic and genetic information. The detection status and the estimated fraction of ctDNA were reported by a machine learning classifier and an independent statistical model, respectively. The calling threshold corresponding to a 99% clinical specificity was verified in a subgroup from the THUNDER study (NCT04820868). Longitudinal data, including vital status, cancer status, and treatment, were collected for up to 5 years. The study was approved by the institutional review board and all participants were required to provide informed consent. **Results:** A total of 289 participants from the MUSETALK-Lung01 study were analyzed. Of these, 49% (141/289) reached the 5-year follow-up, with a median follow-up duration of 59 months. To assess the prognostic value of preoperative ctDNA levels, relapse-free survival (RFS) and overall survival (OS) were evaluated across different stages and pathological subtypes separately. In stage I LUAD patients (N = 179), ctDNA-positive patients (N = 20) had significantly inferior RFS compared to ctDNA-negative patients (2-year RFS: 70% [95% CI: 46%–88%] vs. 94% [95% CI: 90%–97%]; log-rank $p < 0.001$). In contrast, no association was found between preoperative ctDNA detection and RFS in stage II-IIIA LUAD or non-LUAD NSCLC, irrespective of the clinical stage. Specifically, among the 179 stage I LUAD patients, 11 relapsed within 2 years, and 6 of these had positive ctDNA test results. This rate was significantly higher than in patients who relapsed between 2 and 5 years (1/12) or never relapsed (13/156; χ^2 test, $p < 0.001$). **Conclusions:** These findings indicate that presurgical ctDNA can serve as a prognostic indicator in early-stage NSCLC. Tumor-naive ctDNA testing may enhance the standard workflow by identifying high-risk patients who could benefit from innovative treatments. Clinical trial information: NCT04820868. Research Sponsor: None.

Improved detection of circulating tumor DNA in patients with leiomyosarcoma with fragment size restriction.

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Background: Prior work has shown that detection of circulating tumor DNA (ctDNA) at time of diagnosis of leiomyosarcoma (LMS) is associated with lower likelihood of objective response and patients with detectable ctDNA after two cycles of chemotherapy have worse survival. However, because ctDNA exists at much lower concentrations in plasma compared to cell-free DNA of non-tumor origin, the sensitivity of these prognostic measures to tumor signals remains unclear. With increasing evidence of ctDNA fragments being shorter than the background non-tumor cell-free DNA, we sought to test whether restricting our analysis to smaller fragment sizes would improve detection of ctDNA in LMS. **Methods:** Plasma was serially collected from patients with LMS undergoing chemotherapy. Cell-free DNA extracted from these samples was profiled by ultra-low-passage whole-genome sequencing (ULPWGS). Copy number alterations were identified and used to detect ctDNA using the ichorCNA algorithm before and after restricting the dataset to fragments of 90-150bp (short). We compared detectability of ctDNA via ichorCNA between analyses using all sequencing data and those using data restricted to short fragments. **Results:** From 28 patients, 126 plasma samples were profiled. The median fragment length of cell-free DNA was 240bp (IQR 142-349) for patients with LMS, compared to 307bp (IQR 171-465, $p < 0.001$) in samples collected from healthy controls. Short fragments made up 19.48% of LMS libraries at diagnosis when ctDNA levels were highest, 15.27% of all LMS samples, and 12.96% of libraries from healthy controls. While ctDNA was detectable by ULPWGS in 17% of all samples, detection increased to 40% when analyzed using only short cell-free DNA fragments ($p < 0.0001$). The proportion of diagnostic samples with detectable ctDNA was nominally higher when analyzed by short fragments (39% vs. 64% with 90-150bp size restriction, $p = 0.1078$, $n = 28$) and was significantly higher in samples collected after two cycles of chemotherapy (5% vs. 40% with 90-150bp size restriction, $p = 0.0197$, $n = 20$). Increases in ctDNA detectability with fragment size restriction were also observed in each of localized and metastatic subgroups (metastatic: 16% without restriction, 38% with restriction, $n = 97$, $p = 0.0012$; localized: 17% vs. 45%, $n = 39$, $p = 0.04$). **Conclusions:** Our results demonstrate that detection of ctDNA is improved by analyzing short fragments of cell-free DNA in samples collected from patients with LMS. These findings represent a potential to increase the sensitivity of an affordable, low-coverage liquid biopsy assay and may enhance the prognostic value of ctDNA detection in these patients. Further study of the association between ctDNA detection and outcome is needed to fully validate the impact of fragment size restricted analysis of cell-free DNA samples in patients with LMS and is currently ongoing in a prospective study. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Accurate differentiation of malignant and benign gastric lesions using cell-free DNA biomarkers.

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Background: Early detection of gastric cancer is challenging due to the invasive nature of current diagnostic methods and the difficulty in distinguishing cancer from benign gastric conditions. Cell-free DNA (cfDNA) features have emerged as promising biomarkers for non-invasive detection. This study aims to develop and evaluate a machine learning model utilizing cfDNA features for early gastric cancer detection. **Methods:** We developed an ensemble machine learning model incorporating four cfDNA features: repeat elements, fragment-based methylation, focal copy number variation, and fragment size pattern. The model was trained using cfDNA data from 150 gastric cancer patients and 153 individuals with stomach-related conditions. The ensemble model was validated using a cohort of 149 cancer patients, 149 individuals with high-risk benign lesions, and 50 low-risk benign lesions. Risk is stratified according to the Correa's Cascade. **Results:** The ensemble machine learning model developed using four cfDNA features achieved an AUROC of 0.913 in the training cohort and 0.912 in the testing cohort for distinguishing gastric cancer patients from individuals with stomach-related complications, which outperformed individual cfDNA features. A decision threshold of 0.418, established via cross-validation, was set to ensure at least 95% sensitivity in the training cohort. This threshold enabled accurate binary classification in the validation cohort, with model scores correlating with cancer stage and tumor differentiation, supporting its potential for clinical risk stratification. Model scores effectively differentiated cancer from high-risk individuals, with significantly lower scores in non-cancer groups compared to precancerous or Stage I–III cancer cases (Non-cancer group median score = 0.35, precancer group median score = 0.48, cancer group median score = 0.61). Additionally, the model assigned significantly higher cancer prediction scores to gastric cancer cases compared to high-grade intraepithelial neoplasia ($p = 0.003$). In the validation dataset, sensitivities were 92.9% (95% CI: 85.3%–96.7%) for Stage I, 96.3% (95% CI: 81.7%–99.3%) for Stage II, and 100% (95% CI: 83.2%–100%) for Stage III. Sensitivities for well-, moderate, and poorly differentiated tumors were 91.7%, 92.2%, and 100%, respectively. Of note, specificity for the detection of cancer was 66% in the training cohort and 71% in the validation cohort. **Conclusions:** Our findings demonstrate the potential of cfDNA-based machine learning models as a non-invasive and accurate diagnostic tool for early gastric cancer detection. By reducing reliance on invasive procedures, this approach could enhance clinical workflow efficiency and improve patient outcomes. Further validation in larger, independent cohorts is needed to support clinical implementation. Research Sponsor: Heilongjiang Provincial Key R&D Program Projects; "Open competition mechanism" of Heilongjiang Province; "Climbing program" of Harbin Medical University Cancer Hospital.

Development of a methylation-based, tissue-free test for the detection of molecular residual disease by circulating tumor DNA.

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Background: Clinical validation studies support tumor-informed molecular residual disease (MRD) as a prognostic biomarker for disease recurrence across multiple solid tumor types. However, these tests are not always feasible due to the occasional lack of tumor tissue for next-generation sequencing. Here, we discuss the design of a test for tissue-free (tf)MRD detection and its application to a cohort of patients with colorectal cancer (CRC). **Methods:** A targeted panel composed of differentially methylated regions was developed. A machine-learning model was trained on differential methylation patterns in order to classify plasma samples as MRD-positive or MRD-negative. Performance of the trained classifier was assessed in an independent cohort of 246 patients enrolled in the Bespoke CRC trial (NCT04264702). These patients had MRD results available using a tumor-informed circulating tumor DNA (ctDNA) assay (SignateraTM), of whom 163 were persistently MRD-negative without clinical progression, and 83 had MRD-positive results. Tissue-free MRD results were compared to the tumor-informed results by calculating the percent positive agreement (PPA) and negative percent agreement (NPA). Clinical outcomes (recurrence-free survival [RFS]) were evaluated based on tfMRD results in all patients and stratified based on whether the patient received adjuvant chemotherapy (ACT). **Results:** In this clinical cohort from Bespoke CRC (72% non-Hispanic White, 54% male, mean age 61.4±12.3 years), 71 (28%) patients had stage II CRC, and 146 (59%) had stage III CRC. Overall, PPA was 86% (95% CI: 77-93%) and NPA was 98% (95% CI: 95-100%). Patients with tfMRD-positive status showed inferior RFS compared to tfMRD-negative patients ($p < 0.001$). Significant benefit from ACT was observed among tfMRD-positive ($p < 0.001$) but not among tfMRD-negative patients ($p = 0.19$). For patients who did not receive ACT in this cohort, we observed 100% PPV and 100% specificity. **Conclusions:** This is the first study of its kind demonstrating a high concordance between a tfMRD test and a clinically validated tumor-informed ctDNA assay. Similar to recently reported data using a tumor-informed ctDNA assay, patients with tfMRD-positive results appeared to derive benefit from ACT treatment. These findings demonstrate that in cases where tissue is not available or of inadequate quality, a methylation-based tissue-free assay may serve as a potential alternative for MRD detection.
Research Sponsor: None.

Prevalence of androgen receptor ligand-binding domain mutations (AR-LBDm) in circulating tumor DNA (ctDNA) versus tissue biopsies in participants (pts) with metastatic castration-resistant prostate cancer (mCRPC) and other tumor types.

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Background: AR-LBDm is a common mechanism of resistance to AR-directed therapies in patients with mCRPC. However, data on the utility of ctDNA-based versus tissue-based AR-LBDm detection in mCRPC and the prevalence of AR-LBDm in nonprostate cancers are lacking. We evaluated AR-LBDm in ctDNA and tumor tissue samples from pts with advanced solid tumors enrolled in various Merck & Co., Inc. trials. **Methods:** Samples came from pts with mCRPC and 25 other tumor types (eg, bladder, colorectal, ovarian, and pancreatic cancers). AR-LBDm data were available from ctDNA via 2 fixed panel-based ctDNA NGS assays or from tumor tissue samples (mainly archival) via a fixed-panel NGS assay. Data obtained from the 3 assays were nonoverlapping. AR-LBDm prevalence was evaluated in each tumor type and by BRCAm or HRRm status in pts with mCRPC. **Results:** The analysis included 3026 samples assessed by ctDNA assay 1 (mCRPC, n = 1785; other, n = 1241), 2232 samples assessed by ctDNA assay 2 (mCRPC, n = 378; other, n = 1854), and 8181 samples from tissue biopsies (mCRPC, n = 833; other, n = 7348). AR-LBDm was detected in 21.0% of pts with mCRPC by ctDNA assay 1 and 19.8% of pts with mCRPC by ctDNA assay 2. Across all other tumor types, only 1 pt (with hepatocellular carcinoma) had an AR-LBDm in ctDNA. The prevalence of selected AR-LBDm in tissue biopsies was 5.4% (45/833) in pts with mCRPC, 0.6% (1/159) in pts with salivary cancer, and 0% in all other tumor types. AR-LBDm prevalence in pts with mCRPC increased with later-line treatments (Tx) both by tissue and ctDNA analyses and was similar regardless of BRCAm or HRRm status (table). The prevalence of the AR-LBD T878A mutation (by ctDNA) in pts with mCRPC was higher after prior Tx with abiraterone than with enzalutamide (20.9% [43/206] vs 1.7% [3/173]). AR-LBDm was observed in tissues biopsied from the mCRPC setting (prevalence, 12.8% [12/94]) and was associated with higher AR transcriptional activity than in AR-LBD–negative tissues. **Conclusions:** Similar prevalence of AR-LBDm was observed in ctDNA of pts with mCRPC by 2 different ctDNA assays; AR-LBDm prevalence in archival tissue samples was lower than by ctDNA analysis, likely due to the Tx-emergent nature of AR-LBDm. AR-LBDm prevalence was similar regardless of BRCAm or HRRm status in mCRPC, although prevalence of certain AR-LBDm is impacted by the specific prior AR-directed Tx. These data support ctDNA-based (rather than tissue-based) AR-LBDm testing in pts with mCRPC. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

AR-LBDm prevalence, % (n/N)	Frontline Tx	Later-line Tx
ctDNA assay 1	16.6 (122/734)	23.8 (252/1059)
ctDNA assay 2	Not available	19.8 (75/378)
Tissue biopsy	0.6 (3/535)	4.1 (147/3625)
	AR-LBDm +ve*	**AR-LBDm -ve***
BRCA		
Mut	26.5 (9/34)	73.5 (25/34)
WT	27.5 (95/345)	72.5 (250/345)
HRR		
Mut	28.8 (30/104)	71.2 (74/104)
WT	26.9 (74/275)	73.1 (201/275)

*Per ctDNA assay 1.

A high-performance blood-based DNA methylation test for early detection of gastrointestinal cancers.

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Background: Early detection of gastrointestinal cancers (GICs), including esophageal cancer (EC), gastric cancer (GC), and colorectal cancer (CRC), remains suboptimal in China due to low screening adherence and limited access to endoscopic procedures. Multi-cancer early detection (MCED) tests present a convenient alternative, yet the efficacy in detecting early-stage GICs has been inadequate. Accurate tumor localization, particularly differentiating between upper and lower GICs, is crucial for determining subsequent diagnostic procedures. In this study, we report the performance of an MCED assay utilizing targeted DNA methylation sequencing to detect GICs. **Methods:** This multicenter, case-control study prospectively enrolled a cohort of 667 GIC patients (203 EC, 263 GC, 201 CRC; stages: I 20.8%, II 26.7%, III 35.7%, IV 16.8%) and 667 non-cancer participants. Plasma cell-free DNA was sequenced using a panel targeting tumor-specific hyper- and hypo-methylation markers. A total of 5120 GIC-specific methylation features were captured. The GIC model was trained using a gradient-boosted tree model, and nested cross-validation was implemented to determine the optimal parameters and evaluate the model's performance of cancer detection. To predict the tissue of origin (TOO), the top 256 features were first selected based on pairwise mutual information for each cancer type. An XGBoost classifier combined with Synthetic Minority Over-Sampling Technique (SMOTE) was trained to determine the TOO. **Results:** The GIC model exhibited robust performance, achieving an area under the curve (AUC) of 0.959 (95% CI: 0.949-0.970), with an overall sensitivity of 86.4% (83.5%-88.8%) at a specificity of 96.0% (94.2%-97.2%). Notably, for stage I-III GICs, which accounted for 83.2% of cases (a proportion consistent with that seen in prospective observational cohort studies of MCED, such as the SYMPLIFY study), the sensitivity reached 84.1% (80.9%-87.0%). The sensitivities for EC, GC, and CRC were 87.2%, 82.9%, and 90.0% respectively. For stage I CRC, the sensitivity of the GIC model reached 79.1% (64.8%-88.6%), comparable to that of multitarget stool DNA tests, and outperformed fecal immunochemical tests (FIT). Regarding tumor localization, the accuracy of TOO across all positive cases was 89.8% (87.0%-92.0%). For stage I-III GICs, the model maintained a high accuracy of 88.7% (85.5%-91.2%) in predicting TOO. Moreover, the model demonstrated exceptional accuracy in distinguishing between upper and lower GICs, with an accuracy of 95.5% (93.5%-96.9%). **Conclusions:** This study demonstrated the high performance of the MCED test for early detection of GICs in a large-scale, prospective cohort enriched with early-stage cancers. These findings highlight the potential of the GIC model to enhance early detection and precise localization of GICs, thus improving the efficiency of subsequent diagnostic procedures.
Research Sponsor: None.

A novel magnetic bead-based cfDNA extraction method for advanced ctDNA marker discovery and methylation profiling.

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Background: Cell-free DNA (cfDNA) extraction and circulating tumor DNA (ctDNA) enrichment are critical for liquid biopsy-based cancer diagnostics. However, the QIAamp Circulating Nucleic Acid Kit (QIA), despite its widespread use, has limitations, including a labor-intensive manual workflow and suboptimal performance in ctDNA marker enrichment and contaminant removal, potentially affecting downstream methylation analyses. To overcome these limitations, we developed a novel, automatable magnetic bead-based cfDNA extraction method to improve ctDNA enrichment and biomarker discovery. **Methods:** The optimized extraction protocol incorporates refinements in pre-treatment, lysis, and binding steps to enhance cfDNA purity and ctDNA enrichment. Plasma samples from 8 lung adenocarcinoma (LUAD) patients, 10 healthy donors, and five simulated plasma samples spiked with varying proportions of fragmented genomic DNA from H838 (cancer) and NA12878 (healthy) cells were processed using both our optimized assay and the QIA kit. **Results:** The optimized method achieved cfDNA yields comparable to the QIA kit in LUAD and healthy samples but exhibited significantly higher extraction yields in simulated samples (39.91 ng vs. 31.17 ng, $p < 0.05$). Digital PCR demonstrated superior enrichment of 136 bp and 400 bp cfDNA fragments, while library preparation showed a 1-fold and 1.46-fold increase in pre-library yield and a 16.55% and 6.45% increase in mapped ratios for LUAD and healthy donors, respectively. These results demonstrate that our method achieves superior cfDNA enrichment efficiency compared to QIA, making it better suited for NGS-based workflows. Library complexity rose from 24.07% to 31.24% in LUAD samples and from 29.71% to 35.04% in healthy donors, with coverage depth of target regions improving by 56.13% and 22.88%, respectively. This enabled the detection of more CpG sites at equivalent sequencing depths. Simulated sample analysis confirmed that our optimized method better preserved methylation accuracy, achieving higher consistency between extracted and unextracted DNA. Furthermore, the optimized method identified significantly more cancer-specific haplotypes across 1,517 LUAD markers, improving ctDNA detection sensitivity, particularly in low tumor burden samples. **Conclusions:** Our automatable magnetic bead-based cfDNA extraction method outperforms QIA in library quality, complexity, and methylation accuracy while enabling enhanced ctDNA enrichment and biomarker detection. This approach provides a robust and scalable solution for advancing liquid biopsy-based cancer diagnostics. Research Sponsor: None.

	Technique	Protocol	Throughput	Handling time per run (min)	Cost ($)	Beta bias with unextracted DNA	Unmethylated marker counts median	Methylated marker counts median
QIAamp (QIA)	Vacuum-column	Manual	24	180~240	25	0.01319	382	526
Our assay	Magnetic bead	Automatic	24	30	1	0.00365	590	734

Liquid biopsy-informed precision oncology clinical trial to evaluate the utility of ctDNA genomic profiling in patients with advanced or metastatic solid tumors.

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Background: Genomic profiling through liquid biopsies (LB) has enabled precision oncology decision making, however a key challenge lies in critically interpreting LB data to optimize patient care. **Methods:** We report results from the first planned interim analysis of an observational biomarker trial, designed to evaluate the clinical utility of serial LB in patients with advanced/metastatic solid tumors (NCT05585684). Primary endpoints were to determine feasibility, prevalence of actionable alterations in LB and the fraction of patients with enacted genotype-matched therapies. Secondary endpoints included progression-free (PFS) and overall survival (OS), time to subsequent therapy and concordance between LB and tumor next generation sequencing (NGS). Exploratory endpoints included correlation of ctDNA dynamics with survival. Serial LBs were obtained at baseline, 1-3 weeks on therapy and at progression using a CAP/CLIA validated NGS panel (Labcorp, MD). Patient-matched white blood cell (WBC) NGS was utilized to identify clonal hematopoiesis (CH)-derived variants. Actionability of genomic alterations was assessed by an ensemble multi-resource programmatic approach; results were reviewed at the Johns Hopkins Molecular Tumor Board (JH MTB). **Results:** Between March 2023 and July 2024, 51 patients with NSCLC, SCLC and esophageal cancer were enrolled, with 45 evaluable baseline and 12 progression LBs reviewed at JH MTB. Median turnaround time from baseline and progression LB to MTB recommendation was 14 and 13 days respectively. Patient-matched analyses of baseline WBC samples revealed 30.1% (n = 22) CH-derived alterations. The frequency of actionable variants was 28.8% (n = 21) at baseline, 23.3% (n = 7) on therapy and 21.7% (n = 5) at progression. Of the 45 patients reviewed at baseline, 33 received a recommendation for genotype-matched therapies; 48.5% (n = 16) based on tumor molecular profiling, 15.2% (n = 5) based on LB alone and 36.3% (n = 12) based on LB and tissue NGS. Thirteen patients were treated according to MTB recommendations. Patients who were treated with genotype-matched MTB recommended therapies had longer OS and PFS compared to those who received alternate therapies (not reached-NR vs. 14.8 months, log-rank p = 0.028 and NR vs 6.2 months, log-rank p = 0.21 respectively). Among the 12 patients reviewed at progression, 5 received an MTB recommendation for genotype-tailored therapies based on LB alone (n = 3) or in combination with tissue NGS (n = 2). Early on-therapy ctDNA clearance was associated with longer PFS and OS (log rank p = 0.02 and p = 0.06). **Conclusions:** Our findings highlight the value of a multidisciplinary MTB when supported by comprehensive liquid biopsy molecular information to inform therapy selection and improve patient outcomes. Clinical trial information: NCT05585684. Research Sponsor: LabCorp; National Cancer Institute; 1U01CA274631-01A1; Oncology Center of Excellence, Food and Drug Administration (FDA); U01FD0005042.

Real-time clinical validation of a blood cell-free, mRNA-based GeneVerify test for screening and early diagnosis of prostate cancer.

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Background: Prostate cancer screening methods, including prostate-specific antigen (PSA) testing, radiological imaging, and pathological assessments, often fail to achieve reliable early detection. Despite advancements, gene-based diagnostic tests tailored for early detection of prostate cancer remain underdeveloped. To bridge this gap, we evaluated the clinical utility and diagnostic accuracy of the plasma cell-free mRNA-based GeneVerify test. This cutting-edge diagnostic approach aims to deliver faster and more precise results while avoiding the risks and complications associated with surgical biopsies. **Methods:** Blood samples were prospectively collected from patients suspected of prostate cancer who presented with urinary symptoms, persistently elevated PSA levels (>4 ng/mL), and PIRADS 4-5 lesions. All patients were recommended for a transperineal biopsy. Plasma cell-free RNA was isolated and analyzed for 25 prostate cancer-specific genes using the GeneVerify real-time PCR kit (Hayward, USA). The log2 fold change in gene expression for each gene was calculated, and a genetic risk score (GeneVerify Dx) was assigned to each patient. The transperineal biopsy results served as the reference standard. The diagnostic performance of the test in distinguishing between benign and cancerous cases was assessed and ROC (receiver operating characteristic) curve was plotted. **Results:** We tested a total of 45 subjects, comprising 35 suspected prostate cancer cases and 10 healthy controls. The median age of the cases was 66 years (range: 45–85), while the controls had a median age of 41.5 years (range: 39–47). The genetic risk score effectively differentiated prostate cancer patients from benign cases. The Area Under the Curve (AUC) was 0.83 ± 0.07 (P = 0.002; 95% CI: 0.70–0.96), demonstrating the test's strong discriminatory ability. Using a risk score cut-off value of 10, the test achieved a sensitivity of 72% and a specificity of 90%. Additionally, patients with higher Gleason grades and those experiencing chronic inflammation exhibited elevated gene expression levels and higher risk scores compared to benign subjects. **Conclusions:** In summary, this prospective study is the first to validate a blood cell-free RNA-based GeneVerify test for real-time screening and early detection of prostate cancer. The test exhibits high precision in identifying early-stage prostate cancer, with strong concordance to biopsy results. Research Sponsor: None.

Molecular profiling of body fluid cfDNA: Advancing diagnostics and therapeutic decisions.

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Background: Effusions in cancer patients pose several critical challenges for clinicians. In known cancer patients, an effusion may signal recurrence, whereas in newly diagnosed, seemingly localized cases, it indicates a more advanced stage. In many patients the effusion may be secondary to complications of treatment or comorbidities, rather than malignant. Diagnosing malignant involvement of body fluids remains a challenge due to the limitations of conventional cytology. This study explores the potential of molecular profiling of body fluids to identify actionable molecular alterations and its role in diagnosing malignant effusions. **Methods:** We analyzed cfDNA from body fluids—ascitic fluid (N=26), cerebrospinal fluid (N=7), pleural fluid (N=11), and pericardial fluid (N=1), collected from 45 patients with solid tumors, including lung (N=12), breast (N=9), ovarian (N=9), pancreas (N=4), gastrointestinal cancers (N=4), cervix (N=2), and one each of CNS, endometrial cancer, HCC, liposarcoma, and melanoma. In a subset, results from fluid samples were compared with tissue and plasma samples to assess concordance across different sample types. **Results:** Pathogenic alterations were identified in 89% (40/45) of fluid samples. The most frequently mutated genes were *TP53* (53%), *EGFR* (20%), *KRAS* (18%), *PIK3CA* (9%), *CTNNB1* (7%), *FGFR3* (7%), *GNAS* (7%), *MYC* (7%), and *ESR1* (4%). Simultaneous analysis of body fluid and tissue samples (n=11) revealed that 7 patients (64%) had at least one concordant pathogenic alteration. Similarly, analysis of body fluid and plasma samples (n=16) showed that 8 patients (50%) had at least one concordant pathogenic alteration. Body fluid analysis identified acquired resistance alterations, such as *EGFR T790M* and *ALK C1156Y*, which influenced therapy decisions. Among the alterations detected exclusively in fluid samples were *ERBB2* amplification and *ESR1 D538G* mutation in two breast cancer patients. In evaluating molecular profiling against cytology for detecting malignant effusions, 17 of 25 samples were positive by both methods, while 4 of 5 cytology-negative samples were ctDNA-positive. Notably, 3 of 4 ctDNA-negative cases were cytology-positive. These results emphasize the potential role of molecular profiling for diagnosis when cytology is inconclusive. **Conclusions:** This study highlights the importance of body fluid ctDNA profiling (ascites, pleural, pericardial, CSF) in identifying actionable mutations, including unique druggable alterations not found tissue or liquid biopsies. The ability to detect ctDNA in cytology-negative samples underscores the potential of body fluid ctDNA as a valuable complement to fluid cytology for diagnosing malignant involvement. Research Sponsor: None.

ESCAT classification of pathogenic variants identified in body fluids from 45 patients.

Tier Level	Incidence (%)	Number of unique patients
IA	28.9%	13
IIA	0%	0
IIIA	35.6%	16
IIIB	4.4%	2
IVA	55.6%	25
IVB	2.2%	1
X	22.2%	10

Circulating tumor DNA and late recurrence in high-risk, hormone receptor-positive, HER2-negative breast cancer: An updated analysis of the CHiRP study.

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Background: Risk of recurrence for patients (pts) with HR+/HER2- breast cancer persists for decades. Most distant recurrences occur in the 'late' adjuvant setting, > 5 years (yrs) from diagnosis. In CHiRP (ASCO 2022), we showed that minimal residual disease (MRD) was detectable in the late adjuvant setting: ctDNA was detected in 8/83 (9.6%) pts in the cohort and 6/8 (75%) pts with positive ctDNA (+ctDNA) had developed distant recurrence when initially reported (median follow-up 2 years from first plasma sample collected on study). Here, we report updated clinical outcomes and investigate the meaning of a ctDNA test result during surveillance with longer follow-up. **Methods:** In CHiRP, pts with stage II-III HR+/HER2- breast cancer at high risk of recurrence diagnosed > 5 yrs prior with no evidence of recurrence were prospectively identified. All pts provided informed consent for prospective plasma collection every 6-12 months at routine follow-up visits for batched, retrospective ctDNA testing using RaDaR, a tumor-informed whole exome sequencing-based assay. Pts were followed at the discretion of the clinical provider without any routine surveillance imaging, as per guideline-concordant care. See CHiRP ASCO 2022 presentation for additional methods. **Results:** Of 83 pts in the analytic cohort, 57 (68.7%) pts had stage III disease, and most (n = 75, 90.4%) underwent (neo)adjuvant chemotherapy. All pts received endocrine therapy. In this update, median follow-up from first sample collection was 4.4 yrs (interquartile range 4.0, 4.9). 214 plasma samples were collected prior to any known recurrences and included in this analysis. 8/83 (9.6%) pts had +ctDNA at any timepoint including 4/83 (4.8%) with +ctDNA on first study plasma sample. In pts initially ctDNA-negative (-ctDNA; n = 4), median time from first sample collection to MRD detection was 1.29 yrs (range, 0.72 – 3.05). During follow-up, 8 (9.6%) pts developed distant recurrence and 1 (1.2%) pt had a local recurrence. With additional follow-up included in this update, all 8/8(100%) pts with +ctDNA developed distant recurrence with a median lead time of 1.39 years (range 0.01 – 4.24). Among -ctDNA plasma samples with > 2 yrs of follow-up (n = 185), the negative predictive value (NPV) of a -ctDNA test for lack of clinical recurrence for > 2 yrs post-test was 98.4% (3/185). The NPV indicating freedom from recurrence > 1 and > 3 yrs was 100% (0/196) and 96.6% (5/147), respectively. **Conclusions:** In pts with high-risk HR+/HER2- breast cancer in the late adjuvant setting, all pts with +ctDNA developed distant metastasis. A -ctDNA test was strongly associated with lack of recurrence over a 3 yr follow-up period. Future studies are needed to determine if ctDNA-guided intervention can impact clinical outcomes for early-stage breast cancer and to determine the optimal role of MRD surveillance during follow-up. Research Sponsor: None.

A plasma proteomics-based model for predicting response to neoadjuvant chemotherapy in ovarian cancer.

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Background: Neoadjuvant chemotherapy (NACT) is a standard treatment option for advanced high-grade serious ovarian cancer (HGSOC). Following interval debulking surgery, pathologists assess tumor response to initial chemotherapy using a standardized chemotherapy response score (CRS) corresponding with patient survival. We sought to determine the feasibility of developing a proteomic-based biomarker to predict response to NACT based on pre-treatment plasma samples. **Methods:** Pre-treatment samples were collected from 71 HGSOC patients receiving platinum-taxane combination NACT. Deep plasma proteomic profiling was performed using SomaLogic's 7K aptamer-based technology. Based on the proteomic profiles, a computational model was developed to predict CRS, focusing on differentiating between poor CRS (CRS1) versus partial or near-complete CRS (CRS2/3). The model counted the number of response-associated proteins per patient. Patient scores were derived by resampling into training and test sets, averaging test set results. Patients were stratified into groups (i.e., 'Chemo-responsive' or 'Chemo-resistant') based on median score. Bioinformatic analysis of the HGSOC-specific proteomic biomarkers was performed to gain insight into the potential mechanisms driving NACT therapeutic benefit and resistance. **Results:** Our proteomics-based predictive model differentiated between patients with CRS1 versus CRS2/3 (ROC AUC = 0.67, p = 0.008). CRS association with disease-free survival (DFS) and overall survival (OS) in this cohort was consistent with a previous meta-analysis, though not reaching statistical significance (CRS3 versus CRS1/2, HR = 0.62, 95% CI: 0.27-1.42, p = 0.25 for DFS; HR = 0.67, 95% CI: 0.21-2.09, p = 0.48 for OS). Hazard ratios for patient classification as 'Chemo-responsive' versus 'Chemo-resistant' trended in the same direction (HR = 0.70, 95% CI: 0.37-1.30, p = 0.25 for DFS; HR = 0.65, 95% CI: 0.25-1.72, p =0.39 for OS). The predictive model incorporated 62 proteins. Of these, 27 were elevated in the plasma of patients with poor CRS compared to those with partial or near-complete CRS. These proteins were notably enriched in pathways related to cell death resistance. Moreover, several of these elevated proteins have previously been linked to HGSOC, particularly in the context of chemotherapy resistance. Conversely, patients with partial or near-complete CRS showed significant enrichment of proteins associated with genome instability and mutation. **Conclusions:** This study demonstrates the feasibility of CRS prediction using plasma proteomics at baseline, potentially complementing existing imaging approaches. While current treatment options limit immediate clinical utility, these findings provide novel insights into biological determinants of chemotherapy response and may become predictive biomarkers for novel treatment protocols. Research Sponsor: OncoHost; Israel Science Foundation (ISF); 2972/21; Israel Cancer Research Fund (ICRF); 21-302-MI.

NeoCircle: Investigating circulating tumor DNA dynamics as a predictor of survival in primary breast cancer.

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Background: Persistent circulating tumor DNA (ctDNA) detection during neoadjuvant treatment (NAT) of early-breast cancer (EBC) indicates high-risk disease. Following surgical resection, ctDNA-positivity indicates molecular residual disease (MRD) and heralds occult metastatic disease relapse. To incorporate ctDNA into EBC management, scalable and widely accessible diagnostic methods are necessary. Here we apply an ultrasensitive, personalized tumor-informed approach to ctDNA analysis leveraging structural variant (SV) detection using a novel multiplex digital PCR (dPCR) technology. **Methods:** 116 patients with stage I-III EBC (31.0% TNBC, 43.1% HR+/HER2- and 24.1% HER2+) and eligible for NAT were recruited through the prospective SCAN-B study (NCT02306096, substudy NeoCircle) between December 2014 and March 2019 and have been analyzed for ctDNA. Whole genome sequencing was performed on tumor material and personalized multiplex dPCR assays tracking up to 16 SVs were used for ctDNA monitoring. Plasma samples were collected at baseline, during NAT, pre- and post-surgery and at 6-monthly intervals during follow up. **Results:** High baseline detection was observed across all stages and subtypes (90.5% overall), and ctDNA-positivity at end-of-NAT (end-NAT) was a significant predictor of eventual disease relapse and death (relapse-free interval, RFI, hazard ratio, HR, 3.7, 95% CI 1.4-9.7; overall survival HR 7.7, 95% CI 2.2-26.6). A significant association was observed between end-NAT ctDNA clearance and pathological complete response (pCR), whereas non-pCR by itself was not a significant predictor of relapse or death in this cohort. At one or more post-operative timepoints, MRD+ was detected in 10 patients who experienced distant recurrence, with lead times up to 4 years (median 13.9 months, range 1.8-47.7 months). Similarly, ctDNA was detected in 3 of 4 patients with local recurrences and 1 of 2 patients with CNS-only recurrences. For 2 patients without presentation of clinical recurrence to date, ctDNA was detected post-operatively, with subsequent clearance during follow-up. Post-operative MRD associated with poor RFI (HR 45.5, 95% CI 13.0-159.8) and OS (HR 15.3, 95% CI 4.5-52.9). **Conclusions:** In this analysis of 116 patients from a prospective study in patients with EBC receiving NAT, we monitored ctDNA using an ultrasensitive tumor-informed dPCR assay tracking patient-specific SVs. ctDNA detection post-NAT and prior to surgery was associated with high-risk of disease relapse and death, outperforming pCR. Moreover, post-operative ctDNA detection was also significantly associated with disease relapse and death, with long lead-times over standard-of-care clinical assessments. These findings further validate the feasibility of SVs as an MRD analyte and support the clinical use of this approach in EBC. Research Sponsor: None.

Monitoring populations of tumor-macrophage fusion cells in blood prognosticates PFS and OS in pan-metastatic cancers over 2 years.

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Background: Tumor associated macrophages are known to fuse with cancer cells in the blood through a dysfunctional CD47 phagocytic immune pathway resulting in the formation of tumor- macrophage fusion cells (TMFCs) which are observed as heterokaryon (incomplete fusion), synkaryon (full fusion) or hetero-to-synkaryon transition (partial fusion). Previous studies in lung and breast cancer demonstrated that subtypes of TMFCs in blood may correlate with highly aggressive disease unlikely to respond to certain systemic therapies (i.e. chemotherapy). We initiated a prospective study to evaluate the blood of n = 100 metastatic pan-cancer patients (pts) receiving systemic therapy for the presence of full, partial, and incomplete TMFCs to compare their progression-free survival (PFS) and overall survival (OS). **Methods:** We conducted a prospective pilot study of n = 100 pathologically confirmed metastatic cancer pts with breast (n = 23), prostate (n = 21), pancreas (n = 17), colon (n = 19), or lung (20) with active progressive disease, prior to the induction of new systemic therapies, i.e. chemotherapy (n = 39), PD-L1 immunotherapy (n = 27), hormone therapy (n = 20), or targeted therapy (n = 23). TMFCs were isolated from 7.5ml peripheral blood using CellSieve microfiltration and identified by their enlarged multinucleated structure ($>$ 30 μm), which was categorized into 3 distinct subtypes: full fusion marked by a single multinucleated nuclei, partial fusion marked by 2 contacting nuclei, incomplete fusion marked by 2 distinct non-contacting nuclei. TMFC subtypes were compared to pts' PFS and OS by cox proportional univariate and multivariate analysis over 24 months. **Results:** We identified TMFCs in 78% of all pts (n = 78/100), averaging 10 per pt. 37% of pts were found to have more than one TMFC subtype in their sample, with 70 pts having full fusion, 23 partial fusion, and 28 incomplete fusion. At 24 months, pts with incomplete fusion TMFCs had significantly worse PFS (HR, 2.9; 95% CI, 1.5 to 5.7; P = 0.0023) and OS (HR, 2.5; 95% CI, 1.2 to 5.3; P = 0.0202). Interestingly, pts with incomplete fusion and treated with systemic targeted therapy (n = 7) were found to have significantly improved PFS (HR, 4.8; 95% CI, 1.8 to 13.0; p = 0.0052), but not OS (HR, 3.0; 95% CI, 1.0-9.2; p = 0.0999) versus other therapy types. There was no significant PFS differences in pts without incomplete fusion TMFCs being treated with targeted therapies. **Conclusions:** In a pan metastatic cancer setting, we found that incomplete fusion in circulating TMFCs associates with poorer outcomes at 24 months. Further, it appears that pts with incomplete TMFCs may have had better outcomes when treated with targeted therapies compared to other therapy types. These preliminary findings suggest the need for larger scale prospective studies to further evaluate relationships between TMFCs and therapeutic responses in specific disease populations. Research Sponsor: Creatv MicroTech.

Whole-genome bisulfite sequencing of cell-free DNA to investigate molecular contributors to racial survival differences in advanced-stage triple-negative breast cancer.

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Background: Black women are twice as likely to be diagnosed with triple-negative breast cancer (TNBC), a highly aggressive and difficult-to-treat subtype with poor survival outcomes. While well-defined factors such as socioeconomic status have been recognized, the impact of genomic and molecular factors on the racial disparity in TNBC survival remains understudied. Liquid biopsy, a non-invasive and real-time method for studying the molecular landscape of tumors, has yet to be explored in the context of racial survival disparities in TNBC. **Methods:** Ten Black TNBC patients were matched with ten White TNBC patients based on age, family history, tumor stage, grade, and inflammatory breast cancer (IBC) status. Baseline blood samples were collected prior to the initiation of a new therapy. Cell-free DNA (cfDNA) was extracted from plasma, bisulfite-converted, and analyzed through whole-genome bisulfite sequencing (WGBS). After quality control, ichorCNA was used to identify copy number alterations (CNAs), and MethylKit was applied for methylome analysis. Associations between CNAs, differentially methylated regions (DMRs), and progression-free survival (PFS) were evaluated and compared between Black and White patients. **Results:** The Black-White pairs were well-matched across key clinical variables, including age (P = 0.99), family history (P = 1.00), tumor stage (P = 1.00), grade (P = 1.00), and IBC status (P = 0.37). Black TNBC patients had poorer PFS compared to their White counterparts. Significant CNAs were identified on chromosome 1 (chr1: 20400000-23900000_p36.12 and chr1:7200000-9200000_p36.23), regions associated with known breast cancer prognosis genes such as *EPHB2* and *E2F2*. Thirteen DMRs were found to be significantly associated with the racial differences in PFS, with key genes such as *CDH13* and *TMEM132C* identified in these regions. Notably, the methylation status of the *CDH13* promoter has previously been associated with breast cancer risk. The predictive power for PFS was significantly enhanced in a model combining these 13 DMRs with race (Concordance Index [C-index] = 0.96), compared to a model using race alone (C-index = 0.75). **Conclusions:** In this pilot study utilizing WGBS of cfDNA, we identified significant CNAs and DMRs associated with the racial disparity in survival outcomes among advanced-stage TNBC patients. These findings provide insight into the genomic and molecular contributors to this disparity and highlight the potential of liquid biopsy for future studies. Larger studies are needed to validate these results and further investigate the underlying mechanisms. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; R01CA207468; Sidney Kimmel Comprehensive Cancer Center.

Beyond tumor-shed markers: AI driven tumor-educated polymorphonuclear granulocytes monitoring for multi-cancer early detection.

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Background: Tumor educated Polymorphonuclear Granulocytes (tPMNG) are a distinct phenotypic set of Neutrophils (N2) with corrupted programmed death pathways resulting in apoptosis resistance. The presence of tPMNGs in the peripheral blood indicates up-regulation of pro-tumoral factors and resistance to apoptotic signals. Our platform leverages this unique anti-apoptotic characteristic of tPMNGs through a proprietary culture process and AI-based digital imaging analysis to detect cancer in its early stages. This approach represents a paradigm shift from detecting rare tumor-shed analytes such as ctDNA and CTCs to monitoring relatively abundant tPMNGs, whose numbers typically exceed conventional analytes by 3-4 orders of magnitude. We studied detection of tPMNGs in a case-control study to evaluate their suitability for a multi-cancer early detection test (MCED). **Methods:** We collected 10 ml of peripheral blood in EDTA tubes from 892 asymptomatic healthy volunteers above 18 years of age [463, 52% male; 429, 48% females with mean age of 48 (20 to 89) years], 24 individuals diagnosed with non-malignant conditions including prostatitis, polycystic ovarian disease and acute pancreatitis, and 90 individuals recently diagnosed with surgically resectable early stage cancers (Stage 1/ 2) comprising Head and Neck (N=32, 36%), Breast (N=20, 22%), Colorectal (N=14, 16%), others (N=24, 27%). Nucleated cells were isolated from the samples after RBC lysis and centrifugation. These cells were seeded in six well culture plates and subjected to controlled apoptotic stress under serum-free, hypoxic conditions with specific growth factor supplementation for 5 days. Surviving cells were set on imaging slides and stained with H&E. 60X images were obtained and analyzed using a convolutional neural network (CNN) based AI algorithm to detect tPMNGs per ml. **Results:** The mPMNG detection method demonstrated 84% sensitivity (95% CI: 84.44%) across multiple cancer types. The platform demonstrated 97% specificity (95% CI: 97.40%) among healthy asymptomatic cohort. In samples from individuals from individuals with non-malignant conditions, specificity was 96% (95% CI: 95.83%). **Conclusions:** This first-in-class immune cell-based MCED approach offers several advantages over tumor-shed analyte detection: 1. Leverages amplified host response rather than rare tumor products. 2. Provides robust detection across cancer types and stages. 3. Utilizes existing laboratory infrastructure and a scalable protocol. 4. Demonstrates potential for screening, diagnosis, and monitoring applications. The high sensitivity and specificity, combined with practical advantages, suggest potential for clinical implementation in cancer screening and monitoring programs either using tPMNG alone or in conjunction with CTCs / cfDNA evaluation. Research Sponsor: None.

Next-generation U-Net Encoder: Decoder for accurate, automated CTC detection from images of peripheral blood nucleated cells stained with EPCAM and DAPI.

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Background: Direct circulating tumor cell (CTC) detection is a promising biomarker for early cancer detection and monitoring. Traditional fluorescence microscopy and AI-driven methods have limitations such as subjectivity and labor-intensiveness. We developed a deep-learning pipeline using a U-Net–type encoder–decoder architecture for precise pixel-level CTC discrimination in peripheral blood nucleated cells (PBNCs). This method preserves morphological and fluorescence details, overcoming convolutional neural network (CNN) limitations by maintaining fine features through skip connections for better discrimination. We present specificity and sensitivity data from a case-control study. **Methods:** We collected 5 ml of peripheral blood in EDTA tubes from 1383 asymptomatic healthy volunteers (744, 54% male; 639, 46% females with mean age of 49 [(20 to 93) yrs], 38 individuals diagnosed with non-malignant conditions including prostatitis, PCOD and acute pancreatitis, and 143 individuals recently diagnosed with surgically resectable early stage cancers (Stage 1/ 2) - Head and Neck (N=50, 35%), Breast (N=31, 22%), Colorectal (N=17, 12%), Pancreas (N=8, 6%), Prostate (N=8, 6%), Lung (N=5, 3%), Ovary (N=5, 3%) others (N=19, 13%). Nucleated cells were isolated from the samples after RBC lysis and centrifugation and stained with EPCAM and DAPI and set on imaging slides. 60X images were obtained and processed by AI utilizing U-Net–Based Encoder–Decoder Architecture and context discrimination to detect CTCs. The customized U-Net pipeline encodes spatial information through successive convolutional and pooling layers, generating a highly compressed representation of cells in the bottleneck. By employing transposed convolutions in the decoder stage—and incorporating skip connections from the encoder layers—the AI model reconstructs a pixel-wise segmentation mask to identify potential CTCs with cell diameter >10 microns. This approach aims to surpass existing methods that rely on bounding-box–based detection by offering enhanced sensitivity and specificity through end-to-end learned feature extraction. Ground truth annotations were established via expert cytopathology review, and training procedures involved cross-validation to ensure generalizable performance. **Results:** Analysis of total 1564 samples showed that our U-Net–based model achieved a sensitivity of 89% (95% CI: 88.81) and specificity of 97% (95% CI: 97.98) for detecting CTCs. Performance remained consistent across solid tumors, highlighting the flexibility and adaptability of the architecture in various fluorescence staining conditions. **Conclusions:** Our U-Net pipeline uses pixel-level segmentation and skip connections to enhance CTC detection accuracy. Integrating fluorescence and morphology, it can streamline cancer screening and disease monitoring. Research Sponsor: None.

Clinical outcomes of a prospective multicenter study evaluating a combined circulating tumor DNA (ctDNA) and RNA (ctRNA) liquid biopsy assay in metastatic non-small cell lung cancer (NSCLC).

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Background: Genomic profiling of metastatic NSCLC to inform targeted therapy selection is endorsed by numerous guidelines. While tissue biopsy is the mainstay of molecular profiling, liquid biopsy offers a practical real-world approach to non-invasively identify guideline-recommended biomarkers. LIQUIK was a prospective, multicenter, observational cohort study to evaluate the performance of a combined ctDNA and ctRNA liquid biopsy assay, LiquidHALLMARK (LHM ctDNA and ctRNA) in comparison to the ctDNA-only liquid biopsy Guardant360 (G360 ctDNA) and tissue next-generation sequencing (NGS) for biomarker detection in metastatic NSCLC. Diagnostic performance of the primary cohort has been previously presented. Here, we report clinical outcomes after 1-year follow-up of the cohort. **Methods:** LIQUIK (NCT04703153) enrolled 151 non-squamous NSCLC patients across the USA and Singapore from Apr 2021 to Dec 2022. Enrolled patients were genotyped using tissue NGS, LHM ctDNA and ctRNA, and G360 ctDNA for 9 biomarkers (*EGFR*, *ALK*, *RET*, *ROS1*, *BRAF*, *KRAS*, *MET*, *ERBB2*, *NTRK1/2/3*). Patients were treated according to their physician's choice of first-line therapy following biomarker testing. Tumor assessments were performed at baseline and within 6 months (mo) of treatment initiation. Overall response rate (ORR), progression-free survival (PFS), and the clinical utility of ctRNA were investigated. **Results:** Among the 151 patients, 129 were subsequently treated in the first-line setting (49.6% on targeted therapy, 41.1% on chemotherapy, and 30.2% on immunotherapy), with 27 on combination therapy. Of the 64 patients on targeted therapy, 47 had matched biomarker findings from tissue NGS, 47 from LHM ctDNA and ctRNA, and 43 from G360 ctDNA. ORRs of patients on targeted therapy and chemo/immunotherapy were 40.4% and 16.1% respectively. Among patients treated with targeted therapy, ORR was similar between patients with biomarker-matched findings from tissue NGS (45.2%), LHM ctDNA and ctRNA (40.5%), and G360 ctDNA (36.8%). PFS of patients on targeted therapy (median 23.6 mo) was significantly longer than those not on targeted therapy (median 3.8 mo; HR = 0.26; $p < 0.001$). Median PFS was similar between patients with biomarker-matched findings from tissue NGS (23.6 mo), LHM ctDNA and ctRNA (18.6 mo), and G360 ctRNA (20.1 mo). Overall, incorporation of ctRNA into LHM identified 2 additional biomarker-positive patients. Both ctRNA-exclusive biomarkers were confirmed by tissue NGS, and both patients were treated with biomarker-matched targeted therapy. While one patient was lost to follow-up, the second patient had a partial response to treatment. **Conclusions:** Treatment outcomes based on liquid and tissue biopsies are comparable. The inclusion of ctRNA in liquid biopsy increases its diagnostic yield of actionable biomarkers. Clinical trial information: NCT04703153. Research Sponsor: None.

Microbial metabolic pathways to abrogate immunotherapy toxicity and promote anti-tumor response in metastatic renal cell cancer.

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Background: Metastatic RCC has a poor prognosis. Despite improvement in treatment outcomes with ICB and targeted therapy, many patients fail to respond to first line therapy and immune mediated adverse events(irAE) remains a major challenge, often leading to treatment discontinuation. Therefore, mitigating irAE without compromising antitumor immunity is a critical unmet need. Tryptophan microbial metabolic pathway is known to play a major role in immune homeostasis through its action on Aryl hydrocarbon receptor (AhR) balancing immune suppresser with immune effector responses. We hypothesize that microbial metabolism of tryptophan to indole metabolites may play a role in ICB resistance as well in irAE, identification of which may help us predict patients most likely to respond, without life threatening toxicity. **Methods:** We prospectively collected paired stool and blood samples of treatment naïve metastatic RCC patients, treated with ICB +/- Tyrosine kinase inhibitors (TKI) at treatment initiation and at time of first response assessment (12+/-3 weeks). We evaluated stool metagenomics and untargeted stool and plasma metabolomics among responders (R) and non-responders (NR). We focused on kynurenine/tryptophan and indoles/tryptophan ratio to evaluate differential host and microbial metabolism of tryptophan. A responder was classified as progression free survival (PFS) greater than 6 months while patients with grade 3 or higher irAE was classified as serious IrAE. **Results:** Among 120 patients accrued, 49 were treated with combination ICB, while 71 patients were treated with ICB + TKI. Median follow up was 27 months. 28 patients (23%) had a Grade 3 or higher irAE. 3 patients died from complications attributable to irAE. The median duration to development of any irAE was 3.5 months. Using negative binomial regression model evaluating baseline relative abundance of microbial tryptophan metabolites that were associated both with response as well as serious irAE, we noted significant higher abundance of Indole acetic acid (IAA), indole acetonitrile(ACN), indole acetyl phenylalanine (IAAP)and IAA/kynurenine (Kyn) and lower abundance of tryptophol, indole 3 pyruvic (IPA), (coefficient of 6.4, 1.8, 7.15, 4.6, 0.04, 0.46, with adj p value < 0.05) with serious irAE as well as ICB resistance (Coefficient-5.42, 1.83, 6.15, 4.05, 0.03, 0.4, $p < 0.05$). **Conclusions:** This is one of the first studies evaluating microbial metabolic pathways that may play a role in predicting patients who are more likely to respond with lower likelihood of serious irAE in RCC, thus helping to identify strategies to decouple tumor immunity from autoimmunity to improve ICB outcomes. Further the results can be extrapolated to many other solid tumor treated with immunotherapy, as tryptophan metabolism plays a immune homeostatic role across cancers. Research Sponsor: Conquer Cancer foundation-ASCO YIA.

Tumor-educated platelets as a source of potential biomarkers for colorectal cancer.

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Background: Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide. Current diagnostic methods rely on invasive procedures and serum markers with limited sensitivity, highlighting the need for novel, minimally invasive biomarkers. Tumor-educated platelets (TEPs) have emerged as a promising source, as malignant cells reprogram platelets through molecular alterations. This study aimed to identify differentially expressed genes in TEPs from patients with CRC that could serve as potential diagnostic biomarkers. **Methods:** We downloaded gene expression data from platelets from the Gene Expression Omnibus (GEO; GSE183635), tissue gene expression data from TCGA-COAD and TCGA-READ, and vesicle data from Vesiclepedia. The data were preprocessed to remove low-quality reads, and high-quality reads were aligned to the human reference genome GRCh38.p13. We performed differential expression analysis through DESeq2 ($|\log2FoldChange| > 1$, adjusted p-value < 0.05). Gene ontology (GO) enrichment analysis (p-value < 0.05) was conducted, and shared genes between TEPs, tumor tissues, and vesicles were identified. ROC curves (AUC > 0.75) assessed diagnostic potential. **Results:** A total of 3,211 differentially expressed genes were identified in TEPs, with 55 upregulated and 3,156 downregulated. Six genes (*TLN1*, *IGF2*, *IFITM3*, *DKK1*, *MYL9*, *TNNC2*) were consistently upregulated in TEPs, tumor tissues, and observed in microvesicles. These genes exhibited AUC values ranging from 0.76 to 0.83, indicating high sensitivity for distinguishing CRC patients from healthy controls. **Conclusions:** Our study identified six DEGs in TEPs with elevated expression in CRC tissue, highlighting their potential as minimally invasive biomarkers for CRC diagnosis. These findings pave the way for developing more precise diagnostic tools to improve early detection and patient outcomes. Research Sponsor: Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Potential biomarker genes in TEPs for CRC, ranked by Log2FC.

Gene	Log2FoldChange	P-adjusted	AUC
DKK1	2.011554	$1{,}50\times10^{-3}$	0.78
IGF2	1.5006689	$3{,}56\times10^{-9}$	0.81
IFITM3	1.102034	$3{,}01\times10^{-9}$	0.81
TLN1	1.098185	$1{,}24\times10^{-5}$	0.83
MYL9	1.060944	$1{,}91\times10^{-15}$	0.77
TNNC2	1.023068	$7{,}22\times10^{-8}$	0.76

AUC: Area Under the Curve.

3065 Poster Session

Molecular landscape and therapeutic vulnerability of RRAS- and RRAS2-mutant solid tumors.

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Background: The RRAS subfamily of small GTPases shares considerable sequence homology with the canonical RAS oncoproteins KRAS, NRAS, and HRAS. Mutations in *RRAS* and *RRAS2* that are homologous to *KRAS* hotspot mutations promote transformation *in vitro*. Most diagnostic sequencing panels do not profile the RRAS subfamily, and therefore, the prevalence and clinical relevance of these mutations and their treatment have not been fully established. **Methods:** Based on a clinical targeted DNA sequencing assay (MSK-IMPACT), an institutional cohort of 51,040 solid tumor cases prospectively sequenced between 2016-2024 was analyzed to identify *RRAS*/*RRAS2* mutations. Lung cancers were excluded and analyzed in a separate study. Hotspot mutations in *RRAS/RRAS2* were determined based on homology to KRAS hotspot mutations and/or previous literature demonstrating potential oncogenicity (hotspot *RRAS*: G38, G39 and Q87; hotspot *RRAS2*: G23, G24, A70T, Q72 and in-frame insertions in G23/G24). The sensitivity of cells harboring *RRAS* and *RRAS2*-mutations to the clinically active pan-RAS inhibitor RMC6236 was examined *in vitro* and *in vivo*. Western blotting was utilized to determine changes in protein expression and activation. **Results:** Among the 51,040 cases analyzed, hotspot *RRAS* and *RRAS2* mutations were detected in 6 (0.01%) and 270 (0.5%) patients, respectively. Hotspot *RRAS* mutations were seen in various cancer types, and most had other mitogenic drivers (4/6). Amongst tumors with hotspot *RRAS2* mutations, the most common cancer types included endometrial (n = 172), ovarian (n = 27), and germ cell tumors (n = 26); these variants were seen in 5%, 0.9%, and 5% of these respective patient populations. Most endometrial, ovarian, and germ cell tumors lacked other *K/H/NRAS* mutations (83%, 89%, 85%, respectively). Other tumor types with hotspot *RRAS2* mutations included esophagogastric cancers (n = 9), cholangiocarcinomas (n = 5), and breast cancers (n = 5, 2 of which were triple negative). Treatment with RMC-6236 reduced ERK and P90 RSK phosphorylation in CAL-51 (human triple-negative breast cancer line) and A2780 cells (human ovarian carcinoma cell line), both harboring the RRAS2^{Q72L} mutation. Treatment of mice bearing CAL-51 xenograft tumors with RMC-6236 (50 mg/kg, once daily) significantly reduced tumor growth. Growth of cells harboring *RRAS* and *RRAS2* mutations was also blocked by MEK1/2 and ERK1/2 inhibitors. **Conclusions:** Hotspot *RRAS2* mutations are rare but recurrently found in endometrial, ovarian, and germ cell tumors. These mutations are predominantly mutually exclusive with other canonical *RAS* mutations, although co-mutations with *RAS* do occur in a subset. RRAS2^{Q72L}-mutant cancer cells are sensitive to inhibition of the MAPK pathway including pan-RAS inhibition both *in vitro* and *in vivo*. These preliminary findings may inform future therapeutic strategies for patients with *RRAS2*-mutated solid tumors. Research Sponsor: Memorial Sloan Kettering Cancer Center Department of Pathology and Lab Medicine.

Larotrectinib resistance in TRK fusion cancers: Analysis of a tumor-agnostic, global clinical trial dataset.

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Background: Larotrectinib (laro) is the first-in-class, highly selective, TRK inhibitor approved for tumor- and age-agnostic use in TRK fusion cancers. This is the seminal report of primary and secondary laro resistance based on an analysis of the regulatory dataset that supported drug approval across multiple countries. **Methods:** Genomic data from patients (pts) with non-primary CNS TRK fusion cancer enrolled in a global, prospective, multicenter database of three laro clinical trials including adult and pediatric pts were analyzed. Tumor DNA (Illumina TruSight Oncology [TSO] Comprehensive, TSO 500, or FoundationOne CDx) or circulating tumor DNA (Guardant360 or GuardantOMNI) NGS was performed pre-laro (baseline; BL) and post-laro initiation. On-target *NTRK* (solvent front [SF], gatekeeper [GK], xDFG) mutations and COSMIC-classified tier 1/2 off-target alterations were identified. Primary laro resistance analysis set included pts with no meaningful clinical benefit (PD/SD $<$ 4 months). Secondary (acquired) laro resistance analysis set included pts who developed resistance after meaningful clinical benefit (CR/PR/SD $\geq$4 months). Data cutoff: July 20, 2024. **Results:** Of 304 adult and pediatric pts enrolled, 216 had BL genomic data. Primary laro resistance was observed in 24 pts. Only 1 pt had an on-target mutation (*NTRK3* G623R), likely attributable to prior crizotinib; 9 pts (38%) had off-target alterations involving *AKT*, *BRAF*, *FGFR1*, *GNAS*, *KRAS*, *NRAS*, and *PIK3CA*. Secondary laro resistance was observed in 55 pts with valid post-BL ctDNA (the most common of these TRK fusion cancers were infantile fibrosarcoma [22%], other soft tissue sarcoma [18%], thyroid [11%], lung and salivary gland [9% each]); acquired alterations were identified in 16 of these pts. On-target resistance alone was observed in 5 of 16 pts (31%) and were mainly SF or GK single or double mutation-mediated (*NTRK1* F589L, *NTRK1* G595R, *NTRK3* G623R [n = 2], *NTRK3* G623R/G696A). One xDFG mutation was identified. Off-target resistance alone was observed in 7 of 16 pts (44%) and included hotspot *KRAS* G12D/A/S/V or G13D, *PIK3CA* E545K or E542A, *BRAF* V600E, and *GNAS* R844H/C mutations. Complex, combined on-target and off-target resistance was observed in 4 of 16 pts (25%): on-target SF or GK alterations (*NTRK1* G595R, *NTRK1* F589L/G595R, *NTRK3* G623R, *NTRK3* G623R/F617L) co-occurred with *KRAS* G12D or G12D/G13D, and *NRAS* G12D or Q61H. An analysis of resistance profiles by cancer type and age will be presented. **Conclusions:** In this analysis, on-target resistance to laro, including potential double *NTRK* resistance mutations, was commonly observed. Off-target, largely MAPK or PI3K/AKT pathway reactivating resistance, also occurred. In select cases, complex and likely polyclonal resistance including both on-target and off-target alterations were identified. These observations impact novel therapy development for TRK fusion cancers. Clinical trial information: NCT02637687, NCT02576431, NCT02122913. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

Non-invasive PD-L1 prediction in NSCLC patients using 3D self-supervised deep learning and radiomics.

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Background: Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer for ~85% of all cases. Despite therapeutic advances, prognosis remains poor, especially in advanced stages. Immunotherapy has revolutionized NSCLC treatment, with immune checkpoint inhibitors (ICIs) targeting the programmed death-ligand 1 (PD-L1) pathway. While PD-L1 expression is typically measured via immunohistochemistry (IHC), predictive modeling using CT images could offer a non-invasive alternative to enhance patient stratification and treatment planning in hard-to-biopsy cases and tumor follow-up of clonal resistance. We propose a solution for non-invasive prediction of PD-L1 expression leveraging radiomics and AI. **Methods:** This multicentric retrospective study included NSCLC patients from five real-world data sources who underwent CT and biopsy. CT scans were quality-checked and annotated by imaging experts supervised by radiologists (> 5 years' experience) to delineate primary tumors. PD-L1 levels were obtained via IHC. The cohort was randomly split into training and test sets (80/20%), with 5-fold cross validation for model building and fine-tuning. Three methods—radiomics, deep learning, and deep radiomics—were proposed for binary PD-L1 prediction (cut-off > 1%) based on 3D lesion-centered patches. The radiomics pipeline included 3D feature extraction, standardization, dimensionality reduction and classifier selection. The deep learning approach used a self-supervised 3D network, pretrained on 2420 lung lesion patches from 751 CTs by minimizing dissimilarity between augmented pairs and then fine-tuned on the training set to predict PD-L1 expression. The deep radiomics method fused both methods via weighted averaging of predicted probabilities. **Results:** A total of 324 patients (41% women, 63 ± 10 years) with varying PD-L1 expression (63% with levels > 1%), were included. The deep radiomics approach achieved the highest performance, with AUCs of 75.9% ± 5.3% and 70.1%, and F1-scores of 78.1% ± 1.2% and 76.7% on the validation and test sets, respectively, with a per-instance processing time of 1.2 ± 1.3 seconds. Compared to the radiomics method, it improved AUC by 2.6% and 1.2%, and F1-score by 2.7% and 3% on the validation and test sets, respectively. Compared to the deep learning approach, it showed AUC gains of 0.3% and 2%, and F1-score gains of 11.3% and 18.4% on the validation and test sets, respectively. **Conclusions:** This study demonstrates the effectiveness of a novel 3D image-based approach combining radiomics and 3D self-supervised learning to predict PD-L1 expression in a heterogeneous NSCLC cohort using real-world data. The model executes in seconds and could be regulatory cleared and deployed in clinical practice as a medical device performing non-invasive PD-L1 expression identification from CT scans. Research Sponsor: None.

Development and implementation of molecular oncology test e-consult at the VA North Texas Health Care System (VANTHCS).

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Background: The VA National Precision Oncology Program (NPOP), launched in 2016 as part of the White House's Cancer Moonshot Initiative, aimed to revolutionize cancer care through precision medicine for Veterans. Oncologists at the VANTXHCS utilized molecular testing to identify potentially actionable mutations to tailor treatment strategies more accurately. This study aims to evaluate the impact of the identification and impact of potentially actionable mutations with treatment decisions and overall survival. **Methods:** We conducted a retrospective chart review of Veterans with molecular oncology testing (MOT) at VANTXHCS from August 2019 to May 2024 to assess cancer type, prevalence of potentially actionable mutations, treatment decisions, targeted therapy utilization, and overall survival (OS). Potential actionable mutations were determined based on AMP/ASCO/CAP Variant Categorization mapped to the OncoKB FDA-Recognized Human Genetic Variant Database at the time of review. **Results:** 570 Veterans, almost exclusively male (N = 523, 92%) with solid tumors had MOT during the study period. Lung (N = 211, 37%), GI (N = 105, 21%), prostate (N = 49, 9%), pancreatobiliary (N = 46, 8%), head and neck cancers (N = 35, 6%) and GU (N = 30, 5%) were most common with a median overall survival (OS) of 15.93 months. Potential actionable mutations were present in 107 (18.7%) tumors, however only 41 (38%) of the mutations were associated with an FDA approved targeted therapy at the time of testing. Six Veterans (5.6%) received targeted therapy. Reasons for not receiving targeted therapy included secondary mutations (*i.e.*, KRAS), ECOG performance status, hospice or community care and death. Veterans with potentially actionable mutations had significantly worse. **Conclusions:** In the VANTXHCS Veteran population males with lung cancer represents the main tumor type with molecular oncology testing. We observe actionable mutations in nearly 20% of patients tested, with only a minor subset receiving targeted therapy. Our data showed that patients with a potentially actionable mutation have worse overall survival than those that do not. However, treatment with a targeted therapy can significantly improve survival. In conclusion, these findings underscore the need for further research to identify barriers to increase appropriate use of targeted therapies in a timely fashion to improve patient outcomes and advance precision oncology practices. Research Sponsor: None.

3069 Poster Session

Phase 2 multicenter clinical trial to evaluate the safety and efficacy of abenacianine for injection (VGT-309), a tumor-targeted, intraoperative molecular imaging agent, for patients undergoing surgery for cancer in the lung.

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Background: Molecular targeted agents have revolutionized cancer diagnosis and treatment. Intraoperative molecular imaging (IMI) is a novel technique that entails performing real-time, in vivo optical imaging during surgery to ensure cancer clearance. A multicenter clinical trial was conducted using abenacianine, a cathepsin targeted near-infrared (NIR) IMI agent to visualize pulmonary nodules during surgery. The primary objective was to assess the efficacy of abenacianine in localizing pulmonary lesions, evaluating surgical margin, and identifying unsuspected disease. **Methods:** Participants scheduled to undergo surgery for known or suspected cancer in the lung received abenacianine (0.32 mg/kg intravenous) preoperatively 12 to 36 hours before surgery. During a standard-of-care surgery, the lung underwent IMI and additional disease not identified by conventional methods were identified and analyzed. Efficacy was measured by frequency of clinically significant events (CSEs) defined as localization of lesions not found by standard surgical techniques, identification of additional cancers, identification of positive surgical margins confirmed by histology, and detection of cancerous lymph nodes. **Results:** 89 participants were included in the study. The mean age was 67 years and 57 (64%) were female. Of 89 participants administered abenacianine who underwent standard of care surgical resection for known or suspected cancer in the lung, 40 (45%) had at least one CSE. Abenacianine with NIR imaging identified lesions that were not found by standard surgical methods in 34 (38%) participants, synchronous and occult cancers that were not found by pre-operative imaging in 2 (2%), margins within 10 mm of the closest staple line in 8 (9%), and lymph nodes determined to be cancerous in 1 (1%) participant. Tumors visualized by IMI with abenacianine included non-small cell lung cancers (adenocarcinoma, squamous cell carcinoma, neuroendocrine tumor) and cancers that metastasized to the lung (breast, colorectal, prostate, thymoma, renal cell, sarcoma). Abenacianine was safe and well tolerated in this study; there were no drug-related serious adverse events. **Conclusions:** This Phase 2 multicenter study demonstrated that using IMI with abenacianine during standard-of-care lung cancer surgery markedly improved clinical outcomes. Abenacianine localized tumors intraoperatively, identified synchronous and occult lesions, helped assess negative margin status, and identified cancerous lymph nodes enabling a more complete oncologic resection. Clinical trial information: NCT06145048. Research Sponsor: Vergent Bioscience, Inc.; Vergent Bioscience Australia Pty Ltd.

Analysing the impact of size of NGS panel in defining first line therapeutic strategies in NSCLC.

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Background: NCCN recommends the analysis of 8 genes (EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, ERBB2, and NTRK1/2/3) for NSCLC patients to identify efficacious target therapies. Concerned with the rising incidence of sub-optimal response to first-line therapy and rather early progression of disease we performed retrospective analysis in a subset of patients treated at our hospital in order to streamline molecular evaluation strategies. **Methods:** In this study, we retrospectively evaluated the impact of NGS panel sizes in therapy-naïve NSCLC patients. 242 therapy naïve patients evaluated for molecular genetic profiling were stratified into three groups based on gene panel size: a) Small panel (<20 genes): Focused on NCCN-recommended genes, b) Medium panel (50–100 genes): Included organ agnostic genes, c) Comprehensive panel (>100 genes): Included genomic signatures like TMB, MSI & HRD scores. **Results:** Of 242 therapy-naïve NSCLC patients, 60% (145/242) were evaluated using a small panel of which 13% (19/145) had no detectable genetic alterations while 37% (54/145) had 1st line targetable mutations, 31% (45/145) exhibited both targetable and resistance causing mutations, and 19% (28/145) showed only resistance causing mutations. In the 50–100 genes Panel, comprising 29% (70/242) of patients, 10% (7/70) had no genetic alterations, while 26% (18/70) had 1st line targetable mutations, 30% (21/70) demonstrated both targetable and resistance mutations, and 34% (24/70) harboured only resistance causing mutations. Finally, in the comprehensive NGS group (>100 genes), which accounted for 11% (25/242) of cases, only 4% (1/25) lacked detectable genetic alterations; while, 12% (3/25) had 1st line targetable mutations, 32% (8/25) exhibited both targetable and resistance causing mutations, and 52% (13/25) showed only resistance causing mutations. **Conclusions:** a. Increase in gene panel size results in reduction of true negatives. Hence smaller panels may not necessarily capture resistance causing mutations. b. As the gene panel size increases, the detection of actionable driver mutations (e.g., EGFR, ALK) remains consistent; however, there is a notable shift in the mutation profile, with a decrease in cases harbouring only targetable mutations and an increase in those exhibiting both actionable and resistance causing mutations. Hence opting for comprehensive NGS profiling at baseline may increase diagnostic costs marginally, but will have significant impact in designing more effective 1st line therapeutic strategies. Research Sponsor: None.

Evaluation of ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT for the primary staging of non-small cell lung cancer (NSCLC).

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Background: Fibroblast activation protein inhibitor (FAPI) radiolabeled with Gallium-68 or Fluorine-18 have emerged as promising tracers for targeting cancer-associated fibroblasts (CAFs) within the tumor microenvironment. Previous studies in lung cancer demonstrated that FAPI PET/CT is more sensitive in detecting metastases in the brain, lymph nodes, pleura, and bone. This study aimed to evaluate the clinical utility of FAPI PET/CT compared to FDG PET/CT for the primary staging of newly diagnosed NSCLC patients. **Methods:** This prospective study was done at Amrita Institute of Medical Sciences, Kochi between August 2022 to December 2023 among patients with newly diagnosed NSCLC who consented to undergo both scanning i.e. FDG as well as FAPI PET CT before initiating any treatment. This study was approved by institutional review board. Kolmogorov Smirnov one sample test was used to check the normality of data. To test the statistical significance of the difference in the average values of tumor volume, standardized uptake value (SUV), target to background ratio (TBR) and background uptake between FAPI and FDG, paired sample t test was used for normality and Wilcoxon signed rank test was used for non-normality. **Results:** In this study, 42 patients with newly diagnosed NSCLC (32 with adenocarcinoma (AC) and 10 with squamous cell carcinoma (SCC)) were included. Comparison of the results between FAPI and FDG PET in parameters like TBR, SUVmax and background value in metastatic lesions, FAPI performed better. In case of lymph nodes FAPI vs FDG, mean TBR was (5.06 ± 4.19 v/s 3.02 ± 2.89) p value=0.002 and in SUVmax value was (9.07 ± 5.1 v/s 6.59 ± 4.2) p value=0.01. Similar benefits were seen in TBR and SUVmax with FAPI on metastatic site like pleura and bone. In the primary lung lesion, mean tumour volume (MTV) was larger with FAPI but there was no difference in SUVmax, TBR and back ground uptake value. If we compare AC vs SCC cases, there was no advantage for SCC with FAPI in metastatic lesions as well as primary lesions. Driver mutated AC cases performed extremely well with FAPI. In brain, mean SUV max with FAPI was 4.52 ± 0.89 compared to 8.45 ± 3.31 with FDG. But the brain lesions identified with FAPI were higher than FDG due to higher TBR. In liver, SUV max was similar between FAPI and FDG but higher TBR was seen with FAPI. **Conclusions:** ^{68}Ga-FAPI PET/CT performed better than ^{18}F-FDG PET/CT in the primary staging of NSCLC. FAPI PET may be considered instead of FDG PET in staging of NSCLC. Patient compliance was also better because fasting and glycemic control was not required prior to FAPI. This is the only study where histology (AC and SCC) has been directly compared with both FAPI/PET vs FDG/PET – it shows FAPI/PET performs better with AC, and this South East Asian study showed FAPI/PET performs better with driver mutated NSCLC. Research Sponsor: None.

Clinical utility of comprehensive transcriptome testing in advanced solid tumors.

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Background: Despite breakthroughs in genomically-matched therapies, many patients lack actionable genomic alterations. Consequently, innovative new strategies to identify targets for effective therapies are imperative. To assess the potential of comprehensive whole transcriptomic sequencing (WTS) in clinical decision-making, we conducted a prospective trial to perform WTS in patients with metastatic or advanced solid tumors who had prior DNA-based panel testing (≥100 genes) with no reported AMP/ASCO/CAP Tier 1 actionable genomic alterations; along with whole exome sequencing (WES) to compare RNA expression to copy number alterations. We also developed an informed actionability classification scheme to determine actionability of transcriptomics findings. **Methods:** Between August 2022 and December 2024, 100 patients at MD Anderson Cancer Center with advanced cancers were enrolled and underwent comprehensive profiling. Alterations in RNA expression of 147 genes were considered as potentially actionable if the gene's protein product is the direct target of a clinically available therapy (including cell surface targets of antibody-drug conjugates (ADCs)) and/or CNAs of the gene are predictive of response or resistance to a clinically available therapy. A clinical trial was considered a match if RNA expression was an enrollment criterion, or the gene alteration can be directly or indirectly targeted with a therapy utilized within the trial. **Results:** Actionable RNA expressions (AREs) were detected in all patients (100%). In total, 2,216 AREs were detected from 17,800 selected-reported RNA expressions; a median of 22 ARE changes were reported per patient [interquartile range (IQR), 17.0-26.0]. The majority (86.0%) of AREs were RNA overexpressions, defined as the distribution of *tpm* values of the gene expression > 83% of the pan-cancer reference cohort. A median of 13 RNA expression-matched trials were identified per patient [IQR, 10.0-16.0]. The most frequent drug class of actionable RNA overexpressions were ADCs, with a median of 10 ADC targets per patient. Out of 11 distinct genes of which at least 1 amplification is reported, a concordance rate of 61.5% and a Concordance Correlation Coefficient (CCC) value of 0.70 (95% CI, 0.56-0.84) between the actionable gene amplifications (n = 13) and the actionable RNA overexpressions detected in the same patient sample from the tumor profile, indicates a substantial concordance by transcriptional profiling with copy number gain. **Conclusions:** WTS identified actionable RNA expressions in all patients– including for novel ADC targets. These results underscore the utility of comprehensive transcriptional profiling to identify additional actionable targets beyond DNA-based comprehensive profiling. Clinical trial information: MDACC 2021-1049. Research Sponsor: Strategic Alliance: BostonGene–MD Anderson Cancer Center Feasibility and Clinical Utility of Combined Genomics/ Transcriptomics with Systems Biology for Personalized Cancer Therapy; MD Anderson Cancer Center Support grant; Center for Clinical and Translational Science.

Application of an epigenomic-based classifier to identify cancer signal of origin on liquid biopsy in cancer of unknown primary cases.

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Background: Cancer of unknown primary (CUP) lacking resolution to a cancer type (Cancer Signal Origin; CSO) leads to suboptimal outcomes. While several approaches currently exist for identifying a cancer type for CUP samples, they rely on clinical approaches that often require tissue biopsies for immunohistochemistry (IHC), and even still they often fail to resolve a CSO (reported to occur in 50-80% clinical cases). This requirement for tissue, and typically lengthy diagnostic journey, create a large unmet need for CSO identification in CUP individuals. Here, we present feasibility data from a high accuracy Liquid Biopsy method for CSO identification in CUP, bypassing the need for a tissue biopsy and quickly returning a CSO to individuals with CUP. **Methods:** We developed a CSO prediction algorithm on Guardant360 utilizing DNA methylation signatures across thousands of cancer-specific differentially methylated regions for 14 cancer types. We applied the CSO classifier to 1,128 CUP samples in which circulating tumor DNA was detected. Accuracy was assessed by comparing CSO predictions to suspected diagnoses based on clinicopathologic and molecular findings. **Results:** The CSO prediction algorithm was evaluated on 1,128 CUP samples; lung (285/1128, 25.3%) and bile duct (166/1128, 14.7%) were the most common predicted CSOs, aligning with reported prevalence in the literature. Of the 1,128 samples, 12 had a suspected clinical diagnosis. These 12 spanned 8 tumor types. The top CSO prediction aligned with suspected diagnosis in 91.6% (11/12) of cases. The CSO algorithm also provides confidence scores to quantify the confidence of CSO prediction. Out of the total 12 cases, 7 CSOs had high confidence, 3 had moderate confidence, and 2 had low confidence. 7/7 high, 2/3 moderate, and 2/2 low confidence predictions were correct. The single incorrect moderate sample was diagnosed as CRC but predicted to be lung. **Conclusions:** These findings show the feasibility of using plasma-based epigenomic profiling to assign CSO with acceptable accuracy. While interventional clinical studies are necessary to demonstrate clinical utility, this has significant potential for guiding treatment decisions and improving outcomes in CUP patients without ready access to tissue. Research Sponsor: Guardant Health, Inc.

HRD status prediction in patients with advanced breast, prostate, ovarian and pancreatic cancers in a liquid biopsy assay.

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Background: Homologous recombination and repair (HRR) deficiency (HRD) is characterized by genomic instability associated with mutations in BRCA1/2 or other HRR genes. HRD can also be detected by copy number variant (CNV) features, indels, and SNVs (HRD signature). Patients with canonical BRCA-associated cancers harboring an HRD signature with or without HRR mutations derive clinical benefit from PARPi therapy. Here, we present a method of predicting HRD status using Guardant Infinity in patients with these advanced cancers. **Methods:** We developed an ensemble logistic regression model to predict HRD status, inferred from genome-wide somatic SNV and CNV signatures indicative of deficiency in HRR genes, including ploidy-adjusted large-scale state transitions (LST), whole-genome tumor loss of heterozygosity (LOH) and telomeric allelic imbalance (TAI). The model was trained on clinical samples processed on Guardant Infinity, a next-generation platform evaluating both genomics and epigenomics, to assess the sensitivity and accuracy of detecting biallelic loss-of-function in BRCA1/2. The aggregated model was tested on an independent pan-tumor clinical cohort and pre-treatment samples from a subset of patients enrolled in TRITON2, a phase 2 single arm study evaluating rucaparib in metastatic castration resistant prostate cancer (mCRPC) patients with HRR mutations. HRD status association with radiographic progression free survival (rPFS) was evaluated with Cox-proportional hazards model. **Results:** Our model demonstrated high sensitivity in patients with BRCA1/2 biallelic loss and high specificity in HRR-wildtype patients, with an AUC of 0.95 in a pan-tumor cohort with tumor fraction (TF) >10%. In an independent cohort of breast prostate ovarian and pancreatic samples, HRD detection ranged from 79-100% in samples with BRCA1/2 biallelic loss and >10% TF. In breast (n = 703) and prostate (n = 655) cancers, HRD was detected in 14.9% and 13.5% of samples with > 10% TF (3.6% and 3.7% in all TF), with 5.5% and 6.2% attributed to samples not harboring deleterious mutations in HRR genes, respectively, potentially reflecting non-genomic drivers of HRD. In a pilot cohort (n = 15) from TRITON2, HRD was detected in 100% of patients enrolled with either BRCA1/2, or PALB2 mutations (n = 10), where rucaparib demonstrated meaningful activity as measured by independent radiology review objective response rate. HRD was not detected in patients with mutations in CDK12, FANCA, or NBN (n= 5). HRD detected status was associated with prolonged rPFS (HR = 0.07, p = 0.03). **Conclusions:** Guardant Infinity can predict HRD status in patients with advanced canonical BRCA-associated cancers, with preliminary results indicating potential for predicting PARPi benefit in mCRPC. Further studies are warranted to determine PARPi response for breast, prostate, ovarian, and pancreatic cancers with detected HRD status. Research Sponsor: None.

Efficacy and safety of distinct regimens for individuals with advanced EGFR-mutated non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitors: A systematic review and network meta-analysis.

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Background: Targeted therapy with EGFR tyrosine-kinase inhibitors (TKIs) is the preferred first-line treatment for EGFR-mutated advanced non-small cell lung cancer (NSCLC), but acquired resistance inevitably occurs in almost all responding individuals. We aimed to comprehensively review the literature to investigate the efficacy and safety of distinct regimens in the subsequent-line setting, thereby identifying the optimal regimen for these TKI-resistant NSCLC patients. **Methods:** The PubMed, Embase, Cochrane Library databases, and abstracts of ASCO, ESMO, and WCLC were searched from database inception to 3 November 2024, to identify eligible randomized controlled trials (RCTs) that assessed distinct regimens for individuals with advanced EGFR-mutated NSCLC who progressed on TKIs. The outcomes of progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and grade 3 or higher adverse events (≥3AEs) were compared and ranked in overall patients and various subgroups among 8 regimens by network meta-analysis and the surface under the cumulative ranking curve, respectively. The protocol is registered with PROSPERO, CRD42024601619. **Results:** 14 RCTs, involving 3177 participants and 8 treatment regimens (chemotherapy plus ivonescimab (PD-1/VEGF inhibitor) [CT+IVO]; CT+amivantamab+lazertinib [CT+AMI+LAZ], CT+immunotherapy+bevacizumab [CT+IO+BEV], CT+AMI, CT+BEV, CT+IO, CT, and IO), were included. In overall patients, the most pronounced PFS benefit was observed with the CT+IVO, followed by CT+AMI+LAZ, CT+IO+BEV, and CT+AMI, ranked second, third, and fourth, respectively. In terms of OS, the regimen of CT+AMI ranked the best, followed by CT+IVO. However, the comparisons of OS among different regimens did not reach statistical significance, possibly due to immature data. The results for ORR and DCR were similar to those for OS, with CT+AMI topping the rankings, followed by CT+AMI+LAZ. In terms of safety, the incidence of ≥3AEs was highest in CT+AMI+LAZ, followed by CT+AMI. In subgroup analysis, CT+IVO demonstrates stable PFS benefits across clinicopathological characteristics, ranking first in most subgroups. Due to the unavailability of OS subgroup data in most RCTs, many regimens were missing in the OS subgroup analysis. **Conclusions:** Integrating the results of different clinical outcomes and subgroup analyses, we conclude that CT+IVO is the optimal treatment option with an acceptable safety profile for patients with advanced EGFR-mutated NSCLC who have progressed on TKIs. CT+AMI+LAZ and CT+AMI are alternative subsequent line options as well, with superior efficacy compared to immunotherapy-based or chemotherapy regimens, yet elevated toxicity profiles requiring vigilant management. Research Sponsor: None.

Preliminary results of a first-in-human phase 1b (aCCeleR8-001) study of S-531011, a humanized anti-CCR8 monoclonal antibody, in patients with advanced solid tumors.

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Background: C-C motif chemokine receptor 8 (CCR8) is selectively upregulated in tumor-infiltrating regulatory T cells (TI-Tregs) in multiple cancers, inhibiting anti-tumor activity of the host immune system. S-531011, a humanized IgG1 monoclonal antibody, is anticipated to deplete CCR8-positive TI-Tregs, restoring anti-tumor immunity without inducing auto-immunity. **Methods:** An aCCeleR8-001 study is a Phase 1b/2, multicenter, open-label study of S-531011 which consists of Phase 1b Dose Escalation part (Parts A-1 and A-2) and Phase 2 Dose Expansion part. The safety/tolerability, pharmacokinetic (PK), pharmacodynamic, and anti-tumor activity of S-531011 as monotherapy and in combination with pembrolizumab (Merck & Co., Inc.) were evaluated in patients with various types of locally advanced or metastatic solid tumors. S-531011 monotherapy was administered at 8, 24, 80, 240, 800, or 1600 mg/kg intravenously every 3 weeks (Q3W) in Part A-1, whereas patients in Part A-2 received S-531011 at 80, 240, 800, or 1600 mg/kg in combination with pembrolizumab 200 mg/kg Q3W. The data were analyzed when all patients in Dose Escalation cohorts completed the dose-limiting toxicity (DLT) observation period. **Results:** As of the data cutoff date (30 Sep 2024), 40 and 35 patients were enrolled in Parts A-1 and A-2, respectively. No DLTs were reported at any dose level and the maximum administered dose of S-531011 was 1600 mg in both parts. One patient reported an infusion-related reaction in Part A. Immune-related adverse events (irAEs) were reported in two patients (5.0%; Grade 1/2 only) in Part A-1, whereas 15 irAEs were reported in 10 patients (28.6%; including four Grade 3 irAEs in four patients) in Part A-2. PK of S-531011 was approximately dose proportional with a terminal elimination half-life of 10 to 12 days regardless of dose level. CCR8 receptors in PBMCs were occupied at doses of 80 mg or higher. PK/CCR8 receptor occupancy modeling analysis indicated that $>$ 90% of receptors in tumor tissues were occupied in the range of 80 to 800 mg. Multiplex immunohistochemistry analysis demonstrated proof of mechanism as evidenced by CCR8-positive Treg depletion in tumor tissue at doses of 24 mg or higher. Among 62 evaluable patients dosed at 80 to 1600 mg in Part A, four patients (6.5%) had confirmed partial response, three of whom had colorectal cancer (CRC). Twenty patients (32.3%) had disease control for $\geq$ 6 weeks. Response rate was not correlated with dose (80 to 1600 mg). Following a comprehensive data review, tentative recommended Phase 2 doses were determined to be 80 to 800 mg in both parts. **Conclusions:** S-531011 was well tolerated up to 1600 mg as monotherapy and in combination with pembrolizumab. A higher response rate in patients with CRC warrants further exploration of this tumor type in Phase 2 Dose Expansion part. Phase 2 CRC cohorts are currently ongoing. Clinical trial information: NCT05101070. Research Sponsor: Shionogi & Co., Ltd.

First report of ROR2 directed therapy with a conditionally active antibody drug conjugate in advanced melanoma.

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Background: The receptor tyrosine-kinase like orphan receptors (ROR) are mediators of noncanonical WNT signaling and tissue patterning. ROR2 upregulation is observed in malignancy and has been implicated in metastasis. Development of ROR2 directed conditionally active antibodies with enhanced affinity in the tumor microenvironment is a promising treatment strategy. Here we report our institution's experience treating 5 patients with advanced cutaneous or uveal melanoma treated with the anti-ROR2 antibody drug conjugate ozuriftamab vedotin (MMAE) on the first in human phase 1 trial. (NCT03504488). **Methods:** Adults with advanced solid tumors naïve to vinca binding site therapies who had failed all standard of care therapy were eligible. The charts of all 5 patients with advanced melanoma treated at our institution were reviewed. Patients were treated with ozuriftamab vedotin at concentrations of 1.8 mg/kg or 3.0 mg/kg IV Q2W. Safety and efficacy data were collected. Patient samples were evaluated for pharmacokinetics and clinical correlates. **Results:** 4 out of the 5 patients achieved an objective response in target lesions, per RECIST v1.1 (Table 1). Two of these patients have maintained disease control, including one patient in complete remission (CR) >5 years and the other responding >1 year after starting treatment. Adverse events requiring dose reduction or interruption included neuropathy and neutropenia, both of which recovered with reduced dosing and/or colony stimulating factor. No patients discontinued therapy for adverse drug reactions. Pharmacokinetics showed predictable plasma concentrations of both drug and free MMAE. Anti-drug antibodies were not identified. Biopsies were assessed by IHC for ROR2. The biopsy belonging to the patient who achieved CR was strongly positive for ROR2. All other biopsies showed low/negative ROR2 staining of malignant cells. **Conclusions:** Ozuriftamab vedotin showed early promising antitumor activity in this first report describing ROR2 directed treatment in refractory advanced cutaneous and uveal melanoma. Clinical trial information: NCT03504488. Research Sponsor: None.

Efficacy and safety of ozuriftamab vedotin.

	Case 1	Case 2	Case 3	Case 4	Case 5
Melanoma Subtype	Uveal	Uveal	Cutaneous	Cutaneous	Cutaneous
Initial Dose (mg/kg)	1.8	1.8	3.0	1.8	1.8
Final Dose (mg/kg)	1.5	1.5	1.8	1.8	1.8
Best Target Lesion Response	10% increase	31.9% decrease (PR)	89% decrease (CR, w/ lymph nodes < 5 mm)	38.2% decrease (PR)	43.7% decrease (PR)
Time to Progressive Disease (days)	35	+475*	+2079*	127	84
Major Adverse Events	G3 Neutropenia	G2 Neuropathy	G2 Neuropathy, G4 Neutropenia	None	None
Other Adverse Events	G2 Transaminitis, G2 Myalgia, G2 Arthralgia	None	G1 Salivary Inflammation, G1 Alopecia	G2 Neuropathy	G2 Neuropathy

*Patient has not developed progressive disease since starting treatment.

Glutaminase isoform expression in cancer: Implications for metabolic adaptation and therapy.

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Background: Glutamine is a critical amino acid involved in various metabolic pathways, particularly in cancers where its importation is significantly elevated via multiple transporters. Glutaminase, the enzyme catalyzing the deamination of glutamine to glutamate, has two isoforms: kidney-glutaminase 1 (GLS1) and liver-glutaminase 2 (GLS2). This study investigates the expression of glutaminase isoforms in cancers originating from tissues with high glutaminase activity—namely, clear renal cell carcinoma (KIRC), chromophobe renal carcinoma (KICH), papillary renal carcinoma (KIRP), hepatocellular carcinoma (LIHC), and glioblastoma (GBM)—to understand the fate of the imported glutamine. **Methods:** The Cancer Genome Atlas (TCGA), Tumor Immune Estimation Resource ([TIMER] 2.0), Gene Expression Profiling Interactive Analysis ([GEPIA] 2.0), and the University of Alabama at Birmingham Cancer Data Analysis ([UALCAN]) Portal were used to investigate GLS1 and GLS2 expression. TIMER 2.0 analyzed 533 KIRC (72 normal), 66 KICH (25 normal), 290 KIRP (32 normal), 153 GBM (5 normal), and 371 LIHC (50 normal) samples. GEPIA 2.0 analyzed 523 KIRC (100 normal), 66 KICH (53 normal), 286 KIRP (60 normal), 163 GBM (207 normal), and 369 LIHC (160 normal). UALCAN analyzed 533 KIRC (72 normal), 66 KICH (25 normal), 290 KIRP (32 normal), 153 GBM (5 normal), and 371 LIHC (50 normal) samples. Additionally, datasets from NCBI GEO were used, including GSE15641 (23 normal, 32 KIRC, 6 KICH, and 12 KIRP), GSE7696 (4 normal, 40 GBM), and GSE41804 (20 normal, 20 LIHC). These platforms detected GLS1 expression in KIRC, KICH, KIRP, and GBM and GLS2 in LIHC by comparing tumor and normal samples. **Results:** GLS1 was significantly downregulated in KIRC, KICH, KIRP, and GBM across TIMER 2.0, GEPIA 2.0, and UALCAN ($P < 0.05$). GLS2 was also significantly downregulated in LIHC ($P < 0.05$). NCBI GEO datasets (GSE15641 for kidney cancers, GSE7696 for GBM, and GSE41804 for LIHC) supported these results, showing consistent GLS1 downregulation in KIRC, KICH, KIRP, and GBM, and GLS2 downregulation in LIHC (adjusted $P < 0.05$; $|Log2FC| > 1$). **Conclusions:** The tissue-specific downregulation of glutaminase isoforms—GLS1 in kidney and brain cancers, GLS2 in liver cancer—highlights an adaptive mechanism in cancer cells to limit glutamine deamination and preserve imported glutamine for other metabolic needs. Enhancing the deamination process could deprive cancer cells of essential precursors for nucleotide synthesis, disrupting their growth and survival. These isoforms represent potential diagnostic markers and therapeutic targets. Research Sponsor: None.

3079 Poster Session

A phase 1 study of PARP inhibitor (niraparib) plus HSP90 inhibitor (pimitespib) in solid tumors: Dose-expansion results from the NiraPim (EPOC2102) study.

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Background: Heat shock protein 90 (HSP90) inhibitors have shown potential in destabilizing homologous recombination repair (HRR) proteins, thereby inducing homologous recombination deficiency and enhancing PARP inhibitor efficacy. The NiraPim (EPOC2102) study is a phase 1 study to evaluate this combination therapy in humans, investigating the safety and efficacy of combining niraparib, a PARP inhibitor, with pimitespib, a novel HSP90 inhibitor, in patients with advanced solid tumors. Following establishing the recommended dose (RD) in the dose-escalation part, we present primary analysis results from the dose-expansion part. **Methods:** In the dose-expansion part, patients received pimitespib 80 mg (5-day on/2-day off) combined with niraparib 200 mg daily. Cohort A included patients with BRCA-associated cancers (breast, ovarian, prostate, and pancreatic) harboring *BRCA* pathogenic variants and immediately after progression to prior PARP inhibitors. Cohort B included patients with breast/pancreatic cancer without g*BRCA*, prostate cancer without t*BRCA*, and other solid tumors (excluding ovarian cancer) not previously treated with PARP inhibitors. **Results:** As of August 2024, 30 patients were enrolled: 14 in cohort A and 16 in cohort B. Cohort A included breast (n=6), ovarian (n=5), prostate (n=2), and pancreatic (n=1) cancers. Cohort B included breast (n=3), prostate (n=4), pancreatic (n=4), and other tumors (n=5). The median follow-up period was 6.0 months. The median treatment cycle was 2 (range 1–18). Treatment-related adverse events ≥Grade 3 occurred in 33.3%. Common adverse events (≥20.0%) included nausea (73.3%), diarrhea (40.0%), anorexia (23.3%), vomiting (20.0%), fatigue (20.0%), and decreased platelet count (20.0%). No treatment-related deaths occurred during the study period. The objective response rate was 10.0% (95% CI: 2.1, 26.5), with disease control rate of 36.7% (19.9, 56.1) and 3-month PFS of 27.7%. In cohort A, one patient with hormone receptor-positive breast cancer achieved partial response post-olaparib progression. In cohort B, two patients (leiomyosarcoma and urothelial carcinoma) with *BRCA* pathogenic variants achieved partial response, and one prostate cancer patient with *CDK12* pathogenic variant maintained stable disease ≥3 months. **Conclusions:** The dose-expansion part demonstrated a manageable safety profile and potential efficacy at the recommended dose of niraparib plus pimitespib. Clinical benefit was observed in both BRCA-associated cancers resistant to PARP inhibitors and PARP inhibitor-naive non-BRCA associated cancers, supporting further investigation in biomarker-selected populations. Clinical trial information: jRCT2031220179. Research Sponsor: Takeda Pharmaceutical Co., Ltd.; Taiho Pharmaceutical Co., Ltd.

Development and validation of an AI-enabled prediction of prostate cancer (PCa) using urine-based liquid biopsy.

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Background: Prostate cancer (PCa) remains a major cause of malignancy-related mortality among men. Current diagnostic techniques, including PSA testing, lack accurate early detection capabilities, while global barriers include limited access to specialized facilities and cultural sensitivities around transrectal biopsy and digital rectal examination. This study evaluates a non-invasive, urine-based liquid biopsy assay for diagnosing PCa through disease-specific biochemical profiles using an artificial intelligence pipeline. **Methods:** We collected urine from men scheduled for prostate biopsy (biopsy-positive PCa n=197) and healthy controls (n=84). Samples were processed using NUTEC slides, underwent heat cycling, and were converted to digital images for AI analysis. Using 5x2 cross-validation with a random forest classifier, we evaluated cancer detection performance and analyzed cohorts with specific Gleason scores (Gle): Gle 6 (n=70), Gle 7 (3+4) (n=55), Gle 7 (4+3) (n=34), and Gle 8,9,10 (n=38). **Results:** Our classifier demonstrated strong overall performance in distinguishing cancer versus non-cancer subjects (F1=0.843) with notably high recall (R=0.967). Importantly, performance remained robust across Gleason score cohorts (F1=0.799-0.838), maintaining high recall (R>0.89) while preserving clinically relevant precision. The classifier showed particular strength in detecting intermediate- (Gle 7 (3+4): F1=0.838) and low- (Gle 6: F1=0.822) Gleason grade cancers. **Conclusions:** AI-enabled prediction of PCa using urine-based liquid biopsy demonstrates accurate, rapid, and accessible early cancer detection, with consistent performance across disease grades. This non-invasive approach addresses both clinical and cultural barriers to prostate cancer diagnostics. Research Sponsor: None.

TASK	F1	P	R	AUC	ACC
Cancer v. Controls	0.843	0.748	0.967	0.768	0.748
Gle6 v. Controls	0.822	0.770	0.893	0.776	0.746
Gle347 v. Controls	0.838	0.757	0.940	0.752	0.754
Gle437 v. Controls	0.800	0.715	0.913	0.695	0.691
Gle8910 v. Controls	0.799	0.722	0.900	0.695	0.698

AI-enabled prediction of PCa using urine-based liquid biopsy demonstrates accurate, rapid, and accessible early cancer detection, with consistent performance across disease grades. This non-invasive approach addresses both clinical and cultural barriers to prostate cancer screening.

Genomic landscape of 5'methylthioadenosine phosphorylase (*MTAP*) deleted (*MTAP* loss) non-squamous carcinoma of unknown primary site (nsCUP).

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Background: *MTAP*, a key enzyme in the polyamine pathway breaks down 5'Deoxy-5-Methylthioadenosine (*MTA*) into methionine and adenine. *MTAP* loss reduces adenine and accumulates MTA, which inhibits protein arginine methyltransferase 5 (*PRMT5*). This suggests *MTAP* loss cancers may respond to *PRMT5* inhibition. Methionine adenosyl transferase 2α (*MAT-2A*) is a primary producer of donor S-adenosylmethionine (*SAM*) and the depletion of *MAT-2A* has antiproliferative effect in cancers with *MTAP* loss. Based on the synthetic lethality concept, *MTAP* loss is being used as a biomarker for accrual in multiple trials with *PRMT5* and *MAT-2A* inhibitors. We queried the genomic landscape of *MTAP* loss in patients with nsCUP. **Methods:** DNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue of 7,440 nsCUP cases from 2020 to 2024 underwent hybrid capture-based comprehensive genomic profiling (CGP) to assess all classes of genomic alterations (GA). All cases underwent central pathology review to confirm that at the time of sequencing, a primary site for the cases was not established. Microsatellite instability (MSI) status and tumor mutational burden (TMB) were derived from the CGP data. Programmed death-ligand 1 (PD-L1) was determined by immunohistochemistry (IHC) using the DAKO 22C3 system. **Results:** 853 (11.5%) of nsCUP cases had either complete or partial *MTAP* loss with 0.7% 1 exon, 1.2% 2 exons, 2.9% 3 exons, 5.1% 4 exons, 0.5% 5 exons, 2.5% 6 exons, 32.8% 7 exons and 54.3% 8 exons lost. The median age of the *MTAP* loss patients was higher (68 vs 65; $p<.0001$) and the gender distributions were similar (52% to 54% female; not significant (NS)). Cyclin-dependent kinase inhibitor 2A (CDKN2A) loss co-occurred in 99.8% in patients with *MTAP* loss. MSI-high status was uncommon in both *MTAP* loss vs *MTAP* wildtype (0.4% vs 0.7%; NS). The *MTAP* wildtype group had higher tumor mutational burden (TMB) > 10 mutations/mb (15.7% vs 11.1%; p=.0004) and TMB >20 mutations/Mb (5.4% vs 3.5%; p=.017) rates. *MTAP* loss nsCUPs had higher frequencies of *KRAS* GA and *KRAS* G12C, whereas *MTAP* wildtype cases had greater frequencies of *ERBB2*, *PTEN*, *MET* and *EGFR* GA (Table). GA in *BRCA1/2* and *FGFR2* were similar in both groups. GA in *ALK*, *RET*, *ROS1*, *RET* and *TRK* were extremely uncommon in both groups (all less than 1%). **Conclusions:** At 11.5%, nsCUP features a relatively high frequency of *MTAP* loss, with the vast majority involving either all (8 of 8) or nearly all (7 of 8) exons. *MTAP* loss patients are slightly older and have reduced TMB levels which may impact their responsiveness to immunotherapy-based combination regimens with *PRMT5/MAT-2A* inhibitors. Clinical trials for the development of targeted therapies to use *PRMT5* inhibition and *MAT-2A* in nsCUP are warranted. Research Sponsor: None.

	nsCUP *MTAP* Loss (N=853)	nsCUP *MTAP* wildtype (N=6,587)	P value
***KRAS* all/G12C**	45.9%/7.6%	31.2%/4.2%	<.0001/<.0001
***ERBB2* all/amp only**	6.7%/4.3%	10.9%/8.1%	<.0001/<.0001
PIK3CA	6.2%	7.1%	NS
BRAF	6.0%	5.0%	NS
FGFR2	4.3%	4.0%	NS
PTEN	4.1%	6.1%	.02
BRCA1/2	1.8%/2.3%	2.1%/2.4%	NS/NS
MET	2.1%	4.6%	.0004
EGFR	2.6%	4.1%	.031

Preliminary efficacy results from an ongoing phase I/II trial of CTS2190, a PRMT1 inhibitor, in patients with advanced/metastatic solid tumors.

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Background: Epigenetic gene regulation, including arginine methylation holds significant promise in immunomodulation and long survival outcomes. It represents a potential clinical approach to address the highly unmet needs of patients (pts) with advanced solid tumors who failed PD-(L)1 immune checkpoint inhibitors (ICIs) or standard of cares (SoCs) therapies. CTS2190, the orally available, first-in-class small molecule, specifically inhibits arginine methyltransferase 1 (PRMT1) with significant reduction of intra-tumor asymmetric dimethylarginine (ADMA) level, DNA damage response (DDR), androgen receptor (AR) level, and oncogenic proliferation through epigenetic modulation in various solid tumors. Here we present clinical data from an ongoing Phase I/II study of CTS2190 (NCT06224387). **Methods:** Eligible pts in the dose-escalation stage received 60~300 mg of CTS2190 orally, while pts in the dose-expansion stage were treated with 180 or 240 mg until disease progression or intolerable toxicity. Efficacy, safety, PK, PD and biomarker profiles were evaluated. **Results:** As of January 24, 2025, 38 pts had received CTS2190 treatment, 32 of them were response-evaluable. In the PD-(L)1 primarily resistant group, the objective response rate (ORR) and disease control rate (DCR) were 18.2% (2/11) and 72.7% (8/11), respectively. In addition, in PD-(L)1 primarily resistant non-small cell lung cancer (NSCLC) subgroup, the ORR and DCR were 28.6% (2/7) and 71.4% (5/7), respectively, with significantly prolonged median progression-free survival (PFS) (summarized in the table below). Among 2 response-evaluable pts with metastatic castration-resistant prostate cancer (mCRPC), one achieved partial response (PR) while the other exhibited stable disease (SD) with tumor shrinkage. Most treatment-related adverse events (TRAEs) were grade 1/2 and manageable. The only TRAE $\geq$ grade 3 with an incident rate $>$ 15% was platelet count decreased (31.6%). No TRAEs led to treatment discontinuation or death. CTS2190 exposure increased proportionally with escalating doses, and a PK-PD-efficacy model demonstrated a relationship between CTS2190 exposure, efficacy and PD marker changes. The correlation between clinical efficacy and intra-tumor PRMT1 expression, as detected by immunohistochemistry (IHC), is under investigation. **Conclusions:** CTS2190 demonstrated a favorable safety profile and promising efficacy in heavily pretreated pts with advanced solid tumors, particularly in immunologically cold mCRPC and PD-(L)1 primarily resistant NSCLC. These results position CTS2190 as a promising therapeutic option to fulfil unmet medical needs following ICIs therapies. Clinical trial information: NCT06224387. Research Sponsor: CytosinLab Therapeutics Co., Ltd.

PFS of pts with PD-(L)1 primary resistance.

	Patients, n	≥ 3 prior lines of therapy, n (%)	Event	Median PFS (weeks)
All comers	11	7 (63.6%)	7	12.7 (95% CI: 8.0~35.3)
NSCLC	7	4 (57.1%)	5	24.9 (95% CI: 8.0~35.3)

The first-in-human phase 1/2 study of TSN1611, a highly selective KRAS G12D inhibitor, in patients with advanced solid tumors.

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Background: TSN1611 is a novel small molecule KRAS G12D inhibitor targeting both active (GTP-bound) and inactive (GDP-bound) forms of KRAS G12D protein. TSN1611 showed high potency and selectivity against KRAS G12D mutant tumor cells in vitro and effectively inhibited tumor growth in several pancreatic ductal carcinoma (PDAC), colorectal cancer (CRC) and non-small cell lung cancer models (NSCLC) in vivo. **Methods:** A phase 1/2 study of TSN1611 was developed to enroll patients (pts) with advanced solid tumors harboring KRAS G12D mutation. The study comprised a phase 1a dose escalation part following a BOIN design with accelerated titration to determine the maximum tolerated dose (MTD), recommended phase 2 dose and pharmacokinetics (PK), followed by a phase 1b part for dose optimization to compare different recommended doses and a phase 2 part to evaluate the efficacy of TSN1611 across various tumor types. Alternative dose levels or regimens could be explored based on the emerging data. Pts received oral TSN1611 twice daily (BID), until disease progression, unacceptable toxicity, or patient withdrawal. Here we report the preliminary data from phase 1a part. **Results:** As of Jan 05, 2025, 18 pts received TSN1611 from 50 to 600 mg BID (9 with CRC, 5 PDAC, 2 NSCLC, and 1 each with ampullary cancer and gallbladder cancer, all with pre-identified KRAS G12D mutation). Median age was 61 years (range 36-81). The median prior lines of systemic therapy were 3 (range 1-6). No dose-limiting toxicity was reported and MTD was not reached. The most common ($\geq$ 10%) treatment related adverse events (TRAEs) were grade 1 or 2 vomiting (44.4%), nausea and diarrhea (38.9% each), fatigue (16.7%), ALT increased, blood CPK increased, hyperkalemia and hyperuricemia (11.1% each). No treatment related grade 3 or higher AE or SAE was reported. Four (30.8%) out of the 13 evaluable pts demonstrated stable disease per RECIST v1.1. Tumor reductions were observed in 3 pts (CRC, PDAC, and NSCLC, n = 1 each) at 200 or 400 mg BID, with treatment ongoing. Serial assessment of plasma ctDNA revealed declines in KRAS G12D variation allele frequency at 200 mg BID and above, echoing that the exposure at 200 mg BID reached that of ED_{90} in the CRC GP2D model. TSN1611 was rapidly absorbed with T_{max} around 2 hours and half-life around 15 hours. The PK profile indicated a general dose proportionality in exposure across the evaluated dose ranges and low to moderate accumulation after multiple BID dosing. Dose escalation is ongoing, and more data will be available at the conference presentation. **Conclusions:** TSN1611 was well tolerated, demonstrating acceptable PK characteristics as predicted, with preliminary tumor shrinkage observed in pts with refractory KRAS G12D mutant tumors. Phase 1b/2 studies are planned to evaluate TSN1611 both as a monotherapy and in combination with standard of care and/or novel agents treating cancer. Clinical trial information: NCT06385925. Research Sponsor: Tyligand Pharmaceuticals (Suzhou) Limited.

Artificial intelligence (AI)-powered evaluation of protein drug-targetability through subcellular-level expression profiling from immunohistochemistry (IHC) images.

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Background: As a standardized methodology for quantifying the targetability of proteins in drug development has yet to be established, we developed an AI-powered analyzer capable of scalably measuring cellular and subcellular-level expression to assess 74 membrane-specific targets in development. **Methods:** A total of 160K cancer and normal IHC images from Human Protein Atlas (HPA) were analyzed, including 47,591 on 74 target genes. The AI model trained on pathologist-annotated histology images, took the IHC images as input to predict cell types and subcellular compartments (nucleus, cytoplasm, and membrane) along with intensity scores. Target genes were evaluated by 1) Tumor cell specificity (TCS): normalized ratio of positive tumor cells to the total positives, 2) Inverse normal score (INS): inverse ratio of positive normal cells to the total normal cells, 3) Membrane intensity score (MIS) and 4) Membrane specificity (MBS): ratio of MIS to the intensity scores from 3 subcellular compartments. Finally, the targetability score (T score) was calculated as Z_{TCS}x2 + Z_{INS}x2 + Z_{MIS}x0.5 + Z_{MBS}x0.5. Also, Tumor infiltrating lymphocytes (TIL) were compared between Tumor Proportion Score (TPS)≥ 1 and TPS<1 groups in each target. **Results:** The IHC analyzer assessed 528M cells including 147M cancer cells. In 34 cancer types, the average T score for the 74 targets was 0.62, which was higher than -0.07 observed for the other 699 targets that have never been explored as drugs. The average T score of the top 10 targets in pan-cancer was 4.27, which was significantly higher than the average (0.0). Among the top 10 targets in pan-cancer (Table), MUC16 was ranked high in non-squamous lung, ovary, uterine, cervical cancers; and CEACAM5 and TACSTD2 were ranked high in 7 and 10 cancer types, respectively. Most targets showed an association with lower TILs and higher TPS, whereas CEACAM5 demonstrated significantly higher TILs (x1.39) in the TPS≥1 group in bladder cancer. **Conclusions:** We developed a pipeline leveraging AI-powered and big-data-driven approaches to assess the cancer and membrane-specific expression of target proteins in IHC images. The current pipeline reproduces the targetability of developed targets as well as novel targets with a potential synergy with immuno-oncology agents. Research Sponsor: None.

Top 10 targets and their association with TILs.

Targets	T score	Top 5 ranked cancer types	TIL fold change
MUC16	5.82	LUAD, OV, UCEC, CESC	0.37
SEZ6	5.14	CESC, PAAD, Skin, Brain, UCEC	0.33
CLDN4	4.67	PAAD, BLCA, CRAD, PRAD, STAD, UCEC, THCA	0.21
DLK1	4.49	LN, HCC, LUAD, UCEC, RCC, Brain	0.60
TM4SF4	4.27	BLCA, LUSC, BRCA, HNSC, PRAD, CESC, THCA, PAAD	0.26
CLDN1	4.11	STAD, HNSC	0.22
CLDN3	3.77	RCC, UCEC	0.08
CEACAM5	3.76	STAD, CRAD, LUSC, BRCA, HNSC, LUAD, CESC	0.40 1.39 (BLCA)
NECTIN4	3.42	HNSC, BLCA, THCA	0.39
TACSTD2	3.27	BLCA, LUSC, BRCA, HNSC, PRAD, CESC, THCA, PAAD	0.31

Seizure-related homolog 6 (SEZ6) expression and ctDNA methylation profiles in patients with high-grade neuroendocrine carcinomas (NECs)/neuroendocrine tumors (NETs) from a phase 1 study of ABBV-706 in advanced solid tumors.

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Background: SEZ6 is a transmembrane protein with overexpression in small cell lung cancer (SCLC) and other neuroendocrine neoplasms (NENs) and minimal expression in normal tissues, making it a promising therapeutic target for these NENs that have a significant unmet need for treatments. ABBV-706 is a novel SEZ6-targeting antibody-drug conjugate with a potent topoisomerase 1 inhibitor payload and is being evaluated in a phase 1 study (NCT05599984) in patients (pts) with advanced solid tumors. Preliminary data from ABBV-706 monotherapy dose escalation demonstrated a manageable safety profile and promising efficacy in pts with SCLC and NECs/NETs (*JCO* 2024;42[suppl 16]: abs 3001). Herein, we describe SEZ6 expression at the protein and mRNA levels in tumor tissues of pts with NENs outside of SCLC, as well as detection of high-grade NEN cancer signal of origin (CSO) among these pts by investigating ctDNA methylation prior to ABBV-706 treatment. **Methods:** This phase 1, open-label study enrolled pts (≥18 yr) with relapsed/refractory high-grade NECs/NETs (well-differentiated grade 3 NETs and poorly differentiated NECs), atypical lung carcinoid, and medullary thyroid cancer (MTC) in dose-escalation and -expansion cohorts. Pts received ABBV-706 monotherapy IV at 1.3–3.5 mg/kg Q3W. FFPE tumor tissues of these pts, when available, were subjected to a proprietary IHC assay for SEZ6 and RNAseq analysis. ctDNA samples collected prior to ABBV-706 treatment were subjected to the Cancer Research Solution (RUO; GRAIL, Inc.). ctDNA abundance and CSO were assessed by examining cancer-specific methylation patterns of ctDNA. **Results:** As of Aug 27, 2024, in the NEC/NET cohort of 64 pts, median age was 63 yr (range 33–86) and the median number of prior therapies was 3 (range 1–8). High prevalence of moderate to strong SEZ6 expression (SEZ6 cytomembrane IHC H-score ≥100) was observed across NEC/NET histologies: 78% of extrapulmonary small cell NEC of diverse anatomic sites (n = 9); 80% of neuroendocrine prostate carcinoma (n = 5); 43% of large cell NEC of diverse anatomic sites (n = 14); 50% of MTC (n = 4); 40% of gastroenteropancreatic NENs (n = 10); 50% of atypical lung carcinoid (n = 6). *SEZ6* mRNA levels were highly correlative with SEZ6 IHC scores. ctDNA positivity rate was 95% from baseline plasma samples of the NEC/NET cohort (n = 60); 67% of ctDNA-positive samples (n = 57) were predicted to have high-grade NEN as their primary CSO. **Conclusions:** Robust SEZ6 expression was observed with some heterogeneity across histologies of the NEC/NET monotherapy cohort. High ctDNA detection rate at baseline indicates the feasibility of monitoring molecular response longitudinally without an invasive procedure and identifying predictive biomarker(s) for ABBV-706. Clinical trial information: NCT05599984. Research Sponsor: AbbVie, Inc.; n/a.

EphA2 siRNA in DOPC nanoliposomes (EPHARNA): A phase I clinical trial in patients with solid tumors.

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Background: EphA2 overexpression is common in human cancers and has an important role in promoting tumor growth and metastasis. Further, EphA2 has kinase-dependent and independent functions, making it ideal for RNAi-based targeting. EphA2 siRNA incorporated in DOPC nanoliposomes (EPHARNA) was effective in reducing EphA2 protein levels and reducing tumor growth in preclinical studies. This is a first-in-human phase I clinical trial of EPHARNA in patients with solid tumors. **Methods:** Adult patients with advanced solid tumors received escalating doses of intravenous EPHARNA twice weekly in 3-week cycles. A total of 8 dose levels were explored under a BOIN design (Table 1). Study objectives included evaluation of safety, tolerability, maximal tolerated dose, and efficacy. Adverse events were assessed per NCI CTCAE Version 4.03 and efficacy per RECIST v1.1. Patients were evaluable for response if they completed at least 2 cycles. Clinical benefit was defined as objective response or stable disease for 4 or more cycles. **Results:** A total of 48 patients were treated. Most common diagnoses were colorectal (29.2%) and ovarian cancer (12.5%). 20.8% of treated patients were Black and 8.3% were Hispanic. Median age was 60.3 years (range 24.5-78.8). Median number of prior therapies was 4 (range 0-12). Among treated patients, 36 (75%) experienced an AE. Most common AEs (≥20%) were fever (33.3%), infusion-related reaction (25%), and chills (20.8%). 5 (10.4%) treated patients experienced Grade 3 AEs that were dose-limiting toxicities including chills (2.1%), dyspnea (2.1%), hypertension (2.1%), infusion-related reaction (2.1%), and nausea/vomiting (2.1%). No Grade 4 AEs were noted. Of the 25 patients evaluable for response, disease control rate was 44% (95% CI: 24.5-63.5%) with 11 patients demonstrating stable disease for at least 2 cycles. No patients demonstrated partial or complete response. Clinical benefit was observed in 4 (16%, 95% CI: 1.6-30.4%) patients who demonstrated stable disease for at least 4 cycles. One patient received 16 cycles with stable disease before withdrawing consent and discontinuing the trial due to desire for a treatment break. The study was closed to enrollment prior to confirmation of the MTD due to unavailability of the drug. **Conclusions:** EPHARNA demonstrated an acceptable safety profile with manageable adverse events in patients with advanced solid tumors. Further investigation of this novel therapeutic approach is warranted to fully elucidate efficacy and optimal dosing strategy. Clinical trial information: NCT01591356. Research Sponsor: University of Texas MD Anderson Cancer Center; National Cancer Institute; P30CA016672; Gateway for Cancer Research; G-18-300; U.S. National Institutes of Health; 5P50CA098258; T32 Institutional Training Grant; T32CA101642.

Dose levels, patients treated, and DLTs.

Dose Level	EphA2 siRNA-DOPC Dose ($\mu g/m^2$)	Number of Patients Treated	Number of Patients Experiencing DLTs	DLTs
1	450	14	2	G3 chills G3 nausea G3 vomiting
2	675	6	1	G3 hypertension
3	1012.5	5	0	N/A
4	1518.75	5	0	N/A
5	2278.13	7	0	N/A
6	3417.2	2	2	G3 infusion-related reaction G3 dyspnea
7	3600	3	0	N/A
8	7200	6	0	N/A

A phase 2 study of olaparib in IDH1 and IDH2 mutant advanced chondrosarcomas and other solid tumors.

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Background: Pre-clinical data have shown that mutations in isocitrate dehydrogenase (IDH) 1 and 2 can lead to a "BRCAness" phenotype by impairing homologous recombination (HR) repair. Olaparib, a PARP inhibitor effective in BRCA-mutated cancers such as ovarian, prostate, pancreas and breast cancer, may also be effective in IDH1/2 mutant solid tumors. IDH1/2 mutations are frequently present in gliomas and cholangiocarcinomas but also in other solid tumors, such as chondrosarcomas, and melanomas. This study evaluated the efficacy of olaparib in treating advanced IDH1/2 mutated solid tumors other than cholangiocarcinoma and gliomas. **Methods:** NCI 10129 was a 3-arm, open-label Phase II clinical trial performed in the NCIExperimental Therapeutics Clinical Trials Network (ETCTN) evaluating olaparib 300 mg twice daily for IDH mutated solid tumors refractory to standard treatment. Patients with solid tumors, excluding cholangiocarcinoma and glioblastoma, were enrolled in cohort 3 of the Phase II trial. The primary endpoint was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** From March 2019 until January 2024, a total of 26 patients with IDH1/IDH2-mutant tumors were enrolled in the study across 10 sites. Of these, 14 (53%) had chondrosarcomas, with 5 (35%) being dedifferentiated. Following, the most prevalent histologies were gastrointestinal adenocarcinomas (4, 15%), other sarcomas (3, 12%) and other tumors (5, 19%). Most tumors had IDH1 mutations (n = 20, 77%), with R132C (n = 12, 60%) being the most common substitution. The median age was 62 years (range 43-78), and 18 (69%) participants were male. Patients had received a median of 1.5 prior line of therapy (0-9). After a mean follow-up time of 8.6 months (0.8-62.6), no objective responses were seen, leading to the closure of enrollment. The median PFS was 2 months (95% CI 1.8-2.2), and the median OS was 7.5 months (95% CI 1.3-13). Only two patients had a clinical benefit, defined as PFS $>$ 6 months. Olaparib was tolerable, with most adverse events scored as grades 1-2. **Conclusions:** Olaparib did not demonstrate activity in IDH-mutant chondrosarcomas and other solid tumors. This study underscores the remarkably poor outcome associated with IDH mutant tumors, emphasizing the urgent need for additional therapeutic options. Further evaluation of the correlative data, including assessment of HR proficiency, is required to elucidate why pre-clinical evidence suggesting potential efficacy did not translate into clinical benefit in IDH mutant solid tumors. Clinical trial information: NCT03212274. Research Sponsor: National Cancer Institute; NCI-2017-01182.

The effect of HIFU treatment on liver metastasis of colorectal cancer in mice and its impact on immunity.

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Background: The liver represents the predominant site for metastasis in colorectal cancer, with over 85% of cases exhibiting the microsatellite stable (MSS) phenotype, which typically shows limited response to immunotherapy. High-Intensity Focused Ultrasound (HIFU) not only facilitates direct destruction of tumor tissues but also has the potential to remodel the tumor immune microenvironment, thereby enhancing systemic anti-tumor immunity. This study aimed to explore the effects of HIFU on liver metastasis in a murine model and its subsequent impact on immune modulation. **Methods:** A BALB/c mice model of colorectal cancer liver metastasis was established and validated. The animals were treated with HIFU, followed by transcriptomic profiling and immunohistochemical staining to assess immune-related markers (CD8, F4/80, FOXP3, PD-L1, IL-6) in the liver metastasis tissues. **Results:** Transcriptomic sequencing performed on liver metastatic tissues collected seven days after HIFU treatment revealed a notable upregulation of CXCL14 expression, which was corroborated by protein immunoblotting. Immunohistochemical analysis demonstrated an increased infiltration of cytotoxic T cells (CD8+), a reduction in macrophage populations (F4/80), and a significant decrease in T regulatory cells (FOXP3 expression). Additionally, both PD-L1 and IL-6 levels were substantially reduced in the treated tissues. **Conclusions:** Seven days post-HIFU treatment, significant immune modulation was observed in liver metastatic tumor tissues, including enhanced infiltration of cytotoxic T cells, a reduction in immune-suppressive cell populations such as macrophages and Tregs, and the attenuation of inflammatory cytokines. These findings suggest that HIFU not only enhances the anti-tumor immune response but also facilitates the transition of liver metastases from an immune "cold" to a "hot" tumor microenvironment, potentially improving the efficacy of subsequent immunotherapeutic strategies. Research Sponsor: None.

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A phase 2 study of the olaparib and AZD6738, an ATM/ATR inhibitor, in isocitrate dehydrogenase (IDH) mutant solid tumors.

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Background: Pre-clinical data has shown that mutations in isocitrate dehydrogenase (IDH) 1 and 2 can lead to impaired homologous recombination repair. IDH1/2 mutations are frequently present in gliomas and cholangiocarcinomas but also in other solid tumors, such as chondrosarcomas. AZD6738 is an ATR inhibitor, and Olaparib is a PARP inhibitor. Preclinical evidence showed a synergistic effect of this combination in models with DNA damage repair effects. This study aims to evaluate the efficacy of Olaparib and AZD6738 in treating advanced IDH1/2 mutated solid. **Methods:** NCI 10222 is an open-label Phase II clinical trial performed in the NCI National Clinical Trials Network evaluating olaparib 300 mg twice daily with AZD6738 160 mg daily for IDH mutated solid tumors refractory to standard treatment. The primary endpoint was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** From January 2020 until March 2023, a total of 24 patients with IDH1/IDH2 mutant tumors were enrolled in the study across 8 sites. Of these, 14 (58%) had cholangiocarcinoma, 4 (17%) had chondrosarcomas, and 6 (25%) had other tumors. Most tumors had IDH1 mutations (n = 16, 70%). The median age was 59 years (range 29-83), and 15 (63%) participants were male. Patients had received a median of 3 prior lines of therapy (0-6). After a mean follow-up time of 3 months (0.2-ongoing), no objective responses were seen, leading to the closure of enrollment. The median PFS was 2 months (95% CI 2-4), and the median OS was 7 months (95% CI 3-NE). Only three patients had a clinical benefit, defined as PFS $>$ 6 months, with one patient diagnosed with G1 chondrosarcoma still on treatment with stable disease. Combination of Olaparib with AZD6738 resulted in G3 AE in 9 (38%) patients, leading to 4 (17%) discontinuations. **Conclusions:** Olaparib with AZD6738 did not demonstrate activity in IDH mutant solid tumors. However, the stability seen in the patient with low-grade tumors could suggest that the effect is restricted to lower-grade tumors, still dependent on IDH mutations. Further evaluation of the correlative data is required to elucidate why pre-clinical evidence suggesting potential efficacy did not translate into clinical benefit in IDH mutant solid tumors. Clinical trial information: NCT03878095. Research Sponsor: None.

Effect of extrachromosomal DNA (ecDNA) on *MYCN* amplified neuroblastoma and patient outcomes.

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Background: Recurrent cytogenetic abnormalities represent candidate therapeutic targets for children with neuroblastoma (NB). *MYCN* oncogene amplification is associated with significantly worse survival rates for children with NB and remains one of the primary predictors of patient prognosis. *MYCN* amplifications in NB can be found both within the linear genome and on circular extrachromosomal DNA (ecDNA), and therapeutic targeting of the mechanisms underlying *MYCN* amplification represents a novel and promising strategy in NB. However, the molecular features and clinical and biological significance of these amplifications in NB tumors are not sufficiently understood. **Methods:** Whole genome and RNA sequencing data were analyzed for NB cell lines and NCI TARGET NB samples using AmpliconSuite software for ecDNA identification and characterization. GISTIC was used for identification of recurrently amplified regions. Gene expression levels were determined using StringTie, and gene clustering heatmaps were generated using FeatureCounts software. For differential gene expression analyses, samples were divided into ecDNA+ and ecDNA-, and genes contained on ecDNA were compared to the same regions on linear DNA across samples using DESeq2. Associations between ecDNA quantity, content, and patient survival were performed using multivariate Cox regression survival analysis. Associations of gene expression with patient survival were performed using the R2 Platform. The efficacy of targeting ecDNA-associated gene products was assessed using live cell imaging and cell viability assays. **Results:** WGS analysis confirmed 7/20 NB patient tumors from the TARGET database to be ecDNA amplified with 1-5 independent ecDNA elements and *MYCN* gene expression correlated with the ecDNA copy number. ecDNAs in *MYCN*-amplified neuroblastoma cell lines contained distinct gene combinations and possessed unique structures. MYCN overexpression in NB cells has been shown to be associated with replication stress (RS), and tumor cells containing ecDNA are hyper-reliant on the DNA damage response (DDR) kinase CHK1 to manage heightened replication stress. Expression of the *CHK1* gene was associated with neuroblastoma patient outcomes and neuroblastoma was most significantly associated with *CHK1* RNA dependency. We further validated CHK1i as a promising therapeutic strategy in *MYCN* amplified NB, as CHK1 inhibition with the novel inhibitor BBI-2779 was most effective against ecDNA+, *MYCN*-amplified neuroblastoma cell lines. **Conclusions:** Our results emphasize the critical role of ecDNA in NB. We identify a synthetic lethality axis shaped by ecDNA *MYCN* amplification and CHK1 dependence. We further demonstrate the feasibility of targeting this vulnerability through CHK1 inhibition, thus offering new avenues for treatment in *MYCN* amplified tumors. Research Sponsor: Curebound Foundation; Boundless Bio, Inc.

AI-driven design of novel PARP inhibitors.

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Background: Inhibitors of the Poly (ADP-ribose) polymerase (PARP) family play a role in treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 (gBRCA) mutations, as well as in the maintenance treatment of gBRCA-associated metastatic pancreatic ductal adenocarcinoma. However, the design of de novo small molecules targeting proteins like PARP remains time consuming and resource intensive. It is hypothesized that generative models trained on molecular graph encodings could accelerate the design of novel PARP inhibitors. Objective:This study aims to develop a generative model capable of designing novel, orally bioavailable PARP inhibitors. **Methods:** A large language model was pre-trained on 1 million chemical structures sourced from the ChEMBL database. Each structure was represented as a Simplified Molecular Input Line Entry System (SMILES) string, which was tokenized into discrete atomic and functional group-level tokens. The model leverages an Average-Stochastic Gradient Descent Weight-Dropped Long Short-Term Memory (AWD-LSTM) architecture. Transfer learning was applied to adapt the pre-trained model to specific target chemical structures, enabling domain-specific fine-tuning for the de novo design of PARP inhibitors. **Results:** The model demonstrated robust performance in generating chemically valid, unique, novel, and diverse PARP inhibitors. It achieved a validity rate, uniqueness rate, and novelty rate of 100%, along with a diversity score of 81.53%. Furthermore, the generated molecules exhibited favorable physicochemical properties, including a molecular weight of 417.52 Da, a logarithm of the partition coefficient (LogP) of 2.58, a topological polar surface area (TPSA) of 93.21 Angstrom squared, an average of 4.05 rotatable bonds, 1.84 hydrogen bond donors, and 5.14 hydrogen bond acceptors. **Conclusions:** A generative model was developed to design novel, orally bioavailable PARP inhibitors. It provides an efficient and automated tool for de novo small molecule design with tailored molecular and pharmacological properties, potentially accelerating the development of PARP inhibitors. Research Sponsor: None.

A first-in-class KIF11 degrader antibody conjugate (DAC) as a potential therapy targeting a broad spectrum of cancers.

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Background: Kinesin family member 11 (KIF11) plays a critical role in mitotic spindle formation and centrosome separation during cell division, making it an attractive anti-cancer target. Despite its promise, the clinical success of KIF11 inhibitors has been hindered by a narrow therapeutic window, largely due to on-target toxicities, such as myelosuppression. Antibody-drug conjugates present a promising strategy to overcome this limitation by enhancing the therapeutic window of KIF11-targeting therapies. However, creating a KIF11-targeting inhibitor payload with sub-nanomolar potency remains a significant challenge. Using Accutar's chimeric degrader platform, we developed dKIF976, a first-in-class KIF11 degrader with sub-nanomolar potency. This degrader was further used as payload to create DACs demonstrating potent cell growth inhibition coupled with KIF11 degradation, thereby providing a robust foundation for further in vivo evaluation of novel KIF11-targeting therapy. **Methods:** dKIF976, a CRBN-based KIF11 degrader, was designed via Accutar's chimeric degrader platform. Western blot analysis was used to evaluate KIF11 degradation and mitotic arrest, as indicated by Histone H3 phosphorylation, in cancer cell lines. Cell growth inhibition was assessed using ATP-based assays. Mechanism and selectivity of dKIF976 were confirmed through specific cellular assays and proteomic analyses. Cell surface antigen-dependent activity of dKIF976 DACs were evaluated in cell lines with different levels of antigen expression. **Results:** dKIF976 demonstrated rapid, dose-dependent KIF11 degradation and significant upregulation of p-Histone H3 across all tested cell lines, achieving sub-nanomolar potency. In side-by-side comparisons, dKIF976 displayed significantly greater cell growth inhibition than multiple published KIF11 inhibitors. KIF11 degradation and the resulting cell growth inhibition induced by dKIF976 were confirmed to be dependent on the E3 ligase CRBN and the proteasome. Proteomic analysis via mass spectrometry validated the selective degradation of KIF11. When conjugated to antibodies, dKIF976 DACs exhibited antigen-dependent KIF11 degradation and cell growth inhibition, with enhanced potency observed in cell lines with high target expression. **Conclusions:** dKIF976 achieves specific and potent KIF11 degradation, inducing mitotic arrest and robust cancer cell growth inhibition. Its superior efficacy and unique mechanism of action establish it as a highly promising payload for antibody conjugates. dKIF976 DACs demonstrated strong antigen-dependent KIF11 degradation and cell growth inhibition. This innovation highlights the potential of using chimeric degraders as payloads for antibody conjugates, offering a promising strategy to enhance the therapeutic window of KIF11-targeted therapies and pave the way for their future success. Research Sponsor: None.

Comparative analysis of fibroblast activation protein Inhibitor (FAPI) 04 PET/CT versus flurodeoxyglucose (FDG) PET/CT in staging gastrointestinal tumours.

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Background: FAPI 04 PET/CT has emerged as a promising alternative to FDG PET/CT, offering potential advantages in sensitivity, specificity, and patient comfort due to its unique targeting of fibroblast activation protein (FAP), which is up regulated in the stromal cells of many cancers. This study aims to evaluate the diagnostic performance of FAPI 04 PET/CT compared to FDG PET/CT for staging gastrointestinal (GI) tumours. **Methods:** 55 patients with suspected or confirmed GI malignancies underwent both FDG PET/CT and FAPI 04 PET/CT scans within a 7-day window. A total of 115 lesions were identified across the cohort, including colorectal, gastric, pancreatic, and oesophageal cancers. Tumor localization, lesion size, and uptake characteristics were compared between the two imaging modalities. Sensitivity, specificity, and diagnostic accuracy were calculated using histopathology as the gold standard. **Results:** Of the 55 patients, 31 were male and 24 female, with a median age of 58 years (range: 42–78). FAPI 04 PET/CT demonstrated superior sensitivity (92%) compared to FDG PET/CT (84%) for the detection of GI tumours, particularly in pancreatic and colorectal cancers, where stromal fibrosis is prevalent and metabolic activity may be low. Specificity of FAPI 04 PET/CT was also higher (95%) compared to FDG PET/CT (88%), reflecting the lower background activity in non-tumor tissues. Lesion detection rates were significantly improved with FAPI 04 PET/CT, with 112 out of 115 lesions identified, while FDG PET/CT detected 98 lesions ($p = 0.02$). The accuracy of FAPI 04 PET/CT was 94%, whereas FDG PET/CT had an accuracy of 86%. Notably, FAPI 04 PET/CT showed a higher diagnostic yield in detecting metastases in liver, peritoneum, and lymph nodes compared to FDG PET/CT. The average scan time for FAPI 04 PET/CT was 30 minutes, significantly shorter than FDG PET/CT (1 hour 15 minutes). **Conclusions:** FAPI 04 PET/CT outperforms FDG PET/CT in terms of sensitivity, specificity, and diagnostic accuracy for staging gastrointestinal tumours, particularly in cases with abundant stromal involvement. The reduced background activity and higher lesion detection rate enhance the utility of FAPI 04 PET/CT in clinical practice. Additionally, the walk-in basis for FAPI 04 PET/CT with shorter fasting and scan time offers significant improvements in patient comfort and convenience. Given these advantages, FAPI 04 PET/CT represents a promising alternative to FDG PET/CT for staging GI cancers, with potential implications for improved treatment planning and monitoring. Research Sponsor: None.

Role of Lu177 FAPI-09 therapy in combination with chemotherapy or immunotherapy for chemo-resistant progressive cancers: Early clinical experience.

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Background: Chemo resistant progressive tumours represent a major challenge in oncology. These tumours often adapt and develop resistance mechanisms that limit the efficacy of standard treatments. Lu177 FAPI-09 therapy, which targets fibroblast activation protein (FAP) expressed on cancer-associated fibroblasts (CAFs) within the tumor microenvironment, has emerged as a promising treatment option. By binding to FAP, Lu177 FAPI-09 selectively delivers radiation to the tumor stroma, potentially altering the tumor environment and making it more susceptible to subsequent therapies. This study aimed to evaluate the safety, feasibility, and effectiveness of combining Lu177 FAPI-09 therapy with chemotherapy or immunotherapy in patients with advanced chemoresistant cancers. **Methods:** Eighteen patients with advanced progressive and chemo resistant malignancies were included in this study. All underwent Ga-68 FAPI-09 PET/CT scans prior to treatment to confirm FAP expression in their tumors, ensuring that Lu177 FAPI-09 therapy would be beneficial. The patient group consisted of GI(7), ovarian (11). Prior to Lu177 FAPI-09 therapy, all patients had demonstrated resistance to one or more prior lines of chemotherapy or immunotherapy. Following the administration of Lu177 FAPI-09 therapy, patients received chemotherapy or immunotherapy 5 days later, tailored to their specific tumor type. Disease responses were assessed two months after the combined treatment. **Results:** After receiving Lu177 FAPI-09 therapy, 80% of patients showed either stable disease or a positive response to the subsequent chemotherapy or immunotherapy. The safety profile of Lu177 FAPI-09 therapy was favourable, with no major grade 3 or 4 adverse events reported. The most common side effects were mild reductions in blood counts, including neutropenia or anaemia. Overall, Lu177 FAPI-09 therapy in combination with chemotherapy or immunotherapy was well-tolerated by the majority of patients. **Conclusions:** Lu177 FAPI-09 therapy, when used in combination with chemotherapy or immunotherapy, shows promise in enhancing treatment responses in patients with chemo resistant progressive cancers with minimal side effects and no major toxicities. The use of Ga-68 FAPI-09 PET/CT scans to identify patients with tumors expressing FAP ensures appropriate patient selection, optimizing the likelihood of a positive outcome. These findings suggest that Lu177 FAPI-09 therapy could be an effective approach to overcome resistance and improve treatment outcomes in patients with advanced malignancies. Research Sponsor: None.

Dosing tolerability and adverse events (AEs) in dihydropyrimidine dehydrogenase (*DPYD*) variant carriers receiving genotyping-guided fluoropyrimidine (FP) dosing.

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Background: We previously showed that *DPYD* genotype-guided FP (5-FU, capecitabine) dosing reduces severe AEs and hospitalizations in variant carriers. However, optimal dose reduction and tolerability for individual *DPYD* variants are not well understood. This study aims to evaluate dosing tolerability and AEs among *DPYD* variant carriers. **Methods:** This is a retrospective cohort study of patients (pts) receiving FP-based chemotherapy at a multisite cancer center who underwent routine in-house *DPYD* genotyping covering 5 variants (Table). Test results and dose recommendations were provided to oncologists per Clinical Pharmacogenetics Implementation Consortium guidelines (i.e., 50% dose reduction in *DPYD* heterozygous carriers and slow titrations in subsequent cycles based on AEs). Clinicodemographics were collected via chart review, and AEs were graded using Common Terminology Criteria for Adverse Events criteria version 5.0. Data was collected for 3 months of FP treatment unless discontinued early. **Results:** From March 2020-October 2024, 1,645 pts were genotyped with 85 (5.2%) identified as heterozygous *DPYD* variant carriers. This analysis included 49 carriers who were tested pretreatment and started FP chemotherapy (median age 65, 35% male, 67% White, 27% Black, 71% gastrointestinal cancers, 53% 5-FU, 47% capecitabine). All pts started on dose-reduced FP at cycle 1 (Table). Of 49 carriers, 18 (37%) had at least one dose escalation, most occurring in cycles 2 or 3. Of these, 5 were eventually escalated to full dose, 5 had AEs preventing further escalation, 5 had subsequent dose reduction due to AEs, 2 completed therapy while escalating, and 1 had one dose escalation with no documented AE. Dose escalation was not performed in 31 (63%) pts due to the following reasons: any-grade AE (n = 27, of which 5 had further dose reductions due to AEs), poor performance status (n = 1), early discontinuation (n = 2, 1 disease progression, 1 declined further therapy), treatment completion (n = 1). **Conclusions:** This is the largest retrospective cohort study evaluating dosing tolerability and toxicity in *DPYD* carriers using real world data. There is interindividual variability in tolerability within each *DPYD* variant, particularly with decreased function variants. Findings will help inform prospective studies and clinical guidelines on variant-specific dosing strategies. Research Sponsor: None.

Variant	N, %	Median (range) first dose intensity, %	Median (range) final dose intensity, %	Grade 3+ AE	AE related hospitalization	AE related discontinuation
All	49	50 (40-81)	50 (27-100)	13 (27%)	9 (18%)	11 (22%)
c.1236G>A[a]	27 (55%)	50 (40-75)	54 (33-100)	6	3	6
c.557A>G[a]	12 (25%)	50 (40-81)	60 (40-100)	2	1	3
c.2846A>T[a]	6 (12%)	50 (47-54)	50 (47-54)	2	3	2
c.1905+1G>A[b]	3 (6%)	51 (45-54)	38 (27-45)	2	1	0
c.1679T>G[b]	1 (2%)	50	45	1	1	0

[a]Decreased function variant.
[b]No function variant.

Monocentric pilot trial of trametinib in severe extracranial arteriovenous malformations.

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Background: The Mitogen Activated Protein Kinase (MAPK) pathway is crucial for cell growth, proliferation, and survival. Overactivation of MAPK is observed in many cancers leading to evaluation of targeted therapies such as MEK inhibitors. Vascular malformations, including arteriovenous malformation (AVM) share many oncogenic mutations with cancer. For example, AVM present KRAS, RASA1, MAP2K1 mutation that result in excessive activity of the RAS-RAF-MEK cascade. This trial aimed to assess trametinib safety and efficacy in adult patients with stage III AVM refractory to conventional therapy, causing deformities, pain, bleeding, or ulceration. This is the first trial to evaluate targeted therapies in AVM. **Methods:** We conducted a prospective Phase II trial on ten adult AVM patients. Trametinib was administered orally for 12 months, with initial dosage escalation based on patient tolerance. Clinical and radiological outcomes were assessed at baseline, during treatment, and at follow-up. Primary outcomes included safety and clinical efficacy (pain reduction, ulceration healing, thrill and deformation improvement). Secondary outcomes included radiological responses assessed via MRI, Doppler ultrasound, and angiography. **Results:** Of the ten patients (6 female, 4 male), eight had facial AVM, one auricular, and one foot AVM. All experienced deformities, with seven reporting severe pain, five ulceration, and two bleeding. Trametinib was initiated at 2mg daily for three patients but, due to skin toxicities, subsequent patients started at lower doses, with only three reaching the target dose. Trametinib led to clinical improvement in 80% of patients. Pain alleviation occurred in all symptomatic patients (VAS 5–7 to 0–5), deformation improved in 55%, and ulceration healed in 20%. Radiological assessment showed a reduction in vessel size in one patient and nidus disappearance in two. Acneiform rash was the most frequent toxicity (100%), including two cases of grade 3, requiring early drug discontinuation. Severe mucosal bleeding led to premature cessation in two patients with mucosal AVMs. Correlations with genomic-alteration will be presented at congress. **Conclusions:** Trametinib demonstrated clinical benefit in refractory AVMs, supporting MAPK inhibition as a therapeutic approach. Skin and mucosal toxicities necessitate dose adjustment, dermatological co-management, and cautious use in mucosal AVMs. Further studies are warranted to optimize therapeutic regimens and assess long-term outcomes. Clinical trial information: 2019-003573-26. Research Sponsor: None.

Cost analysis of pre-treatment dihydropyrimidine dehydrogenase (*DPYD*) genotyping to reduce hospitalizations at a cancer center in the United States (U.S.).

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Background: Patients with certain *DPYD* variants are at increased risk of fluoropyrimidine (FP) related adverse events (AEs) and mortality at standard doses. We previously showed pre-treatment *DPYD* testing and genotype-guided FP dosing reduced severe AEs and hospitalizations in variant carriers (PMID 38935897), but testing cost remains a barrier to widespread adoption in the U.S. Herein, we performed a cost analysis of pre-treatment *DPYD* genotyping. **Methods:** Variant carrier rates, hospitalization rates, and AEs were derived retrospectively from our institutional cohort (n=442) of patients with no observed variant, dose reduced variant carriers, and standard dose variant carriers (identified reactively) receiving FP primarily for gastrointestinal cancers. All patients were genotyped and followed for three months for FP-related AEs and hospitalizations. Hospitalization cost was the weighted average cost of treating the most expensive AE experienced by the hospitalized patient. Input parameters (Table 1) were modeled using a decision tree to compare the cost of pre-treatment testing (no variant and dose reduced variant carriers) to no pre-treatment testing (no variant and standard dose variant carriers) from a health-system perspective with a three-month time horizon. The model accounted for hospitalization and genotype test costs only. **Results:** Pre-treatment testing resulted in a cost savings of $36.98 per patient compared to no pre-treatment testing (average per patient cost = $1,655.81 and $1,692.79, respectively). Cost savings increase to $124.39 per patient if half of those tested have insurance that reimburses the test cost. Additional savings are expected if costs for outpatient management of AEs and use of uridine triacetate in the inpatient setting are included in the model. **Conclusions:** Pre-treatment *DPYD* genotyping led to cost savings by reducing AE related hospitalizations among variant carriers. Cancer centers should adopt pre-treatment *DPYD* genotyping to reduce severe AEs, hospitalizations, and costs.
Research Sponsor: None.

Model inputs.

Parameter	Value	Source
No variant population prevalence	94%	Institutional cohort
Variant carrier population prevalence	6%	Institutional cohort
No variant hospitalization rate	11%	Institutional cohort
Dose reduced variant carrier hospitalization rate	25%	Institutional cohort
Standard dose variant carrier hospitalization rate	64%	Institutional cohort
No variant hospitalization cost	$12930.67	HCUP NC Inpatient Database 2021
Dose reduced variant carrier hospitalization cost	$8858	HCUP NC Inpatient Database 2021
Standard dose variant carrier hospitalization cost	$8928.29	HCUP NC Inpatient Database 2021
Genotype test cost	$174.81	CMS clinical laboratory fee schedule 2023

HCUP; Healthcare Cost and Utilization Project, NC, North Carolina; CMS, Centers for Medicare and Medicaid Services.

Predicting immunotherapy response in advanced solid tumors using quantitative imaging features from CD8 PET/CT exams.

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Background: CD8-PET/CT imaging with ^{89}Zr crefmirlimab berdoxam (ImaginAb, Inc), which targets CD8-expressing T-lymphocytes, is being explored as an imaging tool to predict responses and monitor immune checkpoint inhibitors (ICI) in patients with advanced solid malignancies. Here we explore how quantitative imaging features from CD8 PET/CT may predict ICI responses. **Methods:** We studied quantitative imaging features (PET parameters and radiomics) in 45 patients from the ImaginAb IAB-CD8-201 phase II trial (NCT03802123). Tumoral lesions, peritumoral ring (ring shaped margin extending 0.5 cm inwards and outwards from the segmented tumor surface), healthy tissue, benign and pathological lymph nodes were segmented from baseline and first on-treatment (4-6 weeks after standard of care treatment including ICI blockade). Imaging features from CD8-PET/CT scans were extracted. Predictive models for best overall response (BOR) according to RECIST 1.1 were developed. Models' performance was evaluated by the ability to distinguish responders (complete or partial response, n = 13) from non-responders (stable or progressive disease, n = 32). A survival random forest analysis was also conducted to estimate time to BOR. **Results:** Significantly greater delta values were identified in the tumor and peritumoral ring compared to healthy tissues, suggesting the tumor and peritumoral ring may reveal early treatment-induced changes important for predicting response. Eighteen predictive models were developed, with models using imaging features from the peritumoral ring showing comparable performance to those using features from lesions and pathological lymph nodes. The simplest BOR predictive model, which yielded the highest performance, used delta values extracted from the peritumoral ring (AUCs = 0.895, sensitivity = 0.900, specificity = 0.615). The inclusion of clinical variables (including age, sex, body mass index, cancer type, received treatments, number of lines of received treatment, white blood cell count) did not significantly enhance model accuracy, emphasizing the robustness of the imaging data alone. A final model integrating key imaging features from multiple regions successfully predicted time to BOR with a C-index, a generalizable AUC that considers censored data, of 0.86. **Conclusions:** This study highlights the potential of quantitative imaging analysis of CD8-PET/CT scans as a tool for predicting responses to cancer immunotherapy. Results suggest the effectiveness of delta imaging features from the peritumoral ring as a potential indicator of patient's ability to respond to ICI treatment, simplifying the analysis without sacrificing accuracy. Further validation in trials with more homogeneous populations and treatment regimens (eg. NCT05013099) is warranted, with the potential to advance personalized cancer care. Research Sponsor: ImagingAb.

Interim safety and efficacy data of [^{212}Pb]VMT01 in MC1R expressing melanoma.

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Background: Immune checkpoint inhibitors (ICI) are effective in melanoma, but many patients experience progression on or after approved ICI +/- MAPK inhibitor therapy. Melanocortin-1 receptor (MC1R) is a novel target for radiopharmaceutical therapy (RPT) and is highly expressed on melanoma tumor cells. VMT01 is an MC1R-targeted RPT that can be radiolabeled with either ^{203}Pb (patient selection and dosimetry assessments) or ^{212}Pb (alpha particle therapy). Here, we present data on the first in-human evaluation of [^{203}Pb/^{212}Pb]VMT01 in patients with metastatic melanoma. FDA granted Fast Track Designation to the product on the bases of preclinical experiments combining [^{212}Pb]VMT01 with immunotherapy. **Methods:** This is a first-in-human dose-finding study to determine the safety, pharmacokinetics, dosimetry and preliminary efficacy of [^{212}Pb]VMT01 in subjects with MC1R-positive metastatic melanoma who progressed on at least 1 approved first-line therapy (NCT05655312). Phase 1 of the trial includes escalating dose cohorts. The first two cohorts incorporate dosimetry evaluations (reported separately) with the imaging surrogate [^{203}Pb]VMT01 prior to receiving up to 3 treatment cycles of [^{212}Pb]VMT01 therapy (injected activity of 111 MBq (3 mCi) or 185 MBq (5 mCi) for Cohort 1 and 2, respectively). Participants are evaluated for any DLT for the first 6 weeks after cycle one. Efficacy is assessed by RECIST 1.1 criteria by the investigator. Following the start of the study the anticipated combination arm with nivolumab was opened as an amendment. **Results:** Cohort 1 (DCO 04Sep24) was completed with 3 enrolled participants who received 3 treatment cycles without any DLTs or SAEs. Cohort 1 participants showed prolonged stabilization of disease from start of treatment (mean: 11.1 months); one participant developed a confirmed objective response (PR) after completion of all three [^{212}Pb]VMT01 administrations and is still on trial after 13.1 months from start of treatment. Cohort 2 has completed with 7 enrolled participants. No DLTs or related SAEs have been observed. All participants in this Cohort progressed after either the first cycle (3 participants) or the second cycle (4 participants).Based on these preliminary results showing anti-tumor effect at the lower dose, additional cohorts for both monotherapy and in combination with nivolumab were introduced at a de-escalated dose of 55.5 MBq (1.5 mCi). Both cohorts are now open for enrollment. Updated safety and efficacy data will be analyzed and presented at ASCO. **Conclusions:** At 111 MBq and 185 MBq activity levels, [^{212}Pb]VMT01 was safe and well-tolerated. An objective response and prolonged stabilization of disease were observed at the 111 MBq activity level while no effect was seen at 185 MBq. The study will continue to explore potentially immunostimulating lower doses of administered activity of [^{212}Pb]VMT01 either as a monotherapy or in combination with nivolumab. Clinical trial information: NCT05655312. Research Sponsor: Perspective Therapeutics.

SPYK04, a novel RAF-MEK molecular glue: Dose escalation (DE) in first-in-human study for MAPK pathway-altered solid tumors.

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Background: SPYK04 is a novel MEK1/2 inhibitor designed to enhance RAF-MEK binding and potentially inhibit feedback activation of MEK1/2. This approach was developed to address the limited efficacy of conventional MEK inhibitors in RAS-mutated cancers, which is thought to be due to feedback activation of the MAPK pathway. **Methods:** This first-in human study of SPYK04 is conducted in the US and Japan (NCT04511845). Patients with locally advanced or metastatic solid tumors harboring MAPK pathway alterations were eligible in its DE part. The primary endpoints included assessment of pharmacokinetics, adverse events (AEs) and dose-limiting toxicities (DLTs); the secondary endpoint was objective response rate (ORR). SPYK04 was administered orally once daily in continuous 28-day cycles. **Results:** A total of 23 patients were enrolled in DE. SPYK04 was evaluated at doses ranging from 0.1 to 1.3 mg/day. An accelerated titration design was employed for doses of 0.1, 0.2, and 0.4 mg/day, followed by a transition to a 3+3 design starting from 0.8 mg/day. Over the dose range of 0.1 to 1.3 mg/day, systemic exposure demonstrated a dose-dependent increase. Grade 3 or higher treatment-related adverse events (TRAEs) were observed in 30.4% of patients. TRAEs observed in >= 20% of patients were: dermatitis acneiform and blood creatinine phosphokinase increased (60.9% each); AST increased (30.4%); nausea and stomatitis (26.1%, each). DLTs were observed in one patient each at dose levels of 0.8, 1.0 and 1.3 mg/day. All DLTs were due to receiving <75% of the planned dose. A decision was made to not escalate beyond 1.3 mg/day. The ORR was 8.7% (n = 2 of 23), with both partial responses (PRs) occurring amongst the 5 enrolled ovarian cancer patients. The disease control rate (DCR; PR+SD) was 52.2% (n = 12 of 23). **Conclusions:** SPYK04 was tolerated at doses up to 1.3 mg/day in patients with advanced solid tumors. PRs were observed in two patients with ovarian cancer. Further evaluation of safety and efficacy will occur in the expansion part of this study. Clinical trial information: NCT04511845. Research Sponsor: Chugai Pharmaceutical Co., Ltd. (Contact Person: Satoe Kawakami, email: kawakamiste@chugai-pharm.co.jp).

SPYK04 dose, mg/day	0.1	0.2	0.4	0.8	1	1.3
Patients, n	1	1	1	8	6	6
Safety, n (%)						
TRAE	0	1 (100.0)	1 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)
Grade 3 or higher TRAE	0	0	0	1 (12.5)	4 (66.7)	2 (33.3)
TRAE leading to discontinuation of study treatment	0	0	0	0	1 (16.7)	0
Confirmed best response, n (%)						
Responders	0	0	0	1 (12.5)	1 (16.7)	0
Partial Response	0	0	0	1 (12.5)	1 (16.7)	0
Stable Disease	0	0	1 (100.0)	2 (25.0)	3 (50.0)	4 (66.7)

Zanzalintinib (zanza) + nivolumab (nivo) ± relatlimab (rela) in patients (pts) with advanced solid tumors: Results from two dose-escalation cohorts of the phase 1b STELLAR 002 study.

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Background: Zanza (XL092) is a novel, multi-targeted tyrosine kinase inhibitor (TKI) that inhibits VEGFR, MET, and TAM kinases. In tumor models, zanza showed antitumor activity alone and in combination with an anti-PD-1 immune checkpoint inhibitor (ICI). The addition of a VEGFR-TKI to ICI combinations of anti-PD-1 + anti-LAG-3 may enhance clinical activity. STELLAR-002 (NCT05176483) is a phase 1b, open-label, dose escalation and expansion study evaluating the safety and efficacy of zanza as monotherapy and in combination with ICIs in pts with advanced solid tumors. Data from dose escalation cohorts treated with zanza + nivo and zanza + nivo/rela are presented. **Methods:** Adults with advanced/metastatic solid tumors were enrolled. Starting doses were zanza 100 mg po qd + nivo 360 mg IV q3w (zanza + nivo cohort), and zanza 60 mg po qd + nivo/rela 480/480 mg IV q4w (zanza + nivo/rela cohort). Pts were enrolled in a rolling six design. Sparse pharmacokinetic (PK) samples were collected. The primary endpoint was safety. Exploratory endpoints included investigator-assessed ORR per RECIST 1.1 and PK. **Results:** Among 19 pts in the zanza 100 mg + nivo cohort, the most common tumor types were prostate cancer (26%) and colorectal cancer (26%). Median number of prior therapies was 6 (range: 2–16). No dose-limiting toxicities (DLTs) were observed in the first 11 DLT-evaluable pts; zanza 100 mg is the recommended dose (RD). The most common treatment-emergent adverse events (TEAEs) were fatigue (68%) and diarrhea (58%). The most common grade (G) 3/4 TEAEs were fatigue (26%) and hypertension (16%). Palmar-plantar erythrodysesthesia (PPE) occurred in 11% of pts (all G1/2). No responses were observed; the disease control rate (DCR: CR+PR+SD) was 42%. In the zanza + nivo/rela cohort, 24 pts received zanza 60 mg + nivo/rela and 25 pts received zanza 100 mg + nivo/rela. One DLT was observed in the first 6 DLT-evaluable pts at zanza 60 mg (G3 ALT increase) and none in the first 5 DLT-evaluable pts at zanza 100 mg. Zanza 100 mg is the RD with nivo/rela. In zanza 100 mg-treated pts, the most common tumor type was renal cell carcinoma (RCC; 56%). Median number of prior therapies was 4 (range: 0–15). The most common TEAEs were diarrhea (68%) and fatigue (56%). The most common G3/4 TEAE was fatigue (20%). PPE occurred in 28% (4% G3/4). ORR was 28% and DCR was 80%; these rates were 36% and 86% in pts with RCC (n = 14). Plasma zanza concentrations 2 hrs after the first dose (C_{max}, mean ± SD) were 595 ± 353 and 838 ± 689 ng/mL for the 60-mg and 100-mg dose levels, respectively. **Conclusions:** The tolerability of zanza + nivo and zanza + nivo/rela was manageable and consistent with each monotherapy agent. Preliminary safety, PK, and response data support selection of the 100-mg zanza dose in combination with nivo or nivo/rela for further investigation. Expansion cohorts are ongoing in various tumor types. Clinical trial information: NCT05176483. Research Sponsor: Exelixis, Inc.

Phase II dose optimization update with EZH2/EZH1 inhibitor tulmimetostat in patients with *ARID1A*-mutated ovarian clear cell carcinoma or endometrial carcinoma.

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Background: EZH2 inhibition antitumor activity occurs through various mechanistic pathways in multiple tumor types, including via synthetic lethality in advanced *ARID1A*-mutated ovarian clear cell carcinoma (OCCC) and endometrial carcinoma (EC). Oral, next-generation, dual EZH2/EZH1 inhibitor tulmimetostat is in Phase II evaluation in multiple disease cohorts (NCT04104776; Oaknin et al. ASCO 2024, ESMO 2024). We report updated efficacy and safety data from the *ARID1A*-mutated OCCC/EC cohorts, including dose optimization and expansion arms. **Methods:** Phase II Stage 1 evaluated tulmimetostat 350 mg once daily (QD). Stage 2 dose-optimization design randomizes further patients with OCCC (M2) or EC (M3) to 200 mg or 300 mg tulmimetostat QD in Stage 2a, with an efficacy gateway for each arm to open Stage 2b. Primary endpoint is objective response rate (complete response [CR] + partial response [PR]), and secondary objectives include safety. **Results:** As of October 15, 2024, enrollment into the M2/M3 200 mg, 300 mg, and 350 mg arms included 20/10, 21/21 and 14/11 patients, respectively. A total of 56.4% M2 and 61.9% M3 patients received ≥3 prior lines of therapy. Most responses were seen in the M2 200 mg arm and in the M3 350 mg arm (n=4 each; Table). The safety profile across arms was consistent with the EZH1/2 drug class. In M2/M3 cohorts, treatment-emergent adverse events (TEAEs) leading to dose modifications were reported in 55.0%/60.0%, 71.4%/85.7%, and 92.9%/90.9% of patients at 200 mg, 300 mg, and 350 mg, respectively. TEAEs leading to treatment discontinuation were reported in 5.0%/20.0%, 4.8%/4.8%, and 14.3%/9.1%, respectively. Serious TEAEs considered at least possibly related (TRAEs) to tulmimetostat treatment were reported in 5.0%/0%, 9.5%/14.3%, and 21.4%/27.3%, respectively. Grade ≥3 TRAEs were mainly hematologic (Table); no TRAEs leading to death were reported. **Conclusions:** Tulmimetostat showed an improved and acceptable safety profile in OCCC and EC at 200 mg and 300 mg doses (versus 350 mg) with promising antitumor activity, supporting further clinical investigation. Clinical trial information: NCT04104776. Research Sponsor: MorphoSys GmbH.

Best confirmed responses and most common grade ≥3 related TEAEs.

	Cohort	M2: OCCC			M3: EC		
	Dose, mg	**200**	**300**	**350**	**200**	**300**	**350**
	Efficacy evaluable*, N	**20**	**20**	**14**	**10**	**15**	**11**
Best confirmed response†, n	CR	0	0	0	0	1	0
	PR	4	2	1	0	1	4
	Stable disease	10	10	7	8	5	2
	Progressive disease	5	7	6	1	7	4
	No post-baseline response assessment	1	1	0	1	1	1
	Safety evaluable, N	**20**	**21**	**14**	**10**	**21**	**11**
Grade ≥3 related TEAEs‡, n (%)	Thrombocytopenia	1 (5)	3 (14)	4 (29)	0	4 (19)	2 (18)
	Anemia	3 (15)	0	7 (50)	0	5 (24)	1 (9)
	Neutropenia	0	0	2 (14)	0	0	4 (36)
	Diarrhea	0	4 (19)	0	0	0	2 (18)

Data cut off: October 15, 2024.

*Patients who received ≥1 dose, had ≥1 post-baseline response assessment, or discontinued treatment prior to first post-baseline assessment for any reason.

†RECIST 1.1.

‡>10% in any M2/M3 arm.

OMX-0407: A novel spectrum-selective small molecule kinase inhibitor in advanced/metastatic solid tumors.

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Background: OMX-0407 is an orally available spectrum-selective kinase inhibitor that targets key oncology-relevant tyrosine kinases and salt-inducible kinases and is being developed as a first-in-class treatment for solid tumor indications. Preclinical investigations indicate a dual mode of action by sensitizing tumor cells to immune cell induced apoptotic cell death as well as direct inhibition of tumor growth promoting kinases. **Methods:** This is a phase Ia/Ib dose escalation and expansion study of OMX-0407 (NCT05826600). Eligible patients for the phase Ia dose escalation part had advanced solid tumors and exhausted available therapies. **Results:** As of the 30th of October 2024, 24 patients have been treated at dose levels 10 through 140 mg p. o. BID and the phase Ia part has been completed. Solid tumor histologies included melanoma, non-small cell lung cancer, sarcoma and colorectal cancer. OMX-0407 was generally well tolerated, adverse reactions were mainly gastrointestinal. Two dose limiting toxicities were observed: One case of facial swelling secondary to drug allergy at the 90 mg BID dose, and one case of fatigue at the 140 mg BID dose. One durable complete response in a patient with cutaneous angiosarcoma secondary to radiotherapy, resistant to two prior lines of chemotherapy treatment, was observed at 30 mg BID which is ongoing at 16 months (at the time of data cutoff). Pharmacodynamic analyses demonstrated phosphorylation inhibition of target kinases. A recommended phase II dose of 100 mg BID was identified. **Conclusions:** OMX-0407 has been well tolerated at pharmacologically and therapeutically active dose levels. One very durable response has been observed in an angiosarcoma patient at a low dose level. The phase Ib expansion part at the recommended phase II dose is currently recruiting patients with angiosarcoma and clear cell renal cell carcinoma. Clinical trial information: NCT05826600. Research Sponsor: iOmx Therapeutics AG.

AI molecular search engine paired with RNA sequencing analysis to develop potent and selective VEGFR-3 inhibitors.

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Background: Tumor angiogenesis (TA) is driven by several VEGF factors and corresponding receptors (VEGFRs). Targeting TA inhibits tumor growth, however there are no selective small molecule TA inhibitors on the market yet. Here we report development of a selective VEGFR-3 inhibitor with potential anti-tumor activity in multiple cancers. **Methods:** The Bioptic virtual screening pipeline employs two models. The first is a SMILES-based LLM fine-tuned on binding affinity data of contrastive molecular pairs. The screening was performed on the ultra-large 40-billion-compound virtual library Enamine REAL. For selectivity, the top-ranked molecules were re-scored using a secondary model, a GNN specifically designed for this task and trained to differentiate activity across similar kinases. The Oncobox algorithm was used to select cancer types with the highest sensitivity to VEGFR1-3 inhibitors based on VEGF(R)s expression and TA pathways activation. It was applied to RNA-seq profiles from TCGA (11428 profiles from 33 primary sites) and the internal relevant RWD cohort (1056 profiles from 89 cancer types). **Results:** Compounds with IC50 $<$ 10 μM in Eurofins VEGFRs Kinase-Profiler were considered active. Among 110 tested compounds, 1 was active against VEGFR-1, 1 - against VEGFR-2, and 4 - against VEGFR-3. One compound was active against all VEGFRs, and 3 - against a single VEGFR. One VEGFR-3 active showed $>$ 45-fold selectivity against both VEGFR1 & 2, while no compound was specific to VEGFR-1 or VEGFR-2. All 3 selective VEGFR-3 inhibitors showed minimal activities ($<$ 50% at 10 μM) against the 12 off-target kinases including B-Raf, c-Raf, c-Kit, FGFR1, FGFR2, FGFR3, FGFR4, Flt3, Met, PDGFR-a, PDGFR-b, Ret. In order to select cancer types for further pre-clinical validation, Oncobox algorithm was used to simulate predicted efficiency of a VEGFR-3 inhibitor in multiple cancer types from TCGA and internal RWD cohort. The highest response rate is expected for papillary thyroid cancer, followed by clear-cell renal, pancreatic, ovarian cancers, and sarcomas. A selective VEGFR-3 inhibitor may be beneficial when compared to already developed pan-VEGFR inhibitors due to lower toxicity. Finally, identification of potential responders to selective anti-VEGFR-3 therapy via RNA-seq analysis may enable patient enrichment in further clinical trials and development of a companion diagnostic for the drug. **Conclusions:** Our results suggest that Bioptic's molecular search engine significantly enhances identification of potent and selective inhibitors for a specific target, and, paired with the Oncobox algorithm, may facilitate development of novel anti-cancer drugs. Research Sponsor: None.

Efficacy and safety of alectinib in pediatric and adult patients with ALK altered advanced solid tumors: Results from the TACKLE phase II trial, a MASTER KEY substudy (NCCH1712/MK003).

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Background: Alectinib is an orally administered tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK) and is approved in ALK-positive non-small cell lung cancers and anaplastic large cell lyphomas in Japan. Beyond these, there is a rare population carrying the same ALK alteration regardless of cancer type, often referred to as "ALKomas". Treatment options are limited for these ALK altered solid tumors. **Methods:** This open-label phase II study evaluated alectinib for ALK altered locally advanced or metastatic cancer. Patients received alectinib as either a capsule or a suspension. Primary endpoint was central-assessed confirmed objective response rate (ORR) according to RECIST v1.1. A Bayesian approach was used to evaluate eligible patients in the main cohort, which were patients able to ingest capsules. Expected ORR was set at 40% and a threshold at 10%. Secondary endpoints included safety, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). **Results:** 26 patients, aged from 8 months to 78 years, across 11 tumor types received treatment. The most common tumor type was soft tissue sarcoma (STS) (n = 11) followed by embryonal neoplasm (n = 5). Alterations included fusion/rearrangements (n = 19), mutations (n = 5), and amplifications (n = 2). The median follow-up was 15.0 months. In the evaluable patients of the main cohort (n = 16), the central-assessed ORR was 43.8% (95% CI, 19.8 to 70.1), meeting the decision criteria of the Bayesian design for the primary endpoint. For the entire evaluable patients (n = 24), the central-assessed ORR was 54.2% (32.8 to 74.4), the DCR was 70.8% (48.9 to 87.4); the median PFS was 24.9 months (3.9 to not estimable); and the median OS was 38.8 months (13.9 to not estimable). In patients with ALK fusions/rearrangements (n = 17), the ORR was 76.5 % (50.1 to 93.2), DCR 82.4% (56.6 to 96.2) and the median PFS and OS were both not reached. All patients with inflammatory myofibroblastic tumor showed a response (ORR 100%, n = 8/8). In pediatric patients aged 15 and under (n = 11), the ORR was 63.6% (30.8 to 89.1) with a DCR of 100.0% (71.5 to 100.0). Although no responses were observed in the patients with ALK mutations or amplifications, a clinically meaningful stable disease was observed in 3 of 5 ALK mutated patients. Grade ≥3 drug-related adverse events were observed in 15.4% (n = 4) among all treated patients (n = 26), with no drug related deaths. **Conclusions:** Our study showed that patients with ALK alterations treated with alectinib achieved sustained clinical benefit, meaningful survival outcomes, and safety consistent with previous data. Greatest benefit was observed for the ALK fusion population including pediatric patients. These data support the potential role of alectinib as a tumor-agnostic therapy for both pediatric and adult patients with ALK altered solid tumors. Clinical trial information: jRCT2091220364. Research Sponsor: None.

Phase 1 study of TT-00973-MS, a highly selective and potent AXL inhibitor, in patients with advanced solid tumors.

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Background: AXL is a member of the TAM family activated by the high-affinity ligand Gas6. The Gas6/AXL signaling pathway plays a critical role in drug resistance, tumor proliferation, metastasis, invasion, epithelial-mesenchymal transition and immune regulation, implicating AXL as an important target in cancer treatment. TT-00973-MS is a highly selective and potent AXL inhibitor which exhibited significant anti-tumor activities in both SK-OV-3 and H1299 derived CDX model with AXL over-expression. Here is first time to present the first-in-human study of TT-00973-MS. **Methods:** Dose escalation is performed using"3+3"design. Adverse events (AE) are evaluated per CTCAE v5.0 criteria. Tumor responses are evaluated per RECIST 1.1. Pts receive TT-00973-MS once daily continuously for 28-day cycles. The primary endpoint is to evaluate dose limiting toxicity (DLT) and identify the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D). **Results:** As of the data cut-off date on December 24, 2024, 18 pts have received TT-00973-MS treatment in 2 mg (n = 1), 5 mg (n = 3), 10 mg (n = 3), 17 mg (n = 7), 25 mg (n = 4) at QD dose levels. Median age was 56.5 (37~69), 8 (44.4%) were males, all had ECOG PS ≤1. 66.6% of pts had Stage III/IV disease. 50% had ≥3 prior lines of systemic therapies. 66.7% had prior immunotherapies. One DLT was observed in a subject at 17 mg QD dose level (Grade 3 peripheral motor nerve disorder). The MTD was not reached. Treatment-related AEs (TRAEs) were reported in all pts, grade 3 in 6 (33.3%), and no grade 4 or 5. The most common TRAE (≥30%) included increased blood lactate dehydrogenase (83.3%), increased aspartate aminotransferase (72.2%), increased alanine aminotransferase (66.7%), hypercholesterolaemia (55.6%), hypoalbuminaemia (38.9%), hypertriglyceridemia (33.3%) and proteinuria (33.3%). Fourteen pts were efficacy evaluable. Two confirmed partial remission (PR) were achieved in pts with renal pelvis cancer (n = 1) and ovarian cancer (n = 1). TT-00973-MS is slowly eliminated from body, with a half-life of about 55 h. After multiple dosing (QD), steady state was reached within 15 days, and the mean accumulation factor of AUC_{0-24h} was approximately 6. Preliminary PK analysis showed a linear increase on exposure. Plasma levels of soluble AXL (sAXL) increased to approximately 1.7 times (range: 0.9~2.8) the baseline levels at C1D28. **Conclusions:** The preliminary findings from this phase I study demonstratedthat the AXL inhibitor TT-00973-MS monotherapy exhibits a well-tolerable safety profile, promising pharmacodynamic activity, with early signs of efficacy in pts with heavily pre-treated advanced solid tumors. Further studies are warranted to comprehensively evaluate the efficacy and safety of TT-00973-MS in large patient populations and specific tumor types. Clinical trial information: NCT05673538. Research Sponsor: None.

A phase 1 dose escalation study of LNP7457 (PRMT5 inhibitor) in patients with advanced or metastatic solid tumors.

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Background: Protein arginine transferase 5 (PRMT5) overexpression plays an important role in pathogenesis of several cancers. LNP7457 is an investigational, orally active, highly potent, S-adenosylmethionine (SAM) competitive PRMT5 inhibitor with wider therapeutic window compared to other investigational PRMT5 inhibitors. Here, we report results of dose escalation (DE) and food-effect (FE) sub-studies of LNP7457 from a Phase 1 study in patients with advanced or metastatic solid tumors. **Methods:** This is first-in-human, multicenter, open-label study in patients with advanced or metastatic solid tumors with failed prior standard therapies or for whom no standard therapy exists. DE followed initial modified acceleration followed by 3+3 design. LNP7457 was administered orally in 21-day cycles [first 16 days (on-period) and last 5 days (off-period)] at escalating doses (1 to 4mg QD). Primary objective was to determine maximum tolerated dose (MTD) assessed by dose-limiting toxicities (DLT) in cycle 1; secondary objectives included safety, pharmacokinetics, pharmacodynamics and preliminary antitumor activity measured by RECIST v1.1. FE study was conducted as a single-dose cross over study at MTD to assess impact of food on PK of LNP7457. **Results:** 17 patients (9 male & 8 females) in DE received LNP745 at doses of 1mg (n = 1), 2mg (n = 8), 4mg (n = 2), 1.5mg (n = 6); median age 51.0 (range 23 - 76) years;Diagnosis included head and neck cancer (n = 9), cervix cancer (n = 2), breast cancer (n = 1), ovarian cancer (n = 1), pancreatic cancer (n = 1), gall bladder cancer (n = 1), prostate cancer (n = 1) and uterine cancer (n = 1). Sixteen patients discontinued treatment; progressive disease (n = 8); consent withdrawal (n = 4); AE (N = 2); death (n = 1) and lost to follow up (n = 1). One patient is ongoing at data cut-off of 31-Oct-2024. A total of 16 (94.1%) patients had at least 1 treatment emergent adverse event (TEAE). The majority of TEAEs were unrelated to LNP7457 (76.4%). Anemia (47.1%) and thrombocytopenia (23.5%) were the most common TEAEs. A total of 6 (35.3%) patients had serious TEAEs, thrombocytopenia (11.8%) being the most common serious TEAE. One patient in 4mg cohort had DLT of thrombocytopenia during cycle 1. None of the patients in 2mg cohort had DLT in cycle 1, hence 2 mg was determined as MTD. After single and multiple dosing in DE study, peak plasma concentrations of LNP7457 were observed between 2-4 hrs. A single-dose cross over FE study (n = 6) at 2mg dose showed no impact of food on PK of LNP7457. Target engagement based on reduction in plasma SDMA levels was observed at all dose levels in DE study. Preliminary efficacy in the form of stable disease was observed in 8 (66.7%) patients across 8 different tumor types. **Conclusions:** LNP7457 was well tolerated with desirable safety, PK/PD and preliminary efficacy profile. Clinical trial information: CTRI/2023/07/054753. Research Sponsor: Lupin Limited, India.

An open-label phase 1 dose-escalation and dose-expansion trial to evaluate the safety, tolerability, and efficacy of TQ-B3234 in adults with neurofibromatosis type 1 (NF1).

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Background: NF1 is an autosomal-dominant genetic disease that can manifest as neurofibromas, including cutaneous neurofibromas (cNFs) affecting almost all NF1 patients (pts), and plexiform neurofibromas (PNs, up to 50%), which are benign nerve sheath tumors. However, PNs can cause substantial pain, disfigurement and impairment in pts and are at risk of transforming into malignant peripheral nerve sheath tumors (MPNSTs). Currently, there is no medical cure for adult pts with NF1-related PN (NF1-PN), and fewer options for adult pts with cNFs. TQ-B3234 is a highly selective MEK1/2 inhibitor. A phase 1 dose-escalation and dose-expansion trial (NCT05107037) evaluated the safety and efficacy of TQ-B3234 in adult pts with inoperable NF1-PN, MPNSTs or cNFs. **Methods:** Eligible adult pts with inoperable NF1-PN, MPNSTs or cNFs were included in the dose-escalation phase using a 3+3 design, while only NF1-PN pts proceeded to the dose-expansion phase. TQ-B3234 was administered as a capsule, with doses ranging from 5 mg to 100 mg, once daily in 28-day cycles during the dose-escalation phase. A dose of 50mg was chosen for the dose-expansion phase. The primary endpoints were safety and objective response rate (ORR). ORR was assessed by investigators using REiNS for NF1- PN pts, RECIST 1.1 for MPNSTs pts, and paper frames for the cNF population. **Results:** As of September 30, 2024, 40 adult pts (31 pts of PNs, 7 pts of cNFs, and 2 MPNSTs) were enrolled. The distribution of doses was as follows: 4 pts at 5 mg, 1 at 10 mg, 3 at 15 mg, 24 at 50 mg, 5 at 70 mg, and 3 at 100 mg. One patient, a cNF case, experienced dose-limiting toxicity (DLT), in the form of G3 diarrhea (16.7%) at the 100 mg dose during the dose-escalation phase. After a median follow-up of 12 months, treatment-emergent adverse events (TEAEs) were observed in 39 pts (97.5%), with the majority were grade 1 or 2. Grade 3 TEAEs were reported in 17.5% of pts; the principal reasons for dose reductions (15.0%) TEAEs included rash acneiform (5.0%), diarrhea (2.5%), and edema (2.5%). No death occurred during the study. Among the 30 pts with NF1-PN who had at least one tumor assessment, 29 pts (96.7%) experienced tumor size reduction, and 11 (36.7%) achieved partial response (PR) based on REiNS criteria. The largest reduction in tumor size was 37.7%. For the 6 cNF pts who had at least one tumor assessment using paper frames, all 6 pts (100%) experienced reduced tumor size, with the largest reduction being 85.2%. **Conclusions:** TQ-B3234 demonstrated manageable safety and a significant ORR in adult NF1- PN pts. These results support the potential of TQ-B3234 to become a new treatment option for NF1- PN pts. Additionally, TQ-B3234 showed deep and durable volume reduction in adult cNF pts, as assessed by paper frames. This method could serve as a valuable tool in clinical research for achieving accurate quantitative phenotype for NF1. Clinical trial information: NCT05107037. Research Sponsor: None.

A phase 1, multicenter, open-label study of HSK42360, a brain-penetrant BRAF inhibitor, in patients with BRAF V600-mutated solid tumors.

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Background: Limitations of approved BRAF V600E inhibitors include toxicity from paradoxical activation of RAF dimerization as well as limited brain penetration. In contrast to approved agents, investigational pan-RAF inhibitors both inhibit mutant RAF proteins and wild-type (wt) RAF proteins, leading to a narrow therapeutic index. HSK42360 is a next-generation, small-molecule BRAF paradox breaker with high brain penetration. It displays significantly less paradoxical activation than approved BRAF inhibitors and spares wtBRAF-containing RAF dimers. Treatment with HSK42360 results in excellent and durable anti-tumor effect in BRAF Class I and II mutant CDX or PDX models. Here we report the interim results from a Phase 1 study of HSK42360 in patients (pts) with BRAF V600 mutations (NCT06536400). **Methods:** This multicenter, open-label, two-part study enrolled adult pts with advanced BRAF V600-mutated solid tumors, including those with recurrent or metastatic solid tumors or primary CNS tumors. Previous BRAF±MEK inhibitor treatment is permitted. In the dose-escalation (Part 1), HSK42360 (200-3600 mg/day) monotherapy was given orally. Escalation followed a "3+3 design" with dose-limiting toxicities assessed during Cycle 1. Part 2 was cohort expansion. Primary objectives were maximum tolerated dose and recommended phase 2 dose of HSK42360. Secondary objectives included safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy. **Results:** As of January 15, 2025, 17 pts (47.1% male; median age 57.0 years) have been treated with HSK42360 monotherapy across five dose levels (200-3600 mg/day). Of these, 64.7% pts experienced adverse events (TEAEs), most frequently increased ALT (23.5%) and increased AST (23.5%). Most (89.7%) of TEAEs were grade 1. Two pts had drug-related grade 3 AEs (increased creatinine and increased ALT) and one had drug-related serious AEs (SAEs) (increased creatinine). There were no DLT, grade 4 TEAEs, treatment-related discontinuations, or treatment-related deaths. Among 11 efficacy evaluable pts, the ORR was 18.2%. Two (1 CRC and 1 ganglioglioma) had a partial response (PR) and three had stable disease (SD) with shrinkage (per RECIST or RANO). This trial is ongoing. **Conclusions:** HSK42360 monotherapy was well tolerated without unexpected safety issues. Preliminary efficacy data demonstrate favorable activity of HSK42360 in pts with BRAF V600-mutated solid tumors, including primary CNS tumors. Clinical trial information: NCT06536400. Research Sponsor: Haisco Pharmaceutical Group Co., Ltd.

Anti-tumor activity of BH-30643, a novel macrocyclic kinase inhibitor, in *EGFR*-mutant lung cancer models.

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Background: Outcomes on tyrosine kinase inhibitor (TKI) treatment in *EGFR*-mutant non-small cell lung cancer (NSCLC) fall short of the durable benefit observed with next-generation targeted therapies in *ALK* and *ROS1*-driven NSCLC. Novel targeted therapies are needed to address treatment resistance and offer prolonged patient benefit with reduced toxicity. We recently described (AACR 2025) the design and discovery of BH-30643, a first-in-class macrocyclic reversible TKI targeting the active conformation of mutant EGFR and offering potent, mutant-selective EGFR inhibition across classical and non-classical *EGFR* mutations. Here we study diverse preclinical models to assess the breadth of activity from this novel approach. **Methods:** Anti-tumor activity of BH-30643 was evaluated in cell-derived xenograft (CDX) or patient-derived xenograft (PDX) tumor models carrying classical or atypical EGFR mutations. CNS activity of BH-30643 was investigated in an intracranial xenograft model. BH-30643 was administered twice daily via oral gavage; osimertinib when used as a comparator was dosed daily. Studies were done with $n \geq 5$. The activity of BH-30643 against diverse *EGFR* exon 20 insertions (ex20ins) was evaluated in 34 engineered Ba/F3 cell lines in cell proliferation assays in vitro. **Results:** In the PC-9 (exon 19 del) CDX model, BH-30643 led to deep tumor regressions, similar to what was observed with osimertinib at the 25 mg/kg dose level. Similarly deep responses with BH-30643 were observed in double mutant CDX models including those derived from H1975 cells (cis L858R / T790M) and Ba/F3 cells engineered with exon 19 del / T790M. In a triple-mutant PDX model (cis exon 19 del / T790M / C797S) and a Ba/F3 triple-mutant CDX model (cis L858R / T790M / C797S), deep responses were observed with BH-30643 while osimertinib demonstrated no anti-tumor effect. BH-30643 activity was also evident in the HCC827-luc (exon 19 del) intracranial xenograft model with 90% tumor reduction. In two Ba/F3 CDX models carrying atypical mutations (cis G719A / S768I and cis G719A /L861Q), BH-30643 maintained strong anti-tumor activity. Finally, we explored the activities of BH-30643 against 34 different *EGFR* ex20ins in engineered Ba/F3 cell lines and BH-30643 showed anti-cell proliferation activity with a median IC_{50} value of 6.06 nM. **Conclusions:** These preclinical studies demonstrate broad activity of BH-30643 against classical and atypical *EGFR* activating mutations, *EGFR* ex20ins, as well as acquired resistance *EGFR* mutations. Such an "OMNI-EGFR" inhibitor may be able to overcome some of the limitations of earlier agents. Supported by favorable ADME and preclinical safety profiles, BH-30643 is now being assessed in a first-in-human study in locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* mutations (NCT06706076, SOLARA). Research Sponsor: BlossomHill Therapeutics, Inc.

Phase II trial of trametinib in patients with advanced solid tumors harboring genomic alterations in the MAPK pathway: Results from the BELIEVE trial (NCCH1901).

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Background: The MAPK pathway is one of the most mutated oncogenic pathways in solid tumors. However, effective treatments targeting this pathway have not been well-established. The BELIEVE trial aimed to evaluate the efficacy of trametinib, a selective MEK inhibitor, in patients with solid tumors harboring genomic alterations in the MAPK pathway. **Methods:** The BELIEVE trial is a multi-cohort, tumor agnostic phase II trial. Eligibility criteria included patients with solid tumors for which no standard treatment was available or those who had shown resistance or intolerance to standard therapies. In the trametinib arm, participants received 2 mg/day of trametinib continuously until disease progression or intolerable toxicity occurred. The primary endpoint was the objective response rate (ORR) within 16 weeks, and secondary endpoints were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. The clinical hypothesis was that patients would respond to the genotype-matched drugs. Bayesian analysis was performed using a prior distribution with an expected response rate of 30% [Beta (0.6, 1.4)]. **Results:** Between October 2019 and October 2023, 60 patients with measurable disease and 9 without measurable disease were enrolled. The top three primary tumor sites were the central nervous system (n=20), pancreas (n=7), and ovary (n=6). The targeted genes for trametinib included non-*BRAF* V600 (n=26), *NF1* (n=18), *MAP2K1* (n=10), *NRAS* (n=6), *KRAS* (n=5), and *RAF1* (n=4). Among the full analysis set of 49 patients with measurable disease, the confirmed ORR was 12.2% (95% CI, 4.6% to 24.8%), and the expected value of posterior distribution [Beta (6.6, 44.4)] was 12.9%. Partial responses were observed in patients with genomic alterations in non *BRAF* V600 (n=3), *KRAS* (n=2), and *NF1* (n=1). However, the confirmed ORR of 12.2% fell below the prespecified threshold of 20%, therefore the primary endpoint was not achieved. The median OS was 11.9 months (95% CI, 8.5 to 22.9 months), and median PFS was 3.9 months (95% CI, 2.4 to 44 months). The DCR was 46.9% (95% CI, 32.5% to 61.7%). Among 59 patients in the safety analysis, severe adverse events (Grade ≥3) were observed in 55.9% of patients. The most frequent adverse effects were acneiform dermatitis (22%), blood creatine phosphokinase increased (20%), and stomatitis (15%). **Conclusions:** The BELIEVE trial demonstrated limited efficacy of trametinib in patients with advanced solid tumors harboring genomic alterations in the MAPK pathway. While the confirmed ORR did not meet the primary endpoint, the outcomes for OS, PFS, and DCR were consistent with the clinical hypothesis, suggesting potential benefit in a subset of patients. Clinical trial information: jRCTs031190104. Research Sponsor: Japan Agency for Medical Research and Development; Health and Labour Sciences Research Grant.

Updated efficacy and safety of zurlectrectinib in adult patients (pts) with locally advanced or metastatic NTRK fusion–positive (NTRK+) solid tumors.

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Background: NTRK gene fusion is one of the most defined driving factors of carcinogenesis, which occurs in various adult tumor types. Zurlectrectinib, a highly selective next-generation TRK tyrosine kinase inhibitor, previously demonstrated encouraging efficacy and manageable toxicity in pts with NTRK+ tumors in a phase I/II clinical trial (NCT04685226). The pivotal phase II clinical trial (NCT05745623) is currently ongoing. Here we present the integrated results of adult pts from both trials. **Methods:** Pts with locally advanced or metastatic solid tumors, who failed from clinical standard of care or for whom there was currently no effective therapy, were enrolled in this study. The primary endpoint was confirmed objective response rate (ORR) per independent review committee (IRC). Tumor responses were assessed by IRC and investigators per RECSIT1.1 and RANO (BM) criteria. Treatment-emergent adverse events were evaluated and graded according to CTCAE v5.0. **Results:** As of 23 Nov 2024, a total of 229 adult pts were enrolled in the two trials. Forty-nine TRK inhibitor naïve adult pts were evaluable for efficacy representing 12 different solid tumor types. Among the efficacy population, the distribution of NTRK1, NTRK2 and NTRK3 fusions was 53.1%, 2.0% and 44.9% respectively. The median age was 51.0 years (range: 18-77). Pts had received a median of two prior lines of systemic therapies, with ECOG performance status between 0-1. Median follow-up was 11.7 months. The confirmed ORR by IRC was 83.7% (95% CI: 70.3, 92.7), 5 pts (10.2%) with complete response. Median duration of response (DOR) and median progression-free survival (PFS) by IRC were not reached. The DOR rate and PFS rate by IRC at 12 months was 92.0% and 90.5%, respectively. Two of the three pts (66.7%) who had brain metastasis at the baseline achieved intracerebral ORR, which is consistent with the good brain penetration and strong intracranial activity of zurlectrectinib. In the safety population of adults (N = 229), treatment-related adverse events (TRAEs) were predominantly grade 1 or 2. The most common TRAEs (≥20%) were anemia (28.4%), increased alanine transferase (27.9%) and increased aspartate transferase (25.8%). Grade ≥3 TRAEs (≥2%) were weight gain (3.5%) and dizziness (2.2%). No Serious TRAEs occurred in ≥2% pts. TRAEs led to dose interruption, reduction and discontinuation in 9.2%, 3.9% and 0.4% of safety population, respectively. **Conclusions:** In line with previously reported results, zurlectrectinib continued to demonstrate a deep and durable responses in adult pts with NTRK+ advanced solid tumors with or without brain metastasis. Zurlectrectinib was also well-tolerated and showed favorable safety profile in adult pts with various tumor types. Clinical trial information: NCT05745623. Research Sponsor: None.

Discovery of potent degraders of pan-KRAS based on a novel KRAS binder.

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Background: As the most frequently mutated oncogene, KRAS alteration occurring in approximately 25% of all malignancies. Despite extensive efforts, targeting KRAS has proven to be challenging due to its structure and complex function. Recently, direct $KRAS^{G12C}$ inhibitors, such as Sotorasib and Adagrasib have occurred first successes. However, therapeutic approaches targeting other variants beyond G12C are under significant unmet needs. Recent developments in protein degradation technologies, such as Proteolysis-Targeting Chimeras (PROTACs), bring new hope for targeting pan KRAS. Based on our novel warheads, potent pan-KRAS degraders were designed and synthesized. **Methods:** The ability of compounds to degrade KRAS protein was evaluated using western blotting. The anti-tumor efficacy was assessed *in vitro* through different mutant cell lines. As a proof of concept study *in vivo*, an experiment in subcutaneous xenograft mouse model was performed. Pharmacokinetic studies were conducted in mice, with serial blood samples analyzed by (LC−MS)/MS. **Results:** A novel series of warheads exhibiting exceptional enzymatic and cellular activity against pan-KRAS has been successfully obtained. Based on these warheads, more than 100 degraders were meticulously designed and synthesized incorporating a diverse array of linkers and E3 ligands. Through a comprehensive evaluation, two series of compounds have demonstrated a remarkable KRAS degradation property and downstream inhibition at concentrations below 10 nM in $SW620^{G12V}$ and $GP2D^{G12D}$ cells. Cell proliferation assay demonstrated that the IC_{50} values of these degraders are ranging from 0.01 to 30 nM in the MIA $PaCa\text{-}2^{G12C}$, $GP2D^{G12D}$ $SW620^{G12V}$ and $LOVO^{G13D}$ cell lines, without affecting the viability of KRAS-independent cell lines (selectivity $>$ 500-fold). These compounds also possess favorable PK properties in mice (clearance $<$ 10 mL/min/kg; IV, 2 mpk, AUC $>$ 5000 ng·hr/mL) and good safety profile (hERG $IC_{50} > 30$ μM). Moreover, these compounds showed strong antitumor activity in xenograft mouse model *in vivo.* **Conclusions:** The innovative linker elongation and branching, coupled with modifications of KRAS binder portion significantly contributed to potent pan-KRAS degraders, which demonstrate excellent pharmacokinetics and exhibit remarkable efficacy both in vitro and in vivo. The IND-enabling studies are being conducted and the regulatory IND filing will be completed in 2025. Research Sponsor: None.

Development and validation of a biology-based novel therapeutic agent targeting the LIN28/*let*-7 pathway in cancer.

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Background: Currently, brain tumors that are diagnosed in infants and young children carry an exceptionally high risk for treatment resistance and toxicities. The LIN28 family of RNA-binding proteins regulate stem cell biology and pluripotency. In addition to embryonic development, they have also been implicated in oncogenesis through interaction with the tumor suppressor micro-RNA (miRNA), *let*-7. In cancer, LIN28 expression leads to *let*-7 loss-of-function, oncogenic activation, and tumorigenesis. Importantly, LIN28 expression has been associated with stemness and subsequent tumor aggressiveness and poor survival in early childhood brain tumors. Thus, LIN28 may offer an effective therapeutic strategy to prevent relapse by specifically targeting cancer stem cells. In this study, we describe a novel therapeutic inhibitor of LIN28 in cancer. **Methods:** Using an *in silico* approach, we designed and synthesized a panel of novel compounds predicted to bind and inhibit the critical molecular interaction between LIN28 and *let*-7. Cytotoxicity was evaluated by alamar blue viability assay in a panel of LIN28-positive cancer cell lines derived from atypical teratoid rhabdoid tumor (ATRT), embryonal tumor with multilayered rosettes (ETMR), and germ cell tumor. LIN28-negative cells were used as control. LIN28 protein expression and *let*-7 miRNA levels were determined by immunoblot and reverse transcription quantitative polymerase chain reaction (RT-qPCR), respectively. Self-renewal capacity was analyzed by sphere formation assay. Mice carrying xenografts were treated to investigate LIN28 inhibition *in vivo*. **Results:** Preliminary screening of small molecule inhibitors identified a lead compound, designated THNB-3, that induces cell death at micromolar concentrations in LIN28-positive cell lines established from various tumors, without affecting LIN28-negative controls. Treatment with THNB-3 increased the level of *let*-7 tumor suppressor, confirming effective inhibition of LIN28. In addition to cytotoxicity, THNB-3 significantly inhibited sphere formation in brain tumor cells, reducing self-renewal and multipotency of cancer stem cells. Lastly, the anticancer activity of THNB-3 was validated *in vivo* against LIN28-positive xenografts and the drug also demonstrated systemic tolerability in mice. **Conclusions:** Our studies provide the first evidence for an effective, targeted therapeutic agent against the LIN28/*let*-7 pathway for the treatment of cancer in the future. THNB-3 selectively induces cytotoxicity in LIN28-positive cancers by restoring *let*-7 miRNA, confirming effective target modulation. Further, LIN28 inhibition by THNB-3 may reduce self-renewal and multipotency of cancer stem cells. Together, our preclinical data supports further development of THNB-3 for the treatment of high-risk LIN28-positive tumors. Research Sponsor: Kids Cancer Care Foundation of Alberta.

A first-in-human, phase 1a/b, dose-escalation/expansion study of BG-68501, a selective CDK2 inhibitor, as monotherapy or in combination with fulvestrant for patients with HR+/HER2- breast cancer and other advanced solid tumors: First disclosure of clinical data.

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Background: CDK2 inhibition could represent a novel treatment (tx) option for patients (pts) with resistance to CDK4/6 inhibitors (CDK4/6i) and/or increased cyclin E1 activity. BG-68501 is a highly potent CDK2 inhibitor with high CDK2 selectivity (~100x) vs other CDK family members. We present dose-escalation data of BG-68501 as monotherapy or in combination with fulvestrant in pts with HR+/HER2- metastatic breast cancer (BC) and advanced solid tumors (NCT06257264). **Methods:** This is the dose-escalation phase of a first-in-human, phase 1a/b, open-label, multicenter study to evaluate the safety/tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles, and preliminary antitumor activity of BG-68501 in pts with advanced, nonresectable, or metastatic solid tumors, including HR+/HER2− BC. During dose escalation, sequential cohorts received increasing doses of BG-68501 as monotherapy or in combination with fulvestrant. Eligible pts are ≥18 yrs, with histologically or cytologically confirmed advanced or metastatic solid tumors associated with CDK2 dependency who have received ≥1 line of tx for advanced or metastatic disease and prior endocrine therapy and a CDK4/6i in either the adjuvant or advanced or metastatic setting for HR+/HER2− BC, or prior standard of care for all other advanced solid tumors. **Results:** As of Jan 22, 2025, 41 pts (median age 63 yrs) have been enrolled. Eleven pts had BC (all received prior CDK4/6i), 12 had ovarian cancer (OC), 7 had endometrial cancer, and the remaining 11 pts had other tumor types. To date, 6 dose levels (DLs) of BG-68501 monotherapy and 1 DL in combination with fulvestrant have been assessed. The median duration of exposure is 1.5 months. Treatment-emergent adverse events occurred in 39 pts (95.1%; grade ≥3, 26.8%), with the most common being nausea (56.1%; grade ≥3, 0%), vomiting (48.8%; grade ≥3, 0%), and fatigue (24.4%; grade ≥3, 0%); no DLTs have been observed. BG-68501 demonstrated a linear PK profile with clinical characteristics consistent with preclinical predictions; signs of TK1 reductions have been observed across DLs tested, including in heavily pretreated pts. Of the 24 efficacy-evaluable pts, 1 extensively pretreated HR+/HER2− BC pt experienced PR and 10 pts showed SD. Dose escalation is ongoing for both monotherapy as well as in combination with fulvestrant. **Conclusions:** BG-68501 demonstrates a favorable safety/tolerability profile, with no DLTs observed to date during dose escalation. Extensively pretreated patients achieving PR and SD with monotherapy, coupled with signs of PD responses and a favorable safety profile, support continued assessment of BG-68501; updated clinical data will be presented at the time of the conference. Clinical trial information: NCT06257264. Research Sponsor: BeiGene, Ltd.

Efficacy and safety of pralsetinib in *RET* fusion-positive solid tumors: Final data from the ARROW trial.

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Background: Pralsetinib is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusion and mutation proteins. *RET* fusions or mutations are present in various tumor types. We report the final results from the phase 2 portion of ARROW, a phase 1/2, open-label, multi-cohort, dose-expansion study evaluating the efficacy and safety of pralsetinib (NCT03037385) in patients with *RET* fusion-positive solid tumors other than non-small-cell lung cancer (NSCLC) and thyroid cancer. **Methods:** Eligible pts were ≥18 years of age with a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic *RET* fusion or mutation, had previously received standard of care appropriate for their tumor type, and were not eligible for any other study groups. Overall response rate (ORR) and safety were primary endpoints of the study. Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). The final database lock was May 20, 2024. **Results:** Twenty-nine patients were enrolled with 11 different solid tumor histologies. Twenty-six (90%) received prior systemic therapy. Median age was 58 years (range 25-75); 59% were female. Twenty-eight patients were included in the efficacy analysis. ORR (by RECIST) was 46.4% (13/28); 10.7% (3/28) achieved complete response (pancreatic cancer, n=2; cancer of unknown primary, n=1) and 35.7% (10/28) achieved partial response. Median PFS was 7 months (95% CI: 3.9, 12.8). Median DOR was 11.1 months (95% CI: 5.5, 25.1). Median OS was 10.3 months (95% CI: 6.8, 25.2). Twenty-five (86%) patients experienced treatment-related adverse events (TRAEs); 19/29 (66%) reported TRAEs ≥grade 3. The most common TRAEs included increased aspartate aminotransferase (11/29; 38%), increased alanine aminotransferase (10/29; 35%), and anemia (9/29; 31%). Four (13.8%) patients experienced hypertension, and 1 (3.4%) patient had ≥grade 3 hypertension. No new safety risks were identified; AEs remained manageable with supportive care and/or dose modifications. **Conclusions:** In the phase 2 portion of this trial, responses were observed in many tumor types (Table). Pralsetinib demonstrated robust and durable anti-tumor activity with an ORR of 46.4%. These data validate *RET* fusions as a tissue-agnostic target with sensitivity to RET inhibition and activity beyond NSCLC and thyroid cancer, further supporting the promising potential of pralsetinib to address the unmet medical need in these patients. Clinical trial information: NCT03037385. Research Sponsor: Blueprint Medicines; Genentech/Roche; Rigel Pharmaceuticals, Inc.

Overall response rate by tumor type.

Cancer Type (patient n)	ORR n (%)
Pancreatic (5)	5 (100)
Cancer of unknown primary (1)	1 (100)
Neuroendocrine (3)	2 (67)
Sarcoma (3)	2 (67)
Head and neck (2)	1 (50)
Small cell lung (2)	1 (50)
Hepatobiliary (4)	1 (25)
Colorectal (5), gastric (1), ovarian (1), thymic (1)	0

Exploring the efficacy and mechanism of action of combined pan-Raf and MEK inhibition in halting the growth of non-V600 BRAF mutated tumors.

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Background: Class 2 & 3 non-V600 BRAF mutations mediate RAF dimerization to hyperactivate the MAPK signaling pathway. Encorafenib (Enco; BRAF monomer inhibitor) + Binimetinib (Bini; MEK inhibitor) elicit responses in <15% of patients with non-V600E BRAF mutations (NCT03839342). We hypothesized that Belvarafenib (Belva), a novel pan-RAF dimer inhibitor, is more potent than Enco in inhibiting the growth of Class 2 & 3 non-V600 BRAF mutated tumors. **Methods:** We performed *in vitro* colonogenic assays to compare the growth inhibitory effect of 5 independent doses of individual inhibitors (Bini, Belva, or Enco) in parallel to 25 different combinations of either Belva+Bini or Enco+Bini in 6 non-V600 BRAF mutated melanoma (WM3629, HMV-II), colorectal (CRC) (NCI-H508, HT55), and lung (NCI-H1666, NCI-H2087) cancer cells. Low nanomolar doses (10-1000 nM) were used to investigate the synergistic potential of either combination using the SynergyFinder tool. Belva+Bini (15 mg/kg each) and Enco+Bini (75 mg/kg + 15 mg/kg) combinations were assessed in 4 non-V600 BRAF (3 Class 3, 1 Class 2) metastatic CRC patient-derived xenograft (PDX) models. The inhibitory effect of Belva and Enco on MAPK activity in the outlined 6 cell lines was assessed by immunoblotting. Transcriptomic (RNA-Seq) analysis was performed on PDXs. **Results:** Belva+Bini was 2-6-fold more effective than Enco+Bini in inhibiting the growth of the 6 cell lines. Belva+Bini achieved overall higher synergy scores in the 6 cell lines and was synergistic in 5/6 cell lines (synergy score > 10) vs. Enco+Bini that was synergistic in 1/6 cell lines. In the 6 cell lines, Belva inhibited MAPK activity more robustly than Enco (assessed by pERK levels). *In vivo*, Belva+Bini was significantly more effective than vehicle or Enco+Bini in halting the growth of 3 out of 4 PDXs. Both Belva+Bini and Enco+Bini significantly inhibited MAPK activity vs. vehicle (as assessed by the transcriptional MAPK Pathway Activity Score). However, there was no statistically significant difference between both combinations. Gene Set Enrichment Analysis revealed that Belva+Bini significantly downregulated genes mediating the interconnected mTORC1 pathway activity and cholesterol metabolism dynamics in the 3 PDXs where Belva+Bini had anti-growth effect. Specifically, among the top downregulated genes by Belva+Bini was *PCSK9*, a druggable key regulator of cholesterol metabolism. **Conclusions:** These results from 10 preclinical models, tested so far, put forward combined Pan-Raf and MEK inhibition as a potential effective treatment choice for patients with non-V600 BRAF mutated tumors to be investigated in clinical trials. In parallel, they unravel novel insights into the mechanism of action of this therapeutic approach and in return the druggable vulnerabilities of the non-V600 BRAF mutated tumors, a notion we are further investigating in the outlined models. Research Sponsor: Canadian Cancer Society; 707457; Conquer Cancer, the ASCO Foundation; Canadian Cancer Society; 708442.

Atropisomeric pyrrolopyrimidine inhibitor as a targeted approach for RET tyrosine kinase in neuroblastoma.

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Background: Increased RET expression is associated with poor prognosis in children with solid tumors such as neuroblastoma (NB), prompting an interest in RET inhibition. A number of kinase inhibitors currently in use for cancer patients have RET inhibitory activity, but these inhibitors also display activity against other kinases, resulting in unwanted side effects and limiting their safety and efficacy. However, developing more specific RET inhibitors remains a drug design challenge due to high levels of conservation between kinase binding pockets. Using novel chiral chemistry leveraging atropisomerism to convert a promiscuous, rapidly interconverting pyrrolopyrimidine compound into an atropisomerically stable analog, we have developed a new atropisomerically stable, highly selective and specific RET inhibitor, getretinib, with similar potency and improved selectivity to that of other next generation RET inhibitors but with half the molecular weight and significantly improved ligand efficiencies towards RET. **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 RET inhibition was assessed against a panel of NB cell lines using live cell imaging and cell viability assays, comparing results with the active and selective RET kinase inhibitor, (R)-getretinib to results with the inactive atropisomer, (S)-getretinib. Mechanisms of cell death and impacts on RET signaling in cells treated with (R)- and (S)-getretinib were evaluated by Western blots. **Results:** (R)-getretinib reduced NB cell confluence in a dose-dependent manner, while (S)-getretinib had no significant effect on cell confluence over time. R-getretinib treatment of NB cells resulted in reduced phosphorylation of RET in a dose-dependent manner, while treatment with (S)-getretinib resulted in paradoxical increase in RET phosphorylation. **Conclusions:** We present (R)-getretinib as an atropisomerically stable and potent inhibitor of RET and have shown its efficacy in *in vitro* models of NB. The high selectivity of (R)-getretinib towards RET has the potential to minimize unwanted side effects caused by off-target kinase binding, thereby increasing its potential for clinical utility.
Research Sponsor: None.

Combined RAF- and MEK-inhibition in solid cancers with kinase-impaired BRAF mutations (SORATRAM phase I trial).

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Background: *BRAF* is a frequently mutated gene in cancer, with most mutations (mut) at the activating hotspot V600 codon. Recently, kinase-inactive class III *BRAF* mut emerged as oncogenic driver and potential therapeutic target, as they lead to paradoxical cross-activation of RAF1- and RAS-dependent downstream signaling. Here we report the Phase I toxicity results of combinatory inhibition of RAF kinases by sorafenib (S), a multi-kinase inhibitor (e.g. RAF1, BRAF, c-KIT, FLT-3) and MEK/ERK signaling by trametinib (T) in patients (pts) with inactivating *BRAF* mut. **Methods:** SORATRAM is a prospective, molecularly stratified, multicenter phase I trial. Primary objective is to determine the maximal tolerated dose (MTD) of T combined with S and the recommended phase II dose (RP2D). Adult pts with metastatic malignancies, confirmed or known impaired kinase *BRAF* mut (according to *in vitro* testing), ECOG $\leq$ 2 and no available therapy options were eligible. S was given in the approved dose (800 mg) from day (d)1 cycle (c)1, combined with T on c1d8 for max 12c or until progression or unacceptable toxicity. Dose levels (DL) are defined by T dose (0.5mg DL1, 1.0mg DL2 and 1.5mg DL3) and escalated in a conventional 3 + 3 design. MTD is defined as highest dose at which 0/3 pts or $<$ 2/6 pts experience a dose limiting toxicity (DLT) during c1. DLT is defined as toxicity related to S+T combination, unrelated to disease progression, intercurrent illness or concomitant medications, that requires dose reduction or drug withdrawal. **Results:** Since 2020, 236 cases from 9 sites were classified for mutational SORATRAM eligibility with 42% being kinase impaired (e.g. D594G, N581I, G466E), 21% known intermediate/high activity (excluding V600E/K) (e.g. L597V, K601E) and 36% with novel/unclear/unknown kinase activity (e.g. G469I, W531S). Eligible pts with inactivating *BRAF* mut proceeded to SORATRAM screening. 15 pts received dose finding treatment: 3 in DL1 and DL2 and 9 in DL3. Median age was 57 years (34-75) with 12f/3m pts. Included entities were colorectal cancer (60%), duodenal carcinoma/carcinoma of papilla vateri (20%), lung adenoid cystic carcinoma (6.7%), bone sarcoma (6.7%) and ovarian cancer (6.7%). 3/3 pts in DL1 and DL2 and 6/9 pts at DL3 fulfilled the minimum safety evaluation requirements ($\geq$ 80% of S+T doses in c1; 28ds observation). No DLT was observed in DL1 and DL2. 1/6 pts in DL3 developed a DLT (reduction of left ventricular ejection fraction (LVEF)). 5/15 pts (33.3%) experienced grade 3 adverse events (AEs) during c1: Hypertension (13.3%), gastrointestinal bleeding (6.7%; rated as SAE), anemia (6.7%), LVEF reduction (6.7%), diarrhea (6.7%) and fatigue (6.7%). 79 AEs grade 1/2 were reported in c1. **Conclusions:** Combination of sorafenib/ trametinib is feasible and can be safely administered to pts. MTD was determined as DL3 (800mg S + 1.5mg T), RP2D as DL2 (800mg S + 1mg T). Dose expansion part of SORATRAM is open for enrollment. Clinical trial information: EU – CT No. 2024-512887-77-00. Research Sponsor: German Cancer Consortium (DKTK); German Cancer Consortium (DKTK) Freiburg site; Sorafenib was kindly supplied by Bayer.

Safety and efficacy of a small-molecule c-Myc degrader WBC100 in solid tumors: A first-in-human, phase I trial.

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Background: *c-Myc* amplification or overexpression is involved in the development and progression of many human cancers, and is often associated with poor outcomes. It is an extraordinarily desirable target, but is also considered undruggable. WBC100 is an oral active molecule glue that selectively degrades c-Myc protein. **Methods:** This is a first-in-human, dose-escalation study conducted in China. Patients with solid tumors that have progressed or relapsed after standard systemic therapy were enrolled. WBC100 was orally administered every other day (QOD) according to 3+3 design. The primary endpoints were safety, dose-limiting toxicity (DLT) and maximal tolerated dose (MTD). **Results:** As of Dec 9, 2024, 28 patients were enrolled in seven dose levels (DLs) from 0.5 to 3.5 mg. The median age was 59 (range, 45-71) years, comprising 15 males and 13 females. Three (11%) patients had an ECOG PS score of 0, while the remaining 25 (89%) had a score of 1. The median number of prior systemic therapy lines was 3 (range, 1 to 6). One DLT of prolonged QT interval was observed in DL7, and MTD has not been reached. Six patients (21%) experienced grade 3 or higher treatment-related adverse events, including five (17.9%) neutropenia and two (7.1%) leukopenia and one (3.6%) prolonged QT interval. Increased aspartate aminotransferase, thrombocytopenia, proteinuria, increased alanine aminotransferase, fatigue, nausea, anemia, and hypoalbuminemia were the most commonly reported grade 1 or 2 adverse events. Nineteen patients were evaluable for efficacy, one (5.3%) showed partial regression (PR), and six (31.6%) showed stable disease (SD), including two patients with hepatocellular carcinoma, one with duodenal adenocarcinoma, and three with pancreatic cancer. Notably, we enrolled eight patients with pancreatic cancer at DL6 and DL7, and six of them were evaluable for efficacy, with one (16.7%) PR and two (33.3%) SD. **Conclusions:** WBC100 showed a tolerable safety profile and preliminary anti-tumor activity in advanced solid tumors especially in PDAC. Dose escalation is ongoing and expected to proceed to dose expansion soon. To our knowledge, this is the first study of a small-molecule c-Myc degrader for further clinical development in cancer. Clinical trial information: NCT05100251. Research Sponsor: Weben Pharma.

In vitro efficacy of CDK9 inhibitor tambiciclib (SLS009) in ASXL1 mutated colorectal cancer cell lines.

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Background: ASXL1 (Additional sex combs-like 1) gene encodes ASXL1 protein thought to disrupt chromatin, enhancing transcription of certain genes while repressing the transcription of others. ASXL1 mutations occur in ~20% of acute myeloid leukemia (AML) patients and ~50% of ASXL1 AML mutations are frameshift or nonsense mutations generating a truncated ASXL1 form with oncogenic gain of function in AML. Recently ASXL1 mutated AML patients were treated with a CDK9 inhibitor tambiciclib (SLS009) with promising results. ASXL1 mutations were also reported in 55% of Colorectal Carcinoma with High Microsatelite Instability (CRC MSI-H) cell lines, but it is not known whether those mutations are similar to ASXL1 mutations observed in AML and whether CDK9 inhibitors have enhanced cytotoxic effect in CRC MSI-H cells with those mutations. **Methods:** Twelve CRC MSI-H cell lines were treated with SLS009 at various concentrations. Staurosporin was used as positive control. Cytotoxicity analysis was performed by CellTiter-Glo 2.0 assay. Data analyses were performed using GraphPad Prism 9. NGS was used to determine mutations in studied cell lines. The experiment was designed to compare ASXL1 mutations in CRC MSI-H cell lines to those observed in AML and determine efficacy of SLS009 cytotoxicity in CRC MSI-H cells with and without ASXL1 mutations. Highly effective concentrations in this experiment were considered those with IC50 values below 100 nM. **Results:** Among the 12 tested cell lines, 8 (67%) had non-synonymous ASXL1 mutations of any kind, similar to the literature reported 55% ASXL1 mutations rate in CRC MSI-H. Among cell lines with ASXL1 mutations, 4 (50%) had high impact frameshift mutations, similar to estimated rate of high impact frameshift mutations in AML (~50%). Among cell lines with high impact frameshift mutations, all had mutations in protein position regions 581-582 and 642-643. Three out four had in addition high impact frameshift mutations in the region of protein position 637-638. Protein positions of these frameshift ASXL1 mutations were similar to those observed in AML (591 – 592 and 635 – 646). Among the cell lines with any ASXL1 mutation, 4/8 (50%) had IC50 values for SLS009 below 100 nM (highly efficacious) vs 0/4 (0%) among cell lines without ASXL1 mutations. Among cell lines with ASXL1 frameshift mutations, SLS009 was highly efficacious in 3/4 (75%) cell lines vs 1/8 (12.5%) in cell lines without ASXL1 frameshift mutations. High efficacy was observed in all cell lines (3/3, 100%) with frameshift mutations in the protein position region 637-638. Presence of high impact TP53 mutations did not appear to significantly affect SLS009 efficacy. **Conclusions:** Results indicate that ASXL1 mutations may be oncogenic drivers in some solid tumors, like CRC MSI-H, similar to those in AML and that efficacy of CDK9 inhibition with SLS009 may be similar in some solid tumors to the efficacy observed in AML. Research Sponsor: None.

Safety and efficacy of EIK1003, a selective PARP1 inhibitor, as monotherapy in participants with advanced solid tumors.

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Background: PARP inhibitors (PARPi) selectively kill tumor cells with genetic mutations in critical DNA repair genes (eg, BRCA1/2). While approved nonselective PARPi may provide antitumor activity, they are associated with hematologic toxicities. Drugs inhibiting PARP1 but not PARP2 may improve the risk-benefit profile by retaining antitumor activity while avoiding PARP2-related toxicities. EIK1003 (IMP1734) is a potent PARP1-selective inhibitor that may widen the therapeutic index in susceptible tumors. **Methods:** EIK1003-001 (IMP1734-101) is an ongoing global, multi-center, Phase 1/2 study evaluating the safety and efficacy of EIK1003 (once daily oral) as monotherapy or in combination with anticancer agents in participants (pts) with advanced solid tumors (NCT#06253130). Pts must be $\geq$ 18 yrs with deleterious or suspected deleterious mutations in select homologous recombination repair genes. This abstract reports the interim safety and efficacy from Part 1 monotherapy (dose escalation). **Results:** At the data cut (10 Jan 2025), 32 pts were treated in the first 4 completed dose levels (DLs; n = 3 to 15 per DL, including backfill) of monotherapy dose escalation. There were no dose-limiting toxicities and a maximum tolerated dose has not been reached. The majority (29/32) of pts were female. Pts had a median age of 60 years (31 to 76), and cancers represented included ovarian (n = 15), HER2-negative breast (n = 10), pancreatic (n = 3), fallopian tube (n = 2), and prostate cancer (n = 1). Pts received a median of 3 (range 1 to 11) prior lines of therapy for metastatic disease with 50% receiving prior PARPi. To date, EIK1003 demonstrated a tolerable safety profile. All pts experienced at least one treatment-emergent adverse event (TEAE), and 13/32 experienced at least one $\geq$ Grade 3 TEAE. 27/32 pts experienced a treatment-related AE (TRAE), 6 of which experienced a $\geq$ Grade 3 TRAE. Hematologic toxicities (Grade 3) included neutropenia (3/32) and anemia (1/32). 7/32 experienced a serious adverse event (including one related case of Grade 3 vomiting). There were no Grade 4 AEs or deaths due to AE, and no trends in AEs by DL were observed. EIK1003 PK was linear, with a half-life $>$ 24 hours. Of the 13 ovarian cancer patients with post-treatment scan assessments, 3 experienced partial response (PR; one each at DL2, DL3, and DL4) and 3 experienced stable disease (SD; one at DL1 and two at DL3) by RECIST v1.1. For these 3 PRs, all had a CA125 response. Of the 6 breast cancer patients with post-treatment scan assessments, there was 1 PR (DL3) and 1 SD (DL1) via RECIST v1.1. **Conclusions:** To date, EIK1001 has demonstrated tolerable safety and encouraging preliminary efficacy. Dose escalation is ongoing. Updated safety and efficacy data will be reported at the time of presentation. Clinical trial information: 06253130. Research Sponsor: None.

A first-in-human phase I/Ib study of ATG-037 monotherapy and combination therapy with pembrolizumab in patients with advanced solid tumors: STAMINA-01.

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Background: ATG-037 is a highly potent oral small molecule inhibitor of CD73. STAMINA-01 is an open-label, first-in-human, phase 1/1b study (NCT05205109) designed to evaluate the safety, pharmacokinetics, and optimal dosing of ATG-037 as monotherapy and in combination with pembrolizumab in patients with refractory/relapsed solid tumors. **Methods:** The study successfully completed enrollment of dose escalation of ATG-037 with optional addition of pembrolizumab following two cycles of monotherapy in May 2024. The primary objectives were to evaluate the safety and define the optimal biological dose of ATG-037 as monotherapy and combination treatment. As of 20 January 2025, 43 patients were enrolled across the following doses - 20mg BID (n=3), 60mg BID (n=6), 120mg BID (n=10), 240mg BID (n=6), 400mg BID (n=12) and 600mg BID (n=6). The trial is currently recruiting the second part of the study for dose optimization of upfront combination therapy at two dose levels (120mg BID and 400mg BID). **Results:** *Efficacy:* As of the data cut-off (20 Jan 2025), 43 patients were enrolled on study and received monotherapy. While on ATG-037 monotherapy, 21 patients had a best response of stable disease (SD) with a disease control rate (DCR) of 49%. Twenty-eight patients with a history of acquired checkpoint inhibitor resistance received combination therapy; 7 of which (5 melanoma and 2 NSCLC patients) achieved a confirmed partial response (PR) with an overall response rate (ORR) of 25% (95% CI: [51.33, 86.78]). Additionally, 15 patients had a best response of SD with a DCR of 79% (95% CI: [8.30, 40.95]). Of the 11 enrolled melanoma patients who received combination, 5 achieved a PR for an ORR of 45% and 6 achieved SD for an DCR of 100%. Of the 9 enrolled NSCLC patients who received combination, 2 achieved a PR for an ORR of 22% and 4 achieved SD for an DCR of 67%. *Safety:* While on monotherapy, 24/43 (56%) patients reported treatment-related adverse events (TRAEs). While on combination therapy, 17/28 (61%) patients reported TRAEs. The majority of TRAEs were grades 1-2. The only dose limiting toxicity was a grade 3 rash which occurred at the monotherapy 400mg BID dose. Only one serious TRAE (grade 3 immune mediated hepatitis) was reported at the data cut-off. **Conclusions:** In relapsed/refractory solid tumor patients, ATG-037 appears to be well tolerated as monotherapy and in combination with pembrolizumab. The preliminary efficacy data is encouraging and suggests that the combination regimen may provide a new therapeutic option for CPI resistant NSCLC and melanoma patients. Clinical trial information: NCT05205109. Research Sponsor: None.

Phase 1 study of zavondemstat (TACH101), a first-in-class KDM4 inhibitor, in patients with advanced solid tumors: Results on safety, pharmacokinetics, and anti-tumor activity.

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Background: Zavondemstat is an epigenetic targeting inhibitor of KDM4 histone demethylase. Dysregulation of KDM4 enzymes (isoforms A-D) has been implicated in various cancers where they drive oncogenesis and resistance pathways by regulating gene transcription. Preclinical studies of zavondemstat demonstrated robust anti-proliferative effects and significant inhibition of tumor growth across numerous xenograft and PDX models. Targeting KDM4 offers the potential to reprogram the epigenetic dysfunction of cancer cells and inhibit drivers of tumor dedifferentiation and proliferation leading to apoptotic cell death. This is the first clinical evaluation of a pan-isoform KDM4 inhibitor. **Methods:** TACH101-CS-0001 (NCT05076552) was an open-label Phase 1 study assessing zavondemstat's safety, tolerability, pharmacokinetics (PK), and recommended Phase 2 dose (RP2D) in patients (pts) with advanced solid tumors. Pts received zavondemstat orally on a weekly schedule in 28-day cycles. Dose escalation followed a Bayesian optimal interval (BOIN) design and explored both intermittent and continuous dosing. Inclusion criteria included heavily pre-treated advanced/metastatic solid tumors that progressed or were non-responsive to available therapies and for which no standard therapy exists. Pts must have measurable disease according to RECIST (v1.1) and ECOG score of 0 to 1. Exclusion criteria included severe hematologic, hepatic, or renal insufficiency. Primary endpoints included safety/tolerability, MTD and RP2D. Secondary endpoints included PK and radiographic response per RECIST v1.1. **Results:** Thirty patients were enrolled across 6 dose cohorts. MTD was not reached; RP2D was not determined. The most common treatment-related adverse events (TRAEs) were diarrhea (12%), fatigue (7%), decreased appetite (7%), nausea (7%), and hyponatremia (7%). All TRAEs were Grade 1 or 2 (no TRAEs $\geq$ Grade 3 were reported). No treatment-related serious adverse events (SAEs) or dose limiting toxicities (DLTs) were reported. In 23 response-evaluable patients, 10 patients (44%) achieved stable disease (SD) across dosing cohorts. Two patients (9%) had SD $\geq$ 6 months, including a patient with castration-resistant prostate cancer (CRPC) and a patient with leiomyosarcoma. Another patient with leiomyosarcoma is continuing to receive zavondemstat under compassionate use, demonstrating SD for a total of 6 months at time of abstract submission. Zavondemstat demonstrated a dose-proportional exposure profile with a short half-life of about 1.5 hours. There was no to minimal drug accumulation observed. **Conclusions:** Zavondemstat was very well tolerated and showed encouraging preliminary signals of clinical benefit in very heavily pre-treated metastatic cancer patients. Continued evaluation of zavondemstat is warranted. Clinical trial information: NCT05076552. Research Sponsor: Tachyon Therapeutics; California Institute for Regenerative Medicine (CIRM).

Phase I dose-escalation study of the safety and pharmacokinetics of PAS-004, a macrocyclic MEK inhibitor, for the treatment of patients with MAPK pathway–driven advanced solid tumors.

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Background: PAS-004 is a small molecule allosteric inhibitor of MEK 1/2 and the first macrocyclic structure MEK inhibitor in clinical development. Macrocycles are large cyclic molecules that can bring increased potency, metabolic stability, and oral bioavailability. PAS-004 was developed to reduce metabolic liabilities and overcome the limited exposure and stability of known MEK inhibitors. We report initial results of an ongoing Phase I dose escalation, multicenter study of PAS-004 in monotherapy in patients with advanced refractory solid tumors. **Methods:** The Phase 1 clinical trial is a multi-center, open-label, dose escalation 3+3 study design to evaluate the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of PAS-004 in patients with MAPK pathway driven advanced solid tumors with a documented RAS, NF1 or RAF mutation, or patients who have failed BRAF/MEK inhibition (NCT06299839).Eligible pts, ≥18 years with MAPK-driven advanced solid tumors, are being enrolled in dose escalation at 8 different dose cohorts in monotherapy. **Results:** As of 3 Jan 2025, a total of 9 patients have been enrolled in dose escalation in 3 dose cohorts (2mg, 4mg, and 8mg). 55.6% of the patients were female with a median age of 60 years. Most common tumor types included colorectal (n = 5, 55.56%), pancreatic (n = 2, 22.22%), gastroesophageal (n = 1, 11.11%), and of unknown type (n = 1, 11.11%). Treatment Related Adverse Events (TRAE) were reported in 44.44% of patients. TRAEs were all low grade (n = 7, 100% were Grade 1-2). No Grade 3, 4 or 5 TRAEs were reported. The most common TRAEs were gastrointestinal disorders (n = 4, 57.14%), dehydration (14.29%), arthralgia (14.29%) and urinary incontinence (14.29%). No rash was observed in any dose cohort. No dose limiting toxicities were detected, and the MTD has not been reached. Preliminary PAS-004 PK analysis suggests linear PK with estimated t1/2 of 70h, Cmax/Cmin ratio of 1.4 at steady state, achieving potentially sufficient exposures for target engagement at the highest dose tested. In the efficacy evaluable population (n = 6), early response evaluation reveals stable disease (SD) by RECIST 1.1 was observed in 2 patients, with progression free survival of up to 159 days and overall survival of up to 253 days. **Conclusions:** To date, PAS-004 is shown to be a safe and well-tolerated novel MEK inhibitor, with dose-dependent PK profile and preliminary clinical activity in monotherapy in patients with heavily pre-treated refractory solid tumors. PAS-004 has the potential to achieve prolonged target inhibition and once-daily dosing (QD) due to its long half-life and low Cmax to Cmin ratio. These findings provide a compelling rationale to continue to test PAS-004 into clinical trials for the treatment of MAPK-driven opportunities. Clinical trial information: NCT06299839. Research Sponsor: Pasithea Therapeutics.

Pertuzumab plus trastuzumab (P+T) in patients (pts) with bladder (BC) and ovarian cancer (OC) with *ERBB2/3* alterations (alt): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating antitumor activity of commercially available targeted agents in pts with advanced cancers with genomic alt. Results of two cohorts of pts with BC or OC with *ERBB2/3* alt treated with P+T 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 performed in CLIA-certified, CAP-accredited site selected labs. Recommended dosing was P at an initial dose of 840 mg intravenously (IV), then 420 mg IV every 3 weeks (wks) and T at an initial dose of 8 mg/kg IV, then 6 mg/kg IV every 3 wks until disease progression. Primary endpoint was disease control (DC) per investigator defined as complete (CR) or partial (PR) response per RECIST v.1.1, or stable disease (SD) of at least 16 wks duration (SD16+). CR was based on radiographic assessment. For both cohorts, Simon 2-stage design was based on a null DC rate of 15% vs. 35% (power = 0.85; α = 0.10). If $\geq$2 of 10 pts in stage I had DC, 18 more pts were enrolled; otherwise, the cohort was closed. If $\geq$7 of 28 pts had DC, the null DC rate was rejected. Secondary endpoints were objective response (OR), progression-free survival (PFS), overall survival (OS), duration of response and SD, and safety. **Results:** 28 pts with *ERBB2/3* alt were enrolled in each cohort. The table shows demographics and outcomes. For the BC cohort, 2 CRs (*ERBB2* amplification [amp, n=1] and *ERBB2* amp and *ERBB3* mutation [mut, n=1]), 5 PRs (*ERBB2* amp [n=3], *ERBB2* amp and mut [n=1], and *ERBB2* mut [n=1]) and 3 SD16+ (*ERBB2* mut [n=3]) were observed for DC rate of 37% (90% CI, 24 to 100) and OR rate of 25% (95% CI, 11 to 45). The null DC rate was rejected (p=0.005). For the OC cohort, 2 PRs (*ERBB2* amp [n=1] and *ERBB2* mut [n=1]) and 3 SD16+ (*ERBB2* amp [n=2] and *ERBB2* amp and mut [n=1]) were observed for DC rate of 25% (90% CI, 10 to 100) and OR rate of 7% (95% CI, 1 to 24). The null DC rate was not rejected (p=0.29). Across both cohorts, 4 pts had 6 tx-related serious adverse events (SAE) including: infusion-related reaction, confusion, diarrhea, and fever, and 2 pts had 1 grade 3 tx-related adverse event (AE) each including: GGT increase and lymphopenia. No pts had grade 5 SAEs. **Conclusions:** P+T met prespecified criteria to declare clinical activity in pts with BC with *ERBB2* alt, but not in pts with OC. Additional study is warranted to confirm the efficacy of P+T in pts with BC with *ERBB2* alt. Clinical trial information: NCT02693535. Research Sponsor: Genentech; Astrazeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck, Pfizer, Seagen (now a wholly owned subsidiary of Pfizer Inc.), Taiho Oncology.

Demographics and efficacy outcomes.

			BC (N=28)		OC (N=28)
ECOG PS, N (%)	0	6	(21)	11	(39)
	1	17	(61)	16	(57)
	2	5	(18)	1	(4)
Prior systemic regimens, N (%)	1-2	6	(21)	13	(46)
	≥3	22	(79)	15	(54)
DC (OR plus SD16+) rate, % (90% CI), p-value		37	(24, 100), p=0.005	25	(10, 100), p=0.29
OR rate, % (95% CI)		25	(11, 45)	7	(1, 24)
Median PFS, wks (95% CI)		13	(7, 22)	8	(8, 16)
Median OS, wks (95% CI)		32	(17, 54)	44	(26, 89)

Digital spatial profiling of advanced solid tumors and lymphomas from a phase 1 trial of copanlisib and nivolumab.

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Background: Digital spatial profiling (DSP) is an innovative technique that facilitates spatially resolved proteotranscriptomic analysis within tissue sections, providing essential insights into the tumor microenvironment (TME). As part of the exploratory objectives in the Phase 1B trial (NCT03502733) evaluating adult patients(pts) with solid tumors and lymphomas copanisib (C), nivolumab (N) + ipilumumab (I), we employed the NanoString-Bruker GeoMx DSP platform to evaluate spatial heterogeneity in differentially regulated biomarkers. **Methods:** The study analyzed samples from pts in the trial's doublet treatment arm, which included C + N. Pts receive C on days 1 and 15 or days 1, 8, and 15 of each cycle and nivolumab on day 1 or days 1 and 15 of each cycle. Core biopsies collected from 8 pts at cycle 1 day 1 pre-dose (C1D1, baseline), cycle 1 day 8 post-dose (C1D8, C only) and cycle 2 day 15 post-dose (C2D15, C+N) were selected for GeoMx analysis. Tissue sections (5-μm) from archival FFPE blocks were prepared on glass slides and hybridized with photocleavable tag-conjugated antibodies (targeting 85 proteins) and oligonucleotide probes (whole transcriptome- WTA) for protein and WTA analyses respectively. Tissue imaging was performed via high-resolution fluorescent microscopy using morphology markers (cytokeratin AE1/AE3, CD45, CD3, CD20, Syto-13 nuclear marker). At least three rectangular (660 x 784 μm) regions of interest (ROI) per timepoint were analyzed using NanoString nCounter for proteomics and NGS for WTA. Data quality control and analysis were conducted using the GeoMx DSP Control Center (V-3.0) with a significance threshold of $\alpha = 0.05$. **Results:** In two lymphoma pts with stable disease (SD) or partial response (PR), PI3K downstream signaling showed downregulation at C1D8 due to C-mediated PI3K-AKT signaling inhibition, possibly through PIK3IP1 overexpression. This signaling returned to baseline by C2D15, likely due to C's elimination half-life. In a follicular lymphoma case (#18, PR), FOXP3 expression decreased at both C1D8 and C2D15, while CD4 and CD8 levels remained constant. Immune marker expression (PD-L1, PD-1, CTLA-4, CD80) progressively declined. However, in diffuse large B-cell lymphoma (#14, SD), no changes in T-cell markers were observed. Solid tumor cases (#12, #24, SD) showed PI3K-AKT signaling downregulation at C2D15, along with CD3+/CD8+ T-cell infiltration into the tumor. FOXP3 levels slightly decreased in tumor and immune compartments. Progressive disease cases showed no change in T-cell markers. **Conclusions:** GeoMx DSP demonstrated its capability to investigate phospho-signaling and immune profiles in tumor and stromal compartments of small biopsies, highlighting its potential to enhance the understanding of TMEs in clinical studies. Further applications may provide critical insights for clinical cancer trials. Clinical trial information: NCT03502733. Research Sponsor: None.

Long non-coding RNA (lncRNA) SNHG11 as a prognostic and predictive biomarker in metastatic colorectal cancer (mCRC): Insights from CALGB (Alliance)/SWOG 80405.

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Background: LncRNAs have emerged as key regulators of cancer progression and therapeutic responses. In CRC, several lncRNAs have been implicated in modulating tumor growth, metastasis and treatment resistance by interacting with critical tumorigenic pathways. Here, we investigate the potential prognostic and predictive value of lncRNA expression in patients (pts) with mCRC enrolled in CALGB/SWOG 80405 (NCT00265850) trial. **Methods:** We analyzed 433 mCRC pts treated with either bevacizumab (bev, n = 226) or cetuximab (cet, n = 207) plus first-line chemotherapy. Tumor RNA expression (Illumina HiSeq 2500) of 13 candidate lncRNAs (SNHG11, HOTAIR, FGF14-AS2, H19, YWHAE, NEAT1, MIR100HG, UCA1, LINC00973, SLC04A1-AS1, POU5F1P4, MALAT1, HCG18) was explored. Median overall survival (mOS) and progression-free survival (mPFS) in months (mo) were compared between pts grouped by tertiles (low [L] vs medium [M] vs high [H]) of gene expression. Likelihood ratio tests, hazard ratios and 95% confidence intervals were computed from multivariable Cox proportional hazards models, adjusting for age, sex, ECOG PS, tumor location, number of metastatic sites, *KRAS*, Consensus Molecular Subtypes (CMS), and treatment. **Results:** Overall, SNHG11 was strongly associated with OS and PFS after adjusting for multiple tests (Benjamini-Hochberg False Discovery Rate < 0.05). High SNHG11 expression (H group, n = 144) was associated with improved mPFS (H: 14.3 vs M: 11.2 vs L: 8.3 mo; p = 0.038) and mOS (H: 39.6 vs M: 31.1 vs L: 20.5 mo; p = 0.033) in the combined treatment analysis. Among cet-treated pts, SNHG11-H showed a numerically longer mPFS (H: 14.2 vs M: 11.1 vs L: 7.6 mo; p = 0.19) and significantly longer mOS (H: 41.1 vs M: 32.4 vs L: 14.3 mo; p = 0.012). In contrast, no statistically significant OS or PFS differences were observed in bev-treated pts. SNHG11-H tumors had a significant OS benefit from cet compared to bev (mOS 41.1 vs 36.5 mo, respectively; p = 0.016), with a nominally significant treatment interaction observed for OS (p = 0.030). No significant differences were observed in the L or M expression groups. Additional analyses showed that SNHG11 expression was high in the CMS2 (canonical) subtype and substantially lower in CMS1 (immune). **Conclusions:** LncRNA SNHG11 plays a significant role in CRC progression and metastasis via tumorigenic pathways, including c-Myc and HIF-1α. Moreover, elevated circulating SNHG11 levels show promise as a non-invasive biomarker for early CRC detection. In CALGB/SWOG 80405, high SNHG11 expression correlated with improved PFS and OS, particularly in cet-treated pts, supporting its role as a prognostic and predictive biomarker. Its strong association with CMS2 aligns with its reported involvement in c-Myc-driven pathways. Further validation is needed to confirm the clinical utility of this biomarker and elucidate underlying mechanisms. Research Sponsor: National Cancer Institute; P30CA014089, U10CA180821, U10CA180882, U10CA180888; Genentech; https://acknowledgments.alliancefound.org.

Using single-cell sequencing to identify endothelial expression of immune checkpoint ligands in advanced hepatocellular carcinoma, pre- and post- atezolizumab plus bevacizumab in the phase II INTEGRATE study.

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Background: Atezolizumab (atezo; anti-PD-L1) plus bevacizumab (bev; anti-VEGF-A) became a standard treatment for advanced hepatocellular carcinoma (HCC) after demonstrating an overall survival advantage over sorafenib (inhibitor of VEGFR2 & other kinases) in the phase III clinical trial, IMbrave150. However, the mechanisms of primary and acquired resistance to atezo-bev are poorly understood. $VEGFR2^+$ endothelial cells (ECs) are potential cellular targets of bev and may play a key immunomodulatory role in response to atezo-bev. In this study, we utilized single-cell sequencing to identify potential mediators of resistance within EC subsets. **Methods:** Eight patients with unresectable HCC were enrolled on the INTEGRATE study, treated with atezo-bev, and underwent intensive biospecimen collection (NCT04563338). Serial tumor biopsies were collected and viably cryopreserved including pre-treatment (n=6), 21-28 days after first dose (n=6), and at disease progression (n=2). Single-cell analysis via cellular indexing of transcriptomes and epitopes (CITEseq) has been performed and data from four patients have been analysed to date. Aggregating their nine biopsies, 8,569 hepatocytes (ALB^+ $FABP1^+$ FGB^+), 29,072 immune cells ($CD45^+$), and 8,028 ECs ($CD31^+$ vWF^+ KDR^+) were annotated. The differential expression of VEGFR2, PD-L1, and other immune checkpoint ligands by tumor vs. immune vs. endothelial cellswere interrogated (Table). **Results:** VEGFR2 (receptor for VEGF-A) is predominantly expressed by ECs, at high prevalence & intensity. PD-L1 and PD-L2 (ligands of PD-1) are expressed by ECs at low prevalence & intensity. Galectin3 (LAG3 ligand) is widely expressed by hepatocytes, immune cells and ECs; while L-SECtin (LAG3 ligand) is predominantly expressed by ECs but at low prevalence & intensity. ECs had the highest prevalence of galectin9 (TIM3 ligand) expression. Nectin2 (TIGIT ligand) is expressed by both hepatocytes and ECs at high prevalence & intensity. **Conclusions:** Liver ECs express a broad array of immune checkpoint ligands, which are more frequent than previously anticipated. These EC subsets may potentially drive resistance by contributing to exhaustion of T cell subsets entering the tumor microenvironment. Complete CITEseq, TCR sequencing, and correlative studies from the full cohort are underway. Clinical trial information: NCT04563338. Research Sponsor: This research was a collaborative effort made possible through support from F. Hoffmann-La Rohce for the imCORE Network.

	Hepatocytes	Immune cells	ECs
VEGFR2 (KDR)	0.06% (<0.01)	0.05% (<0.01)	66% (0.8)
PD-L1 (CD274)	0.2% (<0.01)	4% (0.03)	2% (0.01)
PD-L2 (PDCD1LG2)	0.02% (<0.01)	2% (0.02)	3% (0.02)
L-SECtin (CLEC4G)	0%	0.1% (<0.01)	3% (0.05)
Galectin-3 (LGALS3)	68% (0.8)	39% (0.5)	43% (0.5)
Galectin-9 (LGALS9)	5% (0.04)	28% (0.3)	34% (0.3)
PVR (CD155)	14% (0.1)	1% (<0.01)	18% (0.1)
Nectin2 (CD112)	60% (0.5)	5% (0.04)	44% (0.4)

% = proportion of cells with positive expression. ( ) = normalized mean expression.

Assessment of homologous recombination deficiency and BRCA status in ovarian cancer: Analytical performance and relevance of a decentralized NGS assay for comprehensive genomic profiling.

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Background: Homologous recombination deficiency (HRD) is a complex biomarker with predictive value in ovarian cancer. Understanding both the causes of HRD, such as pathogenic alterations in homologous recombination repair (HRR) genes, and its consequences, like genomic instability (GI), is crucial for exploring various therapeutic strategies, including the potential use of poly (ADP-ribose) polymerase inhibitors (PARPi). This study evaluates the analytical performance and clinical research relevance of the Oncomine™ Comprehensive Assay Plus (OCA Plus), a distributable next-generation sequencing (NGS) research use assay that offers in a single workflow comprehensive genomic profiling, including HRD evaluation. **Methods:** The OCA Plus panel was used for comprehensive genomic profiling of a series of 299 ovarian cancer research samples from the PAOLA-1 trial, part of the ARCAGY biorepository. Research samples were analyzed to assess agreement with orthogonal method, specifically for *BRCA1* and *BRCA2* mutational status, GI status and overall HRD status which combined BRCA1/2 mutational status and GI status. GI status was determined using Genomic Instability Metric (GIM), a quantitative method that characterizes unbalanced copy number changes. Progression-free survival (PFS) was retrospectively studied to determine future clinical relevance. **Results:** The success rate for DNA sequencing was 100%, starting from a minimal sample input of 20ng of genomic DNA isolated from FFPE tissue blocks. The OCA Plus panel provided a detailed genomic profile in a single workflow, achieving high success rates across all biomarkers tested, including single nucleotide variants/indels and HRD (100%). Overall percent agreement (OPA) for HRD status with orthogonal method was 87%. OPA for *BRCA1/2* variants was 98%, while OPA for GI status was 80%. PFS analysis demonstrated a significantly better hazard ratio (HR: 0.51, $p < .005$) for the cases positive for OCA Plus HRD solution compared to the cases negative for the OCA Plus HRD solution (HR: 0.84, $p = 0.43$). **Conclusions:** The OCA Plus solution enables robust and reliable comprehensive genomic profiling with high OPA for *BRCA1/2* and HRD status compared to commonly used orthogonal method. Albeit additional studies are due, overall, the reported data suggests its future clinical utility in predicting treatment outcomes in ovarian cancer. Research Sponsor: None.

Cost-effectiveness of NTRK testing strategies for detecting NTRK fusions in solid tumors in China.

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Background: Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in many solid tumors. With the inclusion of the targeted drug Entrectinib in China's national reimbursement drug list, the demand for NTRK testing has also increased. This study evaluates the cost-effectiveness of a two-step testing strategy (initial pan-TRK IHC testing followed by next-generation sequencing (NGS) confirmation for positive results) compared to directly conducting NGS testing, with treatment of positive cases using Entrectinib. **Methods:** A decision tree model was established from a health system perspective, based on clinical practices in China. The study included 17 cancer types as reported in the latest clinical trial of Entrectinib (n = 194). Diagnostic performance data were sourced from literature and validated by pathologists and clinicians. Clinical efficacy, treatment phase costs, and utility for progression-free survival (PFS) were obtained from open databases and literature. Turnaround time and costs for testing was gathered from expert interviews. The time horizon was set to include the duration of NTRK testing and the period of PFS associated with the medication. A one-way sensitivity analysis was conducted to assess the model's robustness. **Results:** In China, the NGS testing alone produced 0.55507 life years (LY) and 0.42646 quality-adjusted life years (QALY) at a total cost of $5932.57 , whereas the pan-TRK IHC + NGS testing strategy yielded 0.55530 LY and 0.42665 QALY at a total cost of $4176.67. The pan-TRK IHC+NGS testing strategy was dominant, offering higher QALY at lower costs than NGS testing alone. Additionally, the average wait time for pan-TRK IHC + NGS testing was reduced by 10 days. The robustness of the base case results was confirmed through sensitivity analysis. **Conclusions:** Initial pan-TRK IHC testing, followed by NGS confirmation for positive results, is the optimal strategy for NTRK fusion detection in patients with locally advanced or metastatic solid tumors in China, providing superior cost-effectiveness compared to NGS testing alone. Research Sponsor: None.

Cost-effectiveness analysis results.

Testing	Total Cost(USD$)	Effectiveness (LYs)	Effectiveness (QALY)	Incremental cost ($)	Incremental QALYs	ICER (Cost/QALY)
NGS	$5932.57	0.55507	0.42646			pan-TRK IHC +NGS
pan-TRK IHC+NGS	$4176.67	0.55530	0.42665	-$1755.90	0.000187	was dominant

ICER: Incremental cost-effectiveness ratio.

Impact of sample characteristics on RNA-based next-generation sequencing (NGS) for fusion gene detection in non-small cell lung cancer (NSCLC).

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Background: RNA-based next-generation sequencing (NGS) has been widely employed for detecting fusion genes in NSCLC, due to its superior sensitivity and simplified design compared to DNA-based NGS. However, the impact of sample quality on fusion variant detection using RNA-based NGS remains unclear. **Methods:** The study analyzed 5,386 and 5,538 NSCLC samples using DNA- or RNA-based NGS to detect common fusion genes (ALK, RET, ROS1, NTRK, NRG1, MET exon 14 skipping, and FGFR). NGS libraries were constructed using capture-based or amplicon-based methods for DNA and RNA samples, respectively, focusing on pathogenic mutations. **Results:** RNA-based NGS detected 2.44% more fusions than DNA-based NGS [9.50% (526/5538) vs. 7.06% (380/5386)], with notable advantages for NTRK (0.13% vs. 0.02%), NRG1 (0.25% vs. 0.06%), MET exon 14 skipping (2.15% vs. 1.36%), and FGFR fusions (0.40% vs. 0.02%). Tumor cell content analysis showed no significant impact on fusion detection rates within the 20%-90% range for either method. However, higher tumor cell content ($\geq$80%) significantly increased RNA-based NGS detection rates compared to DNA-based NGS, nearly doubling the total detection rate (17.3% vs. 8.88%), primarily due to increased ALK fusion detection (8.97% vs. 5.02%). The type of sampling (surgical, biopsy, or others) did not significantly affect overall fusion detection rates for either method ($p > 0.05$). However, gene-specific analyses showed significantly higher detection rates for ROS1, MET, and RET using RNA-based NGS in biopsy samples compared to DNA-based methods (ROS1: 11.83% vs. 1.18%, MET exon 14 skipping: 2.87% vs. 1.62%, RET: 1.24% vs. 0.79%). Conversely, RNA-based detection of ALK and NRG1 fusions was higher in surgical samples (ALK: 4.00% vs. 3.25%, NRG1: 0.34% vs. 0.08%) compared to DNA-based methods. Regarding sample types, pleural/peritoneal effusions showed higher detection rates than FFPE samples, though not statistically significant. RNA-based NGS consistently showed superior detection rates for ALK and MET exon 14 skipping in all sample types compared to DNA-based methods, with the most substantial increase for MET exon 14 skipping in pleural/peritoneal effusions (2.14% vs. 0.98%). Conversely, RNA-based NGS for NRG1 and ROS1 fusions showed a greater relative increase in detection rate in 10% neutral formalin-fixed tissue/FFPE sections/unstained slides compared to pleural/peritoneal effusions. **Conclusions:** Sample characteristics did not significantly impact the overall detection rate of RNA-based fusion assays. However, detection rates for specific fusions like ALK, NRG1, and MET exon 14 skipping varied with sample type, sampling method, and tumor cell content. Optimizing testing strategies and sample handling is crucial to improving diagnostic accuracy in NSCLC. Research Sponsor: Medical Scientific Research Foundation of Guangdong Province, China; A2022519.

Effect of irradiation on the killing effect of NK cells in colon cancer through MYB/TIM3 axis.

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Background: Natural killer (NK) cells play a crucial role in tumor progression and anti-tumor immunity. However, they often exhibit an exhausted phenotype within the tumor microenvironment (TME), limiting their full cytotoxic potential. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) has emerged as a novel immune checkpoint that is highly expressed on NK cells and suppresses their cytotoxic function. TIM-3 is closely associated with immune evasion and anti-tumor immune tolerance. This study aims to investigate the effects and mechanisms by which radiation modulates NK cell function, providing a foundation for developing strategies that specifically target TIM-3 on NK cells. **Methods:** First, mRNA high-throughput sequencing, RT-qPCR, and Western blot experiments were used to analyze changes in the expression of related genes in NK92 cells after radiotherapy. The LDH release assay was employed to evaluate the effect of radiation on the viability of NK92 cells. ELISA was conducted to detect changes in the release levels of tumor necrosis factor TNF-α and other factors after radiotherapy. Dual-luciferase reporter assays and chromatin immunoprecipitation (ChIP) experiments confirmed that the transcription factor MYB mediates radiation-induced regulation of NK cell activation by targeting and binding to the TIM-3 promoter region. A non-contact co-culture system was established, and flow cytometry demonstrated that radiation combined with MYB overexpression enhanced the cytotoxicity of NK cells against tumor cells. A colon cancer mouse model was constructed to evaluate the anti-tumor effect of combining anti-TIM-3 antibodies with radiotherapy. **Results:** We found that radiation can activate NK92 cells in vitro and enhance TIM-3 expression,promoting the secretion of granzyme B, perforin, TNF-α, IFN-γ, and other cytokines and chemokines that modulate the TME and enhance anti-tumor immune responses. Moreover, the transcription factor MYB inhibits TIM-3 expression by directly binding to the TIM-3 promoter region, mediating the effects of radiation on the TME through NK cell activation. In vivo, the combination of radiotherapy and anti-TIM-3 antibodies effectively controlled the growth of subcutaneously transplanted colon cancer tumors in C57BL/6 mice. However, this combined treatment effect was significantly diminished after NK cells were depleted by the anti-NK1.1 antibody. **Conclusions:** This study elucidates a novel mechanism by which radiation activates NK cells in the tumor microenvironment through the MYB/TIM-3 pathway. It provides new insights for enhancing the efficacy of radiotherapy and offers a theoretical basis for the potential clinical application of these cells in future research. Research Sponsor: None.

Combined prognostic value of post-surgery circulating tumor DNA and tumor-stroma ratio in patients with stage III colon cancer treated with adjuvant chemotherapy.

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Background: Patients with stage III colon cancer (CC) are routinely treated with resection followed by adjuvant chemotherapy (ACT). About half of patients are cured by surgery and hence overtreated with ACT, yet another ~30% experience recurrence and are currently undertreated. Only ~20% of patients are cured by ACT and we are unable to identify these patients. Prognostic value of circulating tumor DNA (ctDNA) and the tumor-stroma ratio (TSR) has been shown in separate studies. This study aimed to integrate these biomarkers with pTNM substage to better predict outcome in stage III CC patients treated with ACT. **Methods:** Patients with stage III CC who received radical resection followed by ACT were selected from the Prospective Dutch ColoRectal Cancer cohort (PLCRC) substudy PROVENC3 (Rubio-Alarcon AACR 2024). Blood was collected between surgery and ACT, to determine ctDNA status using Labcorp Plasma Detect. Based on a diagnostic H&E slide from the CC resection, the TSR was determined by a trained observer according to the United study (Polack ESMO open 2024). A stroma content of ≤50% was considered low and >50% high. The primary outcome was recurrence risk (RR), calculated from date of resection. **Results:** In the overall cohort (N = 207), the 3-year RR was 23.4% [17.3-29.1]. In total, 88 patients (43%) were stroma-high and had a higher recurrence risk (3-year RR 33.1% [22.5-42.3]) than the 119 stroma-low patients (3-year RR 16.0% [8.9-22.5]; HR 2.7 [1.6-4.6]). CtDNA was detectable after surgery in 28 patients (13.5%; HR 5.8 [3.3-10]), of whom 11 (39%) were stroma-high. T4/N2 stage was observed in 82 patients (HR 2.9 [1.7-5.0]), of whom 46 (56%) were stroma-high. TSR (HR 2.6 [1.5-4.6]) had added prognostic value to ctDNA (HR 7.6 [4.3-13]) and pTNM substage (HR 2.9 [1.7-5.0]) in a multivariable cox model (LRT $p<0.001$). Patients with no detectable ctDNA and stroma-low T1-3N1 CC were at low recurrence risk (N = 71; 3-year RR 2.9% [0-6.8]). In comparison, patients with no detectable ctDNA and a tumor that was either stroma-high or T4/N2 were considered intermediate risk (N = 68; 3-year RR 17.2% [7.4-26.0]; HR 5.4 [1.5-19]). Patients with detectable ctDNA and/or stroma-high T4/N2 CC had a high risk (N = 68; 3-year RR 50.2% [36.7-60.8]; HR 19 [5.9-62]). **Conclusions:** The tumor-stroma ratio has added value to post-surgery ctDNA and pTNM substage in predicting outcome in stage III CC patients treated with ACT. The recurrence risk in the third of patients with no detectable ctDNA and stroma-low T1-3N1 CC was only 3%. It is of interest to investigate whether this low risk would persist in a cohort treated with surgery only, to suggest whether these patients could be spared ACT in the future. The third of patients with detectable ctDNA, and/or stroma-high T4/N2 CC, had a 50% recurrence risk despite ACT, highlighting the need for alternative adjuvant treatment options for these patients. Research Sponsor: None.

Regorafenib response prediction in metastatic colorectal cancer by a novel genomic and transcriptomic model.

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Background: The multi-kinase inhibitor regorafenib (Rego) is approved for the treatment of refractory metastatic colorectal cancer (CRC). However, its efficacy is limited, and its use is frequently associated with substantial toxicities. Identifying biomarkers predicting Rego-response could improve therapeutic outcomes and reduce unnecessary treatment-related adverse effects in non-responders. **Methods:** A predictive model for Rego-response was developed based on transcriptomic and genetic data from 41 CRC cell lines. Cell lines were classified into Rego-sensitive *versus* -resistant groups based on drug sensitivity data from the CTRP2 database. Several machine-learning algorithms were evaluated, with the Generalized Linear Model via Elastic Net (GLMNET) achieving the highest predictive performance. Model accuracy was assessed using leave-one-out cross-validation. Further validation was performed using transcriptomic (WTS) data from 24,384 real-world CRC patients assessed by Caris Life Sciences, which included 720 patients treated with Rego. **Results:** The predictive model identified key cell line features associated with Rego-response, including gene expression signatures (e.g., *ZNF441, CCDC82, ZFP69*) and specific mutations (e.g., *RALGAPA1, MORC1*). Transcriptome profiling showed that Rego responders exhibited enrichment in cell-cycle regulation and DNA-repair mechanisms, while non-responders showed a stroma-rich microenvironment with significant endothelial and fibroblast infiltration. External validation using WTS data from real-world Rego-treated CRC patients revealed that predicted responders had a prolonged time-on-treatment ($p = 0.02$, HR = 0.79) and median overall survival ($p = 0.01$, HR = 0.76) compared to predicted non-responders. This association was specific to Rego-response, as there was no survival difference between predicted responders and non-responders among patients not treated with Rego ($p = 0.72$, HR = 1.0). **Conclusions:** This novel predictive model successfully identified and validated molecular features associated with Rego-response in CRC. The transcriptomic and genetic signature holds significant potential for improving personalized treatment strategies by identifying patients most likely to benefit from Rego and prevents unnecessary Rego-associated toxicities in non-responders. Research Sponsor: None.

Relationship between FOLR1 expression and pan-cancer subgroup of tumors with specific transcriptomic profile.

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Background: Mirvetuximab soravtansine is an antibody–drug conjugate currently approved for the treatment of advanced platinum-resistant ovarian cancer. The efficacy of this therapy is correlated with high expression of folate receptor alpha (FRα), encoded by the FOLR1 gene. Treatment requires $\geq$ 75% of tumor cells to be stained positively for FRα by immunohistochemistry (IHC). Here we defined the FOLR1 RNA level that distinguishes ovarian cancers with very high FRα ($\geq$ 75% by IHC), then compared the transcriptomic profile of these cases (FOLR1-H) with the transcriptomic profile of cases with very low FRα expression (FOLR1-L). We further explored the presence similar FOLR1-H signature in various types of cancers. **Methods:** RNA was extracted from 1450 solid tumor FFPE samples and sequenced using a targeted RNA panel of 1600 genes. The RNA expression levels of various genes were quantified and expressed as transcript per million (TPM). IHC for FRα protein was performed on ovarian cancers (N = 49) using VENTANA FOLR1 RxDx assay. **Results:** Based on comparing IHC with RNA expression of FOLR1, FOLR1-H samples were defined with RNA $\geq$ 300 TPM while FOLR1 mRNA $<$ 100 was correlated with very low FRα by IHC and classified as FOLR1-L. Of the 312 ovarian cancers, 21% were classified as FOLR1-H and showed significantly (Log10FDR $<$ -2) higher expression in 39 genes as compared with FOLR1-L. The Log10FDR was $<$ -10 in 19 genes. The top highly expressed genes in FOLR1-H cases were TROP2, NECTIN4, ROR1, ROR2, ACVRL1, and NTHL1. In breast cases (N = 199) FOLR1-H was detected in 14.6% of cases and the most highly expressed genes were ACVRL1, NECTIN4, ROR1, and ACVRL1 (Log10FDR $<$ -5). Of the 932 cases of lung cancer, 21.5% classified as FOLR1-H and had significantly (Log10FDR $<$ -2) high expression of 137 genes, but similar to ovarian cancer TROP2, NECTIN4, ROR1, ROR2, ACVRL1, and NTHL1 were top expressed genes. Of the 174 pancreatic cancers 9.8% were FOLR1-H and top expressed genes were NECTIN4, ROR1, and ACVRL1. In sarcoma (N = 166), 8.4% had FOLR1-H and only three genes (NECTIN4, NTHL1 and SLC47A1) were significantly high. Of the 327 colorectal cancers, 8% met the criteria for FOLR1-H and 16 genes were significantly higher in FOLR1-H including NECTIN4, NTHL1, ACVRL1, ROR1/2. In 64 esophageal cancers 10.9% were FOLR1-H, but only 3 genes (GALNT12, ACVRL1 and NECTIN4) were significantly higher. **Conclusions:** This data suggests that cancers with significantly high expression of FOLR1 mRNA are a special subtype of tumors characterized by the expression of embryonic cell surface markers (FOLR1, TROP2, NECTIN4, ROR1/2). The pan-cancer marked overexpression of these genes suggests that cancers with FOLR1-H represent a subtype of cancers with similar biology. This subtype may benefit from combination therapy targeting more than one of these markers (e.g. anti-FOLR1 with anti-TROP2, or anti-NECTIN4) and clinical trial with such combination may be justified. Research Sponsor: None.

Multi-omics cohort-based prediction model for early relapse of hepatocellular carcinoma post-surgery.

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Background: Postoperative early relapse (PER) of hepatocellular carcinoma (HCC) presents significant challenges in clinical management. Identifying reliable predictive markers and therapeutic strategies for PER is crucial for improving patient outcomes. **Methods:** We constructed a predictive model for PER using multi-omics data from 177 HCC patients with follow-up information. Transcriptomic and proteomic profiling of HCC tissues was performed, followed by differential expression analysis and Weighted Gene Co-expression Network Analysis (WGCNA) to identify molecular markers associated with PER. Univariate, LASSO, and multivariate Cox regression analyses were employed to refine the marker set, resulting in a three-gene signature. The model's accuracy was validated using a proteomic cohort and The Cancer Genome Atlas (TCGA) database. Functional enrichment, drug sensitivity, and immune infiltration analyses were conducted to explore the biological characteristics and therapeutic implications of high-PER risk patients. Patient-derived organoid (PDO) models were used for further validation. **Results:** We identified 31 molecular markers associated with PER, which were narrowed down to a robust three-gene signature (MIK67, GPD1, and MBL2) with an area under the curve (AUC) of 0.868 for predicting early relapse. Functional enrichment analysis revealed that high-PER risk patients exhibited enhanced DNA damage repair and cell cycle pathways. Drug sensitivity analysis suggested potential benefits from gemcitabine and paclitaxel, which were validated using PDO models. Immune infiltration analysis showed reduced NK cell and M2 macrophage infiltration in high-PER risk patients, confirmed by single-cell sequencing and immunohistochemical validation. **Conclusions:** This study provides a novel multi-omics-based predictive model for early recurrence in HCC, highlighting potential therapeutic options for high-risk patients. The findings underscore the importance of DNA damage repair and cell cycle pathways in PER and suggest targeted therapies that could improve clinical outcomes for high-PER risk patients. Research Sponsor: None.

Comprehensive clinicogenomic profiling of signet ring cell carcinoma across multiple organ sites.

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Background: Signet ring cell carcinoma (SRCC) is a rare, aggressive histological subtype of adenocarcinoma that is associated with earlier age of onset and poor prognosis. It most commonly arises from the stomach but can originate elsewhere. Few studies have compared molecular alterations in SRCC across various primary sites. Utilizing the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) v17.0, we performed a comprehensive analysis of clinicogenomic variables in SRCC across different primary sites. **Methods:** The AACR GENIE v17.0 database was used to select tumor samples classified as SRCC by the Oncotree Code. We excluded primary SRCC sites with $<$ 10 tumor samples. Samples were analyzed for clinicogenomic characteristics including gender, race, ethnicity, age at sequencing, and oncogenic molecular alterations by OncoKB classification (somatic mutations, structural variants, copy number alterations). We classified "early onset" SRCC as age of sequencing $<$ 50. Chi-square testing was used to compare categorical variables, and Benjamini-Hochberg procedure was used to control the false discovery rate (statistical significance for $q < 0.05$). **Results:** From 355 patients with SRCC, 358 tumor samples were analyzed, with the following distribution among primary sites: stomach (n = 168), colon/rectum (n = 125), appendix (n = 38), and bladder (n = 27). There were high rates of early onset SRCC in the stomach (29.2%), colon/rectum (47.2%), and appendix (36.8%). Female gender was numerically higher in stomach (56.9%) and appendix (55.3%) SRCC cases compared to colon/rectum (47.2%) and bladder (33.3%) SRCC cases. The most prevalent altered genes included *TP53* (45.0%), *CDH1* (19.4%), *ARID1A* (14.8%), *KRAS* (12.9%), and *SMAD4* (12.3%). There was differential enrichment of molecular alterations across various sites in *TP53*, *CDH1*, *KRAS*, *SMAD4*, *TERT*, *APC*, and *BRAF* ($q < 0.05$). **Conclusions:** To our knowledge, this study represents the largest molecular analysis of SRCC across multiple organ sites, revealing high rates of early onset SRCC and distinctive molecular alteration patterns. These findings underscore the further need to investigate functional implications and potential therapeutic targets for site-specific molecular alterations in SRCC. Research Sponsor: U.S. National Institutes of Health; 5T32CA203703-09.

Highlighted clinicogenomic features.

Clinical Variable/ Alteration	Total	Stomach	Colon/ Rectum	Appendix	Bladder	q-value
Age of Sequencing <50 (%)	34.4%	29.2%	47.2%	36.8%	3.7%	<0.001
Female Gender (%)	51.5%	56.9%	47.2%	55.3%	33.3%	0.24
TP53	45.0%	40.5%	48%	31.6%	77.8%	0.011
CDH1*	19.4%	26.2%	3.4%	7.9%	63%	<0.001
KRAS	12.9%	8.3%	17.6%	26.3%	0%	0.0055
SMAD4*	12.3%	3.6%	20.3%	21.0%	11.1%	<0.001
TERT*	8.7%	1.5%	7.1%	0%	66.7%	<0.001
APC	5.7%	1.2%	15.3%	0%	0%	<0.001
BRAF	3.9%	1.2%	8.8%	2.6%	0%	0.017

*Not all samples profiled for specific alteration; % reflects percentage of samples with alterations of those profiled.

Comparative analysis of T-cell subsets and vessel features in matched primary colorectal tumors and corresponding resected liver metastases.

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Background: Outcome after liver resection for colorectal cancer metastases (CRLM) is partly determined by factors such as the number, size, and vitality of the metastases, as well as the T- and N-stage of the primary tumor. The tumor microenvironment—particularly immune cell infiltration and vascular features—also influences outcome. Data on how these factors compare between paired primary colorectal tumors and matched CRLM are limited. **Methods:** We used TMAs from matched primary tumors and CRLM samples of 50 patients, of which 15 were untreated and 35 had received neoadjuvant therapy (cytotoxic ± VEGF-/EGFR-targeted agents) before liver resection. Each tumor consisted of 1–3 tissue cores (1 mm) from both the tumor center and the invasive margin. Multiplex immunofluorescence was performed to assess T-cell (e.g., CD3, CD4, CD8, PD1, FOXP3, TIM3, Ki67), and vessel (claudin-5, αSMA, PDGFRβ) markers. Nonparametric Wilcoxon signed rank and Spearman correlations were used for cell density comparisons. Cox regression for continuous variables was used for disease-free survival (DFS) associations. **Results:** We observed significantly lower densities of CD3+CD8+Ki67+, CD3+CD4+Ki67+, and CD3+CD4+FOXP3+ cells in CRLM than in paired primary (all $p < .006$) in both untreated and pretreated cohorts. The αSMA+PDGFRβ− vessel subset was more prevalent in CRLM compared with the primary tumor in the untreated cohort ($p < .001$). In the untreated cohort, larger vessel size in CRLM (but not in the primary tumor) showed a positive correlation with CD3+CD8+PD1+, CD3+CD4+PD1+, and CD3+CD4+FOXP3+ densities (Spearman r = .54–.60, p = .02–.04). In the pretreated cohort, higher tumor vitality and/or CDX2+ expression in CRLM (indicative of poor treatment response) were each negatively correlated with cytotoxic (CD3+CD8+) and helper T-cell (CD3+CD4+) subsets (r = -.42 to -.63, $p < .01$). DFS after metastasectomy was associated with vessel and T-cell features. Regarding vessel metrics in the small untreated cohort, αSMA−PDGFRβ− vessel subset in primary showed a negative trend (p = .06) as did smaller vessel size in CRLM (p = .06). CD3−CD4+TIM3+ in CRLM was negatively associated with DFS in pretreated (p = .04), with a trend also in untreated (p = .10). **Conclusions:** Densities of certain T-cell subsets are significantly lower in matched CRLM than in primary tumors indicating immune desert phenotype. Vessel subset profiling suggests differences between primary tumors and CRLM, possibly relevant for treatment response. Poor pretreatment effect, i.e., high vitality and CDX2+ density in CRLM, was negatively correlated with several T-cell subsets, a correlation not seen in untreated. The poor prognosis association of CD3−CD4+TIM3+ cells in CRLM merits further investigation. Research Sponsor: Finska Läkaresällskapet; Sigrid Juselius Stiftelse; Medicinska understödsföreningen Liv & Hälsa; The Finnish Cancer Foundation; The Competitive State Research Financing of the Expert Responsibility Area of Tampere and Helsinki; Tampere University Hospital Fund; Mary and Georg C. Ehrnrooth Foundation; Radiumhemmets fonder; Cancerfonden; Suomen onkologiayhdistys.

Characterisation of ductal carcinoma in situ (DCIS) using mass spectrometry imaging towards near realtime margin assessment.

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Background: Imprecision in breast-conserving surgery leads to high national average high rates of reoperative intervention. In line with updated margin guidelines, accurate differentiation between non-invasive and invasive breast cancer is essential. This study aimed to assess whether mass spectrometry can distinguish between normal breast tissue, benign, non-invasive and invasive disease towards the development of an intraoperative margin assessment tool. **Methods:** Breast tissue samples were collected from patients undergoing mastectomy. Samples were flash-frozen, sectioned, and analysed using a Xevo G2-XS QTof mass spectrometer (Waters Corp.). Selected sections were ionised using a pulsed optical parametric oscillator laser (OpoletteTM 2731/3034, OPOTEK) which operated at 2940 nm wavelength and 20 Hz repetition rate. The laser focused on the tissue through a 20 mm focal distance convex lens generating aerosol which was aspirated into the spectrometer. The data was combined using spatial distribution and chemical information from characteristic ions to generate 2D chemical images and labelled using consecutive H&E-stained sections annotated by a Consultant Histopathologist for ground truth cross-validation. **Results:** Over 1 million mass spectra were collected from imaging 52 breast tissue sections. This includes 720 mass spectra from 31 DCIS breast tissue sections, compared to 6 spectra from 2 DCIS breast tissue samples in previous work. A pixel size of 50 μm and scan rate was 250 μm/s was utilised. An ex-vivo classification model was built using n=6,796 and achieved $>$99% sensitivity for tumour detection (DCIS and IBC) and 100% specificity for identifying normal tissue. Principal Component Analysis demonstrated accurate separation of IBC, DCIS, benign breast disease, and normal breast tissue. Six possible metabolites were identified following Recursive Feature Elimination (RFE) was used to identify the most significant features which differentiate the tissue types, these were annotated using the Lipid Maps database (http://www.lipidmaps.org/) (Table 1). Cancerous tissue showed higher levels of structural lipids (600-900 Da), while normal/benign breast tissue had higher levels of small metabolites (50-300 Da) and fatty acids (200-400 Da). **Conclusions:** Mass spectrometry imaging enables accurate differentiation of IBC, DCIS, benign breast disease, and normal breast tissue. Research Sponsor: NIHR Imperial Biomedical Research Centre.

Biological features identified from the most significant RFE selected features.

m/z value	Annotation	Delta	Theoretical m/z	Ion	Class
255.2324	Palmitic acid	0.0006	255.2330	M-H	Fatty acid
297.2751	FA 19:0	0.0037	297.2799	M-H	Fatty acid
307.2019	FA 16:0	0.0026	307.2046	M+Cl	Fatty acid
766.5392	PE 38:4	0	766.5392	M-H	PE
843.5053	PI 35:4	0.0025	843.5029	M-H	PI
891.7444	TG 52:3	0.0003	891.7447	M+Cl	TG

A minimal comprehensive somatic panel to aid clinical decision making in a low cost setting.

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Background: Large next-generation sequencing (NGS) panels (> 300 genes) offer multiple potential therapeutic options for patients with metastatic cancer. However a large portion of the population in developing countries is unable to avail the benefits of such testing due to limited availability of many drugs or suitable clinical trials, coupled with the high cost of these tests. There is an urgent need to offer a compact, affordable and robust testing solution which can offer expanded but feasible therapeutic options. Hence we decided to develop a custom mid-sized panel to fulfil these unmet requirements. **Methods:** A targeted solid tumor (DNA + RNA) panel comprising 74 genes (SA74) was designed to cover all genes with a Tier 1 drug recommendation for therapy, evaluating single nucleotide variants (SNV), indels, copy number variants (CNV) and gene fusions (GF). We also included certain Tier2 genes for prognosis or added clinical impact. GFs were evaluated by RNA. Inferior sample quality often results in poor quality data, so we added a DNA component for tiling select intronic regions to identify GF which to be used when RNA could not be analyzed. The analytical sensitivity was > 99% for SNV/Indels with a 5% limit of detection, > 99% for CNV and GF. The clinical sensitivity was 100% for SNV, 95% for indels, 84.2% for CNV, 100% for RNA GF and 70% for DNA GF. **Results:** 239 formalin-fixed paraffin embedded tumor samples were evaluated using SA74 and the data was scored for actionability across tumor types. This was compared with data from 706 samples across multiple cancers analyzed using the Illumina TSO500 panel. The average number of actionable alterations was 1.1 in SA74 and 1.6 in TSO500. The overall actionability (cases with at least one Tier1 or Tier2 actionable variant) of SA74 was 63.4%; while that of TSO500 was 78.3%. Of this, the overlap with SA74 was 73.7%. The actionability in the remainder was due to Tier2 genes with lesser evidence altering the same pathway as an approved drug target or targeting investigational drugs. The actionability for each cancer type was calculated and found to be: colon (34.1%; n = 44), non-small cell lung (NSCLC) (78.4%; n = 37), breast (91.7%; n = 24), carcinoma of unknown primary (CUP) (45%; n = 20), uterine (53.3%; n = 15), gallbladder (75%; n = 12) and sarcoma (40%; n = 10), among others. Smaller panels often do not include CNV and GF. Addition of these variant types increased actionability across cancers. The lack of CNV and GF would have decreased total actionability from 62.9% to 54.5%. NSCLC and CUP were most impacted with a difference in actionability of 16.2% and 15% respectively. GF increased actionability mainly in NSCLC, while CNV contributed to increases across all cancers. **Conclusions:** SA74 demonstrated high actionability across cancers. It therefore presents a practical alternative to large panel testing by optimizing actionability and affordability, useful in a cost-sensitive setting. Research Sponsor: None.

Clinical performance of Signatera Genome assay in a cohort of patients (pts) with solid tumors.

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Background: Circulating tumor DNA (ctDNA) has emerged as a powerful, minimally invasive biomarker of treatment response and pt prognosis. Signatera, a tumor-informed, mPCR-NGS ctDNA assay, offers high sensitivity and specificity for detecting molecular residual disease (MRD). Signatera (exome) uses its proprietary approach to select a highly curated set of tumor variants, followed by deep sequencing of plasma libraries at >100,000x per variant. Signatera Genome uses the same proven technology and may provide an advantage over exome in certain cases. However, beyond analytical improvements, it remains unclear if Signatera Genome provides superior performance and utility compared to the clinically validated exome-based version in the clinical setting. In this study, we assessed the clinical performance of the Signatera Genome assay in a cohort of pts with solid tumors. **Methods:** We performed a retrospective analysis of clinically annotated residual pt samples from commercial ctDNA testing (Signatera, exome-based, 16-plex mPCR-NGS assay). Adjuvant treatment decisions and ctDNA-cadence of testing were at the provider's discretion. Signatera Genome assays were designed, consisting of 64 high-quality variants, from the respective pts' matched tumor and normal whole genome sequencing data. These assays were used to detect ctDNA in the associated pts' plasma utilizing a sample calling strategy that combined the target confidences and sample-level noise into a final confidence score. ctDNA concentration was measured in mean tumor molecules per mL of plasma (MTM/mL). Longitudinal plasma samples represented postoperative time points until recurrence/end of follow-up. The correlation between any time postsurgical ctDNA positivity and recurrence-free survival (RFS) was assessed using Cox regression analysis. **Results:** The Signatera Genome assay achieved a high analytical sample-level specificity of 99.8% (healthy subjects). Clinical performance was assessed in a real-world cohort of >300 pts with several cancer types, including breast cancer, non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC). Among pts with relapse, the Signatera Genome assay detected ctDNA ahead of clinical recurrence as confirmed by imaging. Pts with postsurgical ctDNA-positivity demonstrated significantly inferior RFS compared to ctDNA-negative pts. This trend was consistent across all cancer types investigated. Multivariate analysis adjusted for tumor type and stage revealed ctDNA-positivity to be the most significant prognostic factor associated with RFS. Performance metrics by cancer type will be presented. **Conclusions:** Here we report the largest Signatera Genome ctDNA study to date across multiple solid tumor histologies. The data indicate robust performance and concordance with Signatera Exome. Prospective clinical trials are underway evaluating clinical utility. Research Sponsor: None.

Landscape of genomic alterations in genes implicated in the regulation of hypoxia inducible factor (HIF) signaling: A pooled analysis of two pan-cancer cohorts.

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Background: HIF2 alpha inhibitors (HIF2i) have been recently approved for VHL-related tumors, especially clear cell renal cell carcinoma (ccRCC). Alterations in genes that regulate HIF signaling may modulate response to HIF2i and may help identify tumor types that could benefit from new therapeutic approaches targeting HIF activity. Here, we describe the landscape of these alterations across different cancer types. **Methods:** This study included patients (pts) from the TCGA PanCancer Atlas and GENIE Cohort v17.0, across all cancer types. All pts underwent Next Generation Sequencing or OncoPanel analysis of their tumors. Alterations in genes related to the HIF pathway (*VHL*, *EPAS1*, *EGLN1*, and *EGLN2*) and citric acid cycle (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF1*, *FH*, *IDH1*, *IDH2*, and *MDH2*) were screened, and only driver mutations, identified by OncoKB, CIViC Variants, My Cancer Genome, and the available literature, were included. Pts with a mutation in at least one gene were included. Mutation frequencies across different cancer types were analyzed for each cohort, then pooled together. **Results:** We identified a total of 10,953 and 167,073 pts on TCGA and GENIE, respectively. Mutation frequencies for different cancer types are shown in the Table. Among the mutated cases, *IDH1* was the most altered gene in glioma (90.20% [95% Confidence Interval (CI): 90.19; 90.21]), hepatobiliary cancers (75.48% [75.40; 75.56]) and melanoma (55.75% [55.57; 55.92]), and the second most common in leukemia (39.86% [39.68; 40.04]), while *IDH2* was the most altered in leukemia (57.52% [57.34; 57.70]), and the second most common in glioma (5.25% [5.24; 5.25]), and hepatobiliary cancers (19.10% [19.04; 19.17]). *SDHA* was the second most altered gene in melanoma (12.95% [12.87; 13.03]). In RCC, *VHL* was the most mutated gene (92.79% [92.78; 92.79]), followed by *FH* (2.41% [2.40; 2.41]). *EPAS1* was mutated in 64.19% of cases with driver mutations in miscellaneous neuroepithelial tumors (MNET) ([57.07; 71.31]), but not in RCC. Among the altered cases in pheochromocytoma, *SDHB* was the most commonly altered gene (39.71% [35.31; 44.11], followed by *VHL* (18.41% [15.92; 20.91]). *SDHB* was also the second most common gene to be mutated in MNET (23.12% [19.37; 26.86]). **Conclusions:** In this analysis, mutations in HIF-regulating genes were detected in multiple cancers, and were not limited to those studied in the context of HIF inhibitors. Further research is required to elucidate whether these gene alterations sensitize tumors to HIF inhibition. Research Sponsor: None.

Pooled mutation frequencies for all considered genes in different cancer types.

Cancer Type	N	% Pooled Mutation Frequency of any gene	95% CI
RCC	3662	39.76	39.74; 39.77
Glioma	12657	23.67	23.67; 23.67
Leukemia	1857	15.49	15.47; 15.50
Hepatobiliary Cancer	4234	11.18	11.18; 11.19
MNET	253	8.61	8.54; 8.68
Pheochromocytoma	198	5.63	5.56; 5.69
Melanoma	6589	4.34	4.34; 4.34

Analytical validation of EPISEEK, an epigenomic blood-based assay for multicancer detection.

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Background: Early cancer detection significantly improves treatment outcomes and survival rates. However, cancer screening faces key challenges: (1) current tests detect only 14% of new cases and cover a limited range of cancers, (2) each cancer requires its own costly and complex screening process, (3) limited patient awareness of suitable screenings, and (4) poor adoption among marginalized and underinsured groups. EPISEEK was developed for multicancer detection using minimal cell-free DNA from plasma. Here, we present validation study results assessing its robustness and accuracy across 20+ cancer types and stages. **Methods:** EPISEEK is a cfDNA-based methylation assay optimized for 20 ng of cfDNA input from plasma. Plasma cfDNA underwent bisulfite conversion followed by methylation-specific quantitative PCR targeting 10 cancer biomarkers and 3 internal control markers. 251 plasma samples from four cancer stages across 25 cancer types, and 57 samples from individuals over 40 with no known cancer history, were used to establish reference ranges and assess assay specificity and sensitivity. Additional contrived and clinical samples were used to determine the assay's analytical LOD, reproducibility and stability. **Results:** 57 non-cancer samples were used to train the classifier, achieving 99% specificity at a 95% confidence level. Accuracy testing included 251 cancer samples representing $>$ 20 primary cancer sites, including lung, colon, cervix, esophagus, head and neck, kidney, liver, breast, bladder, skin, testis, thyroid, ovary, pancreas, prostate, stomach, brain, bone marrow, and others. The cancer samples spanned all stages: I (29%), II (13%), III (29%), IV (22%), and cases with missing stage data (6.7%). Sensitivity increased with advancing stage, with observed sensitivity rate of 52%. By stage, observed sensitivity was stage I: 42%, stage II: 46%, stage III: 57%, and stage IV: 64%. Due to the limited and non-representative sample distribution for a typical multicancer screening population, SEER data were utilized to estimate EPISEEK's real-world performance by adjusting tumor incidence and stage when estimating positive predictive value and negative predictive value. At 99% specificity and based on adjusted performance, EPISEEK achieved a positive predictive value (PPV) of 40% and a negative predictive value (NPV) of 99%. Seven markers were detectable with $<$ 0.1 ng DNA, while the remaining three markers had an LOD95 of 0.1–0.37 ng. Comparing Ct values of each cancer target both intra and inter runs, EPISEEK demonstrated high reproducibility with standard deviation of 0.383 (high positive), 0.232 (low positive) and 1.063 (negative samples). **Conclusions:** EPISEEK is a sensitive, specific, accurate, and reproducible multicancer detection test. Compared to comprehensive genomic profiling techniques, it offers an affordable testing option for broader populations with a fast turnaround time. Research Sponsor: None.

Small nucleolar RNAs (snoRNAs) expression and effects on patient (pt) outcomes in metastatic colorectal cancer (mCRC): Data from CALGB (Alliance)/SWOG 80405.

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Background: SnoRNAs are non-coding RNAs that primarily guide the chemical modification of ribosomal RNA. Emerging evidence suggests snoRNAs play critical roles in cancer, including CRC, by regulating cell proliferation, apoptosis and tumor progression. Aberrant snoRNA expression has been linked to CRC development and poor prognosis, offering potential as diagnostic biomarkers and therapeutic targets. We investigated whether the tumor expression levels of 3 types of snoRNAs (SCARNA, SNORA, SNORD) affect treatment response in pts enrolled in CALGB/SWOG 80405 (NCT00265850). **Methods:** 433 mCRC pts treated with bevacizumab (bev, n = 226) or cetuximab (cet, n = 207) in combination with first-line chemotherapy were analyzed. RNA was isolated from FFPE tumor samples and sequenced on the HiSeq 2500 (Illumina). 422 snoRNAs were evaluated (23 SCARNA, 140 SNORA, 259 SNORD). Overall survival (OS) and progression-free survival (PFS) were compared across tertiles of gene expression (high [H], medium [M], low [L]) by multivariable Cox proportional hazards models adjusted for age, sex, ECOG performance status, tumor side, number of metastatic sites, *KRAS*, CMS subtypes, and treatment. Interaction tests for the predictive effect (bev vs cet) were performed. *P*-values were corrected for multiple testing using the Benjamini-Hochberg approach ($q < 0.05$). **Results:** Only SCARNA21 achieved statistical significance for OS after false discovery rate (FDR) adjustment. Tumors with H levels of SCARNA21 had shorter survival compared to tumors with M or L expression (median OS 24.4 vs 32.4 vs 33.9 months, respectively; $P = 0.0015$, $q = 0.033$), independent of treatment. No snoRNAs achieved FDR significance for PFS. However, several snoRNAs showed significant treatment interactions with biologic agents. SCARNA6-H and SCARNA5-H tumors had longer PFS and OS when treated with cet, but shorter PFS and OS when treated with bev, compared to the M and L expression groups (PFS interaction $q = 0.0067$ and 0.045, respectively; OS interaction $q = 0.022$ and 0.034, respectively). SCARNA7 also showed significant treatment interaction for OS, favoring cet in the H expression group ($q = 0.018$); the opposite was observed for SNORA63B, SNORA63D, SNORA35B, and SNORA36C ($q = 0.027$, 0.027, 0.027 and 0.047, respectively). No significant results were observed for any of the tested SNORDs. **Conclusions:** SnoRNAs dysregulation affects key pathways such as cell cycle control and immune evasion, making them promising players in CRC biology. Our study highlights the prognostic and predictive potential of specific snoRNAs in mCRC. Notably, high SCARNA21 expression was linked to shorter OS, while SCARNA5 and 6 showed predictive value for treatment response, indicating their potential for guiding treatment decisions. Further validation is needed to confirm these findings, and mechanistic studies are warranted. Research Sponsor: National Cancer Institute; Genentech; https://acknowledgments.alliancefound.org.

Impact of MGMT methylation on overall survival in solid tumors: A systematic review and meta-analysis.

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Background: The protein O6-alkylguanine-DNA-alkyltransferase (AGT), encoded by the MGMT gene, plays a crucial role in DNA repair by singularly removing alkyl lesions from the O6 position of guanine, maintaining genomic stability. Loss of MGMT expression, often due to promoter methylation, is linked to enhanced sensitivity to chemotherapy. While MGMT methylation has been observed in various cancers, its impact on overall survival (OS) in solid tumors remains uncertain. **Methods:** According to PRISMA guidelines, we selected studies from PubMed that examined the impact of MGMT methylation on OS in adult patients with solid tumors. Data were extracted where MGMT methylation status was clearly defined, and OS was reported through hazard ratios (HR) from either uni- or multivariable analyses. We employed R version 4.4.2 and the 'meta' package for our meta-analysis, using both fixed-effects (Mantel-Haenszel method) and random-effects (DerSimonian and Laird's method) models based on the I^2 statistic for heterogeneity. Subgroup analyses were conducted by cancer type, and publication bias was assessed through funnel plot inspection and Egger's regression. Statistical significance was set at $p < 0.05$. **Results:** The meta-analysis included 23 studies, with a total of 3,410 participants across all studies. The studies included an array of cancers, the most common being colorectal (n = 7), then head and neck (n = 6), and lesser-represented groups like pancreatic neuroendocrine (n = 2) and others. The pooled analysis using a random-effects model demonstrated that MGMT methylation status was not significantly related with OS (HR of 1.1967; 95% CI: 0.9004 to 1.5904; p = 0.2040). Subgroup analysis revealed that the impact of MGMT methylation on survival varied significantly across different types of cancer. No significant association was yielded between MGMT methylation and OS for colorectal cancer (HR of 0.9496; 95% CI: 0.6252 to 1.4422), head and neck cancer (HR of 1.1520; 95% CI: 0.8223 to 1.6137), NSCLC (HR of 1.0479; 95% CI: 0.3343 to 3.2841) and pancreatic neuroendocrine cancer (HR of 1.5541; 95% CI: 0.6493 to 3.7195). Conversely, a significant association was yielded for less common cancers, including melanoma, biliary and cervical cancers. The funnel plot and Egger's test for publication bias (t = -0.3999, p = 0.6933) suggested no significant asymmetry, indicating minimal publication bias within this meta-analysis. **Conclusions:** Our findings indicate that MGMT methylation does not universally predict OS across all solid tumors. The variability in survival impact across different cancer types suggests that the prognostic significance of MGMT methylation may be context-dependent, emphasizing the need for tumor-specific studies. Research Sponsor: None.

A phase II basket trial evaluating the efficacy of tasurgratinib (E7090) in patients with advanced solid tumors with fibroblast growth factor receptor (FGFR) gene alteration: FORTUNE study.

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Background: Tasurgratinib is an orally available selective inhibitor of FGFR1-3 tyrosine kinase and is approved in Japan for biliary tract cancer with *FGFR2* fusions or rearrangements based on a global phase 2 study. We previously identified *FGFR* gene alterations that are highly sensitive to tasurgratinib using a high-throughput functional evaluation method (MANO method) (npj Precision Oncology [2021] 5:66). We conducted a single-arm, investigator-initiated multicenter phase 2 basket trial to evaluate the efficacy and safety of tasurgratinib in patients (pts) with advanced solid tumors harboring *FGFR* gene alterations, including alterations identified by MANO method. **Methods:** Pts with advanced solid tumors with *FGFR* gene alterations detected by next-generation sequencing assays received tasurgratinib 140 mg QD. Pts were allocated to each Group based on *FGFR* gene alteration (Group A: *FGFR1-3* fusion, Group B: *FGFR1-3* sensitive mutations to tasurgratinib determined by MANO methods, Group C: *FGFR1-3* activating mutation not applicable to group B or *FGFR1, 2* gene amplification, Group D: cholangiocarcinoma with *FGFR2* fusion and previous treatment with a FGFR inhibitor except for tasurgratinib). The primary endpoint for Groups A, B, and C was objective response rate (ORR) by independent central review (ICR). Group D was an exploratory cohort, and ICR was not performed. The secondary endpoints included ORR by investigator assessment (IA), progression-free survival (PFS), overall survival, and safety. The threshold and expected response rates were 5% and 30%, respectively. With the one-sided significance level of 5%, the target enrolments were 10 (62% power), 15 (87%), and 15 pts (87%) in Groups A, B, and C, respectively. Group D's target number was 1 to 5 pts without a statistical hypothesis. **Results:** From June 2021 to December 2022, 46 pts were registered. The full analysis set includes 41 pts (10, 15, 15, and 1 in Groups A, B, C, and D, respectively). The most common primary sites were brain in 4 pts (40.0%) in Group A, biliary tract in 4 pts (26.7%) in Group B, and esophagus/stomach in 4 pts (26.7%) in Group C. ORRs by ICR in Group A, B and C were 20.0% (90% CI: 3.7-50.7, p = 0.0861), 20.0% (90% CI: 5.7-44.0, p = 0.0362), 6.7% (90% CI: 0.3-27.9, p = 0.5367), respectively. ORRs by IA in Group A, B, C, and D were 20.0% (95% CI: 2.5-55.6), 40.0% (95% CI: 16.3-67.7), 13.3% (95% CI: 1.7-40.5) and 0.0% (95% CI: 0.0-97.5), respectively. Median PFS by IA in Groups A, B, C, and D were 2.5 (95% CI: 1.4-5.7), 7.2 (95% CI: 1.7-8.2), 2.2 (95% CI: 1.9-3.7) and 5.7 months (95% CI: not evaluable), respectively. There was no new safety signal compared to previous reports. **Conclusions:** In Group B, the primary endpoint was met. Tasurgratinib demonstrated clinical activity in pts with selected FGFR-mutated tumors. Further study is needed to validate these findings. Clinical trial information: NCT04962867. Research Sponsor: Eisai; Japan Agency for Medical Research and Development; 20lk1403036h0001.

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

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Background: *NTRK* gene fusions are oncogenic drivers in various tumor types. Larotrectinib (laro) is the first-in-class, highly selective, central nervous system (CNS)-active 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 data in adult and pediatric pts with non-primary CNS TRK fusion cancer treated with laro. **Methods:** Pts with TRK fusion cancer enrolled in 3 laro clinical trials (NCT02637687 [SCOUT], NCT02576431 [NAVIGATE], NCT02122913) were included. Laro was administered at 100 mg twice daily (BID) and 100 mg/m^2 BID in most adult and pediatric pts, respectively. Responses were independent review committee (IRC)-assessed per RECIST v1.1. Pts enrolled in SCOUT were permitted to stop laro in the absence of on-treatment progression ("wait-and-see"). The data cutoff was July 20, 2024. **Results:** At data cutoff,304 pts were eligible for efficacy assessment by IRC; 25 pts had known CNS metastases at baseline. Median age was 45 years (range 0–90). There were 28 different tumor types, including soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung (11%), and thyroid (10%). A total of 101 pts (33%) received no prior systemic therapies in the metastatic/unresectable setting; 115 (38%) received 2 or more. *NTRK* gene fusions were detected by next-generation sequencing (NGS) in 267 (88%) pts. The overall response rate was 65% (95% confidence interval [CI] 59–70): 66 (22%) complete responses (CR), 20 (7%) pathological CR, 112 (37%) partial responses, 56 (18%) stable disease, 32 (11%) progressive disease, and 18 (6%) not evaluable/undefined. Median time to response was 1.8 months (mo; range 0.9–22.9). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 43 mo (95% CI 34–not estimable), 28 mo (95% CI 22–38), and not reached, respectively, at median follow-ups of 45, 42, and 57 mo. The 4-year rates for DoR, PFS, and OS were 48% (95% CI 40–57), 39% (95% CI 32–46), and 63% (95% CI 57–68), respectively. Median duration of treatment was 19 mo (range 0–100+). Fifty-five of 99 pediatric pts in SCOUT had participated in "wait-and-see"; the median duration of the first "wait-and-see" period was 33 mo (range 1–72). At data cutoff, 83 pts (27%) remained on trial (either on treatment or in "wait-and-see"). Treatment-related adverse events (TRAEs) were mainly Grade 1/2 (n = 189; 62%). Grade 3/4 TRAEs occurred in 71 (23%) 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. This data supports the wider adoption of NGS panels that include *NTRK* gene fusions to identify pts who may benefit from treatment with TRK inhibitors. Clinical trial information: NCT02637687, NCT02576431, NCT02122913. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

Early prediction of prognosis in advanced solid tumor patients using tumor growth rates with *g* score in early phase clinical trials.

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Background: The primary objective of early phase clinical trials is to evaluate the safety of investigational drugs, which requires participants to have sufficient expected survival durations. Tumor growth rate using *g* scores, calculated using radiographic measurements and timing after treatment, is gaining attention as a potential tool for treatment efficacy assessment. This study aims to assess the utility of *g* scores before and after treatment in predicting prognosis, and explore suitable trial candidates for accelerating drug development in early phase clinical trials. **Methods:** We retrospectively reviewed patients who participated in early phase clinical trials after standard treatment at the Department of Advanced Medical Development, The Cancer Institute Hospital of Japanese Foundation for Cancer Research between January 2020 to December 2023. A mathematical exponential growth model was applied to estimate tumor growth rates (g) based on radiographic tumor measurements and interval time: $f(t) = \exp(g \cdot t)$, with pre-g scores derived from measurements before the clinical trial and post-g scores from measurements after trial initiation. Pre-g scores were calculated using trial baseline computed tomography (CT)s and the most recent CTs before trial enrollment, while post-g scores were calculated using baseline CTs and the first evaluated CTs after treatment. We defined dichotomized *g* score levels (high/low) using the time-dependent ROC curve procedure. We evaluated independent predictors for survival outcomes according to each *g* score and patient characteristics. **Results:** Of the 173 cases who participated in early phase clinical trials after standard treatment, 162 cases with evaluable CT scans before and after the clinical trial were included in this study. Median time to pre-trial CT was 29 days (range, 5–202), and median time to first post-treatment evaluation was 49.5 days (range, 16–87). Log-rank testing showed both high pre-. and post-. scores correlated to shorter overall survival (OS) compared to low-score groups (HR 2.16; 95% CI 1.22-3.81; $P = 0.0067$, HR 2.68; 95%CI 1.84-3.90; $P < 0.001$). Multivariate analysis showed both high pre-g and post-g scores were independent predictors of shorter OS (HR 2.06, 95% CI 1.13-3.75; $P = 0.019$, HR 3.80, 95% CI 2.44-5.90; $P < 0.001$). **Conclusions:** This study is the first to incorporate pre-. scores as an independent prognostic factor and may serve as a valuable reference for patient enrollment in early phase clinical trials under late-line settings. Additionally, post-. scores were also identified as an independent prognostic factor across multiple cancer types in early phase clinical trials. These results indicate their potential use as surrogate endpoints to, which may help facilitate drug development. Research Sponsor: None.

Picking needles in a haystack: Exploring rare variants of a pan-cancer target in the RET landscape from 229,453 adult cancer patients.

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Background: Advances in precision oncology have led to the approval of tumor-agnostic therapies, and RET, due to its role as a driver of oncogenesis across multiple tumor types, is increasingly recognized as a pan-cancer target. RET alterations, including mutations and fusions, are relatively rare events, however, potent and selective RET inhibitors such as selpercatinib and pralsetinib have demonstrated remarkable efficacy and changed clinical practice in RET-driven NSCLC, thyroid cancer and other cancers. Here, we present a comprehensive analysis of RET alterations in pan-cancer adult malignancies. **Methods:** 229,453 samples from 196,244 patients available from AACR Project GENIE v.17 database were analyzed for the prevalence of RET mutations, fusions and copy number alterations in a range of cancer types. **Results:** A total of 7011 separate RET alterations were identified in 6690 separate pts (3%), including 660 fusions (9.4%), 5553 missense mutations (79.2%), 373 splice site mutations (5.3%), 339 truncating mutations (4.8%), 86 in-frame mutations (1.2%). Most frequent tumor types included NSCLC, colorectal cancer, melanoma, thyroid cancer, endometrial cancer and glioma (23%, 12.2%, 9.5%, 6.6%, 6.4%, 5.3% identified RET alterations, respectively). RET fusions were observed in 0.3% of tumor samples, most identified in NSCLC, thyroid and colorectal cancer (53%, 24% and 4% of identified *RET* fusions). Most fusions were considered driver events using OncoKB database (632, 96%);frequent fusion gene partners included *KIF5B, CCDC6, NCOA4*, and intragenic events (34%, 25%, 9.7%, 8% of 660 fusion samples). Of the 5553 missense mutations, most (89%) were considered variants of uncertain significance; 605 (11%) were considered oncogenic or likely oncogenic. Oncogenic missense mutations occurred across codons, most frequently involving codon 918 (n = 215, 36%; M918M/K/T/V), 648 (n = 41, 6.8%; V648I/A), 886 (n = 28, 4.6%; R886W/Q/L), 630 (n = 21, 3.5%; C630G/R/S/F/Y/W), 891 (n = 31, 5%, S891A/L/W). Documented on-target drivers of multi-kinase RET inhibitor resistance gatekeeper mutations (V804M/L), and selective RET inhibitor resistance mutations were noted in 61 samples, including G810C/S substitutions, solvent-front mutations K809R/N, activation loop mutations Y806C/N (33%, 53%, 3%, 3% of identified samples); most were classified as oncogenic or likely oncogenic (85%). **Conclusions:** RET fusions are rare events across cancers; however, most are characterized as oncogenic. RET missense mutations occur in 2.4% of malignancies, and while most RET missense variants are described as variants of uncertain significance, oncogenic RET variants are diverse, occurring across codons. We confirm multiple documented oncogenic drivers of on-target resistance, and their distinct and diverse mechanisms underline the urgent need to develop next generation RET inhibitors. Research Sponsor: None.

3151 Poster Session

LODESTAR: A single-arm phase II study of rucaparib in solid tumors with pathogenic germline or somatic variants in homologous recombination repair genes.

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Background: To explore PARP inhibitor (PARPi) utility across solid tumors and identify biomarkers that predict sensitivity. **Methods:** This single-arm phase II study assessed rucaparib monotherapy in patients with solid tumors and pathogenic variants (PVs) in *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, *RAD51D* (Cohort A) or *BARD1*, *BRIP1*, *FANCA*, *NBN*, *RAD51B* (Cohort B). The primary endpoint was ORR in Cohort A. Secondary endpoints included DCR, PFS, OS and safety. A scar-based HRD signature (HRDsig) and platinum sensitivity status were explored post-hoc. **Results:** Fifty-one patients in Cohort A and 12 in Cohort B were evaluable for efficacy. ORR of cohort A was 18% (95% CI 10-30%). A significantly higher ORR was observed with HRDsig+ tumors compared to HRDsig- tumors (32%, 95% CI 15-54, vs. 0%, 95% CI 0-14%, $p < 0.01$). In the entire study population: DCR of 65% (95% CI 53-76%), mPFS of 5.5 mo (95% CI 3.68-7.82), and mOS of 12.1 mo (95% CI 10.6 – inf). PFS and OS were significantly longer for platinum sensitive tumors (mPFS: 7.8 mo vs. 3.5 mo, p = 0.02; mOS: NR vs 5.45mo, p = 0.01). Tumor histology was not independently predictive of outcome. Tumors with PVs in Cohort A genes were more likely to be HRDsig+ than tumors with PVs in Cohort B genes. Analysis of a large commercial database showed that in non-canonical tumors with *BRCA* PVs, 30.2% were HRDsig+. **Conclusions:** Rucaparib has activity in HRDsig+ solid tumors with PVs in HRR genes, regardless of histology. Platinum sensitivity correlated with improved outcomes. Clinical trial information: NCT04171700. Research Sponsor: Clovis Pharmaceuticals.

A multicenter, randomized controlled trial of intrapleural drug-loaded vesicle perfusion combined with systemic therapy for malignant pleural effusion.

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Background: This study aimed to evaluate the efficacy and safety of drug-loaded vesicle (DLV) intrapleural perfusion combined with systemic therapy in patients with lung or breast cancer and malignant pleural effusion (MPE). **Methods:** This multicenter, randomized, controlled, open-label clinical trial included patients with pathologically confirmed lung or breast cancer and MPE requiring thoracentesis. In total, 96 patients were randomised 1:1 to arm 1 receiving DLV intrapleural perfusion (50 mL daily for four consecutive days) plus systemic therapy (ST) or arm 2 receiving interleukin-2 (IL-2) intrapleural perfusion (50 mL every three days for three sessions) with ST.The primary endpoint was the objective response rate (ORR) of pleural effusion at 4 weeks post-perfusion, while secondary endpoints included overall survival (OS) and treatment-related toxicity.The difference in ORR between the two cohorts was analyzed using the Chi-square test. Kaplan-Meier survival analysis was performed for OS comparison between the two cohorts. **Results:** A total of 91 patients were evaluated for efficacy (50 in arm 1 and 41 in arm 2). The DLV+ST arm 1 showed a significantly higher ORR for pleural effusion than the IL-2+ST arm 2 (74.0% vs. 53.7%, P = 0.043). In the survival analysis of 83 evaluable patients, median OS was 15.0 months (95% CI: 9.2–26.9) in arm 1 and 6.9 months (95% CI: 5.3–15.8) in arm 2, without a statistically significant difference (HR = 0.75; 95% CI: 0.46–1.24; P = 0.266). The 1-, 2-, and 3-year OS rates for arm 1 were 83.0% (95% CI: 72.9–94.4%), 59.6% (95% CI: 47.1–75.4%), and 51.1% (95% CI: 38.6–67.6%), compared to arm 2's 69.4% (95% CI: 55.9–86.2%), 41.7% (95% CI: 28.3–61.3%), and 33.3% (95% CI: 21.0–52.9%). Both arms had similar safety profiles, with chemotherapy-induced toxicities, including leukopenia, gastrointestinal reactions, and liver dysfunction, being the most common treatment-related adverse events. **Conclusions:** Drug-loaded vesicle intrapleural perfusion combined with systemic therapy is a safe and effective treatment option for malignant pleural effusion in patients with lung or breast cancer. This approach represents a promising treatment strategy for MPE and warrants further clinical investigation and consideration in clinical practice. Clinical trial information: ChiCTR1800017104. Research Sponsor: None.

3153 Poster Session

The efficacy and safety of a selective PARP1 inhibitor ACE-86225106 in patients with advanced solid tumors: Preliminary results from a first-in-human phase 1/2 study.

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Background: ACE-86225106 is a highly selective PARP1 inhibitor, exhibiting high potency in enzymatic and DNA-trapping assays of PARP1, while maintaining significant selectivity over PARP2. Pre-clinical studies with ACE-86225106 have demonstrated strong anti-cancer activities in *in vivo* CDX models, with excellent tolerability. Here we report the preliminary clinical data of ACE-86225106 from the ongoing first-in-human study (NCT06380660). **Methods:** This is a multicenter, open-label, phase1/2 study of ACE-86225106 in adult patients with locally advanced (unresectable) or metastatic solid tumors. Phase 1 includes a typical "3+3" dose escalation and backfill module, followed by a dose expansion module in phase 2. The primary objective is to assess safety, tolerability, PK/PD profile, and pre-liminary efficacy of ACE-86225106 as a monotherapy. **Results:** As the data cut-off (23 Jan 2025), 10 patients received ACE-86225106 at a dose of 5mg, 10mg or 20mg QD, and 5 patients backfilled at a dose of 10mg QD. Median number of prior therapy lines was 3 (range 2-12). Two patients (squamous lung cancer and breast cancer each) did not complete the DLT evaluation period due to disease progression and were replaced. No DLTs were reported as of data cut-off. Among total fifteen patients (10 patients) who received at least one dose of ACE-86225106, no Grade 3 or higher treatment-related adverse events (TRAEs) were reported. There were no treatment discontinuations or dose reductions due to TRAE. The compound exhibited a relatively flat PK curve with mild accumulation after multiple dosing. The steady-state C_{trough} was approximately 5 fold, 24 fold and 36 fold above target effective concentration at dose level of 5mg, 10mg, 20mg respectively. The PARylation inhibition was $>$ 90% confirming target engagement. Of seven patients having post-treatment tumor assessment and being considered efficacy-evaluable, two patients (one fallopian tube cancer patient with BRCA mutation and one prostate cancer patient with BRCA wild type) achieved PR per RECIST1.1. **Conclusions:** Preliminary data indicate that ACE-86225106 is well tolerated and shows promising efficacy in heavily pre-treated advanced solid tumors. Clinical trial information: NCT06380660. Research Sponsor: Acerand Therapeutics (Hong Kong) Limited.

Effect of biopsy requirement on patient enrollment to phase I trials in cancer.

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Background: The need for safer and more effective drugs for patients with cancer is a constant unmet need. Given their narrow therapeutic index, determination of dose and toxicity through phase I clinical trials is confined to patients with cancer. Recently, there has been a trend towards a greater demand for fresh tumor biopsies (Bx) from patients to better understand the pharmacodynamic and target effect of the drugs. We sought to determine whether the requirement for Bx among this vulnerable population had any detrimental effect. **Methods:** The study population included patients who enrolled to phase I trials between June 2022 (new EMR system) through January 2025 at a single NCI-designated comprehensive cancer center. All charts were reviewed and data collected included sex, race, age, diagnosis, and dates of consent, treatment start, last dose of study drug, off treatment, last contact/death; Bx site/approach/complications. Images were reviewed by an interventional radiologist to assess safety, with targets deemed appropriate biopsied under image guidance. For lung lesions or those < 1 cm, 20g core needle was used, while 18g core needle was used for others. Outcomes were analyzed by Mantel–Cox test using Prism GraphPad v 10. **Results:** 146 patients [male (n = 63, 43.2%), age 62, 23-82(median, range), NHW-81 (55.5%), NHB-23 (15.8%), Hispanic-24 (16.4%), and Asian-18 (12.3%)] consented to 25 clinical trials. Of these, 8 mandated paired tumor Bx, 15 were mandatory or optional Bx depending on cohort, and 2 did not require Bx. The most common diagnoses were colorectal (37, 25.3%), other GI (21, 14.4%), pancreas (18, 12.3%), lung (11, 7.5%), breast (6, 4.1%), prostate (3, 2.1%) and others (50, 34.2%). Bx samples were to be collected prior to the first dose of study drug (pre-dose) and repeated after the first 1-2 cycles (on-study). Image guidance included ultrasound (50, 57.5%), CT scans (34, 39.1%), and others (3, 3.4%). Overall, 62 patients (42.4%) provided 87 Bx samples; 25 paired Bx, 20 only pre-dose Bx, and 17 only on-study Bx. Five patients (3.4%) did not undergo Bx because it was deemed unsafe or high risk. The sites of Bx included liver (45, 51.7%), lung (9, 10.3%), lymph node (8, 9.2%), peritoneum (4, 4.6%), and others (21, 24.1%). Two patients experienced pneumothorax and recovered without sequelae. The median (mean) duration from consent to start of study treatment was 20 (20) days among Bx patients vs. 14 (16) among non Bx patients ($p = 0.003$). The median (mean) duration of time on study was 77 (91) days among Bx patients vs. 77 (125) among non Bx patients ($p = 0.046$). **Conclusions:** Over 40% of patients entering phase I trials underwent study specific Bx. The patients who underwent a Bx had a median delay of 6 days in receiving the first dose of study medication. Further in-depth review of medical records will help identify variables that may have led to shorter time on study for patients undergoing clinical trial related biopsies. Research Sponsor: None.

Rapid analysis and response evaluation of combination anti-neoplastic agents in rare tumors (RARE CANCER) trial: RARE 2 talazoparib and temozolomide.

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Background: Preclinical data generated from NIH/NCI Patient-Derived Models Repository (PDMR) demonstrated significant synergistic activity of talazoparib (a PARP inhibitor) combined with temozolomide (an alkylating agent) in patient-derived xenograft models of rare adult and pediatric cancers. This clinical trial aimed to evaluate the objective response (OR) rate of this combination in patients with advanced rare cancers in exploratory fashion. Correlatives include genomic and transcriptomic profiling of tumor tissue, circulating tumor DNA (ctDNA), circulating tumor cells, and assessments of apoptosis and epithelial-mesenchymal transition in relation to treatment activity. **Methods:** This open-label, non-randomized, phase 2 trial used a Simon two-stage design. Patients aged ≥18 years with advanced rare cancers received temozolomide (37.5 mg/m^2 orally, days 2–6) and talazoparib (750 mcg orally, daily) in 28-day cycles. Tumor response was assessed per RECIST v1.1, and adverse events (AEs) assessed using CTCAE v5.0. In the first stage, if 0/14 (across all histologies) responses are observed, the trial will be closed for futility. Otherwise, additional 16 patients were planned to be enrolled. There are no selection criteria based aside from rare tumor to allow for exploration of activity. **Results:** Fourteen patients were enrolled, all evaluable for response and toxicity. Median age was 57 years; 11 were female, and all had ECOG 0–1. Tumor histologies included uterine sarcoma (N = 3), cholangiocarcinoma (N = 2), and one each of adrenocortical carcinoma, adenoid cystic carcinoma, clear cell salivary carcinoma, MPNST, angiosarcoma, carcinoma of unknown primary, squamous urothelial carcinoma, small cell neuroendocrine carcinoma, and SDHB deficient renal cell carcinoma. Best responses included stable disease (N = 6), progressive disease (N = 5), and clinical progression (N = 3). One patient with clear cell salivary cancer and another with cholangiocarcinoma remained on treatment for 8 and 6 cycles, respectively. The median progression free survival is 3.81 months. The most common treatment related AEs (TRAEs) overall as well as ≥Grade 3 were hematologic including thrombocytopenia (13; ≥Grade 3 = 10), anemia (total12; ≥Grade 3 = 10), lymphopenia (total 12; ≥Grade 3 = 5), neutropenia (total 11; ≥Grade 3 = 6), and leukopenia (total 10, ≥Grade 3 = 4). No Grade 5 TRAEs were reported. Although none of the patients discontinued treatment due to TRAEs, planned dose reductions were needed for 7 patients. **Conclusions:** Despite promising preclinical activity, this tumor agnostic exploratory trial did not meet strict goal more design for single histology. Future efforts will focus on correlative analyses, exploring histology-specific expansion cohorts informed by preclinical response data, and optimizing dosing schedules to reduce overlapping toxicities. Clinical trial information: NCT05142241. Research Sponsor: U.S. National Institutes of Health.

Body composition modulations during cyclic fasting-mimicking diet in patients with advanced solid cancers.

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Background: Fasting-mimicking diets (FMD) can induce favorable immune-metabolic changes in humans and preclinical data suggest potential antitumor activity. Cyclic FMD impact on muscle mass and adiposity in patients (pts) is unclear. Here we evaluate body composition changes in pts with advanced solid cancers undergoing FMD in the context of a phase Ib trial (NCT03340935). **Methods:** NCT03340935 study evaluated safety and biological effects of a cyclic FMD consisting of a 5-day, calorie-restricted, plant-based diet repeated every 21-28 days for a maximum of 8 cycles, conducted in oncologic patients receiving concomitant therapies. Here we included pts with advanced solid cancers and Computed Tomography (CT) exams at baseline (BL), FMD end and disease progression (PD). Body composition parameters, i.e. Skeletal Muscle Index (SMI) and Visceral (VAT), Subcutaneous (SAT), Intermuscular (IMAT) Adipose Tissues, were assessed via axial CT scan at 3rd lumbar vertebra using SliceOmatic software. Pts with advanced triple negative breast cancer (TNBC) receiving chemotherapy (ChT) without FMD, having CT scans at BL and PD, were selected as control cohort. Wilcoxon tests were used for comparisons. **Results:** In the FMD cohort (n=36), 61% had BC, 39% had TNBC, 78% received ChT; median age was 54 (IQR 51-65), median completed FMD cycles was 5 (IQR 3-8), median time from FMD end to PD was 3.5 months (IQR 1.0-16.0); 8 pts met criteria for sarcopenia (SMI <38.5 cm^2/m^2) at BL, 6 of whom had TNBC. In the control TNBC cohort (n=17), median age was 54 (IQR 42-68), 6 pts were sarcopenic at BL. In the FMD cohort, between BL and FMD end there was a significant reduction of VAT, SAT and SMI, but no change in IMAT; between BL and PD only SMI was significantly decreased (Table). At FMD end and PD, 12 pts were sarcopenic in the FMD cohort, 7 having TNBC. In the control TNBC cohort (n=17), IMAT was significantly increased between BL and PD, with no changes in other parameters (Table); 8 pts were sarcopenic at PD. **Conclusions:** In advanced cancers pts, cyclic FMD reduces adiposity as well as muscle mass. Tumor/therapy-related factors contribute to sarcopenia in advanced cancer pts, thus future trials involving FMD intervention should detect pts at risk and include supportive measures to preserve muscle mass. Support: Italian Association for Cancer Research (AIRC): AIRC-Bonadonna fellowship (C Sposetti), AIRC fellowship (F Ligorio), AIRC IG 2024 ID 30499 (PI: C Vernieri); Giuliani Foundation. Clinical trial information: NCT03340935. Research Sponsor: Italian Association for Cancer Research (AIRC) / Gianni Bonadonna Foundation; Italian Association for Cancer Research (AIRC); Italian Association for Cancer Research (AIRC); Giuliani Foundation.

	Visceral Adipose Tissue change - % median	*p value*	Subcutaneous Adipose Tissue change - % median	*p value*	Intermuscular Adipose Tissue change - % median	*p value*	Skeletal Muscle Index change - % median	*p value*
FMD end vs BL								
FMD cohort, n=36	-12.4	*0.002*	-11.9	*<0.001*	+0.9	*0.55*	-4.2	*0.014*
PD vs BL								
FMD cohort, n=36	-6.2	*0.25*	-5.5	*0.083*	+1.2	*0.5*	-5.1	*<0.001*
TNBC subset, n=14	-3.2	*0.24*	-5.0	*0.042*	+0.2	*0.9*	-4.7	*0.025*
Control TNBC cohort, n=17	-1.3	*0.64*	-11.0	*0.16*	+11.7	*0.023*	-0.9	*0.24*

TPS3157 **Poster Session**

IDeate-PanTumor02: A phase 1b/2 study to evaluate the efficacy and safety of ifinatamab deruxtecan (I-DXd) in patients (pts) with recurrent or metastatic solid tumors.

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Background: B7-H3 is highly expressed in many solid tumors but has limited expression in normal tissues; high B7-H3 expression is associated with shorter overall survival (OS) in several tumor types. I-DXd is a B7-H3–directed antibody–drug conjugate (anti–B7-H3 mAb covalently linked to a topoisomerase I inhibitor cytotoxic payload [DXd] via an enzymatically cleavable peptide-based linker). It showed promising efficacy in pts with advanced solid tumors in the Phase 1/2 IDeate-PanTumor01 study, with objective responses in 6 of the 7 tumor types with ≥5 pts (small cell lung cancer [SCLC], esophageal squamous cell carcinoma, metastatic castration-resistant prostate cancer, squamous non-small cell lung cancer, head and neck squamous cell carcinoma [HNSCC], and endometrial cancer). I-DXd also showed encouraging antitumor activity in 88 pretreated pts with extensive-stage SCLC in the Phase 2 IDeate-Lung01 study, with greater efficacy at the 12-mg/kg than the 8-mg/kg dose (objective response rates [ORRs] of 54.8% [95% CI, 38.7–70.2] and 26.1% [95% CI, 14.3–41.1], respectively). I-DXd has demonstrated a manageable and tolerable safety profile across tumor types. We describe a study investigating the efficacy and safety of I-DXd in pts with advanced solid tumors with substantial unmet medical needs. **Methods:** IDeate-PanTumor02 (NCT06330064) is a global, multicenter, open-label, single-arm, parallel-cohort, Phase 1b/2 study in ~520 adults with recurrent or metastatic solid tumors (endometrial cancer; HNSCC; pancreatic ductal adenocarcinoma; colorectal cancer; hepatocellular carcinoma [HCC]; esophageal/gastroesophageal/gastric adenocarcinoma; urothelial carcinoma; ovarian cancer; cervical cancer; biliary tract cancer; HER2-low breast cancer [BC]; HER2-negative BC; and cutaneous melanoma). Eligible pts will have received ≥1 systemic therapy for the selected tumor type and have an ECOG PS of ≤1. The study will be divided into 2 parts: Stage 1 and Stage 2 (n≈20 per stage per cohort). Each cohort starts with Stage 1 and may continue to Stage 2 if sufficient safety and efficacy data are observed. All cohorts except the HCC cohort will receive I-DXd 12 mg/kg every 3 weeks (Q3W). The HCC cohort includes a safety run-in part to assess tolerability and the potential need for dose adjustment; the planned starting dose is 8 mg/kg Q3W, which may be escalated. Primary endpoints are ORR per investigator (all cohorts) and safety (HCC safety run-in only). Secondary endpoints are safety, duration of response, progression-free survival, OS, disease control rate, pharmacokinetics, and immunogenicity. The Kaplan–Meier method will be used to estimate time-to-event endpoints, the Brookmeyer and Crowley method for median event times, and the Clopper–Pearson exact method to summarize descriptively endpoints with proportion. Enrollment is ongoing. Clinical trial information: NCT06330064. Research Sponsor: Daiichi Sankyo, Inc., Merck, Inc.

TPS3158 **Poster Session**

REJOICE-PanTumor01: A phase 2 signal-seeking study of raludotatug deruxtecan (R-DXd) in patients with advanced or metastatic gynecologic or genitourinary tumors.

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Background: Cadherin-6 (CDH6), a transmembrane protein involved in cell–cell adhesion and epithelial–mesenchymal transition, is overexpressed in many cancer types. R-DXd is an anti-CDH6 antibody–drug conjugate composed of a humanized CDH6 antibody covalently linked to a potent topoisomerase I inhibitor payload (DXd) via a plasma-stable linker. In an ongoing Phase 1 study (NCT04707248), a subgroup of patients with heavily pretreated ovarian cancer (OC) who received R-DXd 4.8–6.4 mg/kg, had an objective response rate (ORR) of 48.6% (95% confidence interval [CI], 31.9–65.6); median duration of response (DOR) was 11.2 months (95% CI, 3.1–not estimable), and progression-free survival (PFS) was 8.1 months (95% CI, 5.3–not estimable), irrespective of CDH6 expression level (data cut-off: July 14, 2023). The safety profile of R-DXd was manageable. In total, 11.1% of patients discontinued R-DXd due to treatment-emergent adverse events. These promising data warranted further investigation of R-DXd in REJOICE-Ovarian01 (NCT06161025), a Phase 2/3 study in patients with platinum-resistant high-grade serous OC (HGSOC), and in the REJOICE-PanTumor01 Phase 2 study, which is described here. **Methods:** REJOICE-PanTumor01 (NCT06660654) is a global, open-label Phase 2 study in patients with locally advanced or metastatic gynecologic (endometrial cancer [EC], cervical cancer, or non-HGSOC) or genitourinary (urothelial cancer [UC] or clear cell renal cell carcinoma [ccRCC]) tumors. Cohorts are tumor type–specific; patients in all cohorts must have relapsed or progressive disease after receiving ≥1 prior line (and ≤3 prior lines in the EC, UC, and ccRCC cohorts only) of standard treatment. Adult patients with ECOG performance status 0–1 are eligible; there is no selection for tumor CDH6 expression. Approximately 40 patients will be enrolled into each cohort to receive R-DXd 5.6 mg/kg IV every 3 weeks until disease progression per RECIST 1.1, unacceptable toxicity, death, or other reason per protocol. In each cohort, a nonbinding futility interim analysis will be conducted after 20 patients complete a minimum of 12 weeks of follow-up, the results of which may determine whether the remaining (~20) patients will be treated. Primary endpoints are ORR for the gynecological and UC cohorts, disease control rate (DCR) for the ccRCC cohort (both investigator-assessed), and safety and tolerability for all cohorts. Secondary endpoints are ORR (ccRCC cohort only), DCR (except ccRCC cohort), PFS, DOR, time to response (all investigator-assessed per RECIST 1.1), pharmacokinetics, and immunogenicity. No formal hypothesis testing will be performed; ORR and DCR will be analyzed using a Clopper–Pearson method to determine 95% CI. PFS and DOR will be analyzed using the Kaplan–Meier method (2-sided 95% CI). Study enrollment began in January 2025. Clinical trial information: NCT06660654. Research Sponsor: Daiichi Sankyo, Inc., Merck Inc.

TPS3159 **Poster Session**

A phase 1, open-label, multi-center study of the safety, tolerability, and efficacy of IPH4502 as a single agent in advanced solid tumors.

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Background: Nectin-4 is a cell adhesion molecule frequently overexpressed across multiple solid tumor types, including urothelial carcinoma (UC), esophageal cancer, non-small cell lung cancer, and triple-negative breast cancer. It plays a significant role in carcinogenesis and cancer progression and is associated with poor survival in several tumor indications. Targeting Nectin-4 with enfortumab vedotin (EV), an antibody-drug conjugate (ADC) with a monomethyl auristatin E (MMAE) payload, demonstrated clinical benefit in UC, which exhibits the highest Nectin-4 expression among all solid tumor types. EV is now approved for the treatment of UC. IPH4502 is a differentiated Nectin-4 ADC conjugated with exatecan, a topoisomerase-1 inhibitor payload with a drug-to-antibody ratio of 8 via a cleavable hydrophilic linker. IPH4502 has been developed to address the unmet medical need of UC patients who have progressed on, or are ineligible for EV, as well as to treat tumor types with lower Nectin-4 expression beyond UC. In preclinical models, internalization capability and bystander effect of IPH4502 enable an efficient antitumor activity in Nectin-4 expressing tumor models, independent of Nectin-4 expression level, as well as in models resistant to EV. Finally, IPH4502 shows antitumor activity in patient-derived xenograft models from UC and other tumor types. **Methods:** This is a first-in-human, open-label, multicenter, single-arm Phase 1 study to assess the safety profile (DLTs and MTD), tolerability according to NCI-CTCAE v5.0, and RP2D of IPH4502 in patients with advanced solid tumors. Secondary objectives aim to characterize the pharmacokinetic profile and evaluate the immunogenicity and preliminary efficacy of IPH4502. The study is being conducted in participants aged ≥18 years withhistologically confirmed, unresectable, locally advanced, or metastatic solid tumors known to express Nectin-4, including, but not limited to non-small cell lung, triple-negative breast, ovarian, esophageal, gastric, and colorectal cancers, as well as UC. Part 1 (Dose Escalation) will use a Bayesian Optimal Interval Design (BOIN) with backfilling of safety-cleared dose levels. This approach will guide dose escalation and help establish the MTD/MAD. Part 2 (Dose Optimization)will begin after identifying the MTD/MAD, to select the RP2D. It will enroll participants with selected tumor indications (up to 2), for whom a clinical benefit was observed in Part 1. Participants will be randomized at a 1:1 ratio to 2 dose levels, to determine the RP2D. A maximum of 105 participants will receive treatment with IPH4502 in France and the US. Clinical trial information: NCT06781983. Research Sponsor: None.

TPS3160 Poster Session

Design of a first-in-human multicenter open-label study of ZW171, a mesothelin x CD3 targeting bispecific T-cell engager, in participants with advanced solid tumors: ZWI-ZW171-101.

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Background: Mesothelin (MSLN) is a membrane glycoprotein overexpressed in several solid tumors, making it a promising target for cancer treatments, including T cell engagers (TCEs). ZW171 is a humanized trivalent bispecific TCE antibody that targets a threshold level of MSLN expression with 2 binding sites and CD3e receptor on T cells with 1 binding site. Preclinical studies of ZW171 demonstrated favorable pharmacology, pharmacokinetics (PK), and toxicology, showing it preferentially kills MSLN-overexpressing cells, activates T cells without significant toxicity, inhibits tumor growth, and is well tolerated in cynomolgus monkeys, suggesting its potential for treating MSLN-expressing tumors[1] while sparing healthy tissues with low levels of expression. This first-in-human, phase 1, ongoing study (ZWI-ZW171-101) evaluates safety, tolerability, PK, and anti-tumor activity of ZW171 in participants with advanced solid tumors. **Methods:** This 2-part study enrolls eligible adult participants with unresectable MSLN-expressing ovarian cancer (OC), non-small cell lung cancer (NSCLC), or other MSLN-expressing cancers, with measurable disease per RECIST v1.1, ECOG PS score of 0 to 1, adequate organ function, and a minimum life expectancy of 12 weeks. Participants with additional progressing malignancies, recent transplants, clinically significant ongoing toxicity, uncontrolled renal, pancreatic or liver disease, or active autoimmune diseases requiring high-dose corticosteroids or immunosuppressive drugs are excluded. Part 1 evaluates the safety and tolerability of ZW171 and Part 2 evaluates the anti-tumor activity while continuing to evaluate safety and tolerability. Part 1 is dose escalation to identify maximum tolerated dose (using modified toxicity probability interval [mTPI-2] design, n=40) among participants with OC or NSCLC receiving subcutaneous ZW171 monotherapy on days 1, 8, and 15 of 3-week (21-day) cycles. Approximately 6 dose levels will be explored based on safety and tolerability. Step-up dosing will be used for cycle 1. Dose level 1, determined by QSP-based MABEL approach[2], is administered at 4.2 μg (day 1), 12.6 μg (day 8), and 38.0 μg (day 15). Part 2 is dose expansion in participants with OC, NSCLC, and other MSLN-expressing cancers (MSLN expression evaluated retrospectively). Primary objectives are to evaluate safety and tolerability of ZW171 and determine the maximum tolerated dose. Key secondary objectives are to assess PK, anti-drug antibodies, and anti-tumor activity. This is a global study with sites in North America, Europe, and Asia; and actively enrolling participants into Part 1. References: 1. Afacan N, et al. Presented at AACR Annual Meeting 2023; abstract 2942. 2. Afacan N, et al. Presented at SITC Annual Meeting 2024; abstract 1062. Clinical trial information: NCT06523803. Research Sponsor: Zymeworks BC Inc.

TPS3161 **Poster Session**

A phase 1, first-in-human study of AMT-676, an anti-CDH17 antibody-drug conjugate, in patients with advanced gastrointestinal tumors.

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Background: Cadherin-17 (CDH17), also known as liver-intestine-cadherin, is a transmembrane protein that is highly expressed in a variety of gastrointestinal cancers, including colorectal, gastric, esophageal adenocarcinoma, cholangiocarcinoma, pancreatic ductal, and gastrointestinal neuroendocrine tumors. The overexpression of CDH17 is associated with tumor metastasis and progression to advanced tumor stages. AMT-676 is a novel antibody-drug conjugate (ADC) that targets CDH17. It is comprised of a humanized IgG1 monoclonal antibody specific to CDH17, conjugated to the potent topoisomerase I inhibitor exatecan, with a drug-to-antibody ratio of 4, linked through a proprietary T-moiety technology. Preclinical studies have demonstrated significant anti-tumor activity of AMT-676 across multiple gastrointestinal cancer models and great tolerability in safety studies, highlighting its potential as a therapeutic agent for CDH17-expressing malignancies. **Methods:** This phase 1, open-label, multicenter study aims to determine the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D) of AMT-676, as well as to assess its safety, tolerability, anti-drug activity, pharmacokinetics, pharmacodynamics, immunogenicity and preliminary efficacy in patients with advanced solid tumors. Tumor types that express CDH17 including gastrointestinal cancers, treated with or with no standard therapeutic options are to be enrolled. AMT-676 will be administered intravenously on a 21-day cycle. The dose escalation will be guided by the Bayesian Optimal Interval (BOIN) design, incorporating an accelerated titration approach to evaluate 6 cohorts: 1.6, 3.2, 4.8, 6.4, 8, and 10 mg/kg. Three backfilling cohorts at doses that have demonstrated safety will also be included, each enrolling up to 18 patients, to gather additional data on safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy, thereby supporting the selection of an optimized dose for expansion. Mandatory pre-study biopsy sample collection for retrospective immunohistochemistry (IHC) analysis will facilitate a comprehensive exploratory biomarker plan, potentially correlating CDH17 levels with treatment responses. The study is actively enrolling participants for the dose escalation phase. Cohorts 1-4 have been completed DLT evaluation and enrollment of cohort 5 began in December 2024. Clinical trial information: NCT06400485. Research Sponsor: Multitude therapeutics Inc.

TPS3162 **Poster Session**

Phase I multicenter, open-label, dose escalation study of T-1201, a small molecule drug conjugate, to assess safety, pharmacokinetics, and antitumor activity in advanced solid tumors.

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Background: Phosphatidylserine (PS) is a phospholipid critical for maintaining cell membrane integrity and functionality. In rapidly proliferating cancer cells, PS translocates to the outer leaflet of the membrane, making it a promising biomarker and therapeutic target for cancer treatment. The investigational drug T-1201 is a proprietary small molecule drug conjugate combining a bioactive topoisomerase I inhibitor, SN-38, with Zn-DPA complexes, which exhibit high affinity for PS. Preclinical studies have demonstrated T-1201's in-vivo antitumor activity across multiple human tumor xenograft models. This study represents the first clinical evaluation of T-1201 in humans. **Methods:** The primary objectives of this phase I study are to evaluate the safety profile of T-1201, determine dose-limiting toxicities (DLTs), establish the maximum tolerated dose (MTD), and identify the recommended phase II dose (RP2D). Secondary objectives include characterization of pharmacokinetics (PK) and assessment of antitumor activity for T-1201. The study comprises three dose-escalation parts. In Part A, T-1201 is administered intravenously once every four weeks (Q4W), starting at 18 mg/m^2 during Cycle 1. From Cycle 2 onward, the dosing interval can be adjusted to once every two weeks (Q2W) at the investigator's discretion, subject to agreement with the Sponsor. When switching to the Q2W schedule, the dose level is halved compared to the Q4W dose. Each treatment cycle spans four weeks, with dose escalation proceeding via a single-patient cohort design (100% dose increments) initially, transitioning to a modified 3+3 design (40% dose increments) based on DLTs observed in Cycle 1. In Part B, T-1201 is administered intravenously Q2W in a 28-day treatment cycle, starting at 100 mg/m^2, which represents half of the MTD identified in Part A. In Part C, each treatment cycle is reduced to 21 days, with the starting dose not exceeding the highest dose level deemed safe by the Safety Review Committee (SRC) in Part B. Eligible patients are ≥18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and possess radiographically or clinically evaluable tumors. As of now, 27 patients have been enrolled in the Part A dose-escalation stage. This study is registered with ClinicalTrials.gov (NCT04866641). Clinical trial information: NCT04866641. Research Sponsor: Taivex Therapeutics corporation.

Dose escalation/de-escalation rule for the BOIN design.

Number of subjects treated at the current dose*	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	1	1	1	1	2	2
Stay at current dose if # of DLT =	1	NA	NA	2	2	3	3
De-escalate if # of DLT ≥	2	2	2	3	3	4	4
Eliminate if # of DLT ≥	3	3	4	4	5	5	6

*The enrollment may stop when one of the following criteria is met: The planned sample size has been reached; at least 9 subjects have been treated and evaluable for DLT at one dose level; or all doses explored appear to be overly toxic, and the MTD cannot be determined.

TPS3163 **Poster Session**

A phase 1 study to evaluate the safety and tolerability of the antibody–drug conjugate (ADC) MesoC2 (PF-08052666) in patients with advanced solid tumors.

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Background: MesoC2 (PF-08052666) is an ADC that targets mesothelin (MSLN), a cell-surface glycoprotein overexpressed in solid tumors including mesothelioma, ovarian cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), endometrial cancer (EC), and colorectal cancer (CRC), but with limited expression in normal tissues. MesoC2 is constructed from a recombinant human IgG1 anti-MSLN monoclonal antibody conjugated to a cleavable tripeptide linker that carries a topoisomerase 1 inhibitor (TOP1) payload. The average number of TOP1 molecules per antibody is 8. Following high-affinity binding to MSLN on the cell surface, MesoC2 is internalized, the linker is cleaved, and the released payload inhibits DNA religation during amplification, leading to cell cycle arrest and cell death. MesoC2 has shown potent antitumor efficacy in in vitro assays and xenograft models and an acceptable safety profile in cynomolgus monkeys. The aim of this first-in-human study is to explore the safety, tolerability, and preliminary efficacy of MesoC2 in patients with certain advanced solid tumors. **Methods:** In this phase 1, open-label study, up to 365 patients with mesothelioma, platinum-resistant ovarian cancer (PROC), pancreatic ductal adenocarcinoma (PDAC), NSCLC, EC, or CRC will receive intravenous infusion of MesoC2 in dose escalation (n=45), dose and schedule optimization (n=40), and disease-specific dose expansion cohorts (n=280; includes a biology cohort to evaluate exploratory biomarkers). Key inclusion criteria are histologically or cytologically confirmed metastatic or locally advanced mesothelioma, PROC, PDAC, NSCLC, EC, or CRC who have relapsed or progressed following standard therapies; aged ≥18 years; ECOG performance status score of 0 or 1; and available archival tumor tissue (a fresh biopsy is required if unavailable). Key exclusion criteria include prior or current treatment with systemic anticancer therapy or focal radiotherapy within 4 weeks prior to first dose of MesoC2, prior anti-MSLN therapies, and any unresolved toxicities from prior therapy greater than G1 at the time of starting study treatment, except alopecia. Primary endpoints include type, incidence, and severity of adverse events (AEs), frequency of dose modifications due to AEs, incidence of dose-limiting toxicities, cumulative safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity. Key additional endpoints include objective and best response rates per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), duration of response, progression-free survival, overall survival, MSLN expression in blood and tissue, and changes in tumor-specific biomarkers. Enrollment is ongoing; clinical trial information: NCT06466187. A genAI tool (01/06/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Clinical trial information: NCT06466187. Research Sponsor: Pfizer Inc.

TPS3164 **Poster Session**

TUB-030, a novel ADC targeting 5T4: A phase I/IIa multi-center, first-in-human clinical trial (5-STAR 1-01) in patients with advanced solid tumors.

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Background: TUB-030 is a novel antibody-drug conjugate (ADC) targeting 5T4, an oncofetal antigen expressed in various solid tumors with limited expression in healthy tissues. TUB-030 leverages optimized biophysical properties, an effector-silenced antibody, and an exatecan payload to maximize the therapeutic index and minimize off-target toxicities. Preclinical studies demonstrated potent anti-tumor activity, including long-lasting tumor regression at doses as low as 1 mg/kg and durable responses even in tumors with low 5T4 expression. **Methods:** 5-STAR 1-01 is a multicenter, first-in-human dose escalation and dose optimization Phase I/IIa clinical trial designed to investigate safety, tolerability, pharmacokinetics (PK), and efficacy of the anti-5T4 ADC TUB-030 in patients with advanced and metastatic solid tumors. Eligible patients have one of the following tumor types: head and neck squamous cell carcinomas (HNSCC), non-small-cell lung cancer (NSCLC), small cell lung cancer, pleural mesothelioma, triple-negative breast cancer, HR+/HER2- breast cancer, esophageal cancer, gastric cancer, pancreatic adenocarcinoma, colorectal cancer, bladder cancer, prostate cancer, cervical cancer, osteosarcoma, or soft tissue sarcomas and must have exhausted available standard-of-care therapies. Phase I is an open-label, single-arm dose escalation trial, with administration every 21 days. Dose escalation follows an accelerated titration design (ATD) transitioning to Bayesian optimal interval (BOIN) upon predefined toxicity thresholds. Backfill cohorts are planned in NSCLC and HNSCC to further evaluate the safety and efficacy profile at, or near, the maximum tolerated dose (MTD). Primary endpoints include safety and tolerability of TUB-030 as monotherapy, determination of the MTD and the recommended phase II doses; secondary endpoints assess pharmacokinetics, immunogenicity, and preliminary clinical activity using RECIST v1.1 criteria. Exploratory endpoints include analysis of circulating tumor DNA. In phase IIa, dose-optimization will evaluate two dose levels in select indications in order to identify the optimal dose for further development. Enrollment of approximately 130 patients across the US and Canada is planned, with dose escalation currently underway. This study investigates TUB-030, a novel 5T4 targeted ADC as a therapy for advanced/metastatic solid tumors. Clinical trial information: NCT06657222. Research Sponsor: None.

TPS3165 Poster Session

PROCEADE PanTumor: A phase 1b/2, multicenter study of precemtabart tocentecan (M9140), an anti-CEACAM5 antibody-drug conjugate (ADC) with exatecan payload, in patients with advanced solid tumors.

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Background: CEACAM5 is a cell surface glycoprotein that is overexpressed in various carcinomas, notably in gastric cancer (GC), non-small cell lung cancer (NSCLC), pancreatic adenocarcinoma (PDAC), and colorectal cancer (CRC), but shows limited expression on healthy adult cells. Precemtabart tocentecan is an investigational anti-CEACAM5 ADC (drug-to-antibody ratio: 8) that utilizes a unique linker–payload combination to selectively deliver the topoisomerase 1 inhibitor, exatecan, to CEACAM5 overexpressing tumor cells. Preliminary clinical data from the dose-escalation part of the first-in-human study of precemtabart tocentecan in patients with metastatic CRC (PROCEADE CRC-01) demonstrated a manageable and predictable safety profile and promising preliminary efficacy in 40 heavily pretreated patients. The PROCEADE PanTumor study is a Phase 1b/2, multicenter, open-label study that aims to investigate the clinical activity of precemtabart tocentecan, either as monotherapy or in combination with other anticancer agents, in patients with advanced GC, advanced NSCLC and advanced PDAC. **Methods:** The study was designed as a matrix study with a master protocol (applicable to all substudies) and three substudy protocols (GC; NSCLC; PDAC). Based on the master protocol, patients aged ≥18 years, with an Eastern Cooperative Oncology Group performance status ≤1, adequate baseline hematological, renal, and hepatic function, ≥1 lesion that is measurable using RECIST v1.1, who have received ≥1 prior line of treatment are eligible. Patients must have an archival formalin-fixed paraffin-embedded tumor tissue or a fresh biopsy. In the respective substudies, patients with advanced or metastatic, HER2-negative GC or gastroesophageal junction adenocarcinoma; patients with advanced (Stage III; ineligible for resection/curative radiation) or metastatic NSCLC; or patients with advanced or metastatic PDAC will be included. Patient selection will be based on CEACAM5 expression level (both high and low in GC, only high in NSCLC and PDAC [$CEACAM5^{high}$: ≥50% tumor cells with immunohistochemistry [IHC] ≥2+ staining; $CEACAM5^{low}$: <50% tumor cells with IHC ≥2+ staining]), and in patients with NSCLC, *EGFR* mutation status (*EGFR*-wt and *EGFR* mut+). The primary endpoint is objective response (proportion of patients with confirmed complete/partial response [CR/PR] per RECIST v1.1, assessed by investigator). Secondary endpoints include adverse events, duration of response (RECIST v1.1), disease control (CR, PR, stable disease, or non-CR/non-progressive disease [PD] at Week 12), time to response, progression-free survival, and pharmacokinetic assessments. The study is planned to be initiated at multiple sites globally, with an estimated enrollment of 250 patients. Clinical trial information: NCT06710132. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

TPS3166 **Poster Session**

A dose escalation and cohort expansion phase I/IIa study of ACR246, an innovative 5T4- antibody drug conjugate (ADC), in patients (pts) with advanced solid tumors.

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Background: The oncofetal antigen 5T4 is overexpressed in many solid tumors with limited expression in normal adult tissues. Overexpression of 5T4 is associated with poor prognosis. 5T4 on tumor cell surface is rapidly internalized when bound to antibody and is thus an ideal target for the development of ADC drugs. ACR246 is the first next- generation 5T4-ADC consisting of a fully human monoclonal antibody that is site-specifically conjugated to a novel DNA topoisomerase I inhibitor D2102, via a stable and cleavable linker, with a drug-to-antibody ratio (DAR) of 8. ACR246 was carefully designed to improve the safety and efficacy in treating 5T4 positive solid tumors. In preclinical studies, ACR246 demonstrated robust anti-tumor activity, superior to a Dxd-5T4 ADC (as a reference) both in CDX and PDX models, including but limited to NSCLC, gastric cancer, pancreatic cancer and Esophageal cancer, and excellent tolerability, supporting further development for clinical use. **Methods:** This is an ongoing, phase I/IIa, open-label, multicenter, dose escalation and cohort expansion study of ACR246 to be injected intravenously to adult pts with advanced solid tumors. For phase I study, a Bayesian optimal interval design is adopted to assess dose levels of ACR246, 0.6, 1.2, 2.4, 3.6 and 4.5 mg/kg, administered every 3 weeks on a 21-day cycle，and intermediate dose levels of 3.0, 4.0 and 5.0 mg/kg may be evaluated based on emergent safety or pharmacologic data. The primary objectives are to evaluate safety and tolerability and determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D); the second objectives include PK, immunogenicity and preliminary clinical efficacy. Dose limiting toxicity (DLT) will be assessed at each dose level. The DLT evaluation period will be 21 days. Once the RP2D is determined, phase IIa study will be conducted to further evaluate the safety, tolerability, efficacy, PK and immunogenicity of ACR246 in 5T4-positive advanced solid tumor pts (esophageal cancer, NSCLC, ovarian cancer, prostate cancer and other types of tumors) under RP2D. Approximately 77 pts ≥ 18 years of age with advanced solid tumors that have histologically or cytologically been diagnosed recurrent or metastatic unresectable advanced disease and have failed or are intolerant of systemic standard therapy or standard therapy is not available, and having adequate ECOG performance status (0-1), hematologic function, and end organ function are planned to be enrolled, with 37 pts in phase I study and approximately 40 pts in phase IIa study. 5T4 expression is not required for enrollment for phase I, but will be assessed retrospectively. The toxicity will be assessed by Common Terminology Criteria for Adverse Events v5.0 and the tumor response will be determined per RECIST v1.1. Dose levels of 0.6 mg/kg and 1.2mg/kg has completed enrollment with no DLT. Clinical trial information: NCT06238401. Research Sponsor: Hangzhou Adcoris Biopharma Co., Ltd.

TPS3167 **Poster Session**

A phase 1 dose escalation and dose expansion study for LNCB74, a B7-H4 targeted antibody drug conjugate, as monotherapy in participants with advanced solid tumors.

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Background: B7-H4 is a transmembrane receptor of the B7-family of immunomodulatory proteins whose expression correlates with poor clinical outcomes for ovarian and breast cancers. High expression in multiple tumor types and limited expression in normal tissues makes B7-H4 an attractive target for antibody drug conjugate (ADC) therapeutics. LNCB74 is a B7-H4 targeted ADC in which a humanized IgG1κ antibody is conjugated to the microtubule disrupting payload monomethyl auristatin E (MMAE) with a drug-to-antibody ratio of 4 (DAR4). LNCB74 is designed to maximize therapeutic index through three key elements. First, site specific ConjuAll conjugation results in a homogeneous DAR to drive uniform PK. Second, our proprietary glucuronidase-cleavable linker reduces both on- and off-target toxicity. Third, the antibody Fc was "LALA"-mutated to reduce Fc mediated uptake into Fc receptor expressing cells such as immune and endothelial cells. Compared to other B7-H4 targeted ADCs in clinical development, LNCB74 has demonstrated a superior safety profile in nonhuman primate toxicity studies and potent anti-tumor activity in multiple cell line- and patient-derived xenograft in vivo models, making it a promising ADC therapy for B7-H4-expressing solid tumors. **Methods:** LNCB74-01 is a phase 1, open-label, first-in-human study that will include dose escalation, safety, and biomarker backfills (Part 1) and randomized dose expansion/optimization (Part 2). The objectives of the study will be to determine safety and tolerability, define the maximum tolerated dose and/or recommended phase 2 dose, characterize the pharmacokinetics (PK) and pharmacodynamics (PD), and to assess the preliminary efficacy in participants with metastatic solid tumors treated with LNCB74. The tumor types include ovarian, breast, endometrial, biliary tract cancer, and squamous NSCLC. Key eligibility criteria include measurable disease based on RECIST v1.1 and the ability to provide tissue samples to test B7-H4 expression by CLIA-certified immunohistochemistry assay in a central laboratory. Participants will receive LNCB74 on Day 1 of each 21-day cycle. Dose escalation will follow a Bayesian optimal interval (BOIN) design. Dose expansion will occur in up to two tumor types. In each tumor specific dose expansion, participants will be randomized to two dose levels stratifying for prior lines of therapy (1-3 vs ≥4) and B7-H4 expression (intermediate vs high). The PK profile, immunogenicity, preliminary anti-tumor activity per RECIST v1.1, and correlation of baseline B7-H4 expression to anti-tumor activity of LNCB74 will be evaluated as secondary endpoints. Biomarkers will be assessed in peripheral blood and tumor tissue. Enrollment is ongoing in the United States. Clinical trial information: NCT06774963. Research Sponsor: NextCure Inc.

TPS3168 **Poster Session**

The EQUAL study: Utilizing plasma EGFR cfDNA detection as an accessible screening tool for lung cancer in underserved patients ineligible for routine screening.

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Background: Lung cancer (LC) among non-tobacco-users is increasing in the United States, with no routine screening available. Among those patients, EGFR mutations (EGFRm) are common, with the highest prevalence seen in East Asian and Hispanic women. Delays in diagnosis and treatment are exacerbated in these marginalized groups and women, negatively impacting their cancer outcomes. At Dana-Farber Cancer Institute's (DFCI) Belfer Center for Applied Science, we developed a novel droplet digital PCR ctDNA assay to detect EGFR del19 and L858R mutations, which comprise 85-90% of total EGFRm in LC. Here, we report the methodology of EQUAL, a study assessing the feasibility of a diagnostic assay among non-tobacco using, historically marginalized East Asian and Hispanic populations at high risk for EGFRm-LC. **Methods:** To assess the feasibility of our ctDNA screening tool, the EQUAL study is recruiting two cohorts of participants. Cohort 1 (n=500) includes 50–80-year-olds who self-identify as East Asian or Hispanic from the general population, while Cohort 2 (n=500) includes 40–80-year-olds of the same backgrounds with an additional risk factor for LC, with a focus on direct family members of patients with EGFRm-LC. Recruitment is beginning with these family members of patients with EGFRm-LC at DFCI main campus, Beth Israel Deaconess Medical Center, Massachusetts General Hospital, DFCI Merrimack Valley, DFCI regional campuses, and will expand to primary care clinics and community events. Blood samples are collected in clinics or at home via mobile phlebotomy. Positive results are verified in a government-certified CLIA laboratory; a complementary chest CT will be arranged for those with positive assay results, and patients will receive navigation until resolution. Patients with a positive assay but negative chest CT will be followed for 12 months and will receive a second annual chest CT. Recognizing how cultural beliefs and tobacco's association with LC may hinder screening participation, EQUAL includes an optional survey and focus groups to explore perceptions and barriers surrounding LC screening with our tool for future optimization efforts. The study is available in 8 languages including Spanish, Portuguese, Korean, Vietnamese, Japanese, Chinese (simplified and traditional), and Creole. EQUAL is the first study to implement EGFRm-LC blood-based screening for historically marginalized populations who are not eligible for LC screening, thereby allowing for LC identification that can be effectively treated with targeted therapy approved for stages IB-IV. This pilot study seeks to lay the groundwork for future sensitivity and specificity trials that will confirm the value of the assay and expand the scope of current screening guidelines to reduce health disparities and delays in LC diagnosis. Clinical trial information: NCT06716580. Research Sponsor: Dana-Farber Cancer Institute Philanthropic Funds.

TPS3169 **Poster Session**

A phase 1/2 study of FOG-001, a first-in-class direct β-catenin: TCF inhibitor, in patients with colorectal cancer (CRC) and other locally advanced or metastatic solid tumors.

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Background: Activation of the Wnt/β-catenin pathway, often as truncal APC mutations, in 80–90% of CRCs and other solid tumors, is known to be a key driver of cancer progression and has been associated with immune exclusion and resistance to immunotherapy. Development of agents targeting this pathway at the key β-catenin: T-cell factor (TCF) node has eluded the pharmaceutical industry to date. FOG-001 is a Helicon peptide that competitively inhibits interaction between β-catenin and TCF transcription factors. Helicon peptides are hyper-stabilized α-helices that can be tuned for picomolar binding affinities, robust cell penetration, broad tissue distribution, no immune recognition, and long *in vivo* half-lives. In studies in a wide range of patient-derived xenograft (PDX) CRC and HCC models, FOG-001 inhibited tumor growth and promoted tumor regression as monotherapy. Combinations with immune checkpoint inhibitors or standard-of-care therapies, including bevacizumab and 5-FU, showed strong additivity/synergy in PDX CRC models. **Methods:** This first-in-human, phase 1/2, multicenter, open-label, dose-escalation (part 1) and dose-expansion (part 2) study evaluates the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor effects of FOG-001 monotherapy and combined with other anti-cancer therapies in patients with microsatellite stable (MSS) CRC or advanced/metastatic solid tumors known to harbor a Wnt pathway-activating mutation (WPAM). Eligible patients must have received at least one prior systemic anti-cancer therapy and either progressed on, not responded to, or be unfit for available therapies. In Part 1, FOG-001 is administered intravenously every week, at escalating dose levels evaluated sequentially in a standard 3+3 design as monotherapy in patients with MSS CRC or any solid tumor with documented WPAM. PD effects are evaluated in a separate cohort of approximately six patients with MSS CRC. Combination cohorts will evaluate FOG-001 + FOLFOX/bevacizumab (1L MSS CRC), FOG-001 + nivolumab (3L MSS CRC or anti-PD-1/PD-L1-resistant CRC and solid tumors), and FOG-001 + trifluridine/tipiracil + bevacizumab (3L MSS CRC). Part 2 dose expansion will evaluate FOG-001 monotherapy in patients with MSS CRC and other solid WPAM+ tumors. Combination dose expansion will evaluate combinations initially studied in Part 1. Primary endpoints are safety/tolerability of FOG-001 alone or in combination. Secondary endpoints are PK, PD, recommended phase 2 dose and schedule, and preliminary anti-tumor activity (e.g., ctDNA changes, overall response rate, best objective response, duration of response, and progression-free survival). 156 patients are planned to be enrolled in Part 1, which is currently enrolling in the USA. Clinical trial information: NCT05919264. Research Sponsor: Parabilis Medicines.

TPS3170 **Poster Session**

SCRUM-Japan MONSTAR-SCREEN-3: Comprehensive tumor microenvironment analysis via multi-omics in a large-scale prospective study.

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Background: SCRUM-Japan is a multi-institutional, industry-academia collaborative cancer genome screening project launched in 2015, consisting of LC-SCRUM-Asia for lung cancer and SCRUM-MONSTAR for other malignancies. The project has successfully implemented organ-agnostic liquid biopsy-based precision oncology and molecular residual disease (MRD)-guided therapeutic development, resulting in multiple regulatory approvals of therapeutic agents and diagnostics. In 2024, MONSTAR-SCREEN-3 was launched to expand the scope of multi-omics analysis beyond advanced solid tumors to include resectable solid tumors and hematologic malignancies, aiming for a comprehensive understanding of tumor microenvironment (TME) dynamics. The project integrates a multi-omics platform, including spatial transcriptomics, ctDNA analysis, and proteomics, to advance personalized medicine and accelerate drug development. **Methods:** MONSTAR-SCREEN-3 (UMIN000053975) is a large-scale, multi-institutional prospective study involving 55 centers across Japan, aiming to enroll 3,200 patients across three cohorts: Cohort A: Advanced solid tumors undergoing systemic therapy (n=1,700); Cohort B: Resectable solid tumors receiving perioperative treatment (n=1,100); Cohort C: Hematologic malignancies (n=400). Our analysis platform combines spatial transcriptomics with circulating tumor DNA/RNA sequencing, bulk tissue whole exome/transcriptome sequencing, plasma proteomics, and microbiome analyses. For resectable cases, standardized longitudinal monitoring with whole genome sequencing-based MRD analysis is implemented, while disease-specific MRD approaches are applied to hematologic malignancies. Following SCRUM-Japan's quality assurance system, standardized monitoring collects regulatory-grade clinical data, including key indicators such as response rate, progression-free survival, and overall survival. MONSTAR-SCREEN-3 applies standardized protocols for tissue preservation and data acquisition across all centers, ensuring high-quality data. The project leverages the VAPOR CONE supercomputing infrastructure for real-time data integration and AI-driven analysis to identify biomarkers, elucidate resistance mechanisms, and deepen the understanding of tumor-immune interactions. The study aims to establish a framework for next-generation precision oncology. The latest enrollment status and initial operational results will be reported at the ASCO meeting. MONSTAR-SCREEN-3 is expected to contribute to new therapies, cross-cancer MRD assays, and the resolution of drug lags in hematologic malignancies, driving advancements in personalized cancer treatment. Clinical trial information: UMIN000053975. Research Sponsor: None.

TPS3171 **Poster Session**

A first-in-human multi-center phase 1/2 study of a selective FGFR2/3 inhibitor, CGT4859, in patients with intrahepatic cholangiocarcinomas or other advanced solid tumors.

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Background: Genetic alterations in fibroblast growth factor receptors 2 and 3 (*FGFR2/3*) occur in nearly all cancer types. *FGFR2* fusions and rearrangements occur in up to 10-15% of intrahepatic cholangiocarcinomas (iCCA) and alterations in *FGFR3* occur in 15-30% of urothelial cancers. The clinical benefit from currently approved FGFR inhibitors (FGFRi) is often curtailed by development of acquired resistance, which may arise through on-target mutations in the *FGFR2/3* kinase domain. Additionally, off-tumor effects on FGFR1 by pan-FGFRi can lead to hyperphosphatemia and consequently to dose reductions or dose holds. Thus, there is an unmet clinical need for a selective FGFR2/3 inhibitor that has clinical efficacy against activating alterations and resistance mutations without causing FGFR1-mediated hyperphosphatemia. CGT4859 is an orally bioavailable, ATP-competitive, reversible inhibitor of FGFR2/3, with potency against clinically relevant *FGFR2/3* kinase domain mutations. In addition, CGT4859 demonstrates >140 fold selectivity over FGFR1, and shows robust efficacy in target altered *in vivo* tumor models without increases in serum phosphorus. Nonclinical pharmacokinetics (PK) and safety data support evaluating CGT4859 in a first-in-human, open-label, dose-escalation and signal-seeking Phase I/II study (NCT06777316). Safety, tolerability, PK, pharmacodynamics, and antitumor activity of CGT4859 will be assessed in adults with histologically confirmed unresectable or metastatic iCCA or other solid tumors with *FGFR2/3* alterations. **Methods:** CGT4859 will be administered orally continuously in 28-day cycles to patients (N=~50) at a starting dose of 1 mg QD, and dose escalation will not exceed 40 mg QD as determined using a Bayesian optimal interval design with backfill (BF-BOIN). This approach will be used to guide dose escalation and establish the maximum tolerated dose (MTD) and recommended Phase 2 Dose (RP2D). BF-BOIN enables backfilling of participants to doses that are cleared for safety during the dose escalation, generating additional data on safety and tolerability below the MTD. Objective response rate (ORR) and disease control rate will be determined based on investigator assessment using RECIST v1.1. Phase II will enroll up to 4 cohorts, each enrolling ~15 patients. Proposed cohorts will include participants who have iCCA and are either FGFRi-naïve or FGFRi-exposed. Two additional cohorts with other advanced solid tumors harboring *FGFR2/3* alterations may be included based on signals detected in dose escalation. The primary efficacy endpoint for Phase II is ORR per RECIST v1.1. The preclinical data support the study of CGT4859 in this patient population with solid tumors harboring *FGFR2* and/or *FGFR3* genetic alterations. The phase I dose escalation study is currently enrolling at sites in the United States. Clinical trial information: NCT06777316. Research Sponsor: Cogent Biosciences.

TPS3172 **Poster Session**

Phase IB/II study to evaluate safety and preliminary efficacy of the WEE1 inhibitor Debio 0123 in combination with sacituzumab govitecan (SG) in triple-negative or hormone receptor–positive (HR+)/HER2-negative (HER2–) advanced breast cancer (ABC): The WIN-B study.

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Background: SG is a Trop-2 directed antibody drug conjugate that has shown an overall survival benefit for patients (pts) with HER2- ABC in two phase III trials. Unfortunately, most pts become refractory to this treatment, highlighting a critical need for strategies to overcome resistance to SG and improve therapeutic outcomes. WEE1 is a cyclin-dependent kinase 1 regulator, which delays the G2/M transition and maintains genomic stability during the cell cycle. Debio 0123, a highly selective and brain penetrant WEE1 inhibitor, has demonstrated synergistic activity in breast cancer preclinical models with SG. The aim of the WIN-B study is to evaluate the safety and preliminary efficacy of combining the WEE1 inhibitor Debio 0123 with SG in pts with previously treated HER2- ABC. **Methods:** WIN-B (NCT06612203) is an international, multicenter, open-label, single-arm phase Ib/II trial. In phase Ib, 12-24 pts will be assigned to different Debio 0123 dose cohorts (200, 300, 400, or 520 mg orally once daily on days 1-3 and 8-10) plus standard doses of SG (10 mg/kg intravenously on days 1 and 8) given in 3-week cycles. In phase II, 52 pts will be divided into cohorts A (triple-negative breast cancer [TNBC], n = 26) and B (HR+/HER2– tumors, n = 26), and will be treated with the recommended doses determined during phase Ib. Key inclusion criteria are: pts aged ≥18 with TNBC or HR+/HER2- tumors who have experienced disease progression after 1 or 2 lines of systemic therapy for ABC, ECOG performance status of 0-1, with evaluable (for phase Ib) or measurable (for phase II) disease as per RECIST v.1.1. Pts will receive study treatment until progression, death, unacceptable toxicity, or study discontinuation. Primary objectives are: in phase Ib, to establish the recommended phase 2 dose of the combination of Debio 0123 plus SG and, in phase 2, to assess the objective response rate (ORR) as per RECIST v.1.1. Key secondary endpoints are progression-free survival and overall survival, safety and toxicity. In phase Ib, dose escalation will be performed using a Bayesian Logistic Regression Model with overdose control. In phase 2, A'Hern one-stage design will be set at one-sided type I binomial exact test of 5% to attain 80% power. The primary analyses will estimate ORR (H0: ORR≤29% for TNBC and ORR≤19% for HR+/HER2- tumors vs H1: ORR≥55% for TNBC and ORR≥41% for HR+/HER2- tumors). The phase 2 part of the study will be deemed positive if at least 12 (46.2%) and nine (34.6%) pts with TNBC and HR+/HER2- tumors, respectively, achieve an objective response. Clinical trial information: NCT06612203. Research Sponsor: Debiopharm. Gilead will provide the supply of SG.

TPS3173 **Poster Session**

Trial in progress: First-in-human study of PFL-721/STX-721 in participants with locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations.

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Background: Mutations in exon 20 of the *EGFR* gene account for approximately 4% to 10% of all EGFR mutations in Non-Small Cell Lung Cancer (NSCLC). Most of these mutations are insertions (EGFR ex20ins) that reduce the binding of first, second, and third generation tyrosine kinase inhibitors (TKI) to the ATP-binding pocket of the EGFR. Amivantamab, a bispecific anti-EGFR/c-MET-receptor antibody, is approved for the treatment of NSCLC with EGFR ex20ins mutations. However, there is significant unmet need for new oral agents that lack the limitations of intravenous administration and associated infusion-related toxicities and possess improved target engagement, mutant selectivity, and tolerability. PFL-721/STX-721 is an orally bioavailable, irreversible small-molecule inhibitor targeting a broad range of EGFR- and HER2-activating ex20ins mutations. PFL-721/STX-721 is highly selective for EGFR ex20ins mutations compared to wild type EGFR and exhibits greater selectivity compared to other EGFR mutant inhibitors. In addition, PFL-721/STX-721 has demonstrated superior anti-proliferation and antitumor effects compared to other investigational anti-EGFR ex20ins agents in relevant tumor models *in vitro* and *in vivo.* These observations suggest a more robust clinical risk-to-benefit profile and support further clinical investigation of PFL-721/STX-721. **Methods:** PFL-721/STX-721-101 (NCT06043817) is an open-label, first-in-human (FIH), Phase 1/2 study evaluating the safety, tolerability, pharmacokinetic (PK) exposure, and preliminary antitumor activity of PFL-721/STX-721 in participants with locally advanced or metastatic NSCLC harboring EGFR/HER2 ex20ins mutations. It consists of 3 parts: Part 1 Dose Escalation, Part 2 Recommended Phase 2 Dose (RP2D) selection, and Part 3 Dose Expansion. In Part 1, participants with NSCLC harboring EGFR or HER2 ex20ins mutations will be enrolled into sequential cohorts to receive ascending oral doses of PFL-721/STX-721 administered daily in 28-day treatment cycles. The main goal is to identify the maximum tolerated dose (MTD) and optimal biological dose (OBD) of PFL-721/STX-721. In Part 2, participants with NSCLC harboring EGFR ex20ins mutations who have received 1 to 2 prior lines of treatment, including a platinum-containing chemotherapy regimen and excluding EGFR targeted therapies with the exception of amivantamab, will be randomized 1:1 to receive PFL-721/STX-721 at the MTD or OBD in order to determine the optimal RP2D. Finally, Part 3 will further test the anticancer efficacy of PFL-721/STX-721 is administered at the RP2D. PFL-721/STX-721-101 is actively enrolling at 18 sites in 7 countries globally. Clinical trial information: NCT06043817. Research Sponsor: Scorpion Therapeutics, Inc.

TPS3174 **Poster Session**

A phase 1/2 dose escalation study of the oral DNA polymerase theta inhibitor (POLQi) GSK4524101 ± niraparib in adults with advanced or metastatic solid tumors.

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Background: In homologous recombination-deficient (HRd) tumors, use of a PARP inhibitor (PARPi) leads to generation of DNA breaks that cannot be effectively repaired, thus selectively killing cancer cells via synthetic lethality. An alternative DNA repair mechanism, microhomology-mediated end joining, is mediated by DNA polymerase theta (encoded by *POLQ*). In preclinical studies, POLQi + PARPi demonstrated superior efficacy vs PARPi alone in preventing HRd tumor growth. To evaluate the clinical potential of this combination, this first-in-human study investigates treatment with GSK4524101, an investigational POLQi, and niraparib, a PARPi, in patients with solid tumors. **Methods:** This open-label, phase 1/2, multicenter study opened in October 2023 and includes a phase 1a/b, dose-escalation portion (part 1; potential enrollment to n≈75). Sites in the US and Canada are enrolling patients for part 1, which aims to assess the maximum tolerated dose, pharmacokinetics (PK), and safety of oral GSK4524101 ± oral niraparib. Eligibility criteria include age ≥18 years, Eastern Cooperative Oncology Group performance status of 0–2, life expectancy ≥3 months, and diagnosis of advanced or metastatic solid tumor with all standard-of-care treatment options exhausted. Exclusion criteria include unresolved chemotherapy-induced adverse events (AEs) or symptomatic uncontrolled brain or leptomeningeal metastases, uncontrolled hypertension, history of myelodysplastic syndrome or acute myeloid leukemia, or another malignancy that has progressed or required active treatment in the past 2 years. Outcome measures include dose-limiting toxicity (DLT) incidence during the DLT observation periods (up to 28 days; primary); treatment-emergent AEs (TEAEs) and serious AEs (SAEs); percentage of patients receiving all planned doses; and percentage of patients requiring AE-related dose interruptions, reductions, and discontinuations in the DLT observation period. Secondary endpoints include the PK of niraparib and the metabolite of GSK4524101 and incidence and duration of TEAEs and SAEs beyond the DLT observation period. The study is currently recruiting, with 17 patients having received doses across 9 sites in 2 countries as of January 10, 2025. Clinical trial information: NCT06077877. Research Sponsor: GSK.

TPS3175 **Poster Session**

A phase 1 study to evaluate the safety, pharmacokinetics, and efficacy of the first-in-class cyclin A/B RxL inhibitor CID-078, an orally bioavailable, cell-permeable macrocycle.

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Background: The cyclin-dependent kinase (CDK)-RB-E2F axis forms the core transcriptional machinery driving cell cycle progression. Alterations in *RB1* or other key components occur in many cancers, resulting in heightened oncogenic E2F activity. E2F activation relies on the interaction between the cyclin's conserved hydrophobic patch (HP) and the RxL motif found on E2F and other cyclin/CDK substrates. Disrupting this cyclin A/E2F RxL interaction leads to hyperactivation of E2F and synthetic lethality in E2F-driven tumors. CID-078 is a novel, orally bioavailable, passively cell-permeable, potent and selective macrocycle that binds to the HP of cyclins A and B, blocking the RxL motif-mediated binding of E2F1 to cyclin A2-CDK2 and Myt1 to cyclin B1-CDK1. Consequently, CID-078 induces cell cycle arrest at the G2/M phase, leading to apoptotic tumor cell death. In preclinical studies including small cell lung cancer (SCLC) and triple negative breast cancer (TNBC) tumor types, CDX and PDX models with high E2F target pathway scores and high E2F1 expression demonstrated tumor regression following single-agent CID-078 treatment. Pre-clinical species demonstrate a well-tolerated safety profile and 20% oral bioavailability. Preclinical to clinical predictions maintain a 20% bioavailability. **Methods:** This is a phase 1, first-in-human, open-label, multicenter, dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics (PK) pharmacodynamics (PD) and preliminary anti-tumor efficacy of CID-078 in patients (pts) with locally advanced or metastatic solid tumor malignancies (NCT06577987). Pts previously treated with standard of care therapy and for whom no available curative therapy exists are eligible. CID-078 will be administered orally, twice-daily in repeating 21-day cycles and treatment will continue until disease progression, death, unacceptable toxicity or withdrawal from study. Part I dose escalation will be guided by a Backfill-Bayesian Optimal Interval Design (BF-BOIN) based on the incidence of dose-limiting toxicities (DLTs) and all available safety and PK data. Under the BF-BOIN design, additional pts may be enrolled to expand previous cohorts to better characterize the safety, PK, PD and preliminary efficacy activity to support a recommended dose for expansion. A pilot food effect cohort is planned as well. In Part II dose expansion, pts will be enrolled to one or more cohorts defined by histologic tumor type or molecular alteration at the recommended doses of expansion. Based on preclinical data generated to date, the study plans to include patients with SCLC, TNBC, and RB1-mutated tumors with additional tumor types expanded based on observed efficacy. Dose escalation is ongoing with no DLT reported in the initial 3 dose cohorts evaluated. Clinical trial information: NCT06577987. Research Sponsor: None.

TPS3176 **Poster Session**

First in human phase 1 dose escalation and expansion clinical trial to evaluate the safety, pharmacokinetics and antitumor activity of intravenous AROG4-01 in patients with advanced solid tumors.

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Background: AROG4-01 is a synthetic compound with a first-in-class mechanism of action, targeting complex secondary structural elements in mRNA, including G-quadruplexes(G4s). These secondary nucleic acid structures, characterized by Hoogsteen base pairing, play pivotal roles in gene regulation and are abundant in cancer cells due totheir high proliferation rates and dysregulated gene expression patterns. By binding to G4s present in untranslated regions, AROG4-01 modulates gene expression atthe post-transcriptional level, reducing tumor growth and survival. Preclinical studies have demonstrated that AROG4-01 achieves significant antitumor activity,inhibiting cancer cell proliferation, with a strong effect of the compound on inhibit colony formation, evidencing the capacity of AROG4-01 to prevent the long-termsurvival and proliferation of cancer cells. This activity has been validated in vivo across multiple solid cancer models. **Methods:** This study (NCT06652529,EudraCT2024-517569-18) is an open label, Phase 1 dose escalation trial with two expansion cohorts to investigate the safety, tolerability, pharmacokinetics,pharmacodynamics and preliminary antitumor activity of AROG4-01. The study consists of two parts. Part A is a dose escalation that will include 8-20 patients withadvanced solid tumors, covering up to 6 dose levels with the primary objective of determining the safety and tolerability of AROG4-01 and defining an appropriaterecommended phase 2 dose (RP2D) for further evaluation in part B. The study will start with an accelerated-titration dose escalation scheme enrolling one evaluablepatient per cohort for the first 2 dose levels followed by a classic 3+3 design. Part B is a dose expansion, with two cohorts of ten patients: one cohort of patients withadvanced mesothelioma (cohort 1) and a second cohort of patients with other solid tumors (cohort 2). Serum samples collected from patients enrolled in part A whenreceiving the first IMP dose during the first treatment cycle will be used to assess the PK of AROG4-01. Three sites in Spain are expected to participate. Clinical trial information: NCT06652529. Research Sponsor: Applied Research using Omic Sciences.

TPS3177 Poster Session

IMMUNONET: A multicenter, open-label, proof-of-concept phase II trial evaluating NP137 as add-on therapy in advanced/metastatic solid tumors treated with standard immunotherapies.

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Background: PD-1/PD-L1 blockade has transformed oncology by offering durable responses in various cancers. However, many patients develop resistance, highlighting the need for novel therapeutic strategies. Epithelial-to-Mesenchymal Transition (EMT) plays a pivotal role in immune checkpoint inhibitor efficacy, with epithelial tumors exhibiting greater immunoreactivity than mesenchymal ones. NP137, a first-in-class anti-Netrin-1 monoclonal antibody, has shown in phase I study the ability to inhibit EMT, potentially overcoming resistance (Cassier et al., *Nature*, 2023). This phase I data demonstrated NP137's ability to shift tumors toward an epithelial phenotype, supporting its combination with immune checkpoint inhibitor to sensitize tumors and alleviate resistance. The goal of IMMUNONET study (NCT05605496) is to evaluate NP137's ability to re-sensitize advanced solid tumors to anti-PD-1/PD-L1 therapy.
Methods: This proof-of-concept study assess NP137 (14 mg/kg, IV, Q3W) as add-on therapy to standard PD-1/PD-L1 inhibitors across three independent cohorts of patients with advanced/metastatic solid tumors of any histological types: Cohort 1 (Stable Disease [SD]): Radiological SD after ≥12 weeks of anti-PD-1/PD-L1 therapy. Cohort 2 (Primary Refractory): Radiological progressive disease (PD) and no response under anti-PD-1/PD-L1 therapy. Cohort 3 (Secondary Refractory): Radiological PD following initial response under anti-PD-1/PD-L1 therapy. Treatment continues until progression, unacceptable toxicity, or consent withdrawal. The primary endpoint is clinical activity: objective response rate (ORR)-12W for cohort 1 and progression-free rate (PFR)-12W for cohorts 2 and 3. Secondary endpoints include ORR-12W (cohorts 2 and 3), Time to Objective Response (ToR), Duration of Response (DoR) and safety for all cohorts. Evolution of EMT, Netrin-1, and receptor expression will be analysed and correlated with clinical outcomes. An adaptive 2-stage design is being used for this study (Lin and Shih, Biometrics 2004). The target levels of clinical activity are set at 20% (relevant) and 25% (high). In stage 1, 18 patients will be enrolled at 1-sided alpha of 5%. Depending on the observed success rate, additional 11 patients (if 1 or 2 successes) or 5 patients (if >2 successes) could be recruited into stage 2. Null hypotheses will be rejected if ≥4 successes are observed in 29 [test $p_0 = 0.05$ vs. 0.20, 80% power] or 23 patients [test $p_0 = 0.05$ vs. 0.25, 90% power], respectively. Current Status: Cohort 1 has been closed due to non-feasibility. Prespecified goals for the first stage were met, stage 2 enrolment is underway. Cohort 2 has enrolled 21 patients, and cohort 3 has enrolled 19 of 23 planned evaluable patients. Clinical trial information: NCT05605496. Research Sponsor: European Innovation Council.

TPS3178 **Poster Session**

Trial in progress: Phase 1 study of the selective protein degrader ASP4396 in patients with locally advanced or metastatic solid tumors with *KRAS G12D* mutations.

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Background: *KRAS G12D* is the most common *KRAS* mutation at codon 12 found in solid tumors and is difficult to target. There are no approved therapies directly targeting *KRAS G12D*. Targeted protein degradation is emerging as a promising therapeutic approach for undruggable targets. ASP4396, a novel protein degrader, targets KRAS G12D-mutated protein for degradation via the ubiquitin-proteasome system. This mode of action may offer higher efficacy and safety compared with inhibitors by blocking both enzymatic and scaffolding functions of proteins and by higher target selectivity. This first-in-human study aims to evaluate the safety and efficacy of ASP4396 in patients with advanced solid tumors with *KRAS G12D* mutations (NCT06364696). **Methods:** This Phase 1, open-label, multicenter, dose-escalation and dose-expansion study of ASP4396 is enrolling adult patients with locally advanced (unresectable) or metastatic solid tumors with documented *KRAS G12D* mutations who have ≥ 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1, ECOG performance status of 0 or 1, adequate organ function, and who did not respond or who are ineligible for standard therapies. Tumor-specific dose expansion cohorts may be enrolled at the maximum tolerated dose (MTD) and/or candidate recommended phase 2 dose (RP2D). Patients who received prior treatment targeting KRAS G12D will be excluded. Primary endpoints are safety and tolerability (assessed by dose-limiting toxicities [DLTs], adverse events, laboratory and other standard tests), and RP2D and/or MTD of ASP4396. Secondary endpoints are antitumor activity (objective response rate, duration of response, disease control rate, and progression-free survival per RECIST v1.1 by investigator assessment; and overall survival), and pharmacokinetic/ pharmacodynamic assessments. In the dose escalation cohort, patients will receive increasing doses of ASP4396 intravenously in a 21-day cycle. The target enrollment for each dose level is set at 1 DLT-evaluable patient for dose levels 1–3 and ≥ 3 DLT-evaluable patients for each subsequent dose level. The study will consist of 3 periods: screening (up to 28 days), treatment (every 21-day cycle until treatment discontinuation criteria are met), and follow-up. Data will be summarized descriptively (mean, standard deviation, median) for continuous endpoints, and by counts and percentages for categorical endpoints. Study enrollment is ongoing. Clinical trial information: NCT06364696. Research Sponsor: Astellas Pharma Inc.

TPS3180 **Poster Session**

Phase 1 first-in-human clinical trial of AG01, a recombinant monoclonal antibody to progranulin/glycoprotein 88 (PGRN/GP88), to determine the safety, tolerability, pharmacokinetics, and preliminary anti-tumor response in subjects with advanced solid tumor malignancies.

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Background: GP88/PGRN is the largest member of the granulin/epithelin family. We demonstrated GP88's role as an autocrine growth & survival factor in breast cancer (BC): in ER+BC cells, GP88 stimulates proliferation & confers resistance to anti-estrogen therapy & aromatase inhibitors;GP88 is expressed in 80% of invasive ductal carcinomas & is negative in normal mammary tissue; GP88 tumor expression is a prognostic indicator of recurrence & death in BC pts; Elevated GP88 serum level in metastatic BC patients (pts) is associated with disease progression. PGRN/GP88 is overexpressed in several other solid tumors (non-small cell lung carcinoma, colorectal, bladder, ovarian, prostate & brain). In advanced NSCLC & prostate pts, elevated serum PGRN/GP88 have been found. These results make GP88/PGRN an ideal therapeutic & diagnostic target in BC and other solid tumors. An anti-human PGRN/GP88 monoclonal antibody (AG01) inhibiting PGRN/GP88 action was developed & expressed as recombinant antibody in CHO cells. Pharmacology, GMP manufacturing, formulation, stability studies & GLP toxicology studies in non-human primates were done. The IND application was cleared by the FDA to proceed with the first-in-human (FIH) AG01 study in adult subjects with advanced solid tumors. **Methods:** This IRB approved FIH study, will be conducted in 2 stages, dose escalation (1A) and dose expansion (1B). The 1A part is ongoing, with the 1 + (3+3) design. In the 1A part the AG01 is administered intravenously (IV) over 90 min. every 14 days +/- 1 day, 1 cycle = 28days, DLT assessments occur in the first 28 days of treatment. Five dose levels of AG01 & a -1 level are planned (level -1-0.5mg/kg, & 1mg/kg, 2mg/kg, 4mg/kg, 6mg/kg, 8 mg/kg). In 1A part of the study, initially an accelerated titration design (1pt/dose level) was utilized to guide dose progression & estimation of the maximum tolerated and/or administered dose (MTD/MAD). Eligibility criteria for 1A part include pts with advanced relapsed/refractory solid tumor malignancies who failed 1 or more standard of care (SOC) therapies or for whom no SOC treatment exists or is not tolerated, at least 1 RECIST1.1 measurable lesion, ECOG $<$ = 2, Life expectancy $>$ = 12wks, adequate organ & bone marrow function, willing to sign informed consent & follow study procedures. Primary objective (1A) is to determine the MTD and/or MAD of AG01. Secondary objectives: to determine the recommended phase 2 dose (RP2D), safety, tolerability, the PKs, immunogenicity & the preliminary anti-tumor activity of AG01. Exploratory objectives:todetermine PGRN/GP88 expression in tumor tissue & PGRN/ GP88 blood levels (A&G's IHC & ELISA test). This study is registered at NCT05627960. The study is supported by NCI grants NCI R44 CA224718 & CA162629. Clinical trial information: NCT05627960. Research Sponsor: National Cancer Institute; National Cancer Institute.

TPS3181 **Poster Session**

Trial in progress: First-in-human study of ATX-559, an oral inhibitor of DHX9, in patients with advanced or metastatic solid tumors, and molecularly defined cancers.

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Background: DHX9 is a multifunctional RNA helicase that is involved in the maintenance of genomic stability by resolving DNA/RNA secondary structures that may lead to DNA replication stress and DNA damage. High expression of DHX9 is evident in multiple cancer types. ATX-559, an oral inhibitor of DHX9, has been shown preclinically to induce robust anti-tumor activity of a variety of different solid tumors with genomic instability, including models with BReast CAncer gene 1 and/or 2 alterations or deficiency (BRCA deficient) and microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR). **Methods:** This is a first-in-human, Phase 1, open-label, single-arm, dose-escalation and expansion study to evaluate the safety profile of ATX-559 and to determine the recommended phase 2 dose (RP2D). In dose-escalation, patients with locally-advanced or metastatic solid tumors, and molecularly-defined cancers will be enrolled for safety assessment, guided by a model-assisted dose escalation design (Yuan, 2019) to identify an acceptable dose. To assess evidence of preliminary antitumor activity in the expansion study, participants with (1) BRCA deficient, HER2-negative, metastatic breast cancer, and (2) dMMR/MSI-H solid tumors will be enrolled using a Simon 2-stage design (Simon, 1989). Primary endpoints include identification of the RP2D dose that is deemed acceptable per the model-assisted dose escalation design and to evaluate safety and tolerability as noted by the frequency and severity of adverse events (AEs). Secondary endpoints will evaluate pharmacokinetics (PK), pharmacodynamics (PD) peripherally and in a biopsy sub-study, and preliminary anti-tumor activity per RECIST v1.1. Exploratory objectives will explore potential biomarkers in relationship to ATX-559 exposure, as well as those that may correlate with treatment outcomes. A randomized cohort has also been included during dose expansion in recognition of Project Optimus. The study is open and enrollment is ongoing. Clinical trial information: NCT06625515. Research Sponsor: Accent Therapeutics.

TPS3182 **Poster Session**

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

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Background: 5T4, a Type I transmembrane glycoprotein, plays a pivotal role in neonatal development, but its expression in normal adult tissues is limited. In contrast, 5T4 emerges prominently in a broad spectrum of solid tumors, including but not limited to NSCLC, breast, ovarian, endometrial, bladder, pancreatic, esophageal, gastric and colorectal cancers. Furthermore, the expression of 5T4 is confirmed to be associated with advanced disease and worse clinical outcomes in multiple solid tumors. These features make 5T4 an attractive, but as of yet unexploited, target for cancer therapeutics. JK06 is an antibody-drug-conjugate (ADC) targeting 5T4-expressing cancer cells. The antibody moiety of JK06 has a high-affinity tetravalent binding capacity, compensating for generally low 5T4 expression levels. Further, the JK06 binding specificity is biparatopic, targeting two non-overlapping epitopes on 5T4 antigens. In this way, JK06 cross-links 5T4 on the surface of cancer cells, which enhances internalization and increases intracellular release of the cytotoxic payload. The cytotoxic payload of JK06 is the clinically proven microtubule-disrupting agent, MMAE, that inhibits cell division by preventing the polymerization of tubulin, leading to cell cycle arrest and apoptosis. JK06 mediates cytotoxicity in vitro, in a 5T4 receptor density dependent manner, and anti-tumor activity has been demonstrated in several murine xenograft models. JK06 has been shown to bind to recombinant human and cynomolgus 5T4, supporting the translation of pre-clinical toxicology studies. Preclinical toxicology studies showed no toxicity with JK06 at dose levels up to 17 mg/kg single dose and 9 mg/kg repeat dose. Toxicokinetic analysis and PK modeling suggest that a Q3W dosing regimen should provide adequately sustained exposure in clinical studies. In summary, preclinical studies support clinical development of JK06 for the treatment of multiple 5T4 expressing solid tumors. **Methods:** The Phase 1/2 study of JK06 will enroll patients with advanced relapsed/refractory solid tumors. The study will employ a 3+3 escalation design to explore the safety, PK and preliminary anti-tumor activity of JK06. Back-fill enrollment at specific dose levels is permitted but mandates fresh tumor biopsy. Patients will receive treatment with JK06 intravenously once every three weeks until confirmed disease progression or intolerable toxicity. Tumor specific expansion cohorts will be initiated once dose and schedule are established from dose escalation; fresh tumor biopsies will also be collected from patients enrolled in expansion cohorts. Response will be assessed every 9 weeks per RECIST v1.1. Clinical trial information: NCT06667960. Research Sponsor: None.

TPS3183 **Poster Session**

A phase I/Ib study of olaparib and ASTX727 in BRCA 1/2- and HRD-mutated tumors.

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Background: Patients with germline or somatic HRR pathway mutations often develop resistance despite initial response. Overlapping toxicities hinder combination strategies in breast, ovarian, prostate, and pancreatic cancers, creating a need for safer and more effective approaches. Preclinical studies have shown that DNMT inhibition enhances PARP inhibitor efficacy by promoting PARP trapping on DNA. This phase I study aims to assess the safety and tolerability of olaparib and AST727 in HRR-mutated patients and establish the RP2D for a phase II trial, to be supported by the NCI ComboMatch program. Correlative studies include the creation of PDX and organoid models for ex vivo analysis of therapy response. **Methods:** Further studies include cfDNA and tumor tissue assessment to elucidate mechanisms of resistance (reversion mutations, epigenetic markers) and PD markers of HR pathway modulation. Rad51 foci will be measured to determine DNA repair function and CHIP assays (clonal hematopoiesis of indeterminate potential) to study the differential rate of CHIP as an early event in the evolution of AML/MDS. Trial Design: This is a single center phase I/Ib clinical trial evaluating the combination of olaparib and ASTX727 (an oral formulation of decitabine with cedazuridine, a cytidine deaminase inhibitor that allows for oral administration). All participant enrollment and study participation will be conducted at UCSF as single site trial with collaboration from other centers for correlative/exploratory objectives. The phase I dose escalation portion will follow a standard 3+3 design for enrollment and will include adults with advanced/metastatic solid tumor malignancies with germline or somatic mutations in the HRR pathway (i.e., BRCA1/2, PALB2, ATM, and/or CHEK2 mutations). Patients will be treated in 2 escalating cohorts with a 12 patient phase Ib dose expansion in the same population. At least 6 of 12 expansion patients must have germline HRD mutations. Key Eligibility: The participant must have histologically confirmed advanced solid tumors with a germline and/or somatic mutation in one or more of the following genes: BRCA1/2, PALB2, ATM, and/or CHEK2. Patients must have adequate organ function and recovered from prior treatment associated toxicities. Prior treatment with PARP inhibitors is allowed if the participant has not required dose reductions or delays due to toxicity. Participants with treated brain metastases are eligible if follow-up brain imaging shows no evidence of progression for at least 4 weeks. Individuals with a prior or concurrent malignancy are eligible, however participants diagnosed with MDS or AML are excluded from the study. Trial Status: The study is ongoing and 4 patients have been enrolled to date. Clinical trial information: NCT06177171. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

TPS3184 Poster Session

RYZ101 (^{225}Ac-DOTATATE) in patients with estrogen receptor-positive, human epidermal growth factor receptor 2–negative, locally advanced and unresectable, or metastatic breast cancer progressing after prior therapy: The phase 1b/2 TRACY-1 study.

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Background: RYZ101 (actinium-225 [^{225}Ac]-DOTATATE) is a radiolabeled somatostatin analog (SSA) for the treatment of patients with solid tumors expressing somatostatin receptor-type 2 (SSTR2). RYZ101 is composed of the alpha-emitting radioisotope ^{225}Ac, the chemical chelator DOTA (tetraxetan), and SSA octreotate (TATE). RYZ101 binds with high affinity to SSTR2 on the cell surface and is internalized, whereupon the alpha-particle emission of ^{225}Ac results in lethal double-strand DNA breaks. Although SSTR-directed therapy is widely used in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), its relevance in non-GEP-NET SSTR-expressing neoplasms is still emerging. Clinical positron emission tomography (PET) imaging studies have reported SSTR expression in estrogen receptor (ER)-positive breast cancer. Available data support investigating the efficacy of RYZ101 in patients with ER-positive, HER2-negative, locally advanced and unresectable or metastatic breast cancer. **Methods:** TRACY-1 (NCT06590857) is a global, multicenter, open-label, two-part (dose escalation and expansion) phase 1b/2 study. Key inclusion criteria are: age ≥18 years; histologically confirmed, ER-positive, HER2-negative locally advanced and unresectable or metastatic breast cancer not amenable to curative-intent treatment; endocrine-refractory disease; documented progression (per RECIST v1.1) after ≥2 and ≤4 prior lines of chemotherapy and/or ADC (≥1 must be ADC if the patient is a candidate for ADCs and treatment is available); ≥1 RECIST-measurable SSTR−PET-positive lesion and ≥80% of RECIST-measurable lesions being SSTR−PET-positive on screening scan. Key exclusion criteria are: prior radiopharmaceutical therapy; prior anticancer therapy or external beam radiotherapy in past 4 weeks; anticancer hormonal treatments in past 2 weeks. Primary objectives are to determine the recommended phase 2 dose (R2PD) of RYZ101 (dose escalation; anticipated 6−24 patients), and the efficacy of RYZ101 at the RP2D defined as ORR as determined by BICR (dose expansion; approximately 100 patients). During dose escalation, patients will receive RYZ101 by IV infusion every 6 weeks for up to 6 cycles at a starting dose of 6.5 MBq (dose level [DL] 1), with escalation to DL 2 (8.3 MBq) and DL 3 (10.2 MBq), or dose de-escalation to 4.6 MBq if DL 1 is not tolerated, based on dose-limiting toxicity rates. In the expansion phase, patients will receive RYZ101 at the RP2D. Concomitant amino acid IV infusions (containing L-arginine and L-lysine) will be co-infused with RYZ101 for renal protection. The study is ongoing and enrolling patients in the USA. Clinical trial information: NCT06590857. Research Sponsor: RayzeBio.

TPS3185 **Poster Session**

panSOHO: Phase II trial of BAY 2927088 in patients with unresectable or metastatic solid tumors other than NSCLC with *HER2*-activating mutations.

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Background: Human epidermal growth factor receptor 2 (*HER2*) gene mutations occur in approximately 3.5% of solid tumors, with a frequency varying from less than 1% to 9%, depending on the tumor type. BAY 2927088 is an oral, reversible tyrosine kinase inhibitor that potently inhibits HER2 and mutant epidermal growth factor receptor and has shown clinical benefit based on preliminary evidence from the Phase I/II SOHO-01 trial in patients with *HER2*-mutant non-small cell lung cancer (NSCLC; PL04.03 presented at IASLC 2024 World Conference on Lung Cancer), an indication for which the FDA has granted Breakthrough Designation. Here we introduce the panSOHO trial evaluating the efficacy and safety of BAY 2927088 in patients with unresectable, locally advanced or metastatic solid tumors with *HER2*-activating mutations. **Methods:** panSOHO is a Phase II, open-label, multicenter, multinational, single-arm basket trial of BAY 2927088 in patients with unresectable or metastatic solid tumors with *HER2*-activating mutations (NCT06760819), and will be conducted in the USA, Europe, and the Asia-Pacific region. Eligibility criteria include patients aged ≥18 years with: documented histologically or cytologically confirmed, locally advanced or metastatic solid tumor cancer (colorectal, biliary tract, bladder and urothelial tract, cervical, endometrial, or other solid tumor); documented activating HER2 mutation; ≥1 measurable lesion per RECIST v1.1; and previous standard therapy or no satisfactory alternative treatment options. Key exclusion criteria include primary diagnosis of NSCLC, treatment with a HER2 tyrosine kinase inhibitor, untreated active brain metastases, and leptomeningeal disease. Overall, 111 eligible patients will receive BAY 2927088 p.o. 20 mg twice daily in 3-week cycles until disease progression, unacceptable toxicity, or study withdrawal. The primary outcome is BAY 2927088 efficacy on objective response rate per RECIST v1.1 as assessed by blinded independent central review (BICR). Secondary outcomes include BAY 2927088 efficacy on time to response, duration of response, disease control rate, and progression-free survival per RECIST v1.1 by BICR, and overall survival, and BAY 2927088 safety and tolerability. Impact of BAY 2927088 on patient quality of life will be evaluated by EORTC QLQ-C30. Enrollment is open. Clinical trial information: NCT06760819. Research Sponsor: Bayer AG.

TPS3186 **Poster Session**

Molecular residual disease (MRD) in solid tumors.

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Background: Pragmatically designed clinical studies facilitate rapid accrual of representative populations by aligning research with routine care and enabling study execution in community practice settings. In addition, the implementation of technologies to streamline patient ascertainment and data collection further reduce site burden and improve efficiency. Herein we describe the initial cohort under a platform study designed with pragmatic elements initiated within a technology-enabled community oncology research network. This substudy establishes a prospective observational registry that collects routinely documented clinical data plus intentionally collected biomarker samples, including blood, for the purpose of isolating circulating tumor DNA at specified intervals to enable exploration of MRD in patients with early stage solid tumors. **Methods:** This is a prospective, multicenter, observational, biospecimen collection study in participants (pts) diagnosed with early stage cancers in select solid tumors who have planned curative-intent surgery. The scientific objective is to collect tumor tissue, longitudinal blood samples, and associated clinical data to explore applications of blood and/or tissue-based cancer biomarkers for cancer detection, prognosis, therapy selection, surveillance, and therapy response. Approximately 1350 pts will be enrolled across ~30 Flatiron Research Network community oncology sites. Participants are grouped by tumor site of origin and histology into 7 cohorts (Table). Patients provide informed consent and are enrolled before starting neoadjuvant or adjuvant therapy. Study visits correspond with routine care. Research tissue and blood samples are obtained upon enrollment and at study-specified intervals up to 5.5 years or until disease recurrence for analysis by Exact Sciences laboratories. Technology enablement includes near real-time, AI-assisted, centralized patient ascertainment and integrated electronic health record-to-electronic data capture system data transfer. Under the parent protocol mechanism, the study was IRB approved 65 days from commencement of protocol writing. Target enrollments are based on the number needed to enroll to observe at least 30 events in 3 years. Clinical trial information: NCT06605404. Research Sponsor: None.

Study cohorts.

Tumor type	Disease stage	Target enrollment
Muscle invasive urothelial carcinoma	II-III	200
Esophageal	I-III	150
Gastric & gastroesophageal junction	I-III	150
Melanoma	II-III	300
Non–small cell lung cancer	I-III	200
Exocrine pancreatic cancer	I-III	150
Other solid tumors (excluding central nervous system, colorectal, breast, skin squamous and basal cell, gastrointestinal stromal tumors, thyroid, uveal melanoma, and low or intermediate grade neuroendocrine tumors)	II-III	200

TPS3187 **Poster Session**

Beamion PANTUMOR-1: A phase II, multicenter, multicohort, open-label trial to evaluate the efficacy and safety of the oral HER2-selective tyrosine kinase inhibitor zongertinib for the treatment of *HER2*-mutated or overexpressed/amplified solid tumors.

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Background: While it is well known that HER2 overexpression, amplification, and mutation drives various tumors, there remains an unmet need for effective, oral, HER2-targeted therapies. Zongertinib is an irreversible tyrosine kinase inhibitor (TKI) that selectively inhibits HER2 while sparing EGFR, thereby limiting associated toxicities. In the ongoing Phase Ia/Ib trial (NCT04886804), zongertinib showed manageable safety and confirmed responses in patients (pts) with HER2-overexpressed/amplified and *HER2*-mutant tumors (Wilding et al, *Cancer Discov.* 2024). Based on these encouraging data, the Beamion PANTUMOR-1 basket trial (NCT06581432) is evaluating the efficacy and safety of zongertinib monotherapy in pts with *HER2*-mutant or HER2-overexpressed/amplified solid tumors. **Methods:** In this global Phase II basket trial, ~200 pts with HER2-driven (*HER2*-mutant or HER2-overexpressed/amplified) tumors will be enrolled at ~60 sites in 13 countries. Pts will be enrolled to 10 cohorts: 8 cohorts of specific tumor types and 2 tumor-agnostic cohorts (see Table). The specific tumor type cohorts will initially recruit 10 pts, with potential for expansion to up to 20 pts after an interim analysis. In the tumor-agnostic cohorts, 20 pts will be recruited directly without an interim analysis. Pts will receive 120 mg zongertinib until disease progression, unacceptable toxicity, or withdrawal. Patients must be ≥18 years old, have documented HER2-positive (HER2-overexpressed/amplified) status or a *HER2* mutation (established by local testing), ≥1 measurable lesion outside the central nervous system, an ECOG performance score of 0 or 1, and have progressed following prior treatment or have no alternative treatment options. Exclusion criteria include *HER2*-mutant non-small cell lung cancer (NSCLC) and previous/concomitant malignancies. Primary endpoint is objective response, as assessed by central independent review according to RECIST v1.1. Secondary endpoints include duration of response, progression-free survival, disease control, occurrence of treatment-emergent adverse events, and health-related quality of life. Enrollment is ongoing. Clinical trial information: NCT06581432. Research Sponsor: Boehringer Ingelheim.

HER2 overexpression/ amplification cohorts	Tumor type	*HER2* mutation cohorts	Tumor type
Cohort 1	Urothelial cancer	Cohort 7	Urothelial cancer
Cohort 2	Biliary tract cancer	Cohort 8	Breast cancer
Cohort 3	Uterine cancer	Cohort 9	Gastroesophageal cancer
Cohort 4	Cervical cancer	Cohort 10	Other *HER2*-mutant solid tumors†
Cohort 5	Non-squamous NSCLC		
Cohort 6	Other *HER2* overexpressed/ amplified solid tumors*		

*Except breast cancer, gastric, gastroesophageal junction, or esophageal adenocarcinoma.
†Except NSCLC.

TPS3188 **Poster Session**

Perfume trial: Phase II trial of binimetinib in patients with *BRAF* fusion-positive low-grade glioma or pancreatic cancer.

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Background: *BRAF* fusion was reported to be a rare mutation found in 0.3% of all solid tumors, but a high percentage of BRAF fusion has been reported in pilocytic astrocytoma (30-77%) and pancreatic acinar cell carcinoma (24-67%). Although treatment for *BRAF* V600 mutations has been developed, treatment for *BRAF* fusion has not yet been established. Recently, tovorafenib has been granted accelerated approval by the FDA for pediatric low-grade glioma (LGG) with *BRAF* alteration (including *BRAF* fusion). Still, it is not yet approved in Japan, and an unmet need exists. In *BRAF* fusion-positive solid tumors, the constitutively activated BRAF kinase domain forms dimers that cause activation of the MAPK pathway. MEK inhibitors have been reported to show anti-tumor effects against *BRAF* fusion-positive cell lines. Phase I/II trials with selumetinib or binimetinib have shown efficacy in patients with *BRAF* fusion-positive LGG. **Methods:** Perfume trial (NCCH2101/MK011) is an open-label, parallel, 2-cohort, multicenter, phase II, investigator-initiated registration-directed clinical trial to evaluate the efficacy and safety of binimetinib in patients with advanced or recurrent LGG or pancreatic cancer (PC) harboring *BRAF*fusion/rearrangement. Sample sizes of 16 and 11 patients are needed for LGG and PC at a one-sided significant level of 5% to achieve 85% and 70% power, respectively. Key eligibility criteria for LGG (grade 1 and grade 2 tumors according to WHO classification) include age≧12 (body weight ≧40 kg in 12-17 year old) and KPS/LPS≧70, regardless of history of cancer drug therapy. Key eligibility criteria for PC include age≧12 (body weight ≧40 kg in 12-17 year old); ECOG PS 0-1; refractory or intolerant to at least one prior cancer drug therapy. Enrolled patients receive binimetinib 45mgadministered orally twice daily. The primary endpoint is the objective response rate (ORR) using RECIST 1.1 by independent central review. The secondary endpoints include ORR by investigators' assessment, ORR by RANO in LGG, progression-free and overall survivals, disease control rate, duration of response, and safety. This study implemented a decentralized clinical trial system for patients living in remote areas to reduce their time and economic burden. Enrollment started in March 2023 and is ongoing at 6 facilities in Japan. As of Dec 2024, 6 patients with LGG and 3 patients with PC were enrolled. Clinical trial information: jRCT2031230007, NCT06159478. Research Sponsor: None.