First-in-human trial of M9140, an anti-CEACAM5 antibody drug conjugate (ADC) with exatecan payload, in patients (pts) with metastatic colorectal cancer (mCRC).

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Background: CEACAM5 is a cell surface protein with limited expression in adult healthy tissues, but high expression in various adenocarcinomas, particularly in CRC (>90% of pts). M9140 is the first anti-CEACAM5 ADC with a topoisomerase 1 inhibitor (Top1i) payload (exatecan). The ß-glucuronide linker connecting the M9140 antibody backbone to the payload is highly stable in circulation (drug-to-antibody ratio=8). In preclinical models, M9140 has demonstrated strong potency, antitumor activity, and a bystander effect. **Methods:** This Phase 1 trial (NCT05464030) investigated the safety, tolerability, pharmacokinetics (PK), and preliminary clinical activity of M9140 as monotherapy (Q3W [Day 1 of 21-day cycles]; IV) in adults with CRC (ECOG PS ≤1) who had received ≥2 prior lines of treatment. The primary objectives of Part 1A were to determine the maximum tolerated dose (MTD) and/or recommended dose(s) for expansion (RDE). **Results:** At data cutoff (19 Jan 2024), 40 pts from the US, EU, and Japan were treated across 7 dose levels (DLs): 0.6 mg/kg, 1.2 mg/kg (n=3, each), 2.4 mg/kg (n=7), 2.6 mg/kg (n=4), 2.8 mg/kg (n=12), 3.0 mg/kg (n=4), and 3.2 mg/kg (n=7, including 3 pts with primary G-CSF prophylaxis). Most pts were heavily pretreated (80% had ≥3 lines of prior treatment; 100% received irinotecan). Overall, 6 pts experienced dose-limiting toxicities (DLTs); the majority were hematological adverse events at DLs 3.0 and 3.2 mg/kg; 1 patient (at 2.8 mg/kg) experienced a Grade 5 sepsis. The most frequently reported Grade ≥3 treatment-emergent adverse events (TEAEs) were neutropenia in 16 (40.0%) pts, thrombocytopenia and anemia in 11 (27.5%) pts each, and WBC decreased in 10 (25.0%) pts. No events of ocular toxicity/interstitial lung disease (ILD) were reported. The best objective response per RECIST v1.1 was partial response (PR) in 4 (10.0%) pts (3 confirmed) (all at DLs ≥2.4 mg/kg); stable disease (SD) in 17 (42.5%), including 6 (15.0%) lasting for ≥100 days and progressive disease (PD) in 6 (15.0%) pts. For a total of 13 (32.5%) pts, the best overall response was not evaluable, including 6 (15.0%) who had no on-treatment tumor assessment yet. The preliminary median progression-free survival (PFS) was 6.7 months (95% CI: 4.6, 8.4). As of data cutoff, 15 (37.5%) pts are continuing treatment. Based on the safety, tolerability, preliminary clinical activity, PK, and PK/pharmacodynamics modeling data, 2.8 mg/kg was declared as the MTD, and 2.4 mg/kg and 2.8 mg/kg were chosen as the RDEs and have been taken forward into a randomized expansion study. **Conclusions:** M9140 demonstrated encouraging activity in heavily pretreated pts with advanced CRC, with a manageable and predictable safety profile. Contrary to approved ADCs with Top1i payloads, no ILD or ocular toxicities were observed. Evaluation of M9140 in mCRC continues in the dose expansion part of this study. Clinical trial information: NCT05464030. Research Sponsor: EMD Serono (CrossRef Funder ID: 10.13039/100004755).

3001 Oral Abstract Session

First-in-human study of ABBV-706, a seizure-related homolog protein 6 (SEZ6)–targeting antibody-drug conjugate (ADC), in patients (pts) with advanced solid tumors.

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Background: SEZ6 is a transmembrane protein expressed in small cell lung cancer (SCLC) and other neuroendocrine neoplasms (NENs), and central nervous system (CNS) tumors. These malignancies have a high unmet need for novel effective therapies. ABBV-706 is an ADC targeting SEZ6 conjugated to a topoisomerase 1 inhibitor payload at a drug-to-antibody ratio of 6, and is highly efficacious in preclinical models of SCLC, NENs, and CNS tumors. Here, results from ABBV-706 monotherapy dose escalation (DE) are presented. **Methods:** Phase 1, open-label, multicenter, DE and dose-expansion study (NCT05599984) of ABBV-706 as monotherapy or in combination with budigalimab (a programmed cell death 1 inhibitor), carboplatin, or cisplatin. Primary objectives are to determine the safety, PK, preliminary efficacy, and recommended phase 2 dose of ABBV-706. Exploratory objectives are to assess SEZ6 expression retrospectively and its association with safety, PK, and efficacy. DE enrolled adults (≥18 yr) with relapsed/refractory SCLC, high-grade CNS tumors, and high-grade NENs, following the Bayesian optimal interval design. ABBV-706 was administered IV at 1.3–3.5 mg/kg doses Q3W in 21-d cycles. **Results:** As of data cutoff on Nov 15, 2023, 49 pts (SCLC: n=22 [45%]; CNS tumors: n=5 [10%]; NEN: n=22 [45%]) were enrolled and treated with ABBV-706 in DE and backfill cohorts. Median age was 64 yr (range 32–81) and median prior lines of therapy was 2.5 (range 1–6). 2 pts had a dose-limiting toxicity: 1 G4 leukopenia and neutropenia lasting >7 d at 3.0 mg/kg and 1 G4 thrombocytopenia at 3.5 mg/kg. TEAEs occurred in 45 (92%) pts, the most frequent being anemia (51%), fatigue (41%), neutropenia (31%), and leukopenia (31%). G≥3 TEAEs occurred in 28 (57%) pts and were mainly hematologic: neutropenia (29%), anemia (27%), and leukopenia (25%). No pneumonitis/interstitial lung disease was observed. Gastrointestinal TEAEs (all G1/2) were seen in 55% of pts, with the most common being nausea (27%) and vomiting (18%). There were no ABBV-706–related deaths. The maximum tolerated dose was 3 mg/kg IV Q3W. ABBV-706 ADC showed an approximate dose-proportional increase in exposure with an elimination half-life of approximately 7 d across doses. For 33 RECIST-evaluable pts, the confirmed (c) objective response rate was overall 21% (7 partial responses [PRs]); 40% (6/15) for SCLC and 6% (1/18) for NEN. The overall response (c and unconfirmed [u]) rate without confirmation was 45% (7 cPRs/8 uPRs); 73% (6 cPRs/5 uPRs) for SCLC, and 22% (1 cPR/3 uPRs) for NEN. 8 uPRs are pending confirmation and will be reported in the final presentation. The clinical benefit rate was 91% (7 PR, 23 stable disease). No activity was observed in 3/3 pts with high-grade gliomas. **Conclusions:** ABBV-706 demonstrated a manageable safety profile with promising efficacy in SCLC and NENs. Further evaluation of ABBV-706 is ongoing. Clinical trial information: NCT05599984. Research Sponsor: AbbVie; n/a.

Phase I/II first-in-human study to evaluate the safety and efficacy of tissue factor-ADC MRG004A in patients with solid tumors.

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Background: Tissue factor (TF) overexpression is associated with thrombosis, metastasis and poor prognosis in solid tumors, including cervical and pancreatic cancer. MRG004A is a novel anti-TF monoclonal antibody conjugated (ADC) to MMAE payload (drug-to-antibody ratio: 3.8), utilizing Glycoconnect site-specific conjugation technology. Herein, we present the preliminary safety and efficacy data from phase I/II MRG004A-001. **Methods:** This is an interim report (Data cutoff: Dec 15, 2023) of first-in-human, dose-escalation and expansion study ongoing in the USA and China. Pts with ECOG 0-1 with unresectable/metastatic solid tumor with measurable disease per RECIST v1.1 that progressed on prior systemic therapy, received MRG004A monotherapy Q3W intravenously. The primary objectives were to assess the safety, activity, maximal tolerated dose (MTD) and recommended phase 2 dose (RP2D). Baseline tissue was evaluated for the association of TF expression with objective response rate (ORR) and disease control rate (DCR). **Results:** Sixty-three pts were enrolled with 43 in dose-escalation phase (8 dose levels [0.3-2.6mg/kg]) and 20 in dose-expansion phase (15 at 2.0mg/kg and 5 at 2.4mg/kg). Median age 58 (38-75). ECOG0: 8 (13%) pts. Female: 37 (59%) pts. Median 3 prior lines of therapy: 3 (1-10). MTD was not reached. Sixteen baseline samples were evaluated for overall % membrane positivity by immunohistochemistry. Nineteen were pancreatic cancer (PC) and 68% (13/19) had TF $\geq$50% and 2 or 3 (+). Five received dose $<$2 mg/kg Q3W. Significant anti-tumor activity of MRG004A was observed in pts with PC. Among 12 evaluable pts with PC in the 2.0mg/kg cohort, who have received median 3 lines of prior therapy, there were 4 PR and 6 SD. ORR was 33.3% (4/12) and DCR was 83.3% (10/12). Among them, 5 pts with PC of TF expression $\geq$50% and 3+ intensity and $\leq$2 prior lines of therapy received MRG004A at 2mg/kg. 4 of 5 TF-overexpressed PC achieved PR and 1 SD. Also, MRG004A showed efficacy in other cancers. In 4 pts with heavily-treated triple-negative breast cancer (TNBC), ORR and DCR were 25% (1/4) and 50% (2/4), respectively. In 2 pts with cervical cancer with four prior therapy lines, 1 PR and 1 SD. Common treatment-related adverse events (TRAE) of any grade include conjunctivitis (27%), anemia (17%), and hypoalbuminemia (13%) and 7.9% (5/63) pts had serious adverse events. One pt with TNBC treated at 1.8mg/kg experienced G3 Steven Johnson Syndrome, a dose-limiting toxicity (DLT), but resolved. No other DLT was observed and dose expansion and matured outcome evaluation is ongoing. **Conclusions:** MRG004A demonstrated a manageable toxicity and a striking antitumor activity across multiple tumor types with high TF expression in heavily pretreated setting, including pancreatic cancers. These encouraging findings warrant further evaluation of MRG004A, particularly in the context of TF-overexpressed solid tumors. Clinical trial information: NCT03941574. Research Sponsor: Lepu Biopharma.

Efficacy and safety of dendrimer-enhanced (DEP) cabazitaxel (DEP CTX) in patients with advanced solid cancers in a phase 1/2 trial (P1/2).

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Background: DEP CTX is a highly optimized dendrimer nanoparticle formulation of cabazitaxel that achieves sustained cytotoxic drug delivery to tumors via enhanced permeability & retention effects. Unlike standard cabazitaxel (s-CTX), DEP CTX is highly water soluble, does not contain toxic excipients associated with anaphylaxis & does not require steroid/antihistamine premedication. We report the final P2 efficacy and safety results in patients (pts) with advanced/metastatic solid tumors. **Methods:** Pts were treated with DEP CTX at 20 mg/m^2 cabazitaxel, IV 3-weekly. Efficacy was assessed by RECIST v1.1, Prostate Cancer Working Group 3 (PCWG3) guidelines or serum tumor markers; evaluable pts had relevant criteria at baseline and a follow-up assessment per protocol window. Safety was assessed by CTCAE v4.03. (EudraCT 2017-003424-76). **Results:** In P2, 75 pts were enrolled, prioritizing metastatic castration-resistant prostate cancer (mCRPC, s-CTX's only approved indication), esophagogastric (EG) & ovarian (OV) cancers. For all pts, median progression free survival (mPFS) and overall survival (mOS) were 3.8 and 9.0 mths, respectively. Objective response rate (ORR) was 20% in 45 evaluable pts. All 25mCRPC pts were heavily pre-treated with a median of 4 prior lines of anticancer treatment. mPFS was 4.4 mths (radiographic or prostate specific antigen [PSA]); mOS was 14.7 mths. The disease control rate (DCR) was 70.6%; ORR was 16.7%. PSA reduced in 90% pts (by $>$ 50% in 52.4%); 87% with bone metastases had no progression or improved. Of 15 EG pts, 9 were adenocarcinoma (ADENO) (3 gastric, 2 esophageal & 4 EG junction) & 6 were esophageal squamous cell carcinoma (SCC). For all EG pts, mPFS was 4.0 mths, mOS was 8.6 mths. mPFS was 4.0/1.9 mths for ADENO/SCC, respectively. Overall, DCR was 80%; ORR 30%. DCR was 100%/50% and the ORR was 33%/25% for ADENO/SCC, respectively. Of 22 OV pts, 96% were platinum resistant (Pt-R), with a median of 4 prior lines of anticancer treatment, including 59% with $\geq$ 3 platinum lines. mPFS/mOS were 3.1 mths & not reached, respectively. DCR was 66.7%; ORR 17.6%. Treatment related adverse events (TRAEs) were mostly mild/moderate (grade (G) 1/2; 64%/25%). Only 21% of pts had G 3/4 non-hematological TRAEs, while G3/4 lab detected neutropenia was seen in only 23% of pts despite no routine G-CSF. TRAEs observed in $\geq$10% of pts included fatigue, neutropenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, peripheral neuropathy and decreased appetite. **Conclusions:** DEP CTX exhibited clinically meaningful, durable antitumor activity in multiple advanced solid cancers, including mCRPC, Pt-R OV and EG cancers without the need for steroid premedication. The antitumor activity & safety results compare favorably to s-CTX, or standard of care chemotherapy in non-prostate cancers, and highlight the promising potential of dendrimer-enhanced delivery of cabazitaxel. Clinical trial information: 2017-003424-76. Research Sponsor: Starpharma Pty Ltd.

3005 Oral Abstract Session

First-in-human phase I trial of the oral first-in-class ubiquitin specific peptidase 1 (USP1) inhibitor KSQ-4279 (KSQi), given as single agent (SA) and in combination with olaparib (OLA) or carboplatin (CARBO) in patients (pts) with advanced solid tumors, enriched for deleterious homologous recombination repair (HRR) mutations.

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Background: USP1 is a deubiquitinase that regulates DNA damage response pathways, such as Translesion Synthesis and Fanconi Anemia pathways. KSQi is a potent, selective small molecule inhibitor of USP1 with anti-proliferative activity in tumors with HRR mutations. The combination of KSQi and PARP inhibitors (PARPi) showed strong synergy in Ovarian and TNBC PDX models, supporting this clinical trial. **Methods:** This is a 2-part study: Part 1 dose escalation using a BOIN design explored safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary anti-tumor activity of KSQi as SA (Arm 1) and in combination with OLA at 200 mg BID (Arm 2) or CARBO at AUC 4 (Arm 3) to determine the MTD and/or recommended dose for expansion (RDE). Part 2 will assess efficacy and safety of the combinations in expansion cohorts. **Results:** As of Jan 4, 2024, 64 pts (19m/45f; median age 63 y) received KSQi 100 - 1250 mg; Arm 1: 100 mg (3 pts), 150 (3), 200 (4), 300 (6), 450 (5), 650 (9), 900 (7) and 1250 (5); Arm 2: 200 (5), 450 (5) and 900 (5); Arm 3: 200 (3) and 450 (4). Median number of prior therapies was 5, 4 and 3 for Arm 1, 2 and 3, respectively. 29% had prior PARPi in Arm 1, 53% in Arm 2, and 71% in Arm 3. All pts in Arms 2 and 3 had tumors with deleterious HRR mutations. Most common treatment-emergent adverse events (TEAE) were anemia (36%), increased creatinine (33%) as SA, and anemia in combination with OLA (87%) and CARBO (71%). The most common G3+ TEAEs were hyponatremia (12%) as SA and anemia in combination with OLA (73%) and CARBO (29%). DLTs (n = 3) were G3 maculopapular rash at 1250 mg (Arm 1) and G3 WBC decrease at 200 mg, G3 anemia at 450 mg (Arm 2). 30% (19/64) of pts had an interruption in KSQi dosing and 1 (1.6%) discontinued treatment. PK AUC and Cmax increased almost dose-proportionally up to 650 mg. A preliminary review of OLA concentrations following co-administration with KSQi showed no significant impact of OLA at C2D1. Ubiquitinated PCNA induction was observed in paired tumor biopsies from pts receiving KSQi, supporting intra-tumoral USP1 inhibition. A RECIST PR was observed in a fallopian tube cancer pt lasting 7 weeks and SD in 9 pts treated with SA KSQi; best response in combination with OLA was SD in 6 pts and 2 SD with CARBO. Disease control rate at 16 weeks was 28% (Arm 1), 40% (Arm 2) and 29% (Arm 3). **Conclusions:** KSQi is a first-in-class USP1 inhibitor with an acceptable safety profile as SA and in combination. An MTD was not reached in any Arms. PD results support the mechanism of action of USP1 inhibition. The RDE will be determined in additional back-fill cohorts. Clinical trial information: NCT05240898. Research Sponsor: KSQ Therapeutics; Roche Pharma Research and Early Development.

A phase 1 dose expansion study of a first-in-class KAT6 inhibitor (PF-07248144) in patients with advanced or metastatic ER+ HER2− breast cancer.

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Background: Histone lysine acetyltransferase KAT6 regulates lineage specific gene transcription via H3K23 acetylation. PF-07248144 is a novel selective catalytic inhibitor of KAT6 (6A & 6B). We report the clinical safety, efficacy, PK, PD, and biomarker results of a phase 1 dose expansion study (NCT04606446) of PF-07248144 as monotherapy and in combination with fulvestrant in heavily pretreated ER+ HER2− metastatic breast cancer (mBC). **Methods:** Eligible patients (pts) had metastatic ER+ HER2− mBC and had progressed after at least a CDK4/6 inhibitor and an endocrine therapy. Pts received PF-07248144 at the recommended expansion dose of 5 mg QD as monotherapy or in combination with fulvestrant. Primary objective (Obj): safety and tolerability per CTCAE 5.0. Secondary Objs: antitumor activity per RECIST 1.1, PK. Exploratory Objs: PD, predictive biomarkers. Circulating tumor DNA (ctDNA) and gene mutations were evaluated by Guardant 360 assay. **Results:** As of 30 Sep 2023, 35 pts received PF-07248144 as monotherapy and 43 pts in combination with fulvestrant. Median (range) prior lines of systemic therapy in the metastatic setting were 5 (1–13) and 1 (1–6), respectively. In both groups, steady state exposure was similar and maximal H3K23Ac PD inhibition was achieved both in blood and tumor. For monotherapy (n=35), the objective response rate (ORR; 95% CI) was 11.4% (3.2, 26.7), median (range) duration of response (DOR) was 12.0 mos (7.4, NE), and clinical benefit rate (CBR; 95% CI) was 31.4% (16.9, 49.3). For the fulvestrant combination (n=43), with median duration of follow-up of 9.2 mos, the ORR was 30.2% (17.2, 46.1), median DOR was 9.2 mos (7.2, NE), CBR was 51.2% (35.5, 66.7), and the median progression-free survival (mPFS) was 10.7 mos (n=43; 95% CI 5.3, NE). 57% (24/42) of the pts had baseline *ESR1* mutations. Durable activity was observed in pts with both *ESR1* mutant (n=24; ORR 33.3%; mPFS 10.7 mos) and *ESR1* wild-type (n=18; ORR 27.8%; mPFS not reached) tumors.Similarly, antitumor activity was observed in pts with (n=19; ORR 26.3%, mPFS 7.2 mos) and without *PIK3CA/AKT1/PTEN* gene mutations (n=23; ORR 34.8%, mPFS 10.8 mos). After 8-wk treatment, the median reduction in total ctDNA and *ESR1* mutant allele frequency was 95.0% and 100.0%, respectively. In all pts, the most frequent treatment-related adverse event (TRAE) was grade (G) 1/2 dysgeusia (84.6%; 65.4% G1). The G3 TRAEs $>$ 5% were neutropenia (38.5%), leukopenia (11.5%), and anemia (9.0 %). The only G4 TRAE was neutropenia (3.8%), which was reversible and well managed by dose modifications. No G5 TRAEs. **Conclusions:** PF-07248144 demonstrated a tolerable safety profile and durable efficacy in pts with heavily pretreated ER+ HER2− mBC with and without *ESR1* or *PIK3CA/AKT1/PTEN* mutations. We have provided strong clinical proof of concept targeting KAT6, a novel epigenetic target and opened a new avenue to treat ER+ HER2− mBC. Clinical trial information: NCT04606446. Research Sponsor: Pfizer.

Pan-tumor activity of olomorasib (LY3537982), a second-generation KRAS G12C inhibitor (G12Ci), in patients with *KRAS* G12C-mutant advanced solid tumors.

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Background: Olomorasib is a potent and highly selective second-generation inhibitor of GDP-bound KRAS G12C, which preclinically delivers >90% sustained target occupancy. Here, we report updated results from LOXO-RAS-20001, a phase 1/2 study of olomorasib in patients with *KRAS* G12C-mutant advanced solid tumors (NCT04956640). **Methods:** Patients (pts) with advanced solid tumors positive for KRAS G12C (tissue or plasma) were eligible. Dose escalation used a mTPI-2 method, followed by expansion cohorts in NSCLC (with/without prior G12Ci), CRC, and other solid tumors. Safety was evaluated across all pts dosed. Antitumor activity per RECIST v1.1 was studied in all pts who had ≥1 post-baseline response assessment (PBRA) or had discontinued before the first PBRA. Serial ctDNA analysis was performed using FoundationOne Liquid CDx. **Results:** As of 30 October 2023, 157 pts (58 NSCLC, 32 CRC, 24 PANC, 43 other solid tumors) received single agent olomorasib (50-200 mg BID PO); 29 pts with NSCLC had received a prior KRAS G12Ci. Median age was 65 yrs (range, 36-85), median number of prior systemic therapies was 3 (range, 0-11). Any grade TRAEs were 62%; TRAEs ≥10% were diarrhea (24%), fatigue (10%), and nausea (10%); grade ≥3 TRAEs were 5%. TRAEs led to dose hold in 10% of pts, dose reduction in 3%, and discontinuation in 2%. Among 10 pts treated after discontinuing prior G12Ci due to toxicity (5/10 due to LFT increase), 1 pt (10%) required olomorasib dose reduction and none discontinued due to toxicity. 68 pts are ongoing and 89 discontinued treatment. 146 pts were efficacy evaluable (120 G12Ci-naïve; 26 with prior G12Ci) with a median follow-up of 10 months (95% CI, 7-13). As anticipated, ORR was lower in 32 pts with CRC (9%, 3 PR; DCR 84%)[1] and higher in 88 pts with non-CRC tumors (40%, 30 PR and 5 uPR pending/ongoing in 13 unique tumor types; DCR 90%). mPFS ranged across tumor types from 4 months (CRC, 95% CI, 3-7) to 9 months (NSCLC, 95% CI, 3-NE). In the 26 efficacy evaluable NSCLC pts with prior KRAS G12Ci treatment (16 discontinued due to PD, 9 due to AE), the ORR was 39% (9 PR, 1 uPR pending/ongoing; DCR 73%); mPFS was 6 months (95% CI, 3-NE). In 37 pts with ctDNA results at baseline and ongoing, ctDNA response (>50% KRAS G12C VAF reduction) was seen in pts with PR (11/11), SD (17/22), and PD (1/4). **Conclusions:** Olomorasib demonstrates efficacy across a range of KRAS G12C-mutant solid tumors with a favorable safety profile including in pts with prior G12Ci intolerance. Activity of the second-generation G12Ci olomorasib after prior exposure to G12Ci demonstrates the increased potency and target coverage these agents can deliver compared to first generation inhibitors. Phase 2 expansion is currently enrolling pts with PANC, and a global registrational study investigating olomorasib in combination with pembrolizumab in first-line NSCLC is ongoing (NCT06119581).
1. Hollebecque A. et al. ASCO-GI 2024. Clinical trial information: NCT04956640. Research Sponsor: Loxo Oncology, Inc. on behalf of Eli Lilly and Company.

3008 Oral Abstract Session

Updated safety and efficacy data of combined KRAS G12C inhibitor (glecirasib, JAB-21822) and SHP2 inhibitor (JAB-3312) in patients with *KRAS p.G12C* mutated solid tumors.

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Background: Resistance to KRAS G12C inhibitor in non-small cell lung cancer (NSCLC) can be overcome by SHP2 blockade. This concept was tested in Phase I study of glecirasib combined with JAB-3312 in patients (pts) with KRAS p.G12C mutated tumors. Promising preliminary data of safety and response were reported at the 2023 ESMO (653O). Here, we present the updated safety and efficacy data with treatment response and progression-free survival (PFS) of the combination therapy in front-line NSCLC. **Methods:** The phase 1/2a study [NCT05288205] evaluated glecirasib plus JAB-3312 in patients with KRAS p.G12Cmutated solid tumors. The primary objective of the dose-escalation phase was to assess the safety and tolerability of the combination therapy, and the primary objective of the dose-expansion phase was to assess efficacy. Efficacy endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS by investigator per RECIST1.1 and overall survival. Glecirasib 400 mg or 800 mg daily was combined with various JAB-3312 doses and schedules. **Results:** As of December 1st, 2023, 179 pts were enrolled, including 157 with NSCLC, 17 with colorectal cancer, and five with other tumor types. Treatment-related adverse events (TRAE) $\geq$ grade 3 occurred in 41.9% of all pts. There were no treatment-related deaths. Discontinuation of either glecirasib or JAB-3312 due to TRAE occurred in 7.8% of all pts. The AE profile was unchanged from the last ESMO report. The most common ($>$ 20%) TRAEs included anemia, ALT/AST increased, hypertriglyceridemia, bilirubin increased, neutropenia/leukopenia, creatine kinase increased, and edema. No overlapped toxicity was observed for this combination therapy. Amongst all pts enrolled, 88 had NSCLC and received the combination therapy as front-line treatment in seven dosing groups. The median follow-up duration was 6.1 (range:0.5-16.7) months. Eighty pts had at least once post-treatment efficacy assessment. The ORR was 72.5% (58/80) and DCR was 96.3% (77/80). In the group of glecirasib 800mg QD + JAB-3312 2mg one week on/one week off, the ORR was 77.8% (21/27) and DCR was 92.6% (25/27). The median PFS was not mature by the data cut-off date. The 6-month and 12-month PFS rate were 67.3% and 53.7%, respectively. Additional safety and efficacy data will be presented at the meeting. **Conclusions:** Glecirasib plus JAB-3312 has a manageable safety profile and a promising ORR and PFS as a front-line treatment for patients with KRAS p.G12C NSCLC. This combination will be further evaluated in a randomized phase III trial in NSCLC. Clinical trial information: NCT05288205. Research Sponsor: Jacobio Pharmaceuticals.

Performance characteristics of a tissue-agnostic genome-wide methylome enrichment MRD assay for head and neck malignancies.

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Background: Plasma cell-free DNA (cfDNA) tests have emerged as a promising approach for cancer management. cfDNA methylome approaches are well-suited for molecular residual disease (MRD) detection. Here we present data using a tissue-agnostic, genome-wide methylome enrichment platform based on cell-free methylated DNA immunoprecipitation and high throughput sequencing (cfMEDIP-seq) in head and neck cancer (HNC) to predict relapse for purposes of guiding adjuvant therapy after completion of curative-intent treatment and to detect early relapse. **Methods:** The cohort is comprised of biobanked samples from individuals diagnosed with stage I-IVB human papillomavirus (HPV)-negative and HPV-positive HNC with longitudinal data collection and sampling. The full cohort includes 325 unique patients with 1,155 samples. Samples were split into distinct sets to train and test a classifier consisting of differentially methylated regions. Blood collection time points include at diagnosis, and approximately 3 (landmark), 12 and 24 months after curative intent treatment. 5-10 ng of cfDNA isolated from each plasma sample was used for cfMEDIP-seq. MRD signals were quantified from average normalized counts across informative methylated regions and binarized into a positive (above the threshold) and negative groups. Recurrence-free survival (RFS) was compared for patients who tested positive to those who tested negative at 3 months post-curative treatment (i.e., landmark timepoint) and longitudinally. **Results:** A total of 196 post-treatment samples from 80 unique patients [stage I (35%), II (15%), III (24%), IV (26%)] were analyzed and correlated with recurrence, in this interim training result. At the landmark timepoint, patients who tested positive showed significantly worse RFS than those who tested negative (Hazard ratio (HR) 9.69; 95% CI, 4.39-21.4, $P<0.001$). Incorporating serial longitudinal samples, recurrence-free survival was worse in patients who tested positive compared to those that tested negative (HR 14.52; 95% CI, 5.78-36.46, $P<0.001$). **Conclusions:** Interim analysis demonstrates that MRD detection with a tissue-agnostic, genome-wide methylome enrichment platform in HNC patients after curative intent treatment correlates strongly with RFS with hazard ratios consistent with tumor-informed assays previously described. Updated analyses from the cohort will be presented at the meeting. Research Sponsor: Adela, Inc.

Personalized cell-free tumor DNA analysis for patients with HNSCC: Liquid biopsy for minimal residual disease detection in head and neck squamous cell carcinoma (LIONESS).

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Background: Early relapse and development of metastatic disease are some of the primary reasons for the poor prognosis of patients with head and neck squamous cell carcinoma (HNSCC). We conducted LIONESS, a single-center prospective cohort study to assess ctDNA in plasma and saliva from 76 patients with HNSCC receiving primary surgery with curative intent. Our objectives were to determine whether postoperative ctDNA detection can act as a biomarker for surgical tumor clearance and detection of molecular residual disease (MRD) and to evaluate the potential of tumor-informed ctDNA analysis for early molecular-level detection of relapse or prior to clinically confirmed recurrence. **Methods:** Plasma and saliva samples from 76 HNSCC patients (37% stage I/II, 63% stage III/IV; 93% p16-negative) were collected pre- and postoperatively and during clinical follow-up. Whole exome sequencing was performed on FFPE tumor tissue. Tumor-specific variants for personalized assay design (RaDaR, NeoGenomics Laboratories) were selected and used in the analysis of serial samples for evidence of MRD. ctDNA levels were correlated to tumor volumes from staging CT, as well as pathological and other clinical parameters. **Results:** 617 longitudinal plasma and 128 saliva samples were collected pre- and postoperatively and during clinical follow-up (median follow-up time of 805 days). In plasma, ctDNA was detected at a median estimated variant allele frequency (eVAF) of 0.036% (0.000327% - 18.43%). 34% of positive samples had ctDNA levels detected at an eVAF of ≤0.01%. Increased plasma ctDNA levels were detected postoperatively in 96% of cases with confirmed clinical recurrences (21/22) with a median lead time of 160 days (6 – 763 days). Of the remaining 54 patients with no clinically confirmed relapse, ctDNA was detected immediately postop in 7 of them. In 5 patients, adjuvant therapy resulted in persistent ctDNA clearance, while 2 patients are deceased. ctDNA was also detected in baseline saliva samples from patients with HNSCC of various anatomical locations with a 74% overlap with the corresponding plasma ctDNA profiles. There was a strong linear correlation between larger tumor volumes and higher eVAF and a trend towards higher eVAF in cases with regional and distant recurrences in comparison to local relapse. Pathological tumor stage and lymph node involvement were both strongly correlated with preoperative ctDNA shedding. **Conclusions:** The use of ctDNA detection in surgically treated patients with HNSCC has significant potential to guide treatment decisions, improve disease outcome and potentially spare patients unnecessary, partially invasive interventions during clinical follow-up. Our work demonstrates the feasibility of tumor-informed ctDNA assays for detection of MRD postoperatively and for monitoring for early detection of relapse. Research Sponsor: None.

Circulating tumor cells and tumor DNA in patients with resectable colorectal liver metastases: The MIRACLE.

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Background: Recurrence risk after curative surgery for colorectal liver metastases (CRLM) remains high, underlining the need for prognostic markers to detect minimal residual disease after local treatment. The aim of this study was to determine the association between recurrence-free survival (RFS) and detection of circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) before and after surgical treatment of resectable CRLM. **Methods:** The MIRACLE isa prospective, observational biomarker study in patients with isolated, resectable CRLM without (neo)adjuvant chemotherapy, recruited between October 2015 and December 2021. The study was powered to detect at least a 20% difference in one-year recurrence rate between detectable and undetectable circulating tumor load after surgery. Blood samples were collected one day before surgery (T0) and three weeks (T3) after surgery. CTCs were enumerated using the FDA-approved CellSearch system. ctDNA before surgery was measured by next generation sequencing (NGS) using a targeted panel (Oncomine Colon cfDNA assay) and postoperatively by digital PCR (dPCR). **Results:** CTC enumeration resulted in positivity for 43 out of 192 patients (22%) at baseline and 14 out of 161 patients (9%) at T3. ctDNA was detected in 125 out of 191 patients (65%) at baseline, of which 25 (20%) still had detectable ctDNA at T3. Patients with postoperative undetectable CTC had a significantly improved RFS (1-year RFS: 15% vs. 51%, log-rank test p=0.009). Also, patients with postoperative undetectable ctDNA had a significantly improved RFS (1-year RFS: 20% vs. 54%, log-rank test $p<0.001$). In multivariable analysis, at baseline no association was found between RFS and CTCs (HR 1.01; p=0.97) or ctDNA (HR 1.29; p=0.29). In contrast, after surgery a significantly shorter RFS was observed in patients with detectable CTCs (HR 3.09; p=0.002) and ctDNA (HR 3.53; $p<0.001$). Postoperative ctDNA status was a stronger predictor of recurrence compared to known clinical risk factors. **Conclusions:** This is the first study conducted in patients with resectable CRLM without (neo)adjuvant chemotherapy, which demonstrates the impact of detectable circulating tumor load after surgery on RFS. Postoperative ctDNA and CTC detection are a strong predictor for a shorter RFS after local treatment, as opposed to preoperative ctDNA or CTC detection. Research Sponsor: KWF Kankerbestrijding.

Multivariable cox regression for RFS.

Outcome	ctDNA HR (95% CI)	CTC HR (95% CI)
Age	1.03 (0.99 - 1.07)	1.00 (0.97 - 1.03)
N stage +	1.72 (0.93 - 3.18)	1.54 (0.95 - 2.50)
Disease-free interval primary tumor - CRLM (>12 months)	0.43 (0.22 - 0.84)	0.40 (0.23 - 0.70)
Number of CRLM (>1)	2.02 (1.11 - 3.68)	1.87 (1.15 - 3.04)
Preoperative CEA (≥5ug/l)	0.81 (0.42 - 1.54)	1.23 (0.74 - 2.03)
Diameter of largest CRLM (≥5 cm)	1.11 (0.41 - 2.94)	0.65 (0.29 - 1.43)
Resection margin (R1)	1.98 (0.63 - 6.24)	2.58 (0.98 - 6.83)
Postoperative ctDNA	3.53 (1.79 - 6.97)	
Postoperative CTC		3.09 (1.51 - 6.36)

Results of a phase 1/2 study of MHB088C: A novel B7H3 antibody-drug conjugate (ADC) incorporating a potent DNA topoisomerase I inhibitor in recurrent or metastatic solid tumors.

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Background: MHB088C is an investigational B7H3-directed ADC, created by coupling a humanized anti-B7H3 monoclonal antibody with a highly potent DNA topoisomerase I inhibitor (5~10 times more potent than DXd). Preclinical studies demonstrated robust binding affinity, superior internalization rates, powerful tumor killing activities (3~10 times more potent than the DS-7300a analog in CDX models) and a favorable safety profile with no unique toxicities observed in the GLP study as compared to other B7H3 ADCs and no occurrences of interstitial lung disease (ILD). We here present the safety and efficacy results from a first-in-human phase 1/2 study of MHB088C. **Methods:** The study enrolled patients (pts) with recurrent or metastatic solid tumor across two segments: dose-escalation (D-esc) and dose-expansion (D-exp). In the D-esc phase, MHB088C was administrated intravenously at doses of 0.8, 1.6, 3.0mg/kg Q2W; 3.0, 4.0 mg/kg Q3W. **Results:** As of the data cutoff on Dec 31, 2023, 60 pts were enrolled and received at least one dose of MHB088C (D-esc, n=14; D-exp, n=46). 55 pts remain on the treatment and 12 pts had at least one tumor assessment according to RECIST 1.1. Dose-limiting toxicities (DLTs) were platelet count decreased and febrile neutropenia at 4.0 mg/kg Q3W. The MTD was determined to be 3.0 mg/kg Q3W. The most common TRAEs overall in ≥25% of pts were neutrophil count decreased, lymphocyte count decreased, and white blood cell (WBC) count decreased. The most common Grade ≥3 TRAEs (≥5% of pts) were neutrophil count decreased (33.3%), lymphocyte count decreased (30.0%), WBC count decreased (26.7%), platelet count decreased (23.3%), and anemia (15.0%). No ILD was reported. Of12 response-evaluable pts, 5 partial responses (PRs) were observed (ORR: 41.7%). The disease control rate was 91.7% (11/12). In the subset of 3 SCLC pts, all 3 showed PRs (ORR: 100.0%), with one case demonstrating complete response of the target lesion and another with close to 80% tumor volume reduction. The efficacy of 2 SCLC pts was achieved in 1.6 mg/kg Q2W group without major hematologic side effects. All responses among SCLC pts occurred at the first tumor assessment. **Conclusions:** MHB088C exhibited a manageable safety profile, with striking efficacy in SCLC pts. The dose optimization and expansion study is continuing to establish the RP2D for MHB088C. Clinical trial information: CTR20231298. Research Sponsor: None.

9MW2821, a nectin-4 antibody-drug conjugate (ADC), in patients with advanced solid tumor: Results from a phase 1/2a study.

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Background: 9MW2821 is a monoclonal ADC that delivers monomethyl auristatin E to cells expressing Nectin-4. Nectin-4 is an adhesion molecule that highly expressed in variety of solid tumors, especially urothelial cancer (UC), cervical cancer (CC), esophageal cancer (EC) and breast cancer. Here we report the updated safety and efficacy data of 9MW2821. **Methods:** 9MW2821 was administered by intravenous infusion at doses of 0.33-1.5mg/kg on days 1, 8 and 15 of each 28-day cycle. The study included dose escalation, dose expansion and cohort expansion period which included UC, CC, EC, triple negative breast cancer (TNBC) and other Nectin-4 positive solid tumors that progressed after ≥1 systemic treatments (Tx). Primary objectives were assessment of safety and preliminary efficacy. **Results:** As of Jan 15, 2024, 260 patients (pts) were enrolled with doses ranging from 0.33 to 1.5mg/kg. Only 1 out of 6 pts in 1.5mg/kg group had dose limiting toxicity (grade 4 neutropenia lasted more than 5 days). The maximum tolerated dose was not reached up to 1.5mg/kg and the RP2D was selected as 1.25mg/kg for tolerance. 240 pts were enrolled at dose of 1.25mg/kg. The most common TRAEs of 1.25mg/kg dose group (≥20%, all grade/≥5%, ≥G3) were white blood cell (WBC) count decreased (50.8%, 23.3%), neutrophil count decreased (46.3%, 27.9%), anemia (43.8%, 8.3%), aspartate aminotransferase increased (42.1%, 2.9%), alanine aminotransferase increased (35.4%, 2.1%), asthenia (32.1%, 2.9%), rash (30.0%, 5.0%), decreased appetite (28.8%, 1.3%), nausea (26.7%, 0%), hyperglycemia (25.4%, 2.1%), platelet count decreased (24.2%, 4.6%), alopecia (24.2%, 0%), hypoaesthesia (22.5%, 1.7%), constipation (21.3%, 0%), vomiting (20.9%, 1.3%), hypertriglyceridemia (20.4%, 2.1%), gamma-glutamyltransferase increased (15.8%, 5.4%). Among 190 pts treated with 9MW2821 at 1.25mg/kg or above and reached tumor assessment, objective response rate (ORR) and disease control rate (DCR) was 35.3% and 78.4%, respectively. 37 UC pts, 45 CC pts, 27 EC pts and 16 TNBC pts were enrolled at 1.25mg/kg and evaluable for tumor assessment. Median prior lines of Tx were 2 (range, 1-4). All UC, 51% CC and 93% EC pts progressed after platinum-based chemotherapy and immune checkpoint inhibitors, respectively. Objective responses were also observed in pts with other solid tumor types. **Conclusions:** The data indicated encouraging efficacy of 9MW2821 in advanced UC, CC, EC and TNBC. 9MW2821 is the first Nectin-4 targeting ADC showed antitumor activity in patients with CC, EC and TNBC. The safety profile showed adequate tolerability. Clinical trial information: NCT05216965. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

Tumor Type	UC	CC	EC	TNBC
n	37	45	27	16
ORR, %	62.2	37.8	29.6	43.8
(95% CI)	(44.76-77.54)	(23.77-53.46)	(13.75-50.18)	(19.75-70.12)
DCR,%	91.9	84.4	74.1	81.3
(95% CI)	(78.09-98.30)	(70.54-93.51)	(53.72-88.89)	(54.35-95.95)
PFS, months	8.8	4.0	3.7	5.8
(95% CI)	(3.81-NR)	(3.75-5.68)	(1.94-NR)	(2.00-NR)

Dendrimer-enhanced (DEP) SN38 (DEP irinotecan) in patients (pts) with advanced solid tumors: A phase 1/2 trial.

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Background: Dendrimer nanoparticles enable prolonged cytotoxic drug targeting to tumors. DEP SN38 is a water-soluble version of SN38, the active metabolite of irinotecan, attached to a dendrimer, so avoiding usual metabolic pathways of conventional irinotecan (c-IRI). This phase 1/2 (P1/2) trial evaluated safety, tolerability and efficacy of DEP SN38 in pts with advanced solid tumors, including colorectal (CRC), platinum-resistant high-grade serous ovarian (HGSOC) and breast (BC). **Methods:** Pts who had exhausted standard therapy were enrolled in dose assessment (P1)/dose expansion (P2) cohorts of DEP SN38 given IV 3-weekly (Q3W) or Q2W alone or in combination with 5-fluorouracil & leucovorin (5FU/LV combo). Efficacy was evaluated by RECIST 1.1 and serum tumor markers. (EudraCT 2019-001318-40). **Results:** 114 pts were enrolled. The Q3W Recommended Dose (RD) was 12.5 mg/m^2 SN38 with dose limiting toxicity (DLT) in 1/7 pts (grade (G) 4 neutropenia $>$ 7d). The Q2W RD was 12.5 mg/m^2 for SN38 alone or with 5FU/LV. DEP SN38 was well-tolerated for all dose regimens with mostly mild/moderate (G1/2) treatment-related adverse events (TRAEs) & no new events compared with c-IRI. TRAEs in $\geq$ 10% pts included neutropenia, thrombocytopenia, anemia, fatigue, nausea, vomiting, diarrhea, constipation and alopecia. Of734 DEP SN38 cycles only 1 event of G3 diarrhea (0.9% pts) and no cholinergic symptoms have been observed, contrasting with c-IRI (~20% & 47% pts respectively). G3 nausea (1.8% pts) and vomiting (0.9% pts) occurred less frequently than with c-IRI (both ~10% pts). Febrile neutropenia was the DLT at 15 mg/m^2 Q2W monotherapy (2/6 pts), with neutropenia otherwise essentially uneventful and managed with G-CSF. 38 CRC pts received DEP SN38 monotherapy (31 evaluable) and 17 received the 5FU/LV combo (14 evaluable). CRC pts had a mean 4 prior lines with 97% receiving $\geq$ 1 c-IRI containing line. The disease control rate (DCR) in monotherapy was 48% (stable disease (SD) up to 72 wks). The 5FU/LV combo cohort DCR was 85.7%, the objective response rate (ORR) was 14.3%, with disease control observed for at least 35 wks. Several CRC pts continue combo treatment. 23 HGSOC pts with a mean of 6 prior lines received DEP SN38 monotherapy (18 evaluable). The DCR for Q2W was 100% with 33.3% ORR, and 72% DCR for all HGSOC pts. 3 pts have PRs for at least 36 wks; with 1 pt achieving complete tumor & ascites resolution. Reduced CA-125 of up to 98% was observed in 75% pts. Several HGSOC pts continue DEP SN38 treatment. 8 BC pts with a mean of 7 prior lines received DEP SN38 monotherapy Q3W (5 evaluable). The DCR was 100% with SD up to 72 wks. **Conclusions:** DEP SN38 shows promising clinical utility with encouraging antitumor activity including prolonged disease control & durable PRs in heavily pre-treated CRC, HGSOC & BC pts. DEP SN38 is well-tolerated with significantly fewer severe gastrointestinal TRAEs compared to c-IRI, & warrants further clinical assessment. Clinical trial information: 2019-001318-40. Research Sponsor: None.

Diverging acquired resistance evolutionary pathways in fusion-positive patients treated with tyrosine kinase inhibitors.

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Background: Tyrosine kinase fusions are recurrent, actionable oncogenic drivers across cancer types. Multiple tyrosine kinase inhibitors (TKIs) are approved in a disease-specific or tumor-agnostic fashion for these cancers. While TKI resistance includes the acquisition of on-target and off-target alterations, a large subset of resistance remains unexplained and may not simply be mediated by singular emergent alterations. As such, we sought to define how genomic complexity evolves under the selective pressure of TKI therapy. **Methods:** *ALK*, *RET*, *NTRK*, *ROS1* or *FGFR* fusion-positive patient (pt) tumor samples that underwent clinical FDA-authorized tumor-normal panel sequencing (MSK-IMPACT) between April 2015 and January 2023 were selected. Genomic data assessed included chromosomal instability, inferred by the fraction of genome altered (FGA), fraction of loss-of-heterozygosity (F-LOH) and tumor mutational burden (TMB). Samples with low tumor purity (< 0.2) or indeterminate copy number profiles were excluded. Treatment data were obtained from natural language processing of electronic medical records. **Results:** Of 68,920 tumors with sequencing, 49,910 samples met quality requirements. Of these, 1,283 samples (2.6%) from 1,111 pts harbored the queried fusions; among these 64 pts had at least 1 TKI-naïve baseline and 1 or more post-TKI progression of disease (PD) samples, yielding a total of 147 samples usable for evaluating the intra-patient evolution of genomic complexity. The most common cancer types were non-small-cell lung cancer (NSCLC, n = 42), biliary tract cancers (n = 4), and thyroid cancer (n = 4). Paired analysis of TKI-naïve and first post-TKI PD samples in all 64 pts showed increases in FGA (median = 1.1; 0.4~6.6), F-LOH (median = 1.1; 0.2~11.5), and TMB (median = 1.3; 0.2~9.9) upon TKI-resistance ($p < 0.01$). Pts with primary baseline tumors (n = 22) and pts with metastatic tumors (n-42) were next evaluated independently. Increases in FGA, F-LOH and TMB upon TKI PD were statistically significant in both groups ($p < 0.05$). Accounting for tumor type, all 3 metrics showed increase in NSCLCs ($p < 0.05$), whereas only F-LOH was increased in non-lung tumors upon TKI-PD ($p < 0.05$). Post-PD FGA increase was seen in 22 pts, these didn't harbor significant increase in TMB (p = 0.07; 57% increasing, 43% not increasing). Similarly, among the 38 pts with post-PD TMB increase, no significant increase in FGA was seen (p = 0.21; 56% increasing, 44% not increasing). F-LOH was increased in both pt groups ($p < 0.05$). **Conclusions:** Fusion-positive cancers acquire additional genomic alterations post-TKI, potentially via at least two main diverging evolutionary pathways: the acquisition of additional mutations or an increase in chromosomal instability. Improved understanding of pathways by which fusion-positive cancers acquire genomic complexity may yield novel treatment strategies. Research Sponsor: None.

ReNeu: A pivotal phase 2b trial of mirdametinib in children and adults with neurofibromatosis type 1 (NF1)-associated symptomatic inoperable plexiform neurofibroma (PN).

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Background: PN in patients (pts) with NF1 can cause pain, disfigurement, impaired quality of life (QoL), and can undergo malignant transformation. ReNeu (NCT03962543), a multicenter, open-label, Phase 2b study, evaluated efficacy and safety of the highly selective, oral, investigational MEK1/2 inhibitor mirdametinib in adult (≥18 y) and pediatric (2-17 y) pts with inoperable NF1 PN causing significant morbidities. **Methods:** Mirdametinib was administered as a capsule or dispersible tablet (2 mg/m^2 BID, max 4 mg BID) without regard to food in 3 wk on/1 wk off 28-d cycles. The primary endpoint was confirmed objective response rate (ORR; percentage of pts with MRI-assessed ≥20% reduction of target PN volume by blinded independent central review [BICR] within the 24-cycle treatment phase). The minimum clinically relevant ORR (null) was defined as 23% for adults and 20% for pediatrics. Ptscould continue treatment in an optional long-term follow-up (LTFU) phase. Additional key endpoints were duration of response (DoR), time to response (TTR), change from baseline (BL) in target PN volume, pain severity (Numerical Rating Scale-11 [NRS-11]), pain interference (Pain Interference Index [PII]), health-related (HR) QoL (PedsQL), and safety. **Results:** All114 pts (58 adult, 56 pediatric) received mirdametinib. As of the 20 Sept 2023 data cutoff (DCO), BICR-confirmed ORR during the treatment phase was 41% (95% CI, 29-55; $P<.001$ vs null) in adults and 52% (95% CI, 38-65; $P<.001$ vs null) in pediatric pts. Two adult pts and 1 pediatric pt also had a confirmed response in the ongoing LTFU. Median (min, max) target PN volumetric best response from BL was -41% (-90, 13) and -42% (-91, 48) in adult and pediatric pts, respectively. As of the DCO, median treatment duration was 22 mo for each cohort and median DoR was not reached. Median (range) TTR was 7.8 (4-19) mo in adult pts and 7.9 (4-19) mo in pediatric pts. Adult and pediatric pts had statistically significant improvements from BL to cycle 13 in NRS-11, PII, and key PedsQL measures. Most frequent (≥35% pts) treatment-emergent adverse events (TEAEs) were dermatitis acneiform, diarrhea, nausea, and vomiting in adults and diarrhea, dermatitis acneiform, and vomiting in pediatric pts. 16% and 25% of adult and pediatric pts, respectively, had grade ≥3 treatment-related AEs, and 22% and 9%, respectively, discontinued due to TEAEs. **Conclusions:** In ReNeu, the largest multicenter NF1 PN trial reported to date, mirdametinib demonstrated a statistically significant ORR by BICR, with deep and durable PN volume reductions, significant improvements in pain severity, pain interference, and HRQoL, and a manageable safety profile in both adults and children. Together with a dispersible tablet formulation, these results underscore mirdametinib's potential to become an important new treatment option for NF1 PN pts across all ages. Clinical trial information: NCT03962543. Research Sponsor: SpringWorks Therapeutics, Inc.

3017 Rapid Oral Abstract Session

Association between stromal tumor-infiltrating lymphocytes (TILs) and pathologic complete response (pCR) in patients with early breast cancer (BC) treated with neoadjuvant chemotherapy and HER2-directed therapies in NSABP B-41.

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Background: In the phase 3 NSABP B-41 trial, there was an association between pCR and survival in 519 women with early HER2-positive BC treated with neoadjuvant chemotherapy in combination with trastuzumab (T), lapatinib (L), or both (TL). There is a need to identify prognostic biomarkers to tailor patients' treatment, and the quantification of stromal TILs represents a promising, accessible, and reproducible option. In this analysis, we studied the association between TILs and pCR. **Methods:** Eligible patients had a baseline core biopsy sample, known pCR status, and no consent withdrawal for the use of specimens. Slides were scanned using an Aperio GT 450 automated scanner to create whole slide images. TIL analysis was then completed based on the international TIL working group guidelines (RS). Patients were grouped into three TIL score categories based on tumor TIL %: low (1-5%), intermediate (6-30%), and high (31-95%). The dose-response relationship between TIL percentage and pCR was explored via generalized linear models with splines. **Results:** 257 patients were included. 89 (35%) received T, 92 (36%) L, and 76 (29%) TL. 149 (58%) had ER-positive BC. TIL categories in this cohort: 49% low, 22% intermediate, and 29% high. TIL expression was similar across BC intrinsic subtypes and by ER. There was no association between the TIL group and pCR, irrespective of the treatment group (p=0.98). Among tumors with low TILs, T or TL had similar pCR compared to L alone (51.3 *v* 49%; p=0.95). Among tumors with high TILs, T or TL had higher pCR than L (61.2 *v* 40.4%; p=0.04). Among patients with ER-positive BC, high TILs were associated with a numerical increase in pCR rate (56% *vs* 39.6%; p=0.11). Among patients with ER-negative tumors, high TILs were associated with a numerical decreased rate of pCR (50% *v.* 66.7%; p=0.15). The p-value of the Breslow test of homogeneity of the odds ratios across ER status was 0.016, suggesting that the association between TILs (0-30 v. >30) and pCR varies across ER status.No interaction between the TIL percentage and age, nodal status, menopausal status, or histologic grade was noted. **Conclusions:** This analysis revealed that patients with a high TIL percentage treated with T or TL compared to L were more likely to achieve a pCR. These findings can be partially explained by the mechanism of action of the HER2-directed agents. T leads to antibody-dependent cell-mediated cytotoxicity, and a higher percentage of TILs may enhance this mechanism, whereas L has intracellular tyrosine kinase disruption. The association between TILs and pCR varied across ER status. Our next steps include additional studies assessing the interaction between TILs and long-term outcomes, as well as gene expression and TILs to validate this biomarker for future clinical trials in HER2+ early BC. Clinical trial information: NCT00486668. Research Sponsor: BCRF; BCRF-20-156.

A phase I study of highly potent oral ATR inhibitor (ATRi) tuvusertib plus oral PARP inhibitor (PARPi) niraparib in patients with solid tumors.

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Background: Ataxia telangiectasia and Rad3-related (ATR) protein kinase and poly-ADP ribose polymerases (PARPs) are crucial components in the DNA damage response (DDR). Combining tuvusertib and niraparib may synergistically enhance synthetic lethality and increase apoptosis. Part B1 of the DDRiver Solid Tumors 301 study (NCT04170153) assessed this combination. **Methods:** Part B1 of this open-label multicenter dose-escalation phase Ib trial enrolled unselected patients with metastatic or locally advanced unresectable solid tumors refractory to standard treatment. The primary objective was to determine safety (including maximum tolerable dose and recommended dose(s) for expansion [RDE]). Secondary and tertiary objectives included determination of the pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of different dosing regimens of tuvusertib plus niraparib. Multiple continuous and intermittent schedules were explored with tuvusertib doses ranging from 90–180 mg once-daily (QD) and niraparib doses from 100–200 mg QD. A partial ordering continual reassessment method was used to identify the RDEs. **Results:** As of 02 January 2024, 43 patients had been enrolled (all with baseline body weight <77kg or platelet count <150,000/mm^3); 13 patients remained on treatment. Ten (26.3%) patients had dose-limiting toxicities (DLTs). The most common DLT was grade 3 anemia requiring blood transfusion (n=4; 10.5%); the most frequent grade ≥3 treatment-emergent adverse events were anemia (n=18; 41.9%), platelet count decrease (n=6; 14.0%) and fatigue (n=4; 9.3%). The PK of tuvusertib when combined with niraparib was consistent with that of tuvusertib monotherapy, suggesting a lack of any clinically meaningful mutual drug–drug interactions. Dose-dependent ɣ-H2AX inhibition (proximal PD marker) was observed at tuvusertib doses ≥130 mg QD. Preliminary efficacy data show 5 (15.6%) responses (3 confirmed) by RECIST v1.1 in 32 evaluable patients: 2 in patients with epithelial ovarian cancer (EOC; 1 with *BRCA1*-mutant [*BRCA1*m] PARPi-resistant EOC, 1 with *BRCA*-wild type homologous recombination deficiency-positive EOC) and 1 each in patients with non-small cell lung cancer, estrogen receptor-positive HER2-negative *BRCA1*m breast cancer, and *BRCA1*m PARPi-resistant pancreatic cancer. Tuvusertib 180 mg QD and niraparib 100 mg QD or tuvusertib 90 mg QD and niraparib 200 mg QD, both given in a 1 week on/1 week off schedule, were identified as RDEs. **Conclusions:** The combination of tuvusertib plus niraparib, each administered on a 1 week on/1 week off schedule, has a manageable safety profile and is suitable for further investigation. A combination study in patients with PARPi-resistant EOC is planned. Clinical trial information: NCT04170153. Research Sponsor: EMD Serono (CrossRef Funder ID: 10.13039/100004755).

First-in-human phase I clinical trial of RSO-021, a first-in class covalent inhibitor of mitochondrial peroxiredoxin 3 (PRX3), in patients with malignant pleural effusion due to mesothelioma and other advanced solid tumors (MITOPE).

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Background: Malignant cells rely on buffering oxidative stress through mitochondrial PRX3. Oxidative stress is selectively lethal to cancer cells and may be leveraged therapeutically. RSO-021 is a naturally-occurring, sulfur-rich, cyclic oligopeptide of the thiopeptide class, which covalently inactivates PRX3, leading to catastrophic oxidative stress and cell death. We conducted a phase 1 study to explore safety and identify the maximum tolerated dose (MTD) of intra-pleural RSO-021 in patients with mesothelioma, or other predominantly pleural cancer, with pleural effusion. **Methods:** MITOPE was a multicenter trial of weekly intrapleural RSO-021 (90, 120, and 180 mg) with a 3 + 3 dose-escalation design. The primary objective was to assess RSO-021 safety/tolerability. Secondary objectives included establishing local and systemic pharmacokinetic profiles and early anti-tumor activity. We defined dose-limiting toxicity (DLT) as grade (G) ≥3 non-hematological AEs with exceptions for some manageable G3 AEs that resolved within 72 h and complicated G4 hematological AEs or those lasting >7 days. We also studied inflammatory and pharmacodynamic markers in local/systemic samples. Efficacy was assessed using mRECIST 1.1 (mesothelioma) and RECIST 1.1 (other tumors). **Results:** Of 15 patients treated (90 mg/wk, n=7; 120 mg/wk, n=6; 180 mg/wk, n=2), 12 (80%) had ≥3 prior anti-cancer regimens; 12 (80%) had mesothelioma. See table for AE and efficacy data. The commonest all-grade treatment-related AEs (TRAE) were fatigue (33%), pyrexia (20%), and elevated creatinine (20%). Three patients (20%) had DLTs: G3 dyspnea and G3 acute inflammatory response at 120 mg/wk; G3 dyspnea at 180 mg/wk. MTD was 90 mg/wk. Pro-inflammatory cytokines in pleural fluid/serum correlated with AEs suggestive of local inflammation. Prophylaxis mitigated local inflammatory TRAEs. PRX3 target binding in cell pellets from pleural fluid confirmed on-target activity. Systemic exposure was minimal. Disease control was 70% in 10 evaluable patients. The partial response at 90 mg/wk was a 59% reduction in mesothelioma target lesions. Median PFS at MTD was 5.7 months (95% CI, 1.4-NR). Two patients had disease control (DC) >30 wks. **Conclusions:** Weekly intrapleural RSO-021 was safe with signs of anti-tumor activity in patients with pleural mesothelioma. Phase 2 exploration of this novel agent is ongoing at 2 doses, as a single agent and in combination. Clinical trial information: NCT05278975. Research Sponsor: RS Oncology.

Parameter n (%)	90 mg n=7	120 mg n=6	180 mg n=2	All n=15
All grade TRAEs - any	4 (57)	4 (67)	2 (100)	10 (67)
DLTs	0	2 (33)	1 (50)	3 (20)
G3-4 TRAEs - any	1 (14)	2 (33)	1 (50)	4 (27)
Catheter site infection/ inflammation/ pain	1 (14)	1 (17)	1 (50)	3 (20)
Dyspnoea	1 (14)	1 (17)	0	2 (13)
mRECIST 1.1 best response	**n=6**	**n=3**	**n=1**	**n=10**
PR	1 (17)	0	0	1 (10)
SD	4 (67)	1 (33)	1 (100)	6 (60)
DC	5 (83)	1 (33)	1 (100)	7 (70)

Enrichment of somatic mosaic states involving DNA damage response and repair genes in patients treated with ^{177}Lutetium.

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Background: Radioligand therapy (RLT) use has been increasing with the approval of ^{177}Lu-Dotatate for metastatic neuroendocrine tumors (NET) & ^{177}Lu-PSMA-617 for metastatic castration resistant prostate cancer (mCRPC). Therapy-related myeloid neoplasms [tMN, including myelodysplastic syndrome (MDS) & acute myeloid leukemia, (AML)] have been reported after ^{177}Lutetium (^{177}Lu) for NET with rates of 2-20% & median time from first ^{177}Lu to tMN of 2.8yrs [4-12]. Clonal hematopoiesis (CH) is a risk factor for tMN, with the spectrum of CH depending on selection pressures. To describe the prevalence of therapy selected CH & tMN, we performed a retrospective analysis of patients (pts) who had a bone marrow biopsy (BMB) post-^{177}Lu. **Methods:** After IRB approval, we queried the electronic health record for pts with BMB post-^{177}Lu. Pt demographics, treatment history, labs & BMB results were collected. **Results:** Fifty-seven pts met criteria, 41 (72%) with NET & 16 (28%) with mCRPC. . Median age at BMB was 68yrs (range, 28-85). Of the 57pts, prior treatments included: radiation (RT) in 21 (37%), temozolomide in 14 (25%), taxane in 15 (26%), & platinum agents in 10 (18%). The median number of ^{177}Lu cycles was 4 (range, 1-11).Cytogenetics were available in 84% (n = 48) & were normal in 60% (n = 29). Of those with abnormal cytogenetics (n = 18, 38%), the most common abnormalities involved chromosome (chr) 7 (n = 12, 26%), chr 5 (n = 7, 15%), chr 20 (n = 5, 11%) and complex karyotypes in 7 (15%), with 3 (17%) of these patients having no mutations. Diagnoses were assessable in 49 (86%) pts: 15 (31%) with undefined cytopeniasand 16 (33%) with tMDS. Metastatic carcinoma was identified in 17 Fifty-one percent (n = 29), at a median of 0.5yrs (range, 0.04-2.6) after hematologic diagnosis. **Conclusions:** The enrichment of CH involving the DDR pathway in recipients of ^{177}Lu underscores the impact of RLT on bone marrow progenitors. Research Sponsor: None.

Safety and efficacy of biosimilar TDM-1: A real world retrospective study.

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Background: Ado-Trastuzumab emtansine (TDM1), an antibody-drug conjugate demonstrated significant efficacy in both metastatic and adjuvant treatment of HER 2 Positive Breast cancer. Cost of the drug was prohibitive for use in Low and Middle income countries (LMIC). A biosimilar version of TDM1 was introduced in India at a lower price in May 2021. Since then, the use of TDM1 in deserving patients has increased. We aimed to study the safety and efficacy of biosimilar TDM1 in our center. **Methods:** We retrospectively analysed the case records of all patients who were prescribed biosimilar TDM1 at our institute from 01.06.2021 to 20.10.2023. Indication for TDM1, line of therapy in which used, number of cycles used, response rates, adverse events, progression free survival and overall survival were calculated using simple statistical methods. The usage of any TDM1 after May 2021 was compared to the previous years' usage. **Results:** A total of 116 patients were prescribed biosimilar TDM1 in the study period. Out of them, 51 patients received the drug in the adjuvant setting and 65 for advanced stage disease. Early stage (n=51): Out of the 51 patients, 32 (62.7%) completed planned cycles, 14 (27.5%) ongoing; 3 (5.9%) discontinued due to social reasons, 2 (3.9%) changed treatment due to adverse events. All of them tolerated the therapy well. Common adverse effects were fatigue. Only 5 patients (21.7%) required romiplostim for therapy related thrombocytopenia. None of them had grade ≥3 adverse affects. Advanced stage (n=65): At a median follow up of 9 months, 30 patients (46.2%) progressed; 15 (23%) ongoing; 15 (23%) defaulted due to various social reasons; 5 (7.7%) discontinued due to intolerance. The median number of cycles received was 8 cycles (IQR 5-13). Majority of them received TDM1 in the second line (84.6%). Response evaluation was available for 52 patients who completed at least three cycles of TDM1. Objective response rate was noted in 33 patients (50.8%). Clinical benefit rate (CR+PR+SD) was seen in 39 patients (75%). 5 patients (9.6%) had a Complete response, 28 (53.8%) had Partial response and 6 (11.5%) had a stable disease. The median duration of response was 5 months. The median Progression Free survival was 8 months (5.7– 10.2m) and the projected overall survival was 18 months (16.1-19.9 m). No serious adverse event or cardiac compromise was encountered. 3 patients had thrombocytopenia. One patient succumbed to non-neutropenic Septic shock. In a retrospective data analysis, TDM1 was used in 17 patients in one calendar year prior to the availability of generic TDM1. In the subsequent year, 60 patients received TDM1 at least once in either indication. **Conclusions:** The availability of biosimilar TDM1 increased the reach to deserving patients. No new adverse events were identified. The safety and efficacy of the biosimilar TDM1 were comparable. Research Sponsor: None.

A phase 1a/b, multi-regional, first-in-human study of CS5001, a novel anti-ROR1 ADC, in patients with advanced solid tumors and lymphomas.

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Background: Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an embryonic tyrosine kinase-like molecule implicated in multiple pathways promoting oncogenic signaling. ROR1 is overexpressed in a broad spectrum of solid tumors and hematological malignancies while notably absent in normal tissues. CS5001 is an antibody drug conjugate (ADC) composed of a human anti–ROR1 IgG1 monoclonal antibody which is site-specifically conjugated to a pyrrolobenzodiazepine dimer prodrug through a proprietary lysosomal cleavable β-glucuronide linker. Here, we report preliminary phase 1a results of CS5001 in patients (pts) with advanced solid tumors and lymphomas. **Methods:** This is a global, first-in-human, phase 1a/b study evaluating the safety, pharmacokinetics (PK), and anti-tumor activity of CS5001 in pts with advanced solid tumors and lymphomas. CS5001 was administered intravenously Q3W with a 42-day-DLT period. In phase 1a (dose escalation), pts who had progressed on or been intolerant to standard therapies were enrolled without baseline ROR1 expression testing; accelerated titration followed by Bayesian Optimal Interval design was employed; in parallel with dose escalation, additional pts were enrolled to selected dose levels deemed safe to further evaluate safety and efficacy. **Results:** As of 15 Jan 2024, 49 pts with lymphomas (n=17) and solid tumors (n=32) were treated across 8 dose levels (7 to 125 μg/kg). Median age was 57 years. Most (n=40, 81.6%) pts had received ≥3 lines of prior anti-tumor treatment. No DLT was observed and MTD was not reached. Treatment-related adverse events (TRAEs) occurred in 29 pts (59.2%); the most common TRAE was fatigue (n=8, 16.3%). Grade 3 TRAEs occurred in 7 pts (14.3%), with fatigue, gamma-glutamyltransferase increased and pneumonia being the most common (occurring in 2 pts [4.1%] each). No grade 4-5 TRAEs were reported. Drug exposure of CS5001 was proportional to dose in general, with an apparent half-life of about 5 days. The PK profile of CS5001 was similar to that of total antibody, indicating good stability of the ADC in the circulation. Among the 34 pts with post baseline tumor assessment (13 lymphomas and 21 solid tumors), objective responses were observed in pts at dose level 5 or above (n=23), including 2 complete responses (1 Hodgkin lymphoma [HL] and 1 diffuse large B-cell lymphoma) and 3 partial responses (2 HL and 1 pancreatic cancer). Stable diseases were observed in 3 pts (2 colorectal cancer and 1 renal cancer). Dose escalation is still ongoing, and more data will be available at the conference presentation. **Conclusions:** CS5001 was well tolerated with no DLT identified, PK characteristics were as expected, and encouraging antitumor activities were observed in various advanced solid tumors and lymphomas. Current data support continued evaluations for the recommended phase 2 dose and subsequent phase 1b dose expansion. Clinical trial information: NCT05279300. Research Sponsor: CStone Pharmaceuticals (Su Zhou) Co., Ltd.

Clinical landscape of precision oncology for rare cancers among diverse Asian populations: Insights from the MASTER KEY registry.

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Background: Despite considerable strides in novel cancer treatments, disparities in access and care persist globally. This is particularly pronounced for rare cancers and among Asian patient cohorts, presenting a dual challenge. **Methods:** We conducted an analysis on clinical and biomarker data from the MASTER KEY Study, a multi-regional, prospective, observational precision oncology initiative encompassing 3,764 rare cancer patients across Asia. Clinical treatment and biomarker data, inclusive of DNA/RNA sequencing, were scrutinized to compare precision oncology adoption across various countries. **Results:** Within the Japanese cohort (3,268 patients), predominant rare cancer types included soft tissue sarcomas (22.0%), CNS/brain tumors (12.8%), and head and neck tumors (9.2%). The broader Asian cohort (496 patients) included soft tissue sarcomas (14.6%), liver/biliary tract tumors (14.4%), and head and neck tumors (13.8%), drawing patients from Malaysia, Korea, Taiwan, Philippines, Thailand, and Vietnam. Clinical trial participation for these rare cancers was notably higher in Taiwan (8.2%), followed by Japan (6.5%) and Malaysia (2.0%). The utilization of molecular target agents and/or immune checkpoint inhibitors was highest in Japan (20.3%), trailed by Taiwan (18.9%) and Korea (12.8%). DNA/RNA targeted sequencing data was available for 1,852 patients in Japan (56.7%) and 321 patients (64.7%) across the rest of Asia. 19.5% and 7.0% received on-target therapy in Japan and the rest of Asia, respectively. Notably, in Japan, patients harboring detectable targetable genes like *BRAF* V600E, *BRCA1*, and *BRCA2* received BRAF/MEK inhibitors and PARP inhibitors at rates of 78.3%, 37.8%, and 25.0%, respectively, with varying response rates of 33.3%, 18.2%, and 20.2% each. Intriguingly, *TP53* mutation acted as a negative predictor for response to BRAF/MEK inhibitors. Notably, no patients in the Asian cohort received BRAF/MEK inhibitors or PARP inhibitors despite the detection of these genes. **Conclusions:** The MASTER KEY Study demonstrates the feasibility of a prospective precision oncology platform, spotlighting rare cancers and enabling on-label targeted therapy as well as off-label targeted therapy for a subset of patients through trials. However, the broader Asian population outside Japan encounters heightened limitations in accessing precision oncology. Urgent expansion of clinical trials throughout Asia is crucial to effectively address the disparity that lies within Asian rare cancer patients. Research Sponsor: Japan Agency for Medical Research and Development; Chugai Pharmaceutical Co., Ltd.; Nihon Servier Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma, Ltd.; Pfizer R&D Japan G.K.; Bristol-Myers Squibb Company; Astellas Pharma Inc.; Eisai Co., Ltd.; Ono Pharmaceutical Co., Ltd.; Otsuka Pharmaceutical Co., Ltd.; SymBio Pharmaceuticals Limited; Daiichi Sankyo Co., Ltd.; Taiho Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Co., Ltd.

Phase Ia/Ib trial on the safety and efficacy of mobocertinib in combination with T-DM1 for patients with HER2-mutant solid tumors (WJOG16022M).

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Background: Safety and efficacy of HER2 tyrosine kinase inhibitor (TKI) and anti-HER2 antibody-drug conjugate (ADC) in HER2-mutant solid tumors have not been investigated. **Methods:** Mobocertinib, a potent HER2 TKI plus T-DM1, an anti-HER2 ADC was evaluated in this phase I study. In a dose-finding cohort (phase Ia, pIa), the maximum tolerated dose was estimated in patients (pts) irrespective of HER2 mutational status. To further establish safety and evaluate preliminary efficacy, additional pts with HER2 mutations were enrolled in a dose-expansion cohort (phase Ib, pIb). Mobocertinib of 80, 120 to 160 mg was orally administered with intravenous T-DM1 3.6 mg/kg every 3 weeks. The primary endpoint was to determine the recommended dose (RD) (pIa), and to evaluate the confirmed objective response rate (ORR) (pIb). **Results:** Between Nov 2022 and Jun 2023, a total of 28 pts, 6 in the pIa and 22 in the pIb were enrolled to this study (14 NSCLC; 4 cervical; 2 duodenal papilla; 2 pancreatic, median follow-up, 6.4 mo [range, 1.9 to 12.9 mo]). The median age was 54 (range, 40-84) years, 17 pts were female. Among 27 pts with HER2-mutant tumors, mutations in kinase domain were most common (66.7%). In the pIa cohort, 3 DLTs were observed with mobocertinib 120 mg, including grade 3 thrombocytopenia, grade 4 acute kidney injury, and drug withdrawal due to nausea and anorexia, while there was no DLT with 80 mg. The RD was therefore determined to be mobocertinib 80 mg plus T-DM1 3.6 mg/kg. Among 22 pts in the pIb, grade $\geq$ 3 AE occurred in 72.7% of pts; the common events (>5%) being thrombocytopenia (50.0%), diarrhea (13.6%), and anorexia (13.6%). No interstitial lung disease/pneumonitis was observed. The ORR was 28.6%, the disease control rate (DCR) was 71.4%, and median progression-free survival (mPFS) was 3.2 mo (95% CI 1.6, 6.1) in the pIb. In 27 pts with HER2 mutations across all cohorts, the ORR was 42.3%, the DCR was 76.9%, and mPFS was 4.3 mo (95% CI 2.7, 6.7). Additionally, in 13 pts with HER2-mutant NSCLC including those who had developed resistance to trastuzumab deruxtecan, the ORR was 53.8%, the DCR was 84.6%, and mPFS was 6.1 mo (95% CI 2.9, 6.3). **Conclusions:** The RD of this study treatment is mobocertinib 80 mg plus T-DM1 3.6 mg. Combination therapy of HER2 TKI and HER2 ADC demonstrated feasibility and potential efficacy for HER2-mutant solid tumors. Clinical trial information: 2051220070. Research Sponsor: Takeda pharmaceuticals.

The anti-CD20 antibody-drug conjugates TRS005 in relapse/refractory CD20-positive B-cell non-Hodgkin lymphoma: A multicenter, open-label, single-arm, phase I study.

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Background: TRS005 is a novel anti-CD20 antibody-drug conjugate targeting CD20 positive tumor cells to deliver MMAE into the cells via receptor-mediated endocytosis. The aim of this study was to evaluate the safety, pharmacokinetics, and anti-tumor activity of TRS005 in relapse/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). **Methods:** This first-in-human, single arm, multicenter, phase I, dose-escalation and expansion study conducted at 28 hospitals in China. The eligible patient had histologically confirmed CD20 positive B-cell lymphoma and had failed ≥2 prior lines of standard treatment. The dose-escalation phase involved 6 dose cohorts (from 0.1mg/kg to 2.1mg/kg) following a 3+3 design. Patients received TRS005 intravenously on day 1 of each 21-day cycle for 6 cycles. The dose cohort in which partial response (PR) or complete response (CR) was observed entered the dose-expansion phase. The safety, tolerability and efficacy of TRS005 were evaluated every two cycles. The primary endpoints were safety and pharmacokinetics. Secondary endpoints were objective response rate (ORR), disease control rate (DCR) and progression free survival (PFS) assisted by investigators. **Results:** From Aug 24th,2020 to Oct 23th,2023, 130 R/R B-cell NHL patients received treatment. The dose limiting toxicity was observed in the first patient in the 2.1mg/kg dose group during the dose-escalation phase. 70 patients had R/R diffuse large B cell lymphoma (DLBCL). Of the 70 R/R DLBCL patients, the median age was 59 (25-83) years, 82.9% of patients were in stage III-IV and 98.6% of patients received at least 2 lines of treatment (except one patient who only received 1 line of previous treatment). Overall, 88.6% of patients experienced all grades adverse events (AEs). Treatment-emergent adverse events (TEAEs) of ≥grade 3 occurred in 65.7% of patients, hematologic TEAEs were the most common. Two patients withdraw the treatment due to TEAEs and no TEAE related death were observed. At the data cutoff date of Nov 17th, 2023, the median treatment duration was 4 (1-27) cycles. 58 patients were evaluated for efficacy and confirmed ORR was 46.6%, with a DCR of 75.9%. The highest ORR was seen in 1.8mg/kg dose cohort, with an ORR and DCR of 56.7% and 86.7%, respectively. The PFS was 5.6 (95% CI: 4.2-17.4) months and 12-month PFS was 35.1%. **Conclusions:** TRS005 is well-tolerated and exhibits encouraging anti-tumor efficacy in the treatment of R/R DLBCL. Clinical trial information: NCT05395533. Research Sponsor: Development Center for Medical Science & Technclogy National Health commission of the People's Republic of china; 2014ZX09304313006; Development Center for Medical Science & Technclogy National Health commission of the People's Republic of china; 2019ZX09732-001-016.

Baseline characteristics.

Baseline Characteristics	R/R DLBCL (N=70)
Age (median)	59
Range	25-83
≥60	35 (50.0%)
Sex	
Male	35(50.0%)
Female	35(50.0%)
EOCG	
0	23(32.9%)
1	47(67.1%)
Stage	
I	2 (2.9%)
II	10 (14.3%)
III	19 (27.1%)
IV	39(55.7%)
Previous lines of treatment	
1	1 (1.4%)
2	41 (58.6%)
> 2	28 (40.0%)
LDH	
< 250	24 (34.3%)
≥250	46 (65.7%)
Diameter of target lesion	
Longest diameter < 75mm	61 (87.1%)
Longest diameter≥75mm	9 (12.9%)

Phase 1 study (NCT04931823) of CPO100 (albumin bound docetaxel) in patients with advanced solid tumors.

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Background: Docetaxel (Taxotere) is a widely used taxane; the use of docetaxel may have been limited by its original formulation, which contributes to multiple severe adverse effects. Polysorbate-80 in the current formulation has been implicated in several systemic reactions (e.g., hypersensitivity, nonallergic anaphylaxis, rash) and injection- and infusion-site adverse events (pain, erythema, thrombophlebitis). By eliminating polysorbate-80, the use of steroids at the time of infusion may also be eliminated. To improve the safety profile and enhance tumor-targeted drug exposure, CPO-100, an albumin-bound docetaxel formulation without polysorbate-80 was developed. This Phase 1 dose escalation study assessed the maximum tolerated dose (MTD), pharmacokinetics (PK), safety, and efficacy of CPO-100 administered without steroid pretreatment in a weekly schedule (3 weekly doses/ 1-week rest). **Methods:** Patients (pts) were enrolled in a modified 3 x 3 design starting at doses of 6 mg/m^2 and ranging up to 50 mg/m^2 on the weekly schedule (WS). At each visit, safety was assessed. PK data was collected on days 1, 8 and 15 of cycle 1. Efficacy was assessed every 2 cycles (8 weeks) until progression or treatment discontinuation. The MTD was determined with and without the use of granulocyte colony stimulating factor (GCSF) in cycle 1. **Results:** Thirty-four pts with various solid tumors were enrolled. Prior regimens: 2 to 17 (median 4). Prior exposure to taxanes: 18 pts (53%). The most common adverse events (AEs) were fatigue (N=19), nausea (N=18) and anemia (N=15). Grade 3/4 neutropenia (as a term or laboratory finding) for doses above 35 mg/m^2 was 60%. Serious AEs (SAEs) occurred in 13 pts; SAEs regardless of relationship in more than 1 pt were pleural effusion, hypotension and pneumonia. For all evaluable pts, the overall response rate was 2/30 (7%) with two PRs observed in pts with breast and nasopharyngeal cancers. The disease control rate (DCR) was 60%. Among the 18 pts with SD or better, the median (K-M estimate) duration was approximately 10.9 months (mos; range 1.7 to 11.1 mos). A linear relationship between plasma concentrations of total docetaxel and dose was observed. The half-life of total docetaxel ranged from 13 to 39 hrs. Slight accumulation was observed on WS, and steady state was achieved after the second dose. **Conclusions:** Preliminary data with CPO-100 administered on a weekly basis shows potential efficacy in heavily pretreated pts, especially with prior taxane exposure, with a tolerable WS. With a similar dose, CPO-100 demonstrated a better safety profile than docetaxel. The most prominent concern is manageable neutropenia, especially on a dose above 35 mg/m^2, where GCSF supplementation was needed. Further development is warranted, including combinations with agents such as PD-1/PD-L1 inhibitors that might benefit from absence of steroid prophylaxis. Clinical trial information: NCT04931823. Research Sponsor: Conjupro Biotherapeutics.

A phase 1/2 study of LM-302, an anti-claudin 18.2 (CLDN18.2) antibody-drug conjugate in patients with advanced gastric/gastroesophageal junction cancer.

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Background: LM-302 is a novel and potent MMAE antibody-drug conjugate (ADC) targeting CLDN18.2, which is highly expressed in gastric/gastroesophageal junction (GEJ), pancreatic, and biliary tract cancers. Preclinical studies of LM-302 have demonstrated compelling anti-tumor activity in multiple CLDN18.2-positive cell-lines and xenograft models. **Methods:** This phase 1/2 study included dose escalation phase and dose expansion phase. In the dose escalation phase, eligible patients received LM-302 once every three weeks (0.2-2.8 mg/kg Q3W), and once every two weeks (1.8-2.0 mg/kg Q2W) to evaluate the safety, tolerability, and pharmacokinetics. In the dose expansion phase, CLDN18.2-positive patients received LM-302 at recommended phase 2 doses of 2.4 mg/kg Q3W or 1.8 mg/kg Q2W to evaluate the efficacy and safety. The primary endpoints included dose-limiting toxicity (DLT) and adverse events (AEs) in phase 1, and objective response rate (ORR) in phase 2. Here we report the results from safety analysis of LM-302 and efficacy data in gastric/GEJ cancer. **Results:** As of September 23, 2023, 135 patients received LM-302 treatment and the median prior lines of systemic therapy were 2 (range 1-4). In phase 1 and 2, most common TRAEs were white blood cell decreased (51.9%), neutrophil count decreased (51.1%), anaemia (38.5%), vomiting (36.3%), and nausea (34.1%). The most frequent grade ≥3 TRAEs were neutrophil count decreased (22.2%) and white blood cell decreased (17.8%). In phase 2 dose expansion, 52 CLDN18.2-positive (TC ≥ 50%, IHC ≥ 2+) gastric/GEJ cancer patients were enrolled (4 pts at 2.4mg/kg Q3W, 48 pts at 1.8mg/kg Q2W). 1.8mg/kg Q2W was selected for further evaluation based on PK, safety, and efficacy data analysis. Of 36 evaluable gastric/GEJ cancer patients who received at least two or more prior therapies, 11 partial response (PR) and 16 stable disease (SD) were observed. The ORR was 30.6% (11/36), and DCR was 75.0% (27/36). The median PFS was 7.16 months (95% CI 2.72-NA). The median overall survival (OS) was not reached, with an OS rate of 95.0% at the 6-month (as of November 15, 2023). **Conclusions:** LM-302 was well-tolerated with a manageable safety profile and demonstrated promising anti-tumor activity in CLDN18.2-positive patients with third-line and beyond gastric/GEJ cancer. The results support further investigation of LM-302 as a new therapeutic approach to treat CLDN18.2-positive gastric/GEJ cancer. Clinical trial information: NCT05161390. Research Sponsor: LaNova Medicines Limited.

Pooled safety analysis of sacituzumab govitecan (SG) in multiple solid tumor types.

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Background: SG is an antibody-drug conjugate targeted to Trop-2 that received approval for treatment of previously treated metastatic triple negative breast cancer (mTNBC) and HR+/HER2- mBC in multiple countries and accelerated approval for previously treated metastatic urothelial cancer (mUC) in the US. In multiple clinical trials, SG has demonstrated significantly improved efficacy compared to standard of care therapies and a consistent, manageable safety profile with limited treatment discontinuations from adverse events (AEs). We present an analysis of pooled safety data from patients (pts) treated with SG in clinical trials, including differences by *UGT1A1* polymorphisms. **Methods:** Safety data for pts treated with SG (10 mg/kg, days 1 and 8 every 21-day cycle) were pooled from 4 clinical trials of multiple solid tumors, including mTNBC, HR+/HER2- mBC, and mUC: ASCENT (NCT02574455), TROPiCS-02 (NCT03901339), TROPHY-U-01 (NCT03547973), and IMMU-132-01 (NCT01631552). Treatment-emergent AEs (TEAEs) were defined as any AE that started on or after first dose date until ≤ 30 days after last dose date. **Results:** The pooled analysis included 1063 pts; > 99% experienced any-grade TEAEs, and 76% experienced grade ≥ 3 TEAEs (Table). The most common any-grade TEAEs were nausea (64%), diarrhea (64%), neutropenia (61%), and fatigue (51%). The most common grade ≥ 3 TEAEs were neutropenia (46%), anemia (12%), leukopenia (11%), and diarrhea (11%). Febrile neutropenia occurred in 6% of pts (both any-grade and grade ≥ 3). TEAEs led to SG dose reduction in 31% and SG discontinuation in 7% of pts. The most common TEAEs that led to discontinuation were neutropenia, diarrhea, pneumonia, and fatigue (1% each). In pts with available *UGT1A1* genotypes, *28/*28 was associated with a higher rate of grade ≥ 3 TEAEs and TEAEs leading to dose reduction and SG interruption compared to *1/*1 and *1/*28 (Table). **Conclusions:** The results of the pooled safety analysis of pts treated with SG were consistent with previous clinical trials, with neutropenia remaining the most common grade ≥ 3 TEAE. Neutropenia and diarrhea were generally manageable, and the rate of TEAEs leading to discontinuation was low. The *28/*28 *UGT1A1* genotype was associated with higher rates of grade ≥ 3 TEAEs, as previously observed. This is the largest SG safety analysis published to date, providing further support for SG as a treatment with a consistent and manageable safety profile. Clinical trial information: NCT02574455, NCT03901339, NCT03547973, NCT01631552. Research Sponsor: Gilead Sciences, Inc.

		UGT1A1 genotype[a]		
Safety, n (%)	**All pts (N = 1063)**	***1/*1 (n = 416)**	***1/*28 (n = 420)**	***28/*28 (n = 112)**
All TEAEs	1060 (> 99)	415 (> 99)	418 (> 99)	112 (100)
Grade ≥ 3	808 (76)	299 (72)	320 (76)	101 (90)
Led to dose reduction[b]	205/661 (31)	69/268 (26)	89/270 (33)	30/76 (39)
Led to interruption	615 (58)	243 (58)	230 (55)	78 (70)
Led to discontinuation	78 (7)	27 (6)	27 (6)	8 (7)

[a]Other genotypes, n = 13; genotype missing/not done, n = 102. [b]AEs leading to dose reduction not collected in IMMU-132-01; these pts were excluded from total.

Dose optimization and exposure-response analyses to support optimal dose of ABBV-400, a novel C-met–targeting antibody drug conjugate, in patients with metastatic colorectal cancer (mCRC).

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Background: ABBV-400 is an antibody drug conjugate (ADC) consisting of a c-Met targeting antibody conjugated to a potent inhibitor of topoisomerase 1 (Top1) payload. ABBV-400 has shown encouraging activity and demonstrated tolerability of dosages up to 3.0 mg/kg Q3W as monotherapy in patients with advanced solid tumors in an ongoing phase 1 study (1). Dosage optimization is a critical aspect of oncology drug development and FDA Project Optimus has focused on reformulating the dosage selection paradigm for oncology products. The phase 1 study included a dose optimization phase in mCRC patients in which 3 doses were evaluated (1.6, 2.4 and 3.0 mg/kg Q3W) to determine the optimal dose for further development. Herein, exposure-response analyses are reported to determine optimal monotherapy dose in mCRC patients. **Methods:** Data across a range of doses (1.6 – 6.0 mg/kg Q3W) from the phase 1 study (NCT05029882) were used. Population pharmacokinetics (PK) and exposure-response (E-R) analyses were conducted to characterize ABBV-400 conjugate and unconjugated payload PK and the relationship between exposures and efficacy (objective response rate [ORR]) and safety (Grade (Gr) $\geq$ 3 neutropenia, anemia and thrombocytopenia) endpoints. Relative dose intensity (RDI) analysis was performed. **Results:** ABBV-400 conjugate and payload PK were adequately described by a combined multi-analyte population PK model with first order kinetics (n=204). ABBV-400 conjugate average concentration was a better predictor of response and showed that higher exposure correlated with higher probability of response (n=122 CRC, ORR, $p < 0.05$) and safety events (n=204, Gr $\geq$ 3 neutropenia, anemia and thrombocytopenia, $p < 0.001$). Dose intensity analyses showed greater number of dose reductions for 3 mg/kg Q3W with effective (actual) dose received of 2.6 mg/kg Q3W in mCRC patients. E-R analyses for safety and efficacy and dose intensity analyses in mCRC 3L+ patients indicate that both 2.4 and 3.0 mg/kg doses provided meaningful efficacy (ORR); while the 3.0 mg/kg dose may provide higher response rates, the 2.4 mg/kg Q3W dosing regimen provides an optimal balance of safety and efficacy compared to 3.0 mg/kg Q3W. **Conclusions:** Population PK, E-R for efficacy and safety and RDI analyses and totality of clinical data supported the selection of 2.4 mg/kg Q3W as optimal ABBV-400 monotherapy dose for further study in mCRC patients. 1. Sharma M, et al. ASCO 2023. Abstract 3015. Clinical trial information: NCT05029882. Research Sponsor: AbbVie Inc.

Evaluation of the safety, pharmacokinetics, and efficacy of JSKN003 in patients with advanced solid tumors: A phase I/II clinical study.

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Background: JSKN003 is a bispecific HER2-directed antibody-drug conjugate (ADC) conjugated to a topoisomerase I inhibitor via a dibenzocyclooctyne tetrapeptide linker on the glycan of a humanized bispecific antibody. Pre-clinical studies showed that JSKN003 had a good serum stability, that may lead to a broader therapeutic window. **Methods:** JSKN003-102 (NCT05744427) is a phase I (dose escalation and dose expansion) and phase II (cohort expansion) study in Chinese patients (pts) with advanced solid tumors. Pts (ECOG PS 0-1) with HER2-expressing (IHC $\geq$ 1+) or HER2-mutant cancers who failed prior systemic therapies were recruited and received JSKN003 monotherapy intravenously Q3W. The objectives were safety, MTD or RP2D, pharmacokinetics, and preliminary antitumor activity. Here the results from phase I were reported. **Results:** As of 5th Jan 2024, 46 pts (25 breast cancers, 11 gastric cancers, 8 colorectal cancers, 1 lung cancer, and 1 ovarian cancer) were enrolled and received JSKN003 across 6 dose levels, including 2.1 (n=1), 4.2 (n=10), 5.2 (n=14), 6.3 (n=15), 7.3 (n=3), and 8.4 mg/kg (n=3), Q3W, in phase I period. Among the 46 pts, 18 were IHC 3+, 21 were IHC 2+, and 7 were IHC 1+. Most pts (73.9%) received $\geq$ 3 prior lines of therapy, including 60.9% and 45.6% of pts received prior anti-HER2 and anti-HER2 ADC therapy, respectively. The median duration of treatment was 13.1 (range, 2.1 - 42.4) weeks, and 37 pts (80.4%) remained on treatment. Treatment-related adverse events (TRAEs) occurred in 44 pts (95.7%), and the common, mostly grade 1 and 2, were diarrhea (37.0%) and nausea (32.6%). Only 6 pts (13.0%) experienced grade $\geq$3 TRAEs , and the common were lymphopenia (4.3%) and neutropenia(4.3%). 1 pt (2.2%) had treatment related SAE (nausea, grade 3). No pts experienced DLT or interstitial lung disease, and no TRAE led to death or discontinuation. Following a single dose, exposures (C_{max} and AUC) of JSKN003 increased proportionally over a dose range of 4.2 mg/kg to 6.3mg/kg. $T_{1/2}$ of JSKN003 is approximately 3-5 days. No significant accumulation was observed after 4 cycles treatment. The exposure of released payload was very low, demonstrating the stability of the JSKN003 in circulation. 37 pts had at least one post-baseline tumor assessment. The ORR and DCR was 51.4% (95%CI: 34.4, 68.1) and 91.9% (95%CI: 78.1, 98.3), respectively. The ORR in pts with HER2 IHC 1+, 2+ and 3+ was 20.0% (95% CI: 0.5, 71.6), 33.3% (95% CI: 11.8, 61.6), and 76.5% (95% CI: 50.1, 93.2), respectively. For pts who received prior anti-HER2 ADC, the ORR was 57.9% (95% CI: 33.5, 79.7). For HER2 positive breast cancer and gastric cancer, the ORR was 66.7% (95% CI: 38.4, 88.2) in 15 pts and 100% (95% CI: 39.8, 100) in 4 pts, respectively. **Conclusions:** MTD of JSKN003 was not reached yet. And safety of JSKN003 was extremely excellent with encouraging preliminary antitumor activity in heavily pretreated pts with advanced solid tumors. Clinical trial information: NCT05744427. Research Sponsor: Alphamab.

An open-label, multicenter, phase I study of ATG-022 in patients with advanced/metastatic solid tumors (CLINCH).

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Background: Claudin 18.2 (CLDN 18.2) is a tumor associated antigen broadly expressed in gastric, pancreatic, and other solid tumors. ATG-022 is an antibody drug conjugate (ADC), consisting of a humanized monoclonal antibody that binds to CLDN 18.2 with high affinity of sub-nM grade and a conjugated linker-payload vc-MMAE. ATG-022 has displayed promising tumor growth inhibition activity both *in vitro* and *in vivo.* **Methods:** CLINCH is a phase I, multicenter, open-label, dose-finding study (NCT05718895) of ATG-022 in patients with advanced solid tumours. The study design includes a dose escalation phase, enrolling subjects with advanced/metastatic solid tumors, regardless of CLDN 18.2 expression, and a dose expansion phase which will enroll select advanced/metastatic solid tumors with CLDN 18.2-positive expression at the defined maximum tolerated dose and/or recommended Phase 2 dose to further evaluate the safety, tolerability, and efficacy of ATG-022. Other endpoints include pharmacokinetics (PK) and exploratory biomarkers of drug activity. In the dose escalation phase, ATG-022 is administered intravenously every 3 weeks (Q3W) at the starting dose of 0.3 mg/kg, followed by 0.9, 1.8, 2.4, 3.0, and 3.6 mg/kg Q3W using a modified 3+3 dose-escalation design. Efficacy assessments are evaluated per RECIST1.1 criteria. **Results:** As of 9 Oct 2023, 10 patients (pts) with advanced solid tumors have been enrolled to receive ATG-022 at a dose from 0.3 to 2.4 mg/kg. Median age was 59 years. Baseline ECOG scores were 0 (0 pts) and 1 (10 pts); 8 pts had stage IV disease. Three pts had received more than 3 prior lines of systemic therapy. Eight pts (80%) had $\geq$ 1 TRAEs; 1 pt (10%) had $\geq$ 1 Serious TRAEs; 3 (30%) pts had grade $\geq$ 3 TRAEs. The most common grade $\geq$ 3 TRAEs included nausea (30%), vomiting (30%) and decreased appetite (30%). No DLT was reported among the current dose levels. Among 7 pts with gastric cancer, 3 pts are confirmed to be CLDN 18.2 positive. One of these pts has maintained stable disease with tumor shrinkage for more than 6 months (treatment ongoing) at a dose of 0.9 mg/kg, demonstrating tolerability of ATG-022. One PR was observed in a gastric cancer pt (CLDN 18.2 expression to be determined) at the dosage of 1.8 mg/kg. It was noteworthy that a CR was seen in a gastric cancer pt dosed at 2.4 mg/kg, with negative CLDN 18.2 expression. PK analysis of ATG-022 from 0.3 to 2.4 mg/kg revealed that the exposure of total antibody, MMAE and ADC drug is increased as dose increased. No accumulation of ATG-022 was observed. **Conclusions:** ATG-022 demonstrated preliminary anti-tumor activity, tolerability, safety, as well as comparable PK properties at current dose levels. The high affinity of sub-nM grade of ATG-022 in pts with low CLDN 18.2 expression needs further investigation. The dose escalation is ongoing and updated data will be presented. Clinical trial information: NCT05718895. Research Sponsor: Antengene.

YL202/BNT326, a HER3-targeted ADC, in patients with locally advanced or metastatic non-small cell lung cancer and breast cancer: Preliminary results from a first-in-human phase I trial.

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Background: YL202/BNT326 is a novel ADC consisting of an anti-HER3 IgG1 monoclonal antibody linked to 8 molecules of YL0010014, a novel topoisomerase I inhibitor, via a tripeptide linker. We report preliminary safety and efficacy results from a phase I trial of YL202/BNT326. **Methods:** This multinational trial is recruiting patients (pts) with locally advanced/metastatic non-small cell lung cancer (NSCLC) with an EGFR-activating mutation who were previously treated with 3rd generation TKI and platinum-based chemotherapy, and pts with unresectable, locally advanced or metastatic, HR-positive and HER2-negative (IHC 0,1+,2+/ISH-) breast cancer (BC) who were previously treated with CDK4/6 inhibitor and at least one line of chemotherapy. YL202/BNT326 was given at 6 dose levels (DLs, Q3W, iv) in a BOIN dose escalation (D-ESC) scheme, followed by cohort backfill(BF) at selected doses. Primary endpoints are safety and tolerability (dose-limiting toxicities [DLTs] and adverse events [AEs]). Secondary endpoints include pharmacokinetics [PK] and efficacy per RECIST v1.1(ORR, DCR, BOR). **Results:** At data cutoff (4 Feb 2024), 52 pts were enrolled in D-ESC and BF (39 NSCLC, 13 BC). One DLT (grade 3 febrile neutropenia) occurred during D-ESC at the highest dose. Most common TRAEs (>20%, all grade / ≥ G3) were anemia (71%/20%), white blood cell count decreased (67%/31%), neutrophil count decreased (63%/29%), nausea (52%/0%), decreased appetite (42%/4%), lymphocyte count decreased (37%/23%), platelet count decreased (37%/10%), vomiting (37%/0%), dry mouth (25%/0%), fatigue (25%/0%), stomatitis (23%/2%), alopecia (21%/0%). Interstitial pneumonia occurred in 1 (2%) pt after COVID-19 infection. PK exposure was increased through dose escalation, with low systemic exposure of payload and no accumulation of YL202/BTN326 upon repeated administration. In 46 pts with at least 1 tumor assessment were evaluable for efficacy. Of the non-evaluable pts, 5 are on treatment pending first tumor assessment and 1 discontinued treatment prior to first assessment. In DL3 to DL5 dose range, ORR was 41.0% (95%CI, 25.6, 57.9), DCR was 94.9% (95%CI, 82.7, 99.4) across all tumor types; and the ORR in BC pts was 54.5% (95%CI, 23.4, 83.3), DCR was 100% (95%CI, 71.5, 100.0). **Conclusions:** YL202/BNT326 demonstrated encouraging efficacy in heavily pretreated locally advanced/ metastatic NSCLC and BC. The safety profile showed adequate safety and tolerability. Clinical trial information: NCT05653752. Research Sponsor: None.

Analyzed in pts with post-baseline assessment.

	All (N=46)
Median prior treatment line (range)	4 (2-8)
CR/PR/SD/PD	1/16/26/3
ORR*,% (95%CI)	37.0 (23.2, 52.5)
DCR,% (95%CI)	93.5 (82.1, 98.6)
Median DOR, month (95% CI)	8.4 (1.6, -)
Median PFS, month (95% CI)	-(9.7, -)
6-month PFS rate% (95% CI)	61.6 (38.0, 78.5)

*Including unconfirmed response.

The design, preclinical study and phase I dose escalation plan of a HER2 targeted immunoliposome (HF-K1) for HER2 low solid tumor treatment.

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Background: Doxorubicin liposome formulations are being used extensively in the clinic in anthracycline chemotherapy with reduced cardiotoxicity. However, they did not improve clinical outcome because the cancer cell uptake of PEG-coated liposomes is poor. So, the concept of coating antibodies on the liposome surface was initiated and they were named immunoliposomes. There have been numerous studies conducted world-wide for the development of immunoliposomes but none have progressed to late-stage development. Our work draws on the experiences of these prior studies with a new perspective. Since the mechanism of immunoliposomes is similar to those of ADCs, we sought to compare immunoliposomes with ADCs containing the same cancer cell binding domain, for target cell binding capability, binding affinity as well as in vivo distribution, tumor tissue accumulation, and anti-tumor activities. The lessons learned from the success of many ADC products may be applicable to the development of immunoliposomes. **Methods:** The antibody to liposome ratio (ALR) and the drug to lipid ratio (DLR) of the immunoliposomes were selected by in vitro and in vivo anti-cancer activity screening. Cell lines with different HER2 expression levels were used to study immunoliposome binding, cell uptake, drug delivery and cytotoxicity. PK, drug distribution, efficacy and toxicities studies were conducted in respective CDX and PDX mice and non-rodent models. Based on these studies, a phase I dose escalation study plan was designed and the study is now ongoing. **Results:** HF-K1 was designed to have an average of 10 anti-HER2 Fab on each liposome surface and approximately 2300 doxorubicin molecules inside. The equivalent drug to antibody ratio (DAR) is 230. HF-K1 can bind to cancer cells with different levels of HER2 expression with similar kinetics and induces cells death at IC50s of 0.35-6.46 μg/ml Fab concentration. It has a long circulation behavior and enhanced permeability and retention (EPR) in tumor tissues. The clearance T1/2 of HF-K1 in mice and monkey is 12.78 h and 47.12 h, respectively. Evaluation of HF-K1 activity in vivo showed significant tumor growth inhibition $>$95% at the equivalent antibody dose of 3.6 mg/kg in various mouse tumor models including HER2 low and HER2 very low (HER2-). Similar activities were shown by ADCs including T-DM1 and DS-8201a at about 10 mg/kg. **Conclusions:** The encouraging preclinical data supported a clinical trial starting with dose escalation at equivalent antibody doses of 0.72 mg/m2, 2.16 mg/m2, 5.4 mg/m2, 10.8 mg/m2, 16.2 mg/m2, and 21.6 mg/m2. The study is ongoing to determine the safety, tolerability, PK, and preliminary antitumor efficacy in participants with HER2 positive or HER2 low expression advanced solid tumors (NCT 05861895). Clinical trial information: NCT05861895. Research Sponsor: Highfeild Biopharmaceutical Corp.

Safety and efficacy of IBI343 (anti-claudin18.2 antibody-drug conjugate) in patients with advanced pancreatic ductal adenocarcinoma or biliary tract cancer: Preliminary results from a phase 1 study.

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Background: Prognosis for advanced pancreatic ductal adenocarcinoma (PDAC) and biliary tract cancer (BTC) remains poor, with limited treatment options available. Expression of claudin18.2 (CLDN18.2) has emerged as a potential target for anti-cancer treatment. Herein, we report preliminary safety and efficacy results of IBI343, an antibody-drug conjugate (ADC) consisting of anti-CLDN18.2 monoclonal antibody conjugated to exatecan (topoisomerase I inhibitor), in patients (pts) with advanced PDAC or BTC in a phase 1 study. **Methods:** Eligible pts who failed or were intolerant to standard treatment were enrolled. IBI343 were intravenously administered at 6 mg/kg or 8 mg/kg Q3W. In dose escalation, pts were enrolled regardless of CLDN18.2 expression. In dose expansion, pts were required to have CLDN18.2 expression ≥40% (1+/2+/3+ staining intensity by immunohistochemistry). Primary endpoint was safety. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression free survival (PFS) assessed by investigator per RECIST v1.1. **Results:** As of December 19, 2023, 35 pts (1 pt in dose escalation and 34 pts in dose expansion) were enrolled from China and Australia (males: 57.1%, median age: 58.0 years, ECOG PS 1: 71.4%, stage IV: 91.4%, median lines of prior treatment: 2) including 28 PDAC pts and 7 BTC pts. Pts received IBI343 at 6 mg/kg (n=17) or 8 mg/kg (n=18). Median duration of treatment was 7.0 weeks (range: 3.0-23.6) with 23 (65.7%) pts still on treatment. In all pts, treatment-related adverse events (TRAEs) occurred in 28 (80.0%) pts including grade ≥3 TRAEs in 9 (25.7%) pts. Common TRAEs (≥20%) were anemia (42.9%), neutrophil count decreased (28.6%), nausea (25.7%), vomiting (25.7%) and white blood cell count decreased (22.9%). Serious TRAEs occurred in 4 (11.4%) pts. TRAEs leading to dose interruption and treatment discontinuation occurred in 7 (20.0%) pts and 1 (2.9%) pt respectively. No TRAE led to death. Safety profiles of IBI343 in PDAC and BTC were comparable with the whole study cohort and no new safety signal was observed. As of January 15, 2024, 25 pts at 6 mg/kg and 8 mg/kg were efficacy evaluable. Partial response (PR) was observed in 7 pts (5 PDAC and 2 BTC). The ORR was 28.0% (95%CI: 12.1-49.4) and DCR was 80.0% (95%CI: 59.3-93.2). In evaluable pts at 6 mg/kg with CLDN18.2 expression ≥60% (1+/2+/3+, n=13), 5 pts had PR with ORR of 38.5% (95%CI: 13.9-68.4) and DCR of 84.6% (95%CI: 54.6-98.1). Among 10 PDAC pts in this subgroup, ORR was 40% (95%CI: 12.2-73.8). DoR and PFS data were immature. More updated data on safety and efficacy will be presented at the meeting. **Conclusions:** IBI343 was well tolerated with favorable safety profiles and encouraging efficacy in CLDN18.2-positive PDAC and BTC. Clinical trial information: NCT05458219. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Safety and efficacy of JSKN003 in patients with advanced/metastatic solid tumors: A first-in-human, dose-escalation, multicenter, open-label, phase I study.

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Background: JSKN003 is a biparatopic HER2-directed ADC conjugated to a topoisomerase I inhibitor with an average DAR 4. Preclinical studies showed that JSKN003 had a good serum stability and strong anti-tumor activity. Hence JSKN003 could be effective in HER2 expressing tumors with a potentially broader therapeutic window. **Methods:** JSKN003-101 is a first-in-human, dose-escalation and -expansion study in Australian pts with advanced solid tumors. Pts (ECOG 0-1) with histologically documented HER2-expressing (HER2-positive defined as IHC 2+ or 2+/ISH+, HER2 low defined as IHC 1+ pr 2+/ISH-) or HER2-mutation by local testing who failed prior systemic therapies were recruited and received JSKN003 monotherapy intravenously Q3W. The objectives were safety, tolerability, MTD or RP2D, PK, and preliminary antitumor activity. Here the results from dose-escalation part were reported. **Results:** As of 15 Dec 2023, 32 pts were enrolled and received JSKN003 across 7 dose levels (1.0-8.4 mg/kg, Q3W). Among the 32 pts, 9 were IHC 1+, 16 were IHC 2+, and 7 were IHC 3+. Most pts (22/32, 68.8%) received $\geq$ 3 prior lines of therapy. The median duration of treatment was 15.8 (range, 6-54) weeks, and 19 pts (59.4%) remain on treatment. TRAEs occurred in 27 pts (84.4%) and 2 pts (6.3%) in 4.2mg/kg and 7.3mg/kg experienced grade 3 TRAE (anemia and fatigue); the most common TRAEs were diarrhea (62.5%) and nausea (50.0%), which were all grade 1-2. Only 1 pt experienced ILD/pneumonia (7.3mg/kg, grade 2). To date, no DLT events were found yet, and no TRAE led to death or treatment discontinuation. MTD has not been reached in 8.4 mg/kg. Following a single dose, exposures (C_{max} and AUC) of JSKN003 and released TOP1i increased proportionally over a dose range of 4.2 mg/kg to 8.4 mg/kg. $T_{1/2}$ of JSKN003 is approximately 5-6 days for 6.3 mg/kg and higher doses and increases with dose escalation. Accumulation of JSKN003 was minimal within the range of 1.1-1.5. The exposure of released payload was significantly lower than JSKN003 ADC, demonstrating the stability of the JSKN003 in circulation. All pts had at least one post-baseline tumor assessment. 16 pts achieved PR per RECIST 1.1 by investigator. Thus, ORR and DCR was 50.0% (95%CI: 31.9%, 68.1%) and 90.6% (95%CI: 75.0%, 98.0%), respectively. The ORR in pts with IHC 1+, 2+ and 3+ was 55.6% (5/9), 37.5% (6/16), and 71.4% (5/7), respectively. As for the efficacy of the HER2-positive and HER2-low breast cancer, the ORR was 80% (4/5) and 40.0% (4/10), respectively. **Conclusions:** JSKN003 was well tolerated with encouraging preliminary antitumor activity in heavily pretreated pts with advanced/metastatic solid tumors, especially in pts with HER2 expressed tumors. As of the cut-off date, no DLT was observed, MTD has not been reached yet. Clinical trial information: NCT05494918. Research Sponsor: Alphamab Oncology.

Comparison of primary versus metastatic tumor tissue sources when designing panels for whole genome–based tumor-informed ctDNA assays in clear cell renal cell carcinoma.

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Background: Due to low shedding and low tumor-mutation burden, metastatic clear cell renal cell carcinoma (ccRCC) is poorly modeled by current cell-free circulating tumor DNA (ctDNA) assays. Second generation tumor-informed ctDNA approaches may demonstrate improved sensitivity in ccRCC, where somatic variants identified by whole-genome sequencing (WGS) of tumor tissue are tracked in probe panels to monitor molecular residual disease (MRD) in patient plasma. However, intertumoral genomic heterogeneity of input tissue may hinder optimal panel design. Here we evaluated the concordance of ctDNA results using panels designed from primary nephrectomy or metastatic tumors in ccRCC. **Methods:** In five patients with oligo-metastatic ccRCC (≤5 lesions of metastatic disease; median of 1, range 1-4), 13 primary tumor, 24 metastatic lesion subsites and matched buffy coat samples were collected. Baseline plasma was collected prior to radiotherapy. Samples were tested with Myriad Genetics High-Definition MRD assay. Briefly, tumor and normal DNA were whole-genome sequenced (median coverage 30x). A sub-panel with up to 1000 somatic variants was designed for each lesion subsite; variants could be common across sub-panels. Sites were enriched using hybridization capture from patient plasma-derived cfDNA and sequenced to high depth. A statistical model of variant allele counts was used to assess the presence or absence of ctDNA (MRD status) and infer quantitative tumor fraction. **Results:** Median time from nephrectomy or most recent metastasis sample collection to baseline plasma collection was 146 months (71-169) and 32 months (7-48), respectively. Median panel probe count per patient was 4,311 (3,400-5,000) and per tumor sample was 1,545 (102-2,158). Confident calls were emitted for tumor fractions ranging from 0.0004% to 0.027%. Baseline MRD status was fully concordant across sub-panels derived from primary tumor lesion subsites and metastases in three of five patients (3/5; 60%). Of the patients with discordant calls, a single metastasis-derived sub-panel (comprising 20%-25% of metastatic sub-panels) called MRD discordantly in each. Of the three patients MRD positive at baseline, only one was alive at last follow up. All patients MRD negative at baseline are still alive. **Conclusions:** A tumor-informed, WGS MRD assay for ccRCC showed comparable performance between probe capture panels designed from primary tumor and metastatic lesion subsites despite differences in anatomical location and time from plasma collection. This result suggests that intertumoral genomic heterogeneity may not be consequential in MRD assays that leverage large panels to detect ctDNA variants, obviating the need for repeat biopsies of metastatic sites. Work is underway to validate this MRD assay in a larger cohort of patients with ccRCC before and after treatment. Research Sponsor: Myriad Genetics, Inc.

Immune-phenotyping of peripheral blood mononuclear cells from patients with early triple-negative breast cancer: Identification of a systemic immunosuppressive CD3+ CD4+ CD39+ Treg subset.

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Background: Cells of the immune system and malignant cells interact in the tumor microenvironment, influencing response to treatment and survival. The current study was undertaken to assess the prevalence of these immune cells systemically in patients with early triple-negative breast cancer (TNBC). **Methods:** Multi-parameter flow cytometry was used to examine the percentages and phenotypes of cytotoxic T cells, natural killer (NK) cells, monocyte subsets, and regulatory T cell (Treg) subsets in the peripheral blood of 19 TNBC patients (pts) and 10 controls (cnt). Multicolor flow cytometry was carried out using DURAClone IM phenotyping (basic and Treg tubes) with a CytoFLEX Flow Cytometer (Beckman Coulter, California, USA), and data analyzed with FlowJo v 10.10.0 software (BD Life Sciences, USA). The Mann-Whitney U-test was used to compare non-parametric data where appropriate. **Results:** Significant increases in the percentages of immunosuppressive CD3+ CD4+ CD39+ Tregs cells in the setting of a significant decrease of CD19+ B cells were observed in pts with TNBC (Table).Tumour size, nodal status, age and ki-67 did not correlate with the percentages of any type of circulating immune cell. **Conclusions:** TNBC is associated with severe immunosuppression. In this context, percentages of circulating CD19+ B cells were significantly lower, while CD3+ CD4+ CD39+ Tregs were significantly higher in early TNBC pts. The peripheral blood immunome of TNBC pts identified a subset of immunosuppressive Tregs. A study is ongoing to identify the prognostic and predictive values of this systemic subset of Tregs for pCR in early TNBC pts undergoing neoadjuvant chemotherapy. Research Sponsor: None.

			TREGS	ROC (auc)	Group	Median	95% CI	p-value
Lymphocytes			CD45+ lymphocytes | Freq. of Parent	0,2056	TNBC	25,8	11,8-35	0,011
					Cnt	40,95	32-51,8	
	CD3+ CD4+		CD45+ lymphocytes/**CD3+ CD4+**T cells | Freq. of Parent	0,5111	TNBC	34,2	19,4-37,6	0,9437
					Cnt	28,95	24,6-46,4	
		CD25+	CD45+ lymphocytes/CD3+ CD4+ T cells/**CD3+CD4+CD25+** | **Freq. of Parent**	0,3889	TNBC	4,63	3,96-6,55	0,3562
					Cnt	5,9	4,06-6,71	
		CD25-	CD45+ lymphocytes/CD3+ CD4+ T cells/**CD3+CD4+CD25-** | **Freq. of Parent**	0,5000	TNBC	2271	1543-2681	0,0473
					Cnt	2943,5	2283-4823	
		CD4+ FoxP3+	CD45+ lymphocytes/CD3+ CD4+ T cells/**CD4+ FoxP3+** | Freq. of Parent	0,6833	TNBC	8,81	6,21-15,5	0,1205
					Cnt	6,62	4,42-9,67	
		CD4+ Helios+	CD45+ lymphocytes/CD3+ CD4+ T cells/**CD4+ Helios+**| Freq. of Parent	0,6167	TNBC	10,4	4,85-12,3	0,3135
					Cnt	7,9	4,41-11	
		CD4+ CD39+	CD45+ lymphocytes/CD3+ CD4+ T cells/**CD4+ CD39+**| Freq. of Parent	0,7778	TNBC	9,44	6,28-15,5	0,0156
					Cnt	5,3	2,8-8,35	
		CD4+ CD45RA+	CD45+ lymphocytes/CD3+ CD4+ T cells/**CD4+ CD45RA+** | Freq. of Parent	0,2222	TNBC	7,8	4,15-13,4	0,0156
					Cnt	20,3	9,48-41,8	
		FoxP3+Helios+	CD45+ lymphocytes/CD3+ CD4+ T cells/**FoxP3+Helios+** | Freq. of Parent	0,4611	TNBC	7,15	3,41-9,06	0,7595
					Cnt	6,6	3,56-9,53	

Association of *KRAS* G12D vs. G12V circulating tumor DNA variant allele fraction and real-world overall survival in metastatic non-small cell lung and colorectal cancers.

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Background: We previously reported *KRAS* G12D but not G12V variant allele fraction (VAF), as measured in circulating tumor DNA (ctDNA), was associated with overall survival (OS) in metastatic treatment-naïve pancreatic cancer (mPDAC). However, this has not been examined in other RAS-driven cancers. Here we assessed association of real-world OS (rwOS) with *KRAS* G12D and G12V VAF in metastatic colorectal cancer (mCRC) and non-small cell lung cancer (mNSCLC). **Methods:** We queriedGuardantINFORM, a real-world evidence database of aggregated commercial payer health claims and de-identified results from Guardant360 (G360) ctDNA testing from 2014 to 2023, to identify mNSCLC/mCRC patients who were treatment-naive and had *KRAS* G12D or G12V mutations identified $<$ 30 days prior to first-line therapy initiation. Those with co-occurring *KRAS* alterations, *KRAS* amplifications, and/or MSI-H were excluded. Outcomes were assessed as above vs. below median VAF and stratified by treatment type. The Cox regression model was run for continuous VAF, adjusting for age, gender, summary comorbidity score [Elixhauser Comorbidity Index (ECI)], and year of G360. **Results:** For mCRC, *KRAS* VAF above median was significantly associated with shorter rwOS for both G12D and G12V (Table 1); subgroup analysis of the predominant standard-of-care chemotherapy, FOLFOX, showed similar findings. For mNSCLC, *KRAS* VAF above median was associated with shorter rwOS for G12V, but not G12D (Table). Subgroup analysis by first-line treatment type revealed this association to be similar for chemotherapy-containing regimens but not immunotherapy (IO) alone. **Conclusions:** While a variant-specific association of *KRAS* VAF with rwOS was observed in mNSCLC overall (G12V associated, G12D not), above vs below median VAF was not associated with rwOS for the subset of patients receiving IO only. In contrast, for mCRC both G12D and G12V VAF were associated with rwOS, including for the subset of patients who received chemotherapy. These data suggest a complex interplay between *KRAS* variant, ctDNA shedding, first-line treatment, and OS that will be important in the interpretation of the prognostic implications of ctDNA-identified *KRAS* alterations. Research Sponsor: None.

Cancer-Treatment	G12D N	G12D Median VAF	G12D Log-rank P; Cox HR (95% CI)	G12V N	G12V Median VAF	G12V Log-rank P; Cox HR (95% CI)
CRC-All	356	9.0%	0.0002; 2.47 (1.52-4.03)	254	10.50%	0.0108; 2.25 (1.26-4.02)
CRC-FOLFOX	191	10.1%	0.0045; 2.26 (1.11-4.59)	132	14.0%	0.0044; 3.31 (1.41-7.75)
NSCLC-All	643	1.3%	0.4055; 1.12 (0.87-1.44)	790	1.80%	0.0001; 1.64 (1.29-2.09)
NSCLC-IO only	111	1.3%	0.4413; 0.90 (0.47-1.73)	154	1.4%	0.5572; 1.28 (0.73-2.23)
NSCLC-IO+ Chemo	365	1.3%	0.9769; 1.05 (0.73-1.51)	384	2.2%	0.0053; 1.57 (1.11-2.21)
NSCLC-Chemo only	152	1.3%	0.0967; 1.51 (0.93-2.43)	203	1.5%	0.0087; 1.93 (1.16-3.21)

Early clues in the battle against advanced gastric cancer: How plasma ctDNA signals the effectiveness of PD-1 inhibitors with chemotherapy.

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Background: Combination therapy with Programmed Death 1 (PD-1) inhibitors and chemotherapy has shown efficacy in improving survival in advanced gastric cancer, but not all patients derive benefit. We aimed to explore whether early dynamic changes in circulating tumor DNA (ctDNA) can serve as predictors of treatment response and long-term survival in patients receiving first-line PD-1 inhibitors combined with chemotherapy. **Methods:** This is a prospective, single-center trial in which all patients are adults with advanced or metastatic GC/GEJC confirmed by pathology or imaging. 30 eligible patients will receive PD-1 mab (sintilimab/nivolumab (NIVO) Q3W) and chemotherapy (SOX/XELOX Q3W) regardless of programmed death ligand-1 status. Blood samples were collected before treatment and after two treatment cycles for ctDNA analysis. Plasma ctDNA was isolated for evaluating variant allele frequencies (VAF) of somatic mutations in 47 cancer-related genes using next-generation sequencing (NGS), ctDNA response was defined as clearance of maximum VAF (maxVAF) compared to baseline. CT scans were performed after every two cycles and will be categorized as responding (complete response plus partial response) or non-responding (progress disease plus stable disease) according to RECIST v1.1. Overall survival was calculated from the date of first PD-1 mab infusion to the time of death or censored at most recent follow-up; progression-free survival was calculated from the date of first PD-1 mab infusion to the time of death or first documented progression, whichever came first, or censored at most recent follow-up. **Results:** In thirty advanced gastric cancer patients, the dynamic changes in maxVAF demonstrated a significant association with patients attaining either complete response (CR) or partial response (PR) to treatment (P=0.0021), but showed no correlation with stable disease (SD) or progress disease (PD). A substantial agreement was observed between ctDNA response and the best tumor shrinkage rate (Cohen's kappa=0.69). The objective response rate (ORR) among ctDNA responders was 85%, markedly higher compared to the 22% observed in non-responders (P=0.0073). Additionally, patients with ctDNA response had a significantly longer progression-free survival (PFS) compared to patients without ctDNA response (median PFS 15.6 months vs 6.0 months; HR, 0.18; 95% CI, 0.06 to 0.61; p=0.003), overall survival (OS) was also significantly longer among ctDNA responders (median OS not reach[NR] vs 9.0 months; HR, 0.10; 95% CI, 0.01 to 0.88; p=0.011). **Conclusions:** ctDNA response serves as a potential biomarker for assessing treatment efficacy and long-term outcomes in advanced gastric cancer patients treated with first-line PD-1 inhibitors and chemotherapy. Clinical trial information: ChiCTR2200065366. Research Sponsor: BeiJing Bethune Charitable Foundation (BCF-XD-JC-20221205-17); Clinical Ability Improvement Project (JSPH-MB-2020-3).

High-sensitive multi-cancers early detection for 8 cancer types by cell-free DNA targeted methylation sequencing: A retrospective cohort study.

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Background: Early screening effectively reduces mortality associated with cancer. Currently, most cancers lack effective screening paradigms. We developed blood-based multi-cancers early detection (MCED) and cancer signal origin (CSO) approaches in 8 types of cancers including esophageal, stomach, colorectal, pancreatic, liver, lung, breast and ovarian cancer. **Methods:** DNA methylation data generated based on GM-seq by public and internal whole genome methylation data. Based on these data, a panel of 155,362 CpG sites spanning the 2.0M genome was constructed and validated. We enrolled a case-control cohort of 746 participants (522 cancers, 224 non-cancers) for MCED model development. cell-free DNA (cfDNA) was isolated from 10 ml peripheral blood from each participant. A targeted methylation sequencing of cfDNA in plasma baseline was established using 224 non-cancers blood samples for 8 types of cancers. Finally, we developed a MCED model named AMBER for distinguishing cancer from non-cancer individuals. **Results:** DNA methylation data were from 8 types of cancers (cancer tissues: n=812, adjacent/normal tissues: n=416, cancer peripheral bloods: n=624, normal peripheral bloods: n=503) in internal and Infinium Human Methylation 450K array (cancer tissues: n=5000+, adjacent/normal tissues: n=1000+) from public data. 224 non-cancer individuals (healthy: n=196, cancer benign: n=28, male: female, 54.3%: 45.7%) were collected as control, while 522 cancer patients (male: female, 50.0%: 50.0%, stage I 26.9%, II 21.1%) from esophageal (n=56, stage I: n=10), stomach (n=47, stage I: n=11), colorectal (n=72, stage I: n=16), pancreatic (n=64, stage I: n=16), liver (n=69, stage I: n=22), lung (n=103, stage I: n=46), breast (n=41) and ovarian cancer (n=70, stage I: n=17). AMBER showed 99.1% specificity and total sensitivity 77.2% (95% confidence interval (CI): 73.4% to 80.7%). Of them, 56.8% (95% CI: 48.2% to 65.2%) of all stage I cases were detected, 70.6% (95% CI: 61.2% to 79.0%) for stage II, 84.5% (95% CI: 77.6% to 89.9%) for stage III, and 96.7% (95% CI: 91.8% to 99.1%) for stage IV. Strikingly, for stage I cancers, the sensitivity of esophageal, stomach, colorectal, pancreatic, liver, lung and ovarian cancer were 80.0%, 63.6%, 43.8%, 62.5%, 86.4%, 30.4% and 82.4% respectively. The sensitivity of esophageal, stomach, colorectal, pancreatic, liver, lung, breast and ovarian cancer reached 91.1%, 76.6%, 75.0%, 78.1%, 94.2%, 55.3%, 65.9% and 90.0%. For CSO model, the accuracy of TPO1 and TPO2 was 78.9% (95% CI: 74.6% to 82.8%) and 89.1% (95% CI: 85.6% to 92.0%). **Conclusions:** Our MCED tests demonstrated superior performance in detecting 8 types of cancers, especially early cancer screening, by utilizing cfDNA methylation information. It suggests the model can complement lack of multi-cancers early detection.
Research Sponsor: None.

Presence of molecular residual disease after pathologic complete response among patients with inflammatory breast cancer.

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Background: Inflammatory breast cancer (IBC) is known to recur more frequently than non-IBC after pathologic complete response (pCR). The presence of circulating tumor cells (CTCs), a marker of molecular residual disease (MRD), has been associated with higher likelihood of metastasis. We sought to characterize CTCs and its relationship with pCR in IBC patients. **Methods:** Patients diagnosed with IBC were enrolled in a prospective registry from 2005-2022. Serial blood draws were performed before, during, and after neoadjuvant systemic therapy (NST), and 6-months and 1-year post-surgery. CTCs were enumerated using CellSearch™. Patients with ≥ 1 CTC at any timepoint in the post-operative period were included in the positive CTC cohort. T-tests, one-way ANOVA, and chi-squared tests were used to compare differences between groups. Kaplan-Meier analysis was used for survival outcomes. **Results:** A total of 112 patients were included. The median age of diagnosis was 50.5 years (IQR 17) and BMI was 29.3 kg/m^2 (IQR 11.3). Patients were predominantly White (85, 75.9%) with clinical stage IIIB-C (94, 84.9%), node-positive (107, 95.5%), and HER2-negative (66, 59.0%) disease. Almost all patients (109, 97.3%) received trimodality therapy – NST, modified radical mastectomy, and adjuvant radiation. At a median follow-up period of 7.1 years (95% CI: 4.7-9.4), the overall survival (OS) rate was 72.3%. Baseline CTC positivity rate was 61.8% (42/68). More than half of the patients (61, 54.5%) had a positive CTC at some point in the post-operative surveillance period. Among the 39 patients who achieved pCR (34.8%), 15 (38.5%) had positive CTCs during follow-up. There were no differences in age, BMI, menopause status, clinical stage, nodal status, grade, presence of LVI, and number of lymph nodes (LNs) removed by CTC status. However, patients with positive CTCs had a significantly higher number of positive LNs at resection ($p = 0.01$), were more likely to be HER2-negative ($p = 0.001$), and were less likely to achieve pCR ($p = 0.01$). Triple negative disease ($p < 0.0001$), lack of pCR ($p = 0.006$), and positive CTCs (0.007) were associated with poor prognosis. When pCR was combined with CTC status, patients with positive CTCs demonstrated significantly worse survival, despite having achieved pCR, compared to those with pCR and negative CTC status (5-year OS: 35.0% vs. 83.1%, respectively, $p = 0.016$). **Conclusions:** A high proportion of IBC patients who achieved pCR had MRD, as demonstrated by persistent CTCs. CTCs portended worse prognosis in patients with IBC, even after pCR. Future incorporation of longitudinal CTC monitoring may be helpful in identifying patients at risk for relapse despite having achieved a pCR. Research Sponsor: None.

	5-year OS	95% CI	Median OS (months)	95% CI	p-value
pCR, +CTC	35.0%	(0.0-0.70)	60.1	(30.9-89.3)	0.016
pCR, -CTC	83.1%	(0.6 - 1.0)	NR		
No pCR, +CTC	52.0%	(0.32-0.72)	84.8	(32.3-137.3)	
No pCR, -CTC	62.2%	(0.35-0.89)	NR		

Relationship between dynamic changes in circulating tumor fraction and real-world imaging with real-world survival in patients with solid tumors treated with immunotherapy.

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Background: There is an unmet need for a sensitive biomarker that can determine which patients will confer long term benefit from immune checkpoint inhibitors (ICI). While radiologic imaging is the current standard of care for assessing ICI response, imaging can be difficult to interpret and is typically only assessed at 3 month intervals. Dynamic changes in circulating tumor fraction (TF) is a potential biomarker for monitoring ICI response. Here we evaluate the clinical benefit of a molecular biomarker, xM for treatment response monitoring (TRM), in addition to imaging, in a real-world (rw), pan-cancer cohort treated with ICIs. **Methods:** Using the Tempus liquid biopsy assay, ctDNA TF was computed by applying an ensemble algorithm incorporating copy number variant data and pathogenic variant allele frequencies. Deidentified patient records from the Tempus multimodal database were analyzed if patients had a baseline xF test $\leq$ 40 days prior to the start of ICI (alone or in combination with chemotherapy [CT], median = 13 days) and an on-treatment xF test 15-180 days post-ICI (median=93 days) and clinical response evaluated via imaging 15-126 days post ICI (median=77 days). Molecular responders (MR) were defined as patients with a $\geq$ 50% decrease in TF between tests. Rw-imaging, as documented by a provider in their clinical notes, was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), Rw overall survival (rwOS) was defined as time from the imaging date closest to on-treatment xF test to death. A likelihood ratio test at a two-sided 5% significance level was performed to assess if a Cox proportional hazards model incorporating both xM Monitor and rw-imaging as covariates (full model) had predictive power over a reduced model with only rw-imaging as a covariate. **Results:** The evaluable cohort (N=51) – 53% female, median age 64 yrs – had >10 advanced solid tumors (NSCLC 29% and breast cancer 18%). The majority of patients (69%) received ICI + CT, while 31% received ICI alone. 24 patients achieved MR (79% on ICI monotherapy, 21% on ICI + CT). Concordance of response markers is shown in the table. In the full model, xM was a significant predictor of rwOS (HR=0.33 [0.13, 0.84], p=0.02). The added information provided from xM was significant and superior compared to the reduced model of only rw-imaging (p=0.02). For patients with nMR and CR/PR/SD predicted median survival was 10 months whereas for patients with MR and CR/PR/SD predicted median survival was 16 months. **Conclusions:** MRs achieved significantly longer rwOS than nMRs and provides significant power in predicting rwOS beyond rw-imaging response. xM used for TRM can help identify nMRS who can discontinue therapy and be spared ICI toxicity. Research Sponsor: Tempus Labs.

N=51	CR/PR/SD (N=33)	PD (N=19)
MR	19 (59%)	5 (26%)
nMR	13 (41%)	14 (74%)

Classification of HER2 status across multiple cancers using epigenomic profiles from a novel liquid biopsy assay.

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Background: The efficacy of trastuzumab deruxtecan in multiple cancers led to a recent FDA granting of priority review for the treatment of adults with HER2-positive solid tumors. This underscores the critical need for reliable assessment of HER2 expression across cancers. The current standard using IHC/ISH for HER2 scoring is fraught with challenges including scoring discordance and tumor heterogeneity. Here we describe the ability to classify HER2 status from 1 ml of plasma, using epigenomic signatures from a novel multi-analyte liquid biopsy (LBx) platform, offering a minimally invasive approach for patient (pt) selection across cancers. **Methods:** We selected 179 samples from 172 pts with advanced breast (BC), gastro-esophageal (GEA) and ovarian (OV) cancers who had associated HER2 status scored from tissue-based IHC/ISH according to ASCO/CAP guidelines (table). Samples were taken at baseline or at progression and those with detectable cell free DNA, as assessed by iChorCNA, were profiled for genome-wide epigenomic signals across histone modifications associated with active enhancers, promoters and DNA methylation. A regularized regression model developed to classify HER2 status in BC cell lines and was refined and validated for HER2 status prediction for each pt cohort (HER2+ = 3+, 2+/ISH+; HER2- = 2+/ISH-, 1+, 0). The BC cell-line derived HER2 classifier was refined to incorporate GEA and OV cancer specific features before being applied to those samples. Performance was assessed via AUC in a leave-one-out cross-validation schema. We also evaluated HER2 status at progression in a subset of pts with benchmarked HER2 IHC to assess dynamic changes in receptor status by LBx. **Results:** The epigenomic HER2 classifier was applied to all samples with ctDNA detectable by ichorCNA (90 of 179; 50%). HER2 classification of BC pts by epigenomic liquid biopsy was concordant with standard tissue-based IHC for 64/72 (89%) BC samples (AUC 0.9, table). HER2 classifier predictions for all longitudinally collected samples were concordant with IHC-based HER2 status, including the one patient whose status switched from HER2+ to HER2- at progression. Accurate classification of 11/14 (79%, GEA) and 4/4 (100%, OV) pts was achieved using the indication-refined HER2 classifier. **Conclusions:** We demonstrate proof of concept for a HER2 classification approach using comprehensive epigenomic signals from 1 ml of plasma that could be applied across multiple cancers. With further development, our genome-wide profiling approach could alleviate clinical constraints associated with multiple tissue-based HER2 scoring assays (IHC/ISH) and enable longitudinal monitoring of HER2 status on therapy. Research Sponsor: None.

Patient cohort summary and classifier performance.

	BC			OV			GEA		
	Samples	Pts	AUC	Samples	Pts	AUC	Samples	Pts	AUC
Samples processed	119	111	-	14	13	-	46	46	-
Samples with detectable ctDNA	72	68	0.9	4	4	1	14	14	0.93

Using cell-free RNA in monitoring immune system and the demonstration of significant systemic deficiency in lymphoid and myeloid biomarkers in patients with cancer.

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Background: Immune system plays a major role in the clinical course of cancer. Evaluating the local interaction between tumor cells and the immune cells (microenvironment) at the cancer site provides important information. However, currently little is known about the immune system as a whole in patients with cancer. Since cell-free circulating RNA (cfRNA) may reflect the entire body, we hypothesized that cfRNA might provide important information on the health and the status of the immune system. To simplify our approach, we evaluated only cellular biomarkers characteristic for lymphoid and myeloid cells using only the expression of 55 genes typically used in flow cytometry evaluation of hematologic cells. We compared findings between patients with cancer, patients with CHIP (clonal hematopoiesis of indeterminate potential), and normal individuals. **Methods:** cfRNA was extracted from plasma samples of 681 patients with various types of solid tumors, 113 patients with CHIP, and 34 normal individuals. cfRNA was sequenced via a hybrid capture-based panel targeting 55 genes reflecting immune cells including T-cells, B-cells, histiocytes, monocytes, and myeloid cells. The RNA was quantified using TPM (transcript per million). **Results:** There was significant difference ($P<0.0001$) between normal individuals and patients with cancers in the levels of circulating biomarkers specific for immune cells. Surprisingly, expression of B-cell, T-cell, monocytic/histiocytic genes were significantly lower in patients with solid tumors when compared to normal individuals. This included CD19, CD20, CD2, CD22, CD3D, CD3E, CD3G, CD4, CD52, CD7, CD79A, CD79B, CD8A, CD8B,CD33, FCER2(CD23), IL2RA(CD25), ITGAM(CD11B), and ITGAX(CD11C). In contrast, there was no significant difference between CHIP and normal for B- or T-cell markers. After adjusting for multiple testing, no deficiency in immune stimulatory markers was present in patients with CHIP. Patients with CHIP showed significantly ($P<0.001$) lower levels of CD38, CD58, CD16, CD15, CD25, and CD123 mRNA as compared with normal. Furthermore, using 35 immune cell biomarkers in a machine learning algorithm using 2/3 of samples for training and 1/3 for testing predicted the presence of cancer vs no cancer (AUC =0.820), and CHIP from cancer (AUC =0.0830) and CHIP vs normal (AUC =0.871). **Conclusions:** Immune related biomarkers using cfRNA provide important information on the immune system that can be used to monitor patients and to predict the presence of cancer or CHIP. The demonstration that patients with cancer have deficiency in overall systemic immune elements suggests that further studies are needed in monitoring the immune system and exploring means to boost systemic immunity to prevent the development of overt cancers. Research Sponsor: None.

Personalized circulating tumor DNA for minimal residual disease and dynamic assessment in patients undergoing neoadjuvant chemotherapy for breast cancer: Preliminary analysis from MSK-LINC.

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Background: Identification of minimal residual disease (MRD) with circulating tumor DNA (ctDNA) in pts with early-stage breast cancer holds promise to identify risk of relapse. MSK-LINC is prospective ctDNA plasma analysis of breast cancer pts. This pilot study evaluated the utility of serial ctDNA assessment as a biomarker for monitoring MRD and recurrence prediction in clinical stage II-III breast cancer pts undergoing neoadjuvant chemotherapy (NAC). **Methods:** 30 pts who underwent NAC across all subtypes were identified from MSK-LINC. The ctDNA analysis was performed at baseline, on-NAC, post-NAC/pre-surgery, within 8 weeks post-surgery, and during follow-up. Personalized ctDNA RaDaR assays were designed using whole exome sequencing data of paired primary tumor and germline samples from each pt. ctDNA levels were quantified as an estimated variant allele fraction (eVAF). **Results:** ctDNA panels were successfully designed for 29/30 pts (16 Stage II, 13 Stage III), including 6 HR+/HER2-, 12 HER2+, and 11 TNBC, with a median follow up of 4.2 years. The bespoke ctDNA assays targeted a median of 48 variants (21-51), with a median of 43 variants (11-48) passing quality control. A total of 175 plasma samples were analyzed, including 24 baseline and 24 post-surgery. A 100% ctDNA detection rate was observed at baseline in the 24 pts for whom a baseline sample was available (median eVAF 0.33%, range 0.0083% - 8.91%). Pathologic complete response (pCR) was achieved in 11 pts who remained disease free; and of the 18 pts without a pCR, 5 recurred. All patients with a pCR were ctDNA negative post treatment. In 3/5 patients who recurred, MRD detection was achieved, including one patient with persistent ctDNA positivity throughout all timepoints. For the other two pts, ctDNA was first detected in follow-up plasma collected at 4.4 and 9.8 months prior to clinical recurrence. **Conclusions:** This study demonstrates the potential of ctDNA as a dynamic biomarker for monitoring disease burden in pts with high-risk early-stage breast cancer, highlighting its remarkable sensitivity at baseline and its capability for MRD detection preceding clinical recurrence. These findings suggest the need for further research to fully understand the relationship between ctDNA dynamics during and after NACT with prediction of breast cancer outcomes. ctDNA detection rates in plasma samples across collection timepoints. Research Sponsor: NeoGenomics Laboratories.

Timepoints of Plasma Sampling	All pts (n=29)	Pts with Subsequent Recurrence (n=5)	Pts Who Remained Disease Free (n=24)
Baseline	24/24	5/5	19/19
On-NAC*	8/21	2/4	6/17
Post-NAC/Pre-surgery	1/21	1/4	0/17
Post-surgery (<8 weeks)	1/24	1/4	0/20
Follow-up* (collected prior to clinical detection of recurrence)	3/29	3/5	0/24

*Positive cases were counted if at least one of the plasma samples showed ctDNA positivity.

ctDNA as a biomarker in phase II study of tepotinib in advanced solid cancers with *MET* exon 14 skipping mutation or amplification (KCSG AL19-17).

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Background: Tepotinib consistently demonstrated antitumor activity in patients with *MET* exon 14 skipping mutation (*METex14*) and promising activity in various cancers with *MET* amplification, according to previous reports. We assessed plasma ctDNA as a potential biomarker in *MET*-dysregulated advanced cancer patients with tepotinib treatment. **Methods:** KM-08 (KCSG AL19-17, NCT04647838) was a phase 2, multicenter study with tepotinib treatment for patients with advanced or metastatic solid cancers harboring either *METex14* or *MET* amplification detected in tissue-based next-generation sequencing (NGS). For exploratory analyses, we analyzed the genetic profile using liquid-based NGS testing with AlphaLiquid-100 panel (IMBdx Inc. Seoul, KR) at baseline (T0), after six weeks during treatment (T1), and at the time of disease progression (T2). **Results:** Baseline ctDNA NGS data was available in 28 (80%) out of 35 patients enrolled in the trial. Among them, *METex14* or *MET* amplification was detected in 18 patients, with a sensitivity of 64.3%. The most commonly co-mutated gene was *TP53*, followed by *PIK3CA, ATM, MYCN*, and *KRAS*. The objective response rate (ORR) in plasma *MET* positive (PM+) patients was higher (81.2%) than the ORR in plasma *MET* negative (PM−) patients' group (30.0%). In contrast, PM− group had a longer progression-free survival (PFS) and overall survival (OS) than PM+ group. PFS was 11.0 months (95% CI 8.1, 13.9) vs 6.0 months (95% CI 3.6, 8.3) and OS was NR vs 14.0 months (95% CI 4.7, 23.3), respectively. The molecular responder (MR, *MET* alteration variant allele frequency [VAF] T1/T0 $<$50%) was 80.0% (12/15 patients), and the molecular non-responder (MNR, *MET*VAF T1/T0$\geq$50%) was 20.0% (3/15 patients). ORR was higher in the MR group (91.7%) than in the MNR group (33.3%). PFS and OS were longer in the MR group than in the MNR group, 6.0 months (95% CI 0.0, 14.5) vs 3.0 months (95% CI 1.4, 4.6) with P= 0.114 and NR vs 4.0 months (95% CI 2.4, 5.6) with P= 0.067, respectively. Out of the 20 patients with samples available at T2, one had an on-target mutation on *MET* (D1228N, and Y1230H) while two had off-target emerging oncogenic alterations in *KRAS, BRAF,* and *ERBB2* genes. **Conclusions:** In the liquid biomarker analysis in the *MET*-dysregulated cancer patients who were treated with tepotinib, the presence of ctDNA *MET*alteration at baseline was associated with a higher response rate but shorter PFS and OS. The molecular response was well correlated with the radiological response and associated with better outcomes. (Funded by Merck KGaA, Darmstadt, Germany, ClinicalTrials.gov number, NCT04647838.) Clinical trial information: NCT04647838. Research Sponsor: Merck KGaA, Darmstadt, Germany.

Paired matched normal sequencing to accurately identify somatic clonal hematopoiesis mutations (CHm) in solid tumor tissue and plasma specimens.

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Background: Clonal hematopoiesis (CH), characterized by the presence of somatic mutations in blood cells, can be found in cancer-related genes when sequencing tumor tissue or plasma samples. Inability to distinguish somatic, tumor-derived mutations from CHm can lead to inaccurate treatment decisions. In this prospective study, we confirmed potential CHm in solid tumors by sequencing and analysis of paired matched normal (PMN) specimens. **Methods:** We prospectively enrolled 56 patients diagnosed with advanced cancer, including lung (16), colorectal (13), breast (10), gastric (7), ovarian (2), pancreatic (2), liver (2), cervix (1), uterine (1), fallopian tube (1), and perihilar bile duct (1). Targeted next-generation sequencing using a 523 gene panel was performed on paired formalin-fixed paraffin-embedded (FFPE) and circulating tumor DNA (ctDNA) samples. Additionally, whole exome sequencing was performed on PMN buffy coat samples. Analysis of all three specimens was performed to classify somatic mutations as tumor-derived or CHm. **Results:** We identified 21 potential CHm within the FFPE and ctDNA samples of 13 patients (23.2% of the cohort) with lung (7), breast (2), liver (2), colorectal (1), and gastric (1) cancers. CHm were further confirmed when present in buffy coat samples. The VAF of CHm in FFPE and ctDNA samples exhibited a wide range, spanning from 0.85% to 38.4%, with 7 of those identified at $<2\%$ VAF. For these same aberrations, VAF in buffy coat samples ranged from 1.6% to 48%, with seven mutations exhibiting VAF levels $<5\%$. Four of these CHm were classified as oncogenic or likely oncogenic. Four CHm, including an oncogenic *TP53* mutation, were identified in the oldest patient (75 years old, lung cancer), while an oncogenic *DNMT3A* mutation was detected in the youngest patient (42 years old, breast cancer). Both had a 30-year history of smoking. **Conclusions:** Our findings identified somatic CHm in a substantial subset (23.2%) of solid tumors, with four identified as oncogenic or likely oncogenic mutations. The broad spectrum of VAFs for CHm suggests that using VAF as a cut-off to exclude likely CHm may be unreliable. The low VAF CHm found in matched normal specimens indicates low-pass sequencing may not detect critical CHm, even in paired analysis. The diverse age range of patients with CHm (42 to 75 years old) suggests that CHm are not restricted to older populations, and that additional factors, such as smoking history, may play a role. These findings underscore the importance of incorporating routine PMN buffy coat sequencing into clinical practice, to identify somatic CHm that can impact personalized cancer treatment strategies. Research Sponsor: Illumina.

Characterization of molecular response and progression in patients with metastatic HR+/HER2- breast cancer receiving endocrine therapy and CDK4/6 inhibitors using a high-sensitivity tumor-informed assay.

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Background: Tumor-informed circulating tumor DNA (ctDNA) assays, designed to track patient (pt) specific variants identified by tumor sequencing, offer enhanced sensitivity compared to traditional assays focused on driver genes. This approach enables precise ctDNA quantification, facilitating early detection of molecular progression and innovative strategies in metastatic breast cancer (mBC). **Methods:** HR+/HER2- mBC pts receiving standard endocrine therapy + CDK4/6 inhibitors (CDKi) were enrolled in a prospective observational cohort (2018–2023). Plasma samples were collected at baseline (BL), within 30 days (d) and ~q3 months with restaging scans. Archival tumor WES was used to design personalized panels for ctDNA monitoring. The primary endpoint was time to treatment failure (TTF). **Results:** Of 51 pts analyzed (median age 60 years [range 38-88], 1/2L [75/20%], visceral disease 63%, palbo-/ribo-/abemaciclib 76/22/2%), tumor-informed panels were successfully designed for 43 (1 failed WES, 7 failed QC), detecting BL ctDNA in 39 (91%). The median BL estimated variant allele fraction (eVAF) was 0.5% (0.006–17.9) and was associated with liver metastases but no other covariates (e.g. bone-only disease, history of 1ry endocrine resistance [ER]). Higher BL eVAF predicted shorter TTF (HR 1.14 CI 95% 1.05–1.23, $p<0.01$). Most pts had eVAF decreases below BL in the first 30 d (78%) and before the first scan (89%; median 90 d, 23–158). Early increases above BL did not significantly predict TTF, with 3/8 cases showing prolonged responses. ctDNA clearance was observed in 11/39 (28%) pts at a median of 172 d (14–410) and predicted longer TTF (HR 0.06, CI 95% 0.01–0.45, $p<0.01$; median TTF not reached vs 14.5 mo for pts with and without clearance), with treatment failure (TF) rates of 0% vs 40%, and 8% vs 80%, at the 1- and 2-year landmarks, respectively. Clearance was not associated with any clinical covariate (i.e. disease sites, therapy line, CDKi, history of 1ry ER). For any sample irrespective of the trajectory, higher eVAF ratios to BL predicted shorter lead times to TF, though with poor correlation (r^2 0.08, p=0.01). eVAF ratios to BL >1, >0.5 and <0.5 at any timepoint had median lead times to TF of 76 d (Q1–Q3 25–135), 133 d (41–360), and 326 d (174–471). A complete analysis of ctDNA dynamics and operating parameters will be presented along with RECIST 1.1 evaluation and WES-based genomic subgroups. **Conclusions:** ctDNA levels and changes on therapy are prognostic and high sensitivity tumor-informed assays expand the proportion of pts who can be monitored. ctDNA clearance identified pts with better outcome and might inform pt follow up and interventional strategies. Reappraisal of existing early response cutoffs, with limited precision for individual decision making, may be necessary with more sensitive assays. Research Sponsor: ASCO Conquer Cancer Foundation Young Investigator Award; LIBERATE/Princess Margaret Cancer Foundation.

Polyploid circulating stromal cells in blood to identify invasive solid tumors and to prognosticate for highly aggressive cancer subtypes.

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Background: Recently, early studies have identified circulating stromal cells (CStCs), i.e. Cancer Associated Macrophage-Like cells (CAMLs), in patients (pts) with newly diagnosed invasive cancers, which are phagocytic myeloid immune cells emanating from primary tumors. However, no study has evaluated CAMLs as a pan solid tumor screening tool nor their clinical impact on pt outcomes. We analyzed the blood of untreated newly diagnosed cancer pts (n=441), or in non-malignant conditions (i.e. pancreatic cysts, n=77), or healthy controls (n=100). We found that CAMLs are prevalent (82%) in cancer pt blood, absent in healthy controls (0%) and less common in non-malignant conditions (36%), with correlations to worse clinical outcomes. **Methods:** Anonymized peripheral blood was taken from n=441 pts before or after confirmation of invasive malignancy [stage I (n=105), stage II (n=125), stage III (n=114), stage IV (n=97) with pathologically confirmed lung (n=84), pancreas (n=61), breast (n=73), prostate (n=65), esophageal (n=34), Renal Cell (n=29), Sarcoma (n=27), or Other (n=68). In addition, anonymized blood was taken from pts with untreated non-malignant conditions including benign breast masses (n=19), Lupus (n=11), liver Cirrhosis (n=6), rising PSA (n=24), or other benign mass (n=17); and from healthy control volunteers (n=100). CAMLs were isolated by CellSieve microfiltration, defined as enlarged polyploid cells with cytokeratin+ and/or CD45/CD14+. Pts were monitored for 0-8 years (median=2.6) for progression free survival (PFS) and overall survival (OS). **Results:** CAMLs were found in 82% of all cancer pts averaging 5.4 CAMLs, specifically, in 66% of Stage I, 85% Stage II, 84% Stage III, and 92% Stage IV. No CAMLs were found in any healthy controls, but were in 36% of non-malignant pts. CAML sensitivity in cancer vs healthy was 82% (CI95% 78-85%), specificity=100% (CI95% 96-100%), PPV=100% (CI95% 99-100%), NPV=55% (CI95% 50-60%). CAML sensitivity in cancer vs benign was 82% (CI95% 78-85%), specificity=64% (CI95% 32-44%), PPV=93% (CI95% 90-95%), NPV=38% (CI95% 32-44%). CAML presence was significantly associated with worse PFS (HR=2.0, 95%CI 1.4-2.9, $p<0.0001$) & OS (HR=2.2, 95%CI 1.4-3.3, $p=0.0004$), with engorged phagocytic CAMLs (>50um), highly significant for worse PFS (HR=3.3, 95%CI 2.5-4.5, $p<0.0001$) & OS (HR=3.0, 95%CI 2.1-4.3, $p<0.0001$). Further, in benign pts positive for CAMLs, 2 pts were in situ, 16 had histologies with increased cancer risk (i.e. IPMN, atypical hyperplasia), and 5 pts died within 3 years. **Conclusions:** CAMLs appear to be a highly sensitive blood based biomarker that can identify invasive carcinoma in all stages of cancer regardless of subtype, but are not found in healthy controls & rare in non-malignant conditions. Further, enlarged phagocytic CAMLs appeared to correlate with shorter PFS and OS prior to treatment induction. Research Sponsor: DARPA DOD; W911HF14C0098; U.S. National Institutes of Health; NCT04240327, UO1CA214183, & R43CA206840.

Enhancing cancer detection through AI-driven high content analysis of circulating tumor cells.

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Background: The advancements in automated High Content Analysis (HCA) for Circulating Tumor Cells (CTCs) detection necessitate the integration of high-throughput screening (HTS) and Artificial Intelligence (AI) to improve cancer diagnosis efficiency and accuracy. Traditional approaches to cancer detection have faced limitations in speed, cost, and analysis depth, driving the need for innovative solutions in assay development and execution. **Methods:** We obtained peripheral blood from 150 asymptomatic individuals and 63 newly diagnosed cases of solid organ cancers including Lung, Breast, Head and Neck, Colorectal, Pancreas, Esophagus, Gynecologic cancers. We used differential apoptosis based negative enrichment technique and HCS fluorescent imaging for identification of CTCs and CTC like immune cells from the relevant blood samples. We devised AutoML algorithms which were trained on a cohort of 4,135 cropped region of interest (ROI) images of true CTCs and CTC-mimicking immune cells. These images were annotated with the coordinates of the top-left and bottom-right corners of rectangles to specify ROIs. This method employs a combination of automated sample processing, integration with the Laboratory Information Management System (LIMS) integration, digital filtration, and decision matrix algorithms for sample classification and smooth data flow. The image quality criteria were established prior to dataset analysis. The algorithms underwent training, testing, and validation based on expert recommendations, with dataset splitting of 80% for training, 10% for testing, and 10% for validation phases. **Results:** The automated deep learning model achieved remarkable performance metrics, presenting an accuracy of 96.66% (95% CI, 96.07%-97.19%), a specificity of 95.34% (95% CI, 94.37%-96.18%), and a sensitivity of 98.14% (95% CI, 97.44%-98.69%) in detecting true CTCs. Additional analysis included the area under the curve and confusion matrix evaluations, indicating the model's robustness in distinguishing between true positive and true negative specimens. This efficiency and precision in data handling, processing, and analysis demonstrate significant advancements in HCA screening, offering enhanced assay development, execution flexibility, and the facilitation of detailed cell-by-cell analysis for cancer detection from a large set of Peripheral Blood Mononuclear Cells (PBMCs) from samples obtained for screening or diagnosis. **Conclusions:** This study successfully evaluated a deep learning model for the detection of circulating tumor cells (CTCs) in peripheral blood mononuclear cells (PBMCs) using image data from HTS platform. The model achieved superior performance, demonstrating its potential for cancer detection from blood samples. Research Sponsor: None.

Discovery of long non-coding RNA biomarkers for prognosis in pediatric acute lymphoblastic leukemia.

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Background: Acute lymphoblastic leukemia (ALL) ranks among the most prevalent pediatric cancers. Molecular testing, including cytogenetics, has been widely used for prognosticating pediatric ALL. However, cytogenetic testing in pediatric ALL is incapable of detecting submicroscopic genetic changes and suffers from variable sensitivity, which may lead to heterogeneous outcomes within cytogenetic subgroups. In addition to conventional prognostic biomarkers, long non-coding RNAs (lncRNAs) are expressed in both a disease- and tissue-specific manner, emerging as promising biomarkers. However, well-established lncRNA prognostic biomarkers for pediatric ALL have yet to be identified. Therefore, in this study, we discovered three singular lncRNA prognostic biomarkers and a prognostic panel composed of multi-lncRNAs for pediatric ALL using our newly developed BAMBI method. **Methods:** This study utilized RNA-seq data from 561 distinct individuals, comprising 647 blood or bone marrow biospecimens obtained from pediatric patients with ALL from the dbGaP TARGET dataset. Among these individuals with RNA-seq and survival data, 25.8% deceased during follow-up. The average age at enrollment was 8.1 years. Of this cohort, 36.0% were female, and 61.5% were Caucasian white. Initially, our lncRNA identification tool, Flnc (Li Z., et al., Non-coding RNA. 2022), was employed to identify and quantify both novel and known lncRNAs expressed in pediatric ALL. Subsequently, our machine-learning based method, BAMBI, was utilized to discover lncRNAs as new prognostic biomarkers in pediatric ALL. **Results:** Three lncRNAs (ZBTB47 and NKTR antisense RNA, AC097359.2's new isoform, and a novel lncRNA near STXBP5) were identified as individual putative biomarkers for prognosis. Each of these three lncRNA biomarkers exhibited predictive power for survival, with accuracy ranging from 68.2% to 72.8% and AUROC scores ranging from 67.7% to 75%. Furthermore, we established three lncRNA biomarker panels composed of these three lncRNAs along with a few additional lncRNAs, which showed improved prediction power with accuracy ranging from 78.3% to 79.6%, and AUROC scores ranging from 82.1% to 85.2%. **Conclusions:** We discovered both singular lncRNA and panels of multi-lncRNAs as prognostic biomarkers of pediatric ALL patients. These putative lncRNA biomarkers could be further validated through independent cohorts or prospective clinical study designs. Research Sponsor: None.

Clinical impact of molecular profiling in the national prospective cohort Solving Unknown Primary Cancer (SUPER) study.

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Background: Cancer of unknown primary (CUP) is a common cause of cancer death, with a median survival < 12 months. SUPER is a prospective cohort study designed to create a national information and biobank of patients (pts) with no confirmed primary site following diagnostic work-up. We aimed to determine the impact of tumour molecular profiling on treatment decisions. **Methods:** 449 pts were recruited (2013-2021) over 3 phases from 12 Australian sites. Clinical information collected over 12 months included: demographics, treatments, investigations and clinico-pathological characteristics. Molecular tests were centrally performed and included comprehensive panel (CCP) sequencing and gene-expression tissue of origin (TOO) assays in Phase 1&2 and CCP and whole genome sequencing (WGS) in Phase 3. The number of genes reported on increased over the 3 phases. Molecular results were discussed in a molecular tumour board. Clinicians completed clinical management questionnaires before and after receiving molecular results. A combined retrospective evaluation of therapeutic actionability was applied to all DNA sequencing data using the TOPOGRAPH database. **Results:** Median age 63 years [19-86], with 81% ECOG 0-1 and 87% classified as unfavourable CUP subtype. Reporting timelines and rates of successful sequencing improved over time (Table). Clinically actionable genomic abnormalities were detected in 95/331 (29%) pts. Moderate or high match results on TOO assay were consistent with a suspected or later confirmed TOO as reported by clinicians in 81/195 (42%) pts in phase 1 + 2. Germline pathogenic mutations were detected in 34/331 (10%) pts. Molecular tests confirmed clinician's treatment (started while awaiting results) was consistent with the most likely TOO in 170/331 (51%) pts. Clinicians reported that molecular tests resulted in a change in management in 11/118 pts (9%) in phase 1 and 40/213 (19%) pts in phases 2+3, with 17/51 (33%) pts changed treatment based on potential TOO determination. 11/51 (22%) pts could access treatment via standard pathways given a more specific tumour-type diagnosis and 15/51 (29%) pts were potentially eligible for clinical trials; however, only 7 pts were well enough for referral. **Conclusions:** The clinical impact of molecular testing in CUP improved over time as testing became more sophisticated and turnaround times improved. Clinicians suspected TOO pre-profiling was consistent with molecular results in half of the pts. Routine access to novel therapies in CUP remains a challenge. Research Sponsor: Cancer Australia; Victorian Cancer Agency; Australian Genomics Health Alliance.

	Phase 1 (2013-2015)	Phase 2 (2017-2020)	Phase 3 (2020-2021)
Number of genes on CCP (n)	245	462	578
Molecular test successfully completed (n,%)	CCP 98/118 (68) TOO 96/118 (81)	CCP 111/120 (93) TOO 99/120 (83)	CCP 90/93 (97) WGS 44/93 (47)
Median turnaround time for reporting (days, range)	CCP 186 (94-478) TOO 30 (14-245)	CCP 60 (22-339) TOO 58 (13-339)	CCP 49 (16-256) WGS 67 (39-221)

Correlation of ctDNA and radiographic imaging features derived from ^{18}F-FDG PET/CT for patients with metastatic melanoma treated with immunotherapy.

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Background: ^{18}F-FDG PET/CT scans are used to assess tumor response for patients undergoing immunotherapy for metastatic melanoma (MM). Evaluating the relationship between features derived from quantitative medical image analysis and markers in blood samples such as circulating tumor DNA (ctDNA) may present an opportunity to discover imaging and blood biomarkers that can influence future patient care. This study evaluates the correlation of ctDNA and radiographic imaging features derived from FDG PET/CT. **Methods:** Whole-body FDG PET/CT scans from MM patients between 2014-2020 were retrospectively collected under IRB-approved protocol. Patients received pembrolizumab (n=20), ipilimumab (n=4), nivolumab (n=7), or a combination of ipilimumab and nivolumab (n=19). TRAQinform IQ software (AIQ Solutions) identified and quantified regions of interest suspicious of cancer (lesion-ROI), enabling extraction of imaging features including SUV_{max}, SUV_{mean}, and SUV_{total} in baseline ($_{BL}$) and follow-up ($_{FU}$) images and change. Plasma ctDNA concentration (copies/ml) and frequency abundance (FA) were evaluated for the first sample ($_1$) after immunotherapy had started (between baseline and first on-treatment scan), and the next available sample ($_2$). Patients were further grouped by ctDNA mutation for analysis. Correlation between imaging features and ctDNA features was assessed using Spearman coefficient (ρ). **Results:** The patient cohort included 32 males and 19 females with average age of 62 years (range 23-83). For all 51 patients, moderate correlation was observed in $SUV_{max,BL}$ with ctDNA copies/ml_1 ($\rho = 0.48$, $p << 0.001$) and ctDNA FA_1 ($\rho = 0.49$, $p << 0.001$) and in $SUV_{total,BL}$ with ctDNA FA_1 ($\rho = 0.41$, $p < 0.001$). In BRAF mutation patients (N=32), moderate correlations existed between $SUV_{max,BL}$ with ctDNA copies/ml_1 ($\rho = 0.49$, $p = 0.0041$ and ctDNA FA_1 ($\rho = 0.05$, $p = 0.0035$), and $SUV_{total,BL}$ with ctDNA copies/ml_2 ($\rho = 0.42$, $p = 0.017$), ctDNA FA_1 ($\rho = 0.40$, $p = 0.023$), and ctDNA FA_2 ($\rho = 0.43$, $p = 0.012$). All the other combinations displayed weak correlations ($\rho < 0.39$, $p > 0.05$). **Conclusions:** This study shows that in patients with MM receiving immunotherapy, quantitative features from blood biomarkers such as ctDNA correlate with FDG PET/CT imaging features. Combining blood biomarkers with imaging features that are spatially localizable may strengthen prognostication in this patient group. Further analysis is being performed with more types of ctDNA mutations. Research Sponsor: None.

Development of a serum miRNA panel for detection of early stage non-small cell lung cancer.

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Background: Lung cancer remains the leading cause of cancer deaths, largely due to late-stage diagnosis. Early detection significantly improves survival rates, but current methods like chest X-rays and low-dose CT (LDCT) scans face limitations in sensitivity and specificity. MicroRNAs (miRNAs) are small non-coding RNAs whose dysregulation has been widely observed in different stages of cancer. Evidence suggests that circulating miRNAs could be promising biomarkers for early diagnosis of lung cancer. In this study, we developed and validated a 15-miRNA panel as a blood-based minimally invasive test for early detection of non-small cell lung cancer (NSCLC) using the proprietary multiplex quantitative real-time PCR (qPCR). **Methods:** 332 serum samples (182 Stage I&II NSCLC, 150 healthy controls) were divided into training (n=266) and validation (n=66) cohorts. Differentially expressed serum miRNAs were screened with Miseq sequencing followed by qPCR validation. The multi-miR panel was developed with a logistic regression model and validated using an independent cohort. Receiver operating characteristic curves were constructed to evaluate the diagnostic accuracy of the panel. A stem-loop quadruplex qPCR assay was invented for concurrent detection of 4 miRs in a single reaction. **Results:** 15 differentially expressed miRNAs were selected for logistic model construction based on their Ct values (Ct<35) and high diagnostic accuracy of stage I&II NSCLC (AUC>0.7). The 15-miRNA panel model achieved 88.4% sensitivity, 81.7% specificity (AUC = 0.912) in the training cohort (Table), and was validated with 94.4% sensitivity, 73.3% specificity (AUC = 0.892) in the validation cohort. Quantification of 15 miRs and 1 internal control was performed in 4 reactions tubes via quadruplex qPCR assay. **Conclusions:** The serum 15-miR panel developed and validated in this retrospective study exhibited robust performance for detection of early stage NSCLC. The panel demonstrates potential diagnostic applications and clinical utility to be implemented together with LDCT in current lung cancer screening program as a blood biomarker to reduce false positive results. In addition, the proposed stem-loop quadruplex qPCR system offers an efficient and promising approach for miRNA profiling in future clinical applications. Research Sponsor: Miracle Biotechnology Inc.

Training Cohort

		Actual Class	
	Total n = 266	Lung Cancer	Control
Predicted Class	Lung Cancer	129 (True Positive)	22 (False Positive)
	Control	17 (False Negative)	98 (True Negative)

Validation Cohort

		Actual Class	
	Total n = 66	Lung Cancer	Control
Predicted Class	Lung Cancer	34 (True Positive)	8 (False Positive)
	Control	2 (False Negative)	22 (True Negative)

CUPCOMP: A multi-site UK trial in carcinoma of unknown primary: A comparison across tissue and liquid biomarkers.

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Background: Cancer of Unknown Primary (CUP) is a difficult to treat cancer entity for which the tumour origins remain elusive. There is emerging evidence to support a precision medicine approach to aid treatment decisions, however scarcity of tumour tissue for molecular profiling remains a challenge. CUPCOMP sought to compare the feasibility of molecular profiling from both tissue and blood in patients (pts) diagnosed with CUP. **Methods:** A non-randomised prospective feasibility clinical trial conducted across 7 UK sites between 06/2021-02/2023. Eligible pts had a histological confirmed diagnosis of favourable/unfavourable CUP based on clinical, radiological, and pathological review at a CUP Multi-Disciplinary Team meeting and ESMO Guidelines for CUP. Pts had mutation profiling performed from circulating tumour DNA (ctDNA) (FoundationOne Liquid CDx) and tumour tissue (FoundationOne CDX or whole genome sequencing (WGS)). All results were discussed at a dedicated Molecular Tumour Board (MTB) to evaluate the activation state of oncogenic pathways. **Results:** Baseline characteristics of the 117 pts recruited are shown (Table). 114/117 (97%) pts had successful blood (109/117; 93% pts) or tissue (69/117; 59% pts) molecular profiling; both methods were performed in 64/117 (55%) pts. WGS was only successful in 15/21 pts where repeat biopsy was obtained. Where targeted tissue and blood profiling was performed using the same panel (49/117; 42%): 421/550 (77%) Single Nucleotide Variants (SNVs) found in tissue were concordant in ctDNA. ctDNA tumour fraction was ≥10% in 41/109 (35%) pts. In ctDNA, 1556 SNVs, across 271 genes, and 42 rearrangements were identified. 73/114 (64%) of cases carried an actionable alteration in blood or tissue, as determined by MTB. The most frequently reported actionable gene alterations were: KRAS (n=11; 10%); ATM (n=9; 8%); ARID1A (n=9; 8%); PIK3CA (n=10; 9%); NF2 (n=7; 6%); BRAF (n=7; 6%); FGFR2-fusion (n=7; 6%). A tumour mutational burden (TMB) of ≥10 mutations/Mb was detected in 25/117 (22%) of pts. Potential germline variants were found in 8% of pts. 80/114 (70%) pts were alive 6 months after consent to trial. **Conclusions:** Successful tissue-based molecular profiling is challenging in pts with CUP; achieved in only 59% of pts in this cohort. ctDNA analysis was feasible (93% successful) and reliably concordant with tissue. Potentially actionable alterations were found in 64% of pts. ctDNA molecular profiling should be considered as a reliable alternative to tissue-based testing in pts diagnosed with CUP. Clinical trial information: NCT04750109. Research Sponsor: Innovate UK; 50074.

Pt Characteristics		n=117 (%)
Sex	**Female**	66 (56%)
	Male	51 (44%)
Age	***Median***	63
	Range	27-86
Performance status	**0**	35 (30%)
	1	60 (51%)
	2	19 (16%)
	3	1 (1%)
	Not known	2 (1%)
Ethnicity	**White**	99 (83%)
	Other	3 (3%)
	No data	19 (16%)
Histology	**Adenocarcinoma**	60 (51%)
	Carcinoma	21 (18%)
	Squamous	19 (16%)
	Other	7 (6%)
	No data	10 (9%)
Prior lines of SACT	**0**	79 (68%)
	1	20 (17%)
	2-6	18 (15%)

A highly sensitive, low input, and automated assay for molecular residual disease detection (MRD) using whole-genome sequencing (WGS).

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Background: Molecular residual disease (MRD) detection using cell-free DNA (cfDNA) for solid tumors requires a highly sensitive and specific assay that can overcome the limitation of low abundance circulating-tumor DNA (ctDNA) in a standard blood draw with fast sample-to-answer turn-around time (TAT). Here we describe the development and analytical performance of Illumina's TruSight Oncology MRD WGS assay (TSO MRD, for research use only), for detecting MRD using tumor-informed whole-genome sequencing (WGS) of cfDNA extracted from plasma samples across multiple cancer types. **Methods:** The TSO MRD assay was built using Illumina's best-in-class WGS library preparation, informatics and sequencing technologies. The assay is composed of two major steps, fingerprinting and ctDNA detection. At the fingerprinting step, the DNA from tumor tissue and matched normal samples is analyzed through WGS to generate a sample specific somatic variant list. At the ctDNA detection step, the cfDNA extracted from plasma is analyzed through shallow WGS and the presence of ctDNA is detected using the tumor specific fingerprint as an input in the MRD analysis pipeline. The plasma extraction and WGS library preparation workflows are fully automated for high-throughput sample processing with minimum hands-on time and touch points. **Results:** Testing of commercial MRD reference materials and ctDNA-positive samples serially diluted into normal cfDNA background demonstrated a limit of detection of down to 0.001% VAF or 10 parts per million (PPM) in multiple cancer types. Testing of a panel of normal plasma samples from healthy individuals assessed against 20 sets of fingerprints from multiple cancer types demonstrated an analytical specificity of 99.7%. Testing of ctDNA samples with multiple operators, instruments and library prep start days demonstrated high reproducibility in MRD detection. The ctDNA testing works at an optimal input amount of 5 ng and a minimum input amount down to 2 ng, which yields a high sample success rate from one standard 10 ml of blood draw. The TAT of the fingerprinting and the ctDNA detection steps is 5-7 days, respectively. **Conclusions:** The TSO MRD assay demonstrated high analytical sensitivity and specificity in detecting the presence of ctDNA from low input plasma samples with automated workflow and fast TAT. This assay enables a single streamlined solid tumor MRD platform for multiple cancer types. Research Sponsor: None.

RNA-based fusion testing in gastrointestinal (GI) carcinomas: A single-institution experience.

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Background: Molecular profiling with next-generation sequencing is critical to provide appropriate clinical care in most GI cancers. However, outside of biliary tract cancers (BTCs), the utility of routine comprehensive fusion testing in GI carcinomas is not well established. We evaluated fusion testing of GI carcinomas in routine clinical care at Massachusetts General Hospital Cancer Center (MGHCC). **Methods:** Patients with confirmed GI carcinomas who underwent RNA-based tissue fusion testing at MGHCC between Jan 2016 and April 2023 were included. Samples with tumor cellularity <20% or not meeting quality controls were excluded. Fusions of known clinical relevance were evaluated for molecular and histopathologic associations. **Results:** 2300 GI cancers with at least 1 fusion assay were included (see Table). As expected, BTCs had the highest incidence of fusions (13.7%), 80% of which were *FGFR2*. Fusions were detected in 3.9-7.7% of colorectal (CRC), pancreatic ductal (PDAC), esophagogastric (EGC), and small bowel (SBC) carcinomas. Fusions of *BRAF*, *FGFR1-3*, *NTRK1/3*, *RSPO2/3*, and *NRG1* were rare (excepting *FGFR2* in BTCs) but observed in 3 or more cancer types. Consistent with prior studies, the 3 *NTRK1* fusions observed in CRC were associated with MLH1 loss and 15 of 21 (71%) PDAC tumors with fusions were *KRAS* wild-type (WT). *RSPO2/3*fusions were the second most frequent after *FGFR1-3*. *RSPO3*fusions were predominantly seen in CRC and SBC and were associated with poorly differentiated histology (43%), microsatellite stability (100%), *APC* WT (92.6%), and *KRAS* (44.4%), *BRAF* V600E (40%), and *BRCA1/2* mutations (29.6%). Of 5 *RSPO2*fusions, 4 were in EGC and 100% had poorly differentiated histology and *TP53* mutations. No fusions were detected in 47 GI neuroendocrine tumors. **Conclusions:** Although individually rare, in aggregate RNA-based testing identifies clinically relevant fusions in a small but significant fraction of BTC, CRC, PDAC, EGC, and SBC. Molecular selection may identify subpopulations in which fusion testing is higher yield. CRC and SBC harboring RSPO3 fusions have a distinct molecular and pathologic phenotype, including a potentially novel association with *BRCA1/2* mutations. Several detected fusions had novel partners that were nonetheless predicted actionable, highlighting the utility of partner-agnostic fusion testing in this population.
Research Sponsor: None.

	Recurrent fusions, n (%)									
GI Cancer	**BRAF**	**FGFR1-3**	**NTRK1/3**	**NRG1**	**RET**	**RSPO2/3**	**MET**	**CLDN18**	**Other**	**Total**
BTC (n=395)	1 (0.3)	43 (10.9)	0	1 (0.3)	0	1 (0.3)	4 (1.0)	0	4 (1.0)	54 (13.7)
CRC (n=835)	3 (0.4)	1 (0.1)	4 (0.5)	1 (0.1)	2 (0.2)	21 (2.5)	1 (0.1)	0	5 (0.6)	38 (4.6)
PDAC (n=557)	5 (0.9)	6 (1.1)	2 (0.4)	3 (0.5)	0	2 (0.4)	0	1 (0.2)	1 (0.2)	21 (3.8)
EGA (n=346)	1 (0.3)	5 (1.4)	0	1 (0.3)	0	4 (1.2)	0	4 (1.2)	5 (1.4)	21 (6.1)
SBA (n=52)	1 (1.9)	0	0	0	0	3 (5.8)	0	0	0	4 (7.7)
Other (n=115)	0	0	2 (1.7)	0	0	1 (0.9)	0	0	0	2 (1.7)
Total (n=2300)	11 (0.5)	55 (2.4)	8 (0.3)	6 (0.3)	2 (0.1)	32 (1.4)	5 (0.2)	5 (0.2)	19 (0.8)	141 (6.1)

Association of complementing circulating tumor DNA and circulating tumor cells load on stable and progressive disease in treated patients.

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Background: Post curative-intent surgery and therapy, the presence of circulating tumor DNA (ctDNA) load represents Minimal Residual Disease (MRD). Conversely, presence of Circulating Tumor Cells (CTCs) in I-II cancer stage or even in disease free survival (DFS) patients indicates occult Cellular Residual Disease (CRD) with undetectable micro-metastasis. Thus these complementary biomarkers undergoing treatment are the indicators of non-responsiveness outcome suggesting the treatment modifications. **Methods:** Retrospectively, we monitored a cohort of 46 cancer patients for MRD using ctDNA and CTCs- treated or undergoing treatment (e.g. lung, breast, colon, HNC (n = 14, 7, 6, 4, respectively). OncoMonitor test detected single nucleotide variation (SNVs), small insertions and deletions (INDELs), copy number variations (CNVs), and translocations (fusions). Libraries were prepared using a hybridization-capture method covering 1000 targets with mean sequencing depth 5000X on Illumina Nextseq 2000 in a pair-end mode (150 x2). Variant calling was performed using a proprietary bioinformatics pipeline iCare. CTCs were isolated using the OncoDiscover platform possessing anti EpCAM antibody based immunomagnetic system per 1.5 mL blood. CTCs were confirmed with CK18+, PD-L1 and CD45 using a motorized fluorescence microscope. **Results:** From ctDNA, 47.82% (n = 22) of patients identified with at least 1 actionable genomic finding. 13.04% (n = 6) patients showed EGFR driver mutations. Also, 19.56% (n = 9) patients were identified with either EGFR driver/KRAS/PI3K passenger mutations with 4.34% (n = 2) identified with ALK-EML4 fusion. The average ctDNA load obtained in patients with progressive disease (n = 26) was 8.2 molecules per 1mL of plasma. At least 1 CTC was detected in 61.53% (n = 16) of progressive disease patients with the highest of 4 CTCs identified in 7.69% (n = 2) of patients. Only 30% (n = 6) of patients with stable disease were identified with at least 1 genomic finding from a total of 20 patients upon ctDNA analysis with an average ctDNA load of 2.2 molecules per 1mL of plasma. Patients with clinically progressive disease showed ctDNA load ~4 fold higher than in patients with stable disease upon treatment. No patients were identified with 4 CTC in the stable disease cohort as opposed to 7.69% in progressive disease patients upon treatment. **Conclusions:** We observed ctDNA and CTCs complementing MRD status, even post curative-intent surgery and therapy with prophecy for such patients likely to progress. Our findings are strongly indicative of positive correlation between ctDNA load, number of CTC detected, and disease progression from radiological findings for practical and clinical decisions. More studies in this direction are imperative to attain the follow ups for better clinical outcome. Research Sponsor: None.

Analytical validation of the Labcorp Plasma Complete test to enable precision oncology through solid tumor liquid biopsy comprehensive genomic profiling.

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Background: To help guide treatment decisions and enable clinical trial matching for cancer patients, tumor genomic profiling is an essential precision oncology tool. Liquid biopsy may be used as a complementary approach to assess tumor-specific DNA alterations circulating in the blood. The Labcorp Plasma Complete test is a next-generation-sequencing (NGS), cell-free DNA (cfDNA) comprehensive genomic profiling test that identifies actionable and clinically relevant variants in advanced and metastatic solid cancers across 521 genes. **Methods:** The Labcorp Plasma Complete test is a hybrid capture based, targeted NGS test, optimized for 25 ng of cfDNA input and is intended for variant detection in all solid cancer indications. The test interrogates all coding exons of 521 genes to comprehensively detect single nucleotide variants (SNVs) and insertion and deletions (indels). The test also reports copy number amplifications (CNAs) and gene translocations in 12 genes, and microsatellite instability (MSI). In total, 631 cancer patient plasma samples were evaluated by the test including lung, breast, colorectal, head and neck, pancreatic, gynecologic, and prostate cancers among other indications. Well-characterized reference samples (Genome in a Bottle) were utilized to assess analytical specificity. Contrived cell lines and clinical samples were utilized to establish analytical sensitivity, accuracy, as well as precision, reproducibility, and repeatability (PRR). **Results:** The test yielded results for 98.3% (620/631) of cases and identified variants in 94.7% (587/620) with a median of 6 variants per case. Clinically actionable variants were detected in 42.1% of clinical samples. Analytical specificity was $\geq$99.9999% for SNVs and 100% for indels, CNAs, translocations, and MSI. Analytical sensitivity (limit of detection, 95%) was verified for each variant type, with a median variant allele frequency (VAF) of 1.42% for SNVs and 1.43% for indels, 1.7-fold for amplifications, 0.35% fusion read fraction for translocations, and 0.82% VAF for MSI. The intra-laboratory PRR study resulted in 94.9% average percent agreement (APA) and 99.9% average negative agreement (ANA) for sequence variants (SNVs and indels) and 100% APA and ANA for CNAs, translocations, and MSI. Orthogonal assays including other NGS tests and digital PCR were utilized to assess Labcorp Plasma Complete accuracy which demonstrated an aggregate analytical concordance of 96.28% positive percent agreement and >99.9999% negative percent agreement for all variants. **Conclusions:** The analytical validation of the Labcorp Plasma Complete test demonstrates that the liquid biopsy approach is highly sensitive, specific, accurate, reproducible, and robust for comprehensive genomic profiling to complement tissue-based testing and inform clinical decision making. Research Sponsor: None.

Development, comparative study, and external validation of a new deep learning model for predicting genome-wide gene expression from histopathology slides.

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Background: In recent years, the use of tumor molecular profiling in clinical settings has enhanced cancer diagnostics, as well as the delivery of precision oncology. Recently, several methods for predicting gene expression directly from Haematoxylin-and-Eosin-stained (H&E) histology images have offered a new way to leverage the easily obtainable and cost-effective H&E images for multiple precision oncology applications. We previously introduced such a method – DeepPT – and demonstrated how we can leverage its imputed gene expression for successful prediction of drug response, through our ENLIGHT-DeepPT platform. In our previous publication and in an independent study comparing six different methods, DeepPT exhibited the best overall gene expression prediction accuracy. **Methods:** Here we present a new version, *DeepPT 2.0*, with improved architecture, including multi-task learning and a feature space based on a self-supervised pre-trained deep network. We tested both versions of DeepPT and the leading competing methods on patient data from 17 cancer subtypes included in TCGA. In addition, we obtained a new dataset collected at the Medical University of Bialystok (UMB) consisting of matched slide images and mRNA expression from 151 cases representing 7 cancer subtypes. These serve as an external validation to demonstrate that DeepPT generalizes well. **Results:** Our findings indicate that both versions of DeepPT show statistically significant improvement compared with the other methods in terms of median Pearson correlation of top predicted genes - the only metric available for all methods. Moreover, DeepPT 2.0 significantly improves upon version 1.0, demonstrating up to a 3-fold increase in the number of well-predicted genes (defined as genes with Pearson ? $>$ 0.4 between actual and predicted mRNA expressions) for 14 of the 17 cancer subtypes tested. On the external validation data from UMB, DeepPT 2.0 improves gene expression prediction in 6 of 7 of the tested cancer subtypes, with up to a 7-fold increase in the number of well-predicted genes, thus mitigating the concern of overfitting on the training set. Immune genes are particularly well predicted, as we previously observed: using a set of 826 hallmark immune genes, DeepPT 2.0 exhibits up to 3.5-fold and 2-fold increase in the percentage of well-predicted genes in the TCGA and UMB data, respectively, compared to all other genes. **Conclusions:** DeepPT 2.0 significantly improves upon competing methods for predicting mRNA expression from H&E slides across multiple metrics and diverse cancer types. Furthermore, it demonstrates robust generalization to slides from sources not previously seen. The method's good ability to predict the expression of immune genes suggests a potential benefit in predicting response to immunotherapy using the ENLIGHT-DeepPT platform, as indeed demonstrated elsewhere. Research Sponsor: None.

Effect of breast tissue density on cell-free orphan non-coding RNAs secreted by breast cancers.

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Background: Early detection of breast cancer is crucial for improved patient outcomes but cannot always be achieved through mammography for the more than 40% of women with dense breast tissue (BI-RADS C & D). Breast density masks the appearance of tumors, reducing mammographic sensitivity, which can result in false negatives and delayed diagnosis. Orphan non-coding RNA (oncRNAs) are a novel category of small RNAs that are present in tumors and largely absent in healthy tissue. We have recently demonstrated that oncRNAs secreted from breast cancer cells into the bloodstream enable early detection of breast cancer with high sensitivity and specificity. Here, we examine whether these oncRNAs are unaffected by breast tissue density, making them an effective blood-based biomarker in women with dense breast tissue. **Methods:** We prospectively collected serum samples and demographic/baseline characteristics from women being screened for breast cancer and analyzed samples from patients with documented breast cancer. We first assayed the cell-free small RNA content of every sample at an average depth of 50 million 50-bp single-end reads. Reads were then annotated using our proprietary RNA database to quantify oncRNA burden (expressed as the count of oncRNA reads per million mapped, unique reads). A previously developed oncRNA-based AI model for breast cancer detection was applied to calculate an oncRNA score for every sample. We compared both the oncRNA burden and the oncRNA score between breast density groups of fatty breast tissue (BI-RADS A & B) vs. dense breast tissue (BI-RADS C & D) using the Mann-Whitney (MW) *U* test and the Student's *t*-test. **Results:** Of 68 women with breast cancer, 25 women had fatty breast tissue and 43 had dense breast tissue. Cohort characteristics were similar between women with fatty and dense breast tissue (cohort mean age: 58.9±11.6yr, BMI: 30.11±7.57, 74% Caucasian/White, 18% Hispanic, and 9% Black. In the overall cohort, all cancer stages were represented (I: n=36, II: n=18, III: n=10, IV: n=4), T-stage (T1: n=36, T2: n=23, T3: n=4, T4: n=5). The proportion of early stage (I/II) patients is comparable between women in the two breast density groups: fatty breast tissue, (21/25 = 84%) and dense breast tissue (33/43 = 77%). We did not observe a statistically significant difference in oncRNA burden (mean 56,452 counts per million or CPM vs 59,429 CPM in fatty vs. dense tissue, MW p=0.52; t=-0.59, p=0.56) nor in oncRNA score (mean 0.496 vs 0.554 in fatty vs. dense tissue, MW p=0.42; t=-0.79, p=0.43) between breast density groups. **Conclusions:** Taken together, our results indicate that unlike mammograms, the use of oncRNAs for detecting breast cancer are not influenced by breast density. Further research will utilize oncRNA score in determining breast cancer early detection in women with dense breast tissue. Research Sponsor: None.

Non-invasive colorectal cancer detection using multimodal deep learning ensemble classifier.

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Background: The demand for alternative, non-invasive methods for colorectal cancer (CRC) screening is substantial. Cell-free DNA (cfDNA) whole genome sequencing (WGS) offers a promising avenue, utilizing diverse fragmentomic data. We aimed to develop a new approach: integrating fragment end motif by size (FEMS) with genomic coverage (COV) of cfDNA to enhance CRC screening. **Methods:** Participants were comprised of 1,506 colonoscopy verified normal samples, 130 advanced adenoma (AA) patients, 302 CRC patients (stage I: 28.5%, stage II: 25.5%, stage III: 31.1%, stage IV: 14.2%, unknown: 0.7%). We generated low depth cfDNA-WGS data (a minimum 40 million reads per sample) using the Novaseq 6000 sequencer. We minimized batch bias by normalizing with the same samples for each experimental batch. The development set comprised 1,332 samples (1,023 normal, 103 AA, and 206 CRC), while the validation set consisted of 606 samples (483 normal, 27 AA, and 96 CRC). **Results:** Our new algorithm achieved 84.0% sensitivity (95% CI: 81%-86%) for CRC and 69.9% (95% CI: 66%-81%) for AA in the development set, with a specificity of 90.0%. These findings were consistent in the external set with 84.9% specificity (95% CI: 82%-88%) and sensitivities of 80.2% (95% CI: 72%-88%) and 63.0% (95% CI: 44%-82%) for CRC and AA, respectively. The sensitivities across stages (Stage I: 80%, Stage II: 86.8%, Stage III: 78.8%, Stage IV: 96.7%) were similarly reflected in the validation sets (Stage I: 74%, Stage II: 83%, Stage III: 79%, Stage IV: 92%). **Conclusions:** Our multimodal deep learning model shows promise for accurate non-invasive colon cancer and AA detection using low-coverage cfDNA WGS. Its strong performance in detecting not only CRC but also AA lesions suggests its potential for early intervention and improved patient outcomes. The use of colonoscopy-verified normal samples strengthens the study's credibility and paves the way for future clinical translation. Research Sponsor: None.

Nature and distribution of methyl thioadenosine phosphorylase (*MTAP*) genomic loss in human tumors.

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Background: *MTAP* genomic loss, often but not exclusively a bi-allelic homozygous deletion, has recently emerged as important biomarker guiding a novel synthetic lethality mechanism for drugs in the class of PRMT5 and MAT2A inhibitors. In the current study, we assessed the nature and distribution of *MTAP* complete and partial loss in a variety of tumor samples. **Methods:** A total of 291,391 tissue samples underwent comprehensive genomic profiling (CGP) using a hybrid-capture method to evaluate all classes of genomic alterations (GA), and determine the microsatellite instability (MSI) status, tumor mutational burden (TMB), homologous recombination deficiency (HRD) score and genomic ancestry. The distribution of both complete and partial loss of *MTAP* was also determined. **Results:** *MTAP* GA were found in 8.6% of total with 9.3% genomic loss and 0.1% each short variant mutations and rearrangements. Important (not rare) tumor types with the most frequent *MTAP* loss included: 42.6% of glioblastoma (GBM), 13.4% of non-small cell lung cancer (NSCLC), 22.3% of pancreatic ductal and 24.9% of bladder urothelial carcinomas. The most frequently co-altered GA included *CDKN2A* (99.7%), *CDKN2B* (95.1%), *TP53* (55.4%), *KRAS* (30.1%), *TERT*(20.5%) and *PIK3CA* (12%). In tumor types with frequent known targetable driver GA including short variant mutations in *EGFR*, *ERBB2*, *BRAF*, *FGFR2-3*and *MET* and fusions involving *ALK*, *RET*, *ROS1* and *NTRK1-3*, *MTAP* loss was not associated with decreased frequencies of GA in these genes. The frequencies of MSI-high status was 0.3% and of TMB≥10 mut/Mb was 17%. In total, 63.7% of the *MTAP* loss cases involved deletion of all 8 *MTAP* exons (complete loss) with partial loss accounting for 36.3% of cases. All partial loss cases involved loss of multiple exons (35.8%) except for loss of only exon 8 (0.5%). There was no impact of *MTAP* loss status on genomic ancestry, cosmic trinucleotide signature and HRD score. The multiple exon loss frequencies included exons 2-8 loss in 24.7%, exons 5-8 loss in 4.1%, exons 6-8 loss in 3.3%, exons 3-8 loss in 1.6%, exons 7-8 in 1.1%, exon 4-8, 1-5, 2-7,2-5, 1-4, 2-6, 3-7 and 5-7 all at less than 1% frequencies. **Conclusions:** *MTAP*loss is a frequent GA of emerging clinical importance as the trials using PRMT5 and MTA-2 inhibitors progress. *MTAP*loss is frequent in common cancers of the brain, lung, pancreas and bladder and not associated with diminishment of other targetable driver mutations. Although one-third of *MTAP* loss is a partial loss, the partial loss cases involve near total (exons 2-8) loss and may well also be indicative of PRMT5/MAT2A inhibitor benefit. This study strengthens the opportunity to consider a tumor-agnostic approach to targeted therapies. Research Sponsor: Foundation Medicine.

MTAP Status	Frequency
Complete loss	63.3%
Exon 2-8 loss	24.7%
Exon 5-8 loss	4.1%
Exon 6-8 loss	3.3%
Exon 7-8 loss	1.6%
Exon 4-8 loss	0.6%
Exon 8 loss	0.5%
Other less common multi-exon losses	All $<$ 0.15%

Therapeutic implications of phosphoproteomics in molecular cancer diagnostics.

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Background: Precision oncology approaches employing genomics-guided targeted therapies for individual patients have provided significant survival benefits in several cancer types. However, varying response rates in solid malignancies, many patients without actionable genomic lesions, and increasing evidence that non-genomic mechanisms may play an important role in tumors indicate that genomics alone is often insufficient to inform and guide the clinical care of patients. Since most targeted anti-cancer drugs inhibit the activity of protein kinases, measuring the tumor phosphoproteome as a direct readout of oncogenic pathway activity is poised to enhance molecular stratification. **Methods:** We established a clinical (phospho)proteomic workflow for integration into the molecular tumor board (MTB) workflow of the Germany-wide INFORM (for children with relapsed cancers) and MASTER (for young adults with refractory cancers and patients with rare tumors) registry studies and profiled $>$ 1000 tumor tissue specimen from patients enrolled in the DKFZ/NCT/DKTK MASTER study or the INFORM registry trial. To assess the aberrant activity of druggable signaling pathways, we developed a new tumor pathway activity (TUPAC) scoring methodology using expression data of $>$ 8,000 proteins and $>$ 20,000 phospho-sites per patient in a heterogeneous pan-cancer cohort. TUPAC scores integrate protein expression and phosphopeptide abundance data at several levels to detect aberrant signaling pathway activities of several interdependent oncogenic signaling pathways within one tumor specimen. **Results:** We show for the first time that comprehensive (phospho)proteome profiling is feasible and informative in a real-world prospective precision oncology setting. Discussion of (phospho)proteomic data of $>$ 500 prospective patients in weekly MTB meetings revealed that adding a (phospho)proteomic layer can supply critical information for personalized therapies that is not discernible from genomic and transcriptomic data. In an independent value evaluation (329 target recommendations in 104 patients), the phosphoproteome layer was decisive in 22% of all recommended targets. Based on anecdotal cases with available clinical follow-up, we provide evidence that (phospho) proteome profiling carries important diagnostic value by detecting actionable tumor-driving kinase signaling in patients without actionable genomic lesions or by functionalizing genomic variants of unknown significance. **Conclusions:** Measuring the tumor phosphoproteome as a direct readout of oncogenic pathway activity is feasible and adds complementary, therapy-relevant information in a real-world prospective precision oncology setting. Research Sponsor: None.

Development and validation of mFISHseq: A diagnostic test using multiplexed RNA-FISH–guided laser capture microdissection RNA sequencing.

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Background: Breast cancer (BCa) is a heterogeneous disease requiring precise diagnostic tools to guide effective treatment strategies. Current diagnostic assays, including various multigene assays, often fail to adequately address the complex biology of BCa subtypes. To address these limitations and enhance the understanding of BCa biology, we developed and validated a novel diagnostic, prognostic, and predictive tool, called mFISHseq. **Methods:** Our approach, mFISHseq, integrates multiplexed fluorescent *in situ* hybridization (FISH) of the four main BCa biomarkers, estrogen (*ESR1*)/progesterone (*PGR*)/Her2 (*ERBB2*) receptors and Ki67 (*MKI67*), which are used to guide laser capture microdissection (LCM) of regions of interest followed by RNA-sequencing. This technique ensures tumor purity, facilitates interrogation of tumor heterogeneity, consequently permitting unbiased analysis of whole transcriptome profiling data and explicitly quantifying the variability between different tumor regions. We validated mFISHseq on a retrospective cohort study involving 1,082 FFPE breast tumors with detailed clinicopathological data, informed consent, and ethical committee approval. **Results:** mFISHseq demonstrated excellent analytical validity with a 93% accuracy rate compared to standard immunohistochemistry (IHC), while providing more quantitative biomarker expression. Prespecified threshold values for mFISHseq derived from a split 70:30 training/test set showed exceptional concordance with IHC as demonstrated by area under the receiver operating characteristic (ROC) curves for all markers (AUC: *MKI67*=0.98, *ERBB2*=0.95, *ESR1*=0.95, *PGR*=0.93). Both RNA-FISH and -SEQ showed moderate to very strong correlations (Spearman's r; *ERBB2*=0.41, *MKI67*=0.61, *PGR*=0.66, *ESR1*=0.75), thus highlighting the potential to use both orthogonal methodologies to cross-validate results. To demonstrate clinical validity, we developed a 293-gene intrinsic subtype classifier, showing substantial agreement to established classifiers like PAM50 and AIMS (Cohen's κ= 0.75 and 0.73, respectively) and superior prognostic performance. We also report that LCM is an essential component of the mFISHseq workflow, since samples that did not undergo LCM showed reduced biomarker expression, elevated non-tumor gene expression, and misclassification of samples into less aggressive molecular subtypes (e.g., normal-like) and prognostic risk groups (e.g., high to low). **Conclusions:** The mFISHseq method showed excellent concordance with IHC and the use of LCM provides tumor-enriched samples that are devoid of contamination from non-tumor elements, thus providing unbiased spatially resolved interrogation of tumor heterogeneity. Altogether, mFISHseq solves a long-standing challenge in the precise diagnosis and classification of breast cancer subtypes. Research Sponsor: European Commission; Agreement No 946693; National Cancer Institute/U.S. National Institutes of Health; CA24779 01 grant to Fresia Pareja; MultiplexDX.

Utility of [18F]FDG PET/CT in predicting pathological complete response to neo-adjuvant therapy in breast cancer: A prospective study.

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Background: The achievement of a pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) is a major milestone in the treatment of breast cancer (BC), offering an improved prognosis. The new revolutionary frontier is to potentially eliminate the need for surgery in selected cases with an excellent response to NAC. This approach would lead to improved patient outcomes and cost effectiveness. The current standard for assessing residual cancer after NAC is to perform an invasive procedure and biopsy. In this study, we investigate the utility of [18F]FDG PET/CT as a predictive tool for pCR following NAC in BC patients. **Methods:** We conducted a prospective study of patients with newly diagnosed BC who underwent NAC, with [18F]FDG PET/CT assessment at baseline and after NAC prior to surgery. Clinical and pathological data were collected, with response to NAC categorised as pCR or non-pCR based on definitive histopathology, supplemented by assessment using the Residual Cancer Burden (RCB) index. Semi-quantitative parameters including SUVmax and tumour to background ratio (TBRmax) were calculated for the primary tumour at baseline and pre-operative PET/CT scans. Differences between groups were assessed using the Kruskal-Wallis test. Correlations between outcomes and potential predictors were explored using multivariate logistic regression analyses. Statistical significance was set at $p < 0.05$. **Results:** Our study cohort comprised 134 BC patients with a median age of 49.5 years, predominantly HER-2 positive (n=74) and stage II disease (n=104). Of these, 69 patients achieved pCR after NAC. The RCB index was assessed in 94/134 patients, showing varying degrees of residual disease burden (59 RCB-0; 5 RCB-I; 24 RCB-II; 6 RCB-III). Baseline SUVmax and TBRmax showed correlations with key tumour characteristics, including BC subtype (TBRmax was 9.56 vs 5.6 vs 10.2 in luminal, HER-2+ and TNBC, respectively; p=0.005) and ki-67 expression (rho 0.32, p=0.002). However, baseline SUV and TBR parameters failed to discriminate responders to NAC. Conversely, preoperative TBRmax showed significant associations with both pCR (1.09 vs 1.75 for pCR and non-pCR; $p<0.001$) and RCB index (1.09 vs 1.21 vs 1.32 vs 4.25 for RCB-0, I, II, III; $p<0.001$). Logistic multivariate analysis identified TBRmax as a significant predictor of pCR both at baseline (OR 1.07, p=0.04) and at preoperative assessment (OR 0.2, $p<0.001$). In addition, preoperative TBRmax emerged as a significant predictor of response based on the RCB index (OR 5.5, p=0.004). **Conclusions:** Our research shed light on the significant clinical utility of semi-quantitative parameters derived from [18F]FDG PET/CT scans in predicting pCR in BC patients undergoing NAC, potentially advancing the frontiers of BC management and encouraging its integration into the decision-making framework for assessing response to NAC. Research Sponsor: 5x1000 Humanitas Research Grant.

Assessing the value of repeat next generation testing in patients with non-small cell lung cancer: A retrospective review.

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Background: Analyzing a tumor's molecular profile in non-small cell lung cancer (NSCLC) by next generation sequencing (NGS) has been essential in the advancement of precision medicine and has led to development of several targeted therapeutic agents. While their use significantly improves patients' outcomes, patients will inevitably develop progression of disease. Tumor sequencing at the time of progression, whether tissue or liquid biopsy, is important to identify the mechanism of resistance. We sought to investigate which patients benefit from repeat NGS testing which ultimately allowed for changes in their therapeutic management based on its updated molecular profile. **Methods:** We performed a single institution retrospective study of patients with NSCLC between 2014-2023 who have undergone two or more NGS sequencing. Testing was performed through Foundation One tissue CDx or liquid CDx. Data obtained through chart review included NSCLC stage, NGS dates and results, and treatments received. We evaluated clinically meaningful results from repeat testing if patients were continued on their targeted therapy, were switched to or received additional targeted therapy, detected a target when prior tests were negative, had a change in their systemic therapy, or confirmed recurrence or a second primary. **Results:** A total of 277 subjects with NSCLC were identified to have had more than one NGS sequencing. The average number of NGS obtained was 2.90. The average number of liquid NGS was 2.15 and tissue based NGS was 0.75. Out of the 277 patients, repeat testing was clinically meaningful in 134 (48%) patients. Of the 134 patients, 67 (50%) harbored EGFR, 16 (11.9%) ALK, 9 (6.7%) KRAS, 6 (4.5%) ROS1, 6 (4.5%) MET exon 14 skipping, 3 (2.2%) ERBB2, 1 (0.7%) BRAF, and 1 (0.7%) RET as their primary driver alteration upon initial testing. 25 patients (18.7%) had other alterations or no alterations. NGS was repeated for early stage localized recurrence in 8 patients (6%), stage I-III who developed new metastasis in 18 patients (13.4%), and recurrent metastasis in 108 patients (80.6%). Of the patients who clinically benefited from repeat testing, 77 patients (57.5%) were continued or resumed on their targeted therapy, 19 (14.2%) were switched to or received additional targeted therapy, 12 (9%) detected a target when prior tests were negative, and 3 (2.2%) had a change in their chemotherapy or immunotherapy. In 23 patients (17.1%), repeat NGS either confirmed recurrence (n=14) or second primary (n=9). **Conclusions:** Repeat NGS testing in NSCLC can be clinically meaningful to guide management, such as in detecting a target when prior tests were negative, allowing for switch in, continuation of or addition of targeted therapy, or providing confirmation of a recurrence or a second primary. Further research is warranted in this field to evaluate if repeat NGS can ultimately improve clinical outcomes in these patients. Research Sponsor: None.

Clinical validation of Northstar Select, a novel liquid biopsy assay for comprehensive genomic profiling of solid tumors.

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Background: Comprehensive Genomic Profiling (CGP) liquid biopsy tests are vital tools for oncologists that enable the non-invasive detection of diverse somatic mutations, many of which correspond to targeted therapies, in circulating tumor DNA (ctDNA). However, these tests have less utility when ctDNA signal is low, which is common even in late-stage cancer patients. BillionToOne's Northstar (NS) Select assay is a novel CGP test that seeks to leverage proprietary technology and novel calling algorithms to address this limitation by achieving higher sensitivity. **Methods:** Clinical samples for 182 unique patients with stage III or IV solid tumors were obtained via a prospective validation study assessing head-to-head concordance with widely adopted, commercially available 'comparator' liquid biopsy CGP assays. The study cohort was recruited from 1 large hospital center and 6 community clinics across the US and was diverse in patient demographics and clinical presentations. Over 15 different cancer types were represented in the cohort, with the majority of patients having either Lung, Breast, Colorectal, or Prostate cancer, all of which are commonly tested using liquid biopsies in the US. Pathogenic (including likely pathogenic) variants called by NS Select and/or the comparator assay were analyzed for concordance. For a subset of samples (N=28), white blood cell-derived genomic DNA was also processed to identify which variants were detected due to clonal hematopoiesis of indeterminate potential (CHIP). **Results:** In the head-to-head comparison, a large number of variants (N=380) were concordant between the two assays. In addition, NS Select detected 43% (N=147) more pathogenic variants than comparators when controlling for matched coverage regions. The majority of these variants were detected below the reported limit of detection of the comparator assays, but above the limit of detection of NS Select. The rate of CHIP mutations was not significantly different in the variants detected by NS Select (19.0% ± 7.6%) vs. comparators (17.2% ± 9.2%). Finally, the proportion of patients with no pathogenic variants detected was shown to be lower by 45% when using NS Select vs. the comparator assays (20/182 vs. 36/182). **Conclusions:** NS Select reported clinically useful information about the tumor for most patients. For patients in which ctDNA signal was high, NS Select had very high concordance with comparator tests. Furthermore, additional low-VAF pathogenic mutations identified by NS Select translated to a higher diagnostic yield compared to other CGP assays, and CHIP was ruled out as an explanation for these additional detections. This suggests that some patients with low levels of ctDNA would derive clinical benefit from testing with NS Select due to its high sensitivity. Research Sponsor: None.

A pan-cancer analysis of SMARCA4 alterations and the unique clinicogenomic characteristics associated with SMARCA4 mutation types.

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Background: SWI/SNF complexes are regulators of cell lineage and alterations in these proteins occur in >20% of solid tumors with *SMARCA4*being the most common. *SMARCA4* mutations are associated with worse clinical outcomes in various cancer types but are also vulnerable to novel SMARCA2 inhibitors currently being evaluated in clinical trials. We examined *SMARCA4* alterations across cancer types to understand their interplay with other genomic abnormalities and clinical consequences. **Methods:** We analyzed the Memorial Sloan Kettering (MSK) institutional cohort profiled by MSK-IMPACT tumor-normal sequencing. *SMARCA4* mutations were annotated based on OncoKB and literature. FACETS resolved zygosity and genomic metrics of complexity including tumor mutational burden (TMB) and fraction genome altered (FGA). The pan-cancer landscape of somatic *SMARCA4* mutations was mapped by both category (Class I vs II) and zygosity (mono- vs biallelic). DISCOVER was employed to evaluate mutational signatures and frequency-adjusted co-occurring and mutually exclusive mutations. We then extracted progression-free (PFS) and overall survival (OS) to systemic therapy using natural language processing. **Results:** We identified 3,385 tumors from 3,049 patients across cancer types with a total 3,965 oncogenic somatic *SMARCA4* alterations. Copy number estimation was successful for 2,343 (69%). Non-small cell lung cancer (NSCLC) was the most abundant *SMARCA4*-alteredhistology (n=493, 7.1% of all NSCLC), and the majority (87%) were biallelic. Other common histologies were colorectal (n=163, 2.9%), bladder (n=122, 5.5%), uterine (n=88, 4.3%), pancreatic (n=81, 3.2%) and esophagogastric (n=92, 4%). *SMARCA4*biallelic mutated tumors had higher chromosomal instability compared to WT (FGA = 0.53 vs 0.47; $p<0.001$), while monoallelic had lower (FGA = 0.3; $p<0.001$). Monoallelic *SMARCA4* altered tumors had a higher TMB (10.5) than both WT (4.4) and biallelic cancers (6.1; $p<0.001$). Monoallelic and biallelic *SMARCA4* cancers exhibited distinct mutational signatures in most tumor types. Patients with biallelic *SMARCA4* mutations had worse outcomes with both immune checkpoint blockade (ICB) and platinum chemotherapy across in certain tumor types, whereas monoallelic uterine cancers were associated with improved outcomes with ICB. **Conclusions:** This pan-cancer clinicogenomic analysis demonstrates that monoallelic and biallelic *SMARCA4*-mutated tumors have distinguishable genomic features. In addition, biallelic SMARCA4 alterations correlated with poor outcomes across different cancer-types and classes of therapy, while improved outcomes to ICB in monoallelic *SMARCA4*alterations were potentially due to higher representation of MSI-H tumors in this subset. Our findings suggest *SMARCA4* zygosity may be important biomarkers for ongoing clinical trials in SMARCA4-deficient tumors. Research Sponsor: None.

Preliminary results from a phase 1 study of AC699, an orally bioavailable chimeric estrogen receptor degrader, in patients with advanced or metastatic breast cancer.

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Background: Endocrine therapy is a critical component of treatment for over 200,000 patients diagnosed yearly with estrogen receptor positive (ER+)/HER2- breast cancer. Although selective ER degraders (SERDs) have improved progression-free survival in this patient population, as monotherapy they have shown very limited overall response rates (ORR). AC699 is a novel chimeric degrader that binds, ubiquitinates and degrades ERα by bringing it into close proximity with an E3 ligase. This mechanism of action may result in greater specificity and more complete target blockade compared to SERDs. Initial results from the ongoing first-in-human dose escalation study of AC699 (NCT05654532) are presented here. **Methods:** The study employed a 3+3 design, with the option of adding backfill patients to each cohort cleared and deemed safe. Patients must have had locally advanced or metastatic ER+/HER2- breast cancer and received at least 2 prior lines of endocrine treatment, or at least 1 prior line if combined with a CDK4/6 inhibitor. AC699 was administered orally once daily in 28-day cycles. Tumor responses were assessed every 2 cycles using RECIST v1.1 criteria. The relationship between ESR1 mutational status and anti-tumor activity was investigated as an exploratory analysis. **Results:** A total of 22 patients had received AC699 in 3 dose cohorts (100, 200 and 300 mg) at the time of data cutoff. The median age was 61 years and the median lines of prior therapy was 5 (range 2-10). Prior treatments included CDK4/6 inhibitor (100%), aromatase inhibitor (91%), fulvestrant (82%), novel oral SERD or covalent antagonist (SERCA) (23%), and ER chimeric degrader (14%). Eighteen patients had measurable disease while 4 had bone lesions only. There were no dose-limiting toxicities, dose reductions or discontinuations for treatment-related AEs, and the maximum tolerated dose was not reached. The most common treatment-emergent AEs were fatigue (23%), dehydration (18%) and nausea (18%). All treatment-related AEs were Grade 1 or 2, including nausea (18%) and hot flushes (14%). Fifteen patients had at least 1 scan before the data cutoff date and of these, 3 were not evaluable for ORR due to having bone lesions only. Among the 12 evaluable patients, 4 (33%) achieved partial response: 3 confirmed and one unconfirmed. The clinical benefit rate (CBR) which also includes patients with stable disease ≥24 weeks was 42% (5/12). In the subgroup of evaluable patients harboring a confirmed ESR1 mutation, the ORR was 67% (4/6), the CBR was 83% (5/6) and the median time on treatment was 168 days (range 56-336), with 4 of 7 patients still receiving AC699. **Conclusions:** Preliminary data from the ongoing phase 1 trial evaluating AC699 indicate promising safety, tolerability, and anti-tumor activity, at doses up to 300 mg orally once daily. A phase 2 study will begin enrolling in early 2024. Clinical trial information: NCT05654532. Research Sponsor: None.

A novel MRI-based tumor-targeting theragnostic agent: Magnetoelectric nanoparticles in an in vivo murine *KRAS/P53* pancreatic flank tumor model.

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Background: Magnetoelectric nanoparticles (MENPs) are a novel material with a magnetoelectric (ME) property that allows for conversion of an external magnetic field to a local electric field (EF) that can be exploited to generate a Coulomb force to target and electroporate the relatively non-polarized tumor cell walls. We hypothesized that their local EF and superparamagnetic cores can be exploited as an MRI-based anti-cancer theragnostic agent for solid tumors. **Methods:** 35 immunocompetent C57BL/6 mice were inoculated with KPC961 pancreatic adenocarcinoma cells in their flank. The 27 mice with the largest tumors at 4 weeks were randomized into 5 cohorts based on treatment: 300 μg of MENP (300; n=6), 600 μg of MENP (600; n=6), 300 μg of low-ME coefficient MENP (LM; n=5), 300 μg of MENP without M1 MRI (NM; MRI field control, n=5), and normal saline (NS; MENP causal effect control; n=5). The 300, 600, LM, and NS cohorts had T_2 MRI maps (M0) on a 7T MRI. NM had T_2 weighted MRIs at M0. All mice had a neodymium magnet placed over their tumors for 12 hours after tail vein injections (300 μl for all mice) for targeting. The 300, 600, LM, and NS cohorts then underwent MRI mapping (M1) after magnet removal (No M1 MRI for NM). MRI mapping was repeated 5 days after (M2). NM had a T_2 weighted MRIs at M2. M1 and M2 data were used to assess relaxation time (contrast effect) and tumor volume from M0, respectively. Student t and ANOVA tests were used to compare differences for tumor volume and relaxation time data and one-sided Fisher's exact test was used for complete response (CR) data. **Results:** The median M0 tumor volume was 109.6 mm^3 for all mice, and there were no differences between any cohort (p = 0.978; Table). The 300 and 600 MENP cohorts demonstrated a 102.7% reduction in volume (M2/M0; 56.7% vs. 159.4% for NS and NM controls, p = <0.001) and a 7.2% T_2 negative contrast effect (M1/M0; 94.2% vs. 101.3% for NS, p = 0.046) compared to controls. Six mice in 300, 600, and LM (2 each) achieved a clinical CR (between 1 to 2 weeks after M1) vs. none in the NS and NM control cohorts (p = 0.0418), without any recurrences until end of study (6 weeks after M2). **Conclusions:** This is the first report demonstrating the theragnostic effects of MENPs having both T_2 contrast and locally ablative therapy properties as an in vivo tumor targeting agent. These results confirm prior pilot study and point towards irreversible electroporation as the likely mechanism of action (MOA) since the antitumor effect is not seen within the NM cohort. Additional studies characterizing the MOA, dose-response relationships, and immunomodulatory effects are needed to better understand their full clinical potential. Research Sponsor: Radiological Society of North America; RR2327; Departmental.

Median volumes and relaxation times.

	M0 Tumor Volume, mm^3	M2 Tumor Volume, mm^3	M2/M0 Tumor Volume, %	M1/M0 Tumor T_2, %
300	137.1	97.5	56.7%	97.4%
600	108.0	86.5	73.7%	85.8%
LM	83.7	78.8	148.8%	102.0%
NS	109.6	166.0	165.3%	101.3%
NM	84.9	140.3	159.4%	

A phase I study of ATR inhibitor BAY1895344 (elimusertib) plus topotecan (ETCTN 10402): Results of dose escalation.

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Background: Ataxia telangiectasia and Rad3-related (ATR) protein kinase is activated by replication stress and recruited to stalled forks or single strand DNA abnormalities in various cancers. The topoisomerase-I (Top1) inhibitor topotecan induces DNA damage. The ATR inhibitor BAY 1895344 (elimusertib) has demonstrated cytotoxic potential in small cell lung cancer and gastrointestinal cancer xenografts when combined with Top1 inhibitors. **Methods:** This is phase Ia study of elimusertib combined with topotecan in adult patients with refractory advanced solid tumors for whom topotecan can be considered as part of standard care. Patients with previous topotecan exposure were excluded. The study combination was assessed starting at Topotecan 1 mg/m^2 IV (D1-D5) plus elimusertib 20 mg BID (D2, D5) (Cycle=21 days). Dose escalation utilized a 3+3 design. Primary objectives were to assess safety and tolerability and estimate the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of the combination. Secondary objectives included estimating pharmacokinetic (PK) profiles and assessing anti-tumor activity of the combinations. **Results:** Eight patients were treated in dose escalation. Participants were a median of 63 years old and had received 2 median lines of previous therapy. The initial two patients enrolled into dose level (DL) 1 had dose-limiting toxicities with one of patient experiencing respiratory failure and cardiac arrest in setting of pancytopenia related to study drug. Six patients were subsequently enrolled in and received DL-1 (elimusertib decreased from 20 mg BID to 20 mg Daily) and no DLTs were observed. Notable grade 3+ treatment-related adverse events and summary best response are summarized in Table. Disease control rate was 43% among evaluation patient including one unconfirmed partial response. Median progression-free survival in the RP2D cohort was 3.45 months. PK studies are in process and results will be presented at time of meeting. **Conclusions:** RP2D and MTD was established for elimusertib in combination with Topotecan: Topotecan 1 mg/m^2 IV [D1-D5] plus elimusertib 20 mg Daily [D2, D5] every 3 weeks. Dose escalation was notably limited by myelotoxicity. Due to sponsor decision, the study was halted prior to planned expansions cohorts but the concept of ATR + topo I inhibition remains relevant. Clinical trial information: NCT04514497. Research Sponsor: NCI Cancer Therapy Evaluation Program; Bayer.

	Topotecan + BAY1895344
Select Grade 3+ TrAEs	**N=8**
Neutropenia	4 (50%)
Thrombocytopenia	3 (37.5%)
Cardiac Arrest	1 (12.5%)
Best Response	**N=7**
Partial Response	1 (12.5%) [DOR 1.4 mo]
Stable Disease	2 (25%)
Progressive Disease	4 (50%)

A phase I study of irinotecan combined with BAY1895344 (ATR inhibitor) in advanced solid tumors: Results of ETCTN 10402 dose escalation.

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Background: ATR protein kinase is activated by replication stress and recruited to stalled forks or single strand DNA defects in various cancers. The topoisomerase-I (Top1) inhibitor irinotecan induces DNA damage. The ATR inhibitor BAY1895344 (elimusertib) has demonstrated cytotoxic potential in SCLC and GI cancer xenografts when combined with Top1 inhibitors. **Methods:** This phase Ia trial assessed elimusertib in combination with irinotecan in adult patients with refractory advanced solid tumors for whom irinotecan can be considered standard care. Patients with previous irinotecan exposure were excluded. Two dosing schedules were used: 1) Biweekly - irinotecan IV (starting at 150 mg/m^2) D1 + elimusertib (starting dose 20 mg PO BID) D1,D2 (cycle=14 days); 2) Weekly - irinotecan (starting at 50 mg/m^2) IV on D1,8,15 with elimusertib (starting at 20 mg PO daily) on D2,D3,D9,D10 and D16,D17 (cycle=21 days). Dose escalation utilized a 3+3 design. Primary objectives were to assess safety and tolerability and estimate the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Secondary objectives included estimating pharmacokinetic (PK) profiles and assessing anti-tumor activity. **Results:** A total of 21 patients were enrolled in dose escalation (N=9 [Biweekly] and N=12 [Weekly], median age 58 and 2 lines of prior therapy. For the Biweekly cohort: 3/3 patients enrolled at dose level (DL) 1 experienced hematologic dose-limiting toxicity (DLT); 6 patients received DL-1 without any DLTs. The weekly regimen escalation comprised of 12 patients: 6 enrolled in DL1 with 2/6 having hematologic DLT and 5/6 unable to complete ≥75% of cycle 1 dosing; 6 enrolled in DL-1 with no DLTs observed. Notable grade 3+ treatment-related adverse events and summary best response are summarized (Table 1). The majority of evaluable patients in both schedules had initial disease control (56% [biweekly] and 67% [weekly]). One confirmed partial response was seen in the biweekly RP2D. Median progression-free survival was 2.1 mo [biweekly] and 2.5 mo [weekly]. PK results will be presented at time of meeting. **Conclusions:** Both RP2D and MTD of elimusertib in combination with irinotecan were reached for both dosing schedules: irinotecan 150 mg/m^2 IV D1 + elimusertib 10 mg BID PO D1,D2 (biweekly) and irinotecan 25 mg/m^2 IV on D1 + elimusertib (20 mg PO daily) on D2,D3 (weekly). Dose escalation was notably limited by myelotoxicity. Due to sponsor decision, the study was halted prior to planned expansion but the concept of ATR + topo I combination remains scientifically relevant. Clinical trial information: NCT04514497. Research Sponsor: NCI Cancer Therapy Evaluation Program; Bayer.

	Irinotecan Biweekly	Irinotecan Weekly
Select Grade 3+ TRAEs	**N=9**	**N=12**
Neutropenia	5 (55.6%)	7 (58.3%)
Febrile Neutropenia	1 (11%)	1 (8.3%)
Thrombocytopenia	2 (22.2%)	1 (8.3%)
Sepsis	0	1 (8.3%)
Best Response	**N=9**	**N=9**
Partial Response	1 (11.1%) [DOR 4.1 mo]	0
Stable Disease	4 (44.4%)	6 (67%)
Progression	4 (44.4%)	3 (33%)

A first-in-human trial of selective CDK7 inhibitor Q901, in patients with advanced solid tumors: Interim results of a phase I study (QRNT-009).

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Background: Q901 is a potent, covalently binding CDK7 inhibitor with excellent specificity for CDK7 against other protein kinases. Transcriptional regulation by CDK7 inhibition in cancer cells leads to DNA damage repair response inhibition and increased genomic instability. Q901 also regulates cell cycle checkpoints by inhibiting T-loop phosphorylation and transcriptionally downregulating CDK1, 2 and 4. In preclinical *in vivo* models, intravenous (iv) administration of Q901 once a week and once every three-week dosing regimen was well tolerated and showed significant antitumor activity. The safety profile, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy data for 18, 36 and 60 mg/m^2 are presented. **Methods:** QRNT-009 (NCT05394103) is an ongoing Phase 1/2 multicenter, open-label, dose escalation and expansion study. Q901 is administered iv once weekly for four weeks, then once every two weeks thereafter in patients with advanced or metastatic ovarian cancer, castration-resistant prostate cancer (CRPC), breast cancer, endometrial cancer, colorectal cancer, small cell lung cancer (SCLC), or pancreatic cancers. **Results:** As of data cutoff (12Jan2024), 17 patients received Q901 across 3 dose levels: 5 patients at 18 mg/m^2, 4 patients at 36 mg/m^2, and 8 patients at 60 mg/m^2. The median prior lines of systemic therapy were 4 (range 2 - 17). Of 17 patients who received Q901 across all doses, there were no treatment related SAEs, treatment discontinuations, or dose reductions. Most common TRAEs $\geq$ 15% were nausea (29.4%), anemia (23.6%) and fatigue (23.5%). As of data cutoff, no DLTs were observed. All plasma PK analyses across dose levels showed dose dependent increase of AUC_{0-last} and C_{max}. No major metabolite was observed. POLR2A, which is a CDK7 target engagement marker showed biologically effective change starting from 18 mg/m^2. 1 patient with pancreatic cancer who received 18 mg/m^2 had a partial response with CA19-9 reduction from 4,632 to 219. 2 patients at 18 mg/m^2 and 2 patients at 36 mg/m^2 had stable disease. Additional safety and efficacy data will be presented. **Conclusions:** Preliminary data from QRNT-009 study showed that selective CDK7 inhibitor Q901 is well tolerated. Preliminary antitumor activity and pharmacodynamic observations are encouraging. Dose escalation is ongoing to identify MTD or recommended dose for further studies. Clinical trial information: NCT05394103. Research Sponsor: Qurient Co., Ltd.

Focus on human epidermal growth factor receptor 2 (HER2) positive metastatic colorectal cancer (HER2+ mCRC): A real world retrospective analysis.

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Background: HER2+ mCRCs, displaying HER2 overexpression or *ERBB2* amplification, represent a rare molecular subset, accounting for 2- 6% of all mCRCs. HER2+ mCRCs are thought to be enriched in *KRAS*wt pts and associated with distal primary tumor location. While its prognostic value is debated, HER2 seems a negative predictor for antiEGFR agents. Recently, its role as a potential actionable target has emerged, with promising results in refractory mCRC. Despite that, nowadays HER2 testing is not routinely included in the diagnostic workup of mCRC. **Methods:** This is an observational, retrospective, multicenter study, aiming to investigate and describe clinical and molecular features and prognostic value of HER2+ mCRCs from real world pts. Pts with mCRC tested for HER2 status who received at least one line of therapy (tx) at 11 Italian Institutions within the Lazio Region between Mar2011 and Jan2024 were enrolled. HER2 status was assessed either for HER2 overexpression using IHC according to the HERACLES diagnostic criteria or for *ERBB2* amplification using NGS, followed by IHC confirmation for positive cases. Differences between groups for categorical variables were compared using the Chi Square test. Endpoint for prognostic assessment was OS, estimated with the Kaplan-Meier method and compared using log-rank test. Endpoints for predictive assessment were RR and DCR. Statistical significance was set at p .05. **Results:** 422 pts were included, of those 38 pts had a HER2+ mCRC (9%). HER2 positivity was more frequent among patients with *RAS*wt tumor compared to *RAS*mt (12.2 *vs* 6.1%; p .029), lung metastasis (p .013) and synchronous metastatic disease (p .044). No correlation with age, sex, primary tumor location, peritoneal spread, histologic grading and mucinous histology was observed. At a median FU of 19 months, OS was significantly shorter in HER2+ compared to HER2- mCRCs (HR 2.17, 95%CI 1.14-4.13; p .017). 104 pts with *RAS*wt mCRC received an antiEGFR-based first line tx and were evaluable for response; of those 96 were HER2- and 12 HER2+. RR was higher for HER2- tumors (80 *vs* 42%; p .003), while no difference was observed for DCR (96 *vs* 83%; p .085). Of 38 HER2+ tumors, 14 received an antiHER2 tx, of those 11 were *RAS*wt and 3 *RAS*mt. *RAS* status did not impact on antiHER2 activity (DCR 64 *vs* 33% for *RAS*wt and *RAS*mt; p .347). **Conclusions:** We showed that HER2+ mCRCs are more frequently, although not exclusively, *RAS*wt, display a lung tropism, present with synchronous metastases and have a negative prognosis. Moreover, in accordance with results from DESTINY-CRC02, the target actionability seems to be retained irrespective of *RAS* status. Given also the possible use in first line of antiHER2 tx in the near future, the baseline molecular diagnostic workup of mCRC must include HER2 status assessment, irrespective of *RAS* mutational status and primary tumor location. Research Sponsor: None.

Long-term efficacy, safety and PK data of TH1902 (sudocetaxel zendusortide) in solid tumors: A novel SORT1-targeting peptide-drug-conjugate (PDC).

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Background: TH1902 is a novel SORT1 targeting PDC. It exploits the natural function of SORT1, a scavenger receptor, which rapidly internalizes its natural ligands via endocytosis (internalization half-life $\leq$4 min). SORT1 is highly expressed in multiple solid tumors compared to normal healthy tissues making it an attractive target for rapid delivery of anti-cancer therapeutics. In this updated analysis, further data on long-term efficacy, safety and PK is presented from Parts 1&2 of Ph1 with focus on the 300 mg/m^2 q3w. Due to safety observations in 6 patients (pts) enrolled at 420 mg/m^2 dose level (Gr 3 neuropathy [n=2], Gr 4 neutropenia [n=2], Gr 3 ocular [n=1] and Gr 2 skin [n=3] toxicities, the dose was reduced to 300 mg/m^2 in Part 2. **Methods:** Primary objective of the study was to characterize the safety/tolerability of TH1902. Part 1 (modified intrapatient dose escalation) included pts with recurrent/refractory advanced solid tumors (all comers) with no limit on number of previous therapies, including taxanes. Part 2 (dose expansion) included pts with known high SORT1 expression (e.g. OVC, endometrial, TNBC, melanoma). **Results:** Twenty-five heavily pretreated pts were enrolled in the 300 mg/m^2 group. At least one TRAE was observed in 80% of pts. Grade 3 (Gr 3) events of interest were neuropathy (12%), keratitis (8%), anemia (8%), and neutropenia (4%), for an overall incidence of 32%. All grade neuropathy was 28%. Most TRAEs were mild to moderate severity and manageable with standard supportive care or dose reductions. Safety profile of TH1902 was different from that of docetaxel. PK measures of Cmax and AUC showed that exposure to free docetaxel was much lower than that of TH1902; Cmax = 0.58 μM for free docetaxel vs 30.4 μM for TH1902 and AUC24 = 3.1 h.nmol/mL for free docetaxel vs 74.8 h.nmol/mL for TH1902. Three pts exhibited RECIST 1.1 confirmed long-term stabilizations of disease, even after drug discontinuation, which ranged from 8 to 19 mos from treatment initiation, of which one OvC pt had overall PR (with RECIST 1.1 confirmed CR in target lesions) and remained on treatment for a total of 5 months. In addition, one endometrial cancer (part 1) was dose escalated from 60-360 mg/m^2 and completed 11 cycles in total. Pt remained in SD during the 8 mos of treatment, up to time of consent withdrawal. All 4 pts had prior taxane exposure. **Conclusions:** TH1902 induces durable disease stabilization that lasts beyond treatment completion, suggesting a unique, multimodal mechanism of action (MOA) that differs from other cancer therapeutics. TH1902 has a manageable safety profile at 300mg/m^2 with few Gr3 AEs. Low levels of free docetaxel in human plasma may in part explain the low rate of taxane related AEs (i.e. neutropenia, no alopecia). Next phase of the study involves dose optimization to further limit toxicity and improve efficacy. Clinical trial information: NCT04706962. Research Sponsor: Theratechnologies Inc.

Final results of a first-in-human phase I dose escalation trial of daily oral zelenirstat, a n-myristoyltransferase inhibitor, in patients with advanced solid tumors and relapsed/refractory B-cell lymphomas.

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Background: Myristoylation, the N-terminal modification of proteins with the fatty acid myristate, regulates multiple membrane-bound signal transduction pathways important in cancer cell biology, including Src and Src family of protein tyrosine kinases. This modification is catalyzed by two N-myristoyltransferases (NMT), NMT1 and NMT2. Zelenirstat is a first-in-class oral small molecule NMT inhibitor with strong affinity for both NMT1 and NMT2 proteins. Transcriptomic analysis of zelenirstat treated cell lines identified a myristoylation inhibition sensitivity signature in cancer cells most likely to respond to NMT inhibitor therapy; high sensitivity scores were seen in a range of solid cancers and diffuse large B-cell lymphoma. Based on tumor regression and safety in preclinical models, we hypothesized zelenirstat would be safe to administer and show anticancer activity. **Methods:** Patients (pts) with advanced solid tumors and relapsed/refractory (R/R) B-cell lymphomas were enrolled in a multicenter, open label, phase I dose escalation trial of oral daily zelenirstat, administered in 28-day cycles until disease progression or unacceptable toxicity (NCT04836195). The primary endpoints were to evaluate dose-limiting toxicities (DLT) to establish a maximum tolerated dose (MTD). Secondary endpoints were to characterize the pharmacokinetic parameters of zelenirstat and assess anticancer activity. **Results:** Twenty-nine pts (17 females; 12 males; median age 65 years; median prior systemic treatments 4; 25 advanced solid tumor; 4 R/R B-cell lymphoma) were enrolled and 24 pts were DLT-evaluable. Dose cohorts ranged from 20 mg once daily (OD) to 280 mg OD without DLT until the 280 mg cohort where three DLTs were observed: Gr 3 diarrhea, Gr 3 diverticulitis, and Gr 3 dehydration. MTD and recommended phase 2 dose was established at 210 mg OD. Common adverse events were Gr $\leq$ 2 nausea, vomiting, diarrhea, and fatigue. Plasma concentrations peaked between 1 and 4 hours across the cohorts with terminal half-lives ranging from 6.7 to 12 hours. Steady state was achieved by Day 8 to 15, and in the higher dose cohorts, trough concentrations exceeded the levels predicted to be therapeutic. Stable disease as best response was seen in 8 (28%) heavily pre-treated pts (3 colorectal, 2 ovarian, 1 pancreatic, 1 appendiceal, and 1 bladder). Progression-free survival, overall survival, and weighted health status were significantly better in pts receiving 210 mg OD compared to those receiving lower doses. **Conclusions:** Zelenirstat is well-tolerated, reaches plasma concentrations highly active in preclinical models, and shows preliminary signs of encouraging anticancer activity. NMT inhibition represents a new target for ongoing research efforts and further clinical development of zelenirstat is warranted. Clinical trial information: NCT04836195. Research Sponsor: Pacylex Pharmaceuticals Inc.

Phase 1/2 trial of the HPK1 inhibitor NDI-101150 as monotherapy and in combination with pembrolizumab: Clinical update.

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Background: NDI-101150 is a potent, selective, oral inhibitor of hematopoietic progenitor kinase 1 (HPK1), with a different immunotherapy mechanism to other checkpoint inhibitors. NDI-101150 reactivates anti-tumor activity of T-cells, B-cells and dendritic cells (DCs), even under immunosuppressive conditions. **Methods:** Safety and preliminary efficacy (primary endpoints) of NDI-101150 alone (50–200 mg once-daily in 28-day cycles) and in combination with pembrolizumab are being assessed in patients (pts) with relapsed or metastatic solid tumors. NDI-101150 monotherapy expansion cohorts in renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and gastric/gastroesophageal (G/GEJ) cancer are also being assessed. **Results:** Dose escalation/expansion data as of Dec 13, 2023 are presented. Treatment (tx)-related adverse effects (TRAEs) in the safety set (N=39) for NDI-101150 monotherapy are presented in the table. 30 (76.9%) pts reported ≥1 TRAE and 5 (12.8%) pts reported grade ≥3 TRAEs. Most common TRAEs were nausea, vomiting, diarrhea and fatigue. Combination tx TRAEs (N=7) recapitulate the monotherapy profile (data not shown). NDI-101150 induced clinical benefit in 4/24 (16.7%) response-evaluable pts: complete response in 1 pt with clear cell RCC; stable disease (SD) ≥6 months in 3 pts (RCC [21 months], pancreatic cancer and endometrial cancer). Unconfirmed SD was noted in 2 pts with RCC, and in 1 pt each with NSCLC and G/GEJ cancer. Nearly dose-proportional increases in exposure were observed on Day 1 of Cycle 1 (C1) across 50–200 mg, with steady state achieved between Days 15 and 28 of tx. Pharmacokinetic profiles of monotherapy and combination tx cohorts were similar. Sustained inhibition of pSLP76 of >50% relative to pre-tx levels (predicted to achieve efficacy in non-clinical models) was observed at all doses tested by Day 15 of C1. Using a custom 12-plex immunofluorescence assay to monitor changes in the tumor immune microenvironment, an on-tx biopsy assessment from a pt with RCC showed increased infiltration of activated CD8+ T-cells and DCs compared to archival biopsy, aligning with the proposed mechanism of action. **Conclusions:** The observed clinical benefit and safety profile support continued evaluation of NDI-101150 as a viable next-generation immunotherapeutic. Clinical trial information: NCT05128487. Research Sponsor: Nimbus Therapeutics (Nimbus Discovery on behalf of Nimbus Saturn Inc.).

TRAEs by PT[a] N=39	Any grade[b] n (%)	Grade ≥3[c] n (%)
Patients reporting TRAEs, n (%)	30 (76.9)	5 (12.8%)
Nausea	15 (38.5)	0
Vomiting	15 (38.5)	0
Diarrhea	14 (35.9)	1 (2.6)
Fatigue	9 (23.1)	2 (5.1)
Colitis	2 (5.1)	1 (2.6)
Acute kidney injury[d]	1 (2.6)	1 (2.6)
Immune-mediated lung disease	1 (2.6)	1 (2.6)
Hypokalemia	1 (2.6)	1 (2.6)

[a]Pts reporting >1 event are counted only once for each PT
[b]Only TRAEs occurring in ≥10% pts or those with grade ≥3 TRAEs are listed
[c]Occurring in any pt; no grade 4 or 5 TRAEs were reported
[d]In the setting of severe dehydration PT, preferred term; pt, patient; TRAE, treatment-related adverse event.

Safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of KT-253, a targeted protein degrader of MDM2, in patients with relapsed/refractory (R/R) solid tumors, lymphoma, high grade myeloid malignancies and acute lymphoblastic leukemia (ALL).

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Background: The tumor suppressor p53 is mutated in approximately 50% of cancers. In those cancers with wild-type p53, its activity is controlled by mouse double minute 2 (MDM2), an E3 ligase that tags p53 for degradation. KT-253 is a novel, highly potent heterobifunctional MDM2 degrader that upregulates p53 activity and overcomes the p53-MDM2 feedback loop, resulting in >200-fold higher potency compared to MDM2 inhibitors. In preclinical PDX models of sensitive $p53^{WT}$ solid tumors, AML and ALL, KT-253 robustly activates p53, induces apoptosis, and results in tumor regressions with every 3-week dosing. The ability to rapidly induce an acute apoptotic response and dose intermittently may result in a therapeutic index that has eluded previous MDM2 targeting agents. **Methods:** The ongoing open-label Phase 1 study evaluates safety, PK, PD and preliminary efficacy of IV KT-253 administered on Day 1 of 21-day cycles. Patients (pts) with advanced (≥2 prior therapies) solid tumors (ST)/lymphomas (Arm A) and relapsed/refractory (R/R) high grade myeloid malignancies (AML, high/very-high risk myelodysplastic syndrome (MDS), MDS/myeloproliferative neoplasms) and ALL (Arm B) are eligible. Blood samples are collected for KT-253 PK/PD analyses. **Results:** As of 26 January 2024, 18 pts have been treated, 13 in Arm A dose levels (A: DL) 1-4 and 5 in Arm B dose levels (B: DL) 1-2, with mean number of 3 and 2 doses, respectively. The most common solid tumor types were Merkel cell carcinoma ((MCC) n=3), adenoid cystic carcinoma ((ACC) n=2) and uveal melanoma (n=2). Arm B included 5 pts with R/R AML. The median age was 61 years (yrs) (range 42, 81) in Arm A and 66 yrs (range 57, 70) in Arm B. The most common adverse events (AEs) in > 20% of pts included nausea, fatigue, headache, and vomiting. There was 1 DLT of AEs leading to discontinuation that included Grade (G) 2 nausea and fatigue in A: DL4. There were no neutropenia or thrombocytopenia AEs in either arm. KT-253 related SAEs included G3 hypotension in a pt with decreased oral intake (A: DL1). Overall best response: 1 CR (B: DL2, AML); 2 PRs (A: DL1, MCC; B: DL1, AML); 3 SD (A: DL1, fibromyxoid sarcoma; DL2, ACC; DL3, renal cell cancer). PD data from A: DL1-4 and B: DL1-2 demonstrated rapid upregulation of plasma GDF-15 protein and upregulation of CDKN1A and PHLDA3 mRNA levels in blood. KT-253 demonstrated dose-dependent increase in plasma exposure with levels approximating efficacious doses. **Conclusions:** KT-253 results in potent upregulation of p53-dependent biomarkers and has demonstrated early signs of anti-tumor activity including objective responses in MCC and AML at doses that are well tolerated. Dose escalation is ongoing at DL4 in Arm A and at DL2 in Arm B and analyses from additional pts will be presented at the meeting. Clinical trial information: NCT05775406. Research Sponsor: None.

Standard atezolizumab leads to severe overexposure in real-world patients with lung cancer: How far could we go in extending dosing intervals and saving money?

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Background: Immune checkpoint inhibitors are given as fixed doses, which may lead to drug exposure exceeding the plasma concentrations required for target engagement. If confirmed, this could pave the way for de-escalating treatments without compromising efficacy while reducing drug-costs. **Methods:** We monitored plasma concentrations of Atezolizumab in 40 real-world patients. A final set of 33 patients with SCLC or NSCLC were available for full PK/PD analysis. Individual PK parameters were derived using a population pharmacokinetics approach. Individual PK parameters allowed to simulate the full concentration-time profiles and to further simulate for each patient the time to reach the target threshold after the first dose of Atezolizumab. In addition, efficacy (RECIST criteria) and immune-related adverse events, (IRAEs, CTCAE grading) were monitored and statistical analysis was performed to search for possible exposure-response relationships. **Results:** Overall Response Rate was 55% and no severe IRAEs were observed. All patients had Cmin levels significantly above the target threshold on the first cycle of Atezolizumab. The mean Cmax after the first dose on cycle 1 was 426.1 μg/ml and the mean Cmin was 68.5 μg/ml, i.e. 11-time higher than the target threshold associated with target engagement (i.e., 6 μg/ml). The mean AUC at the first cycle was 4763 μg.d/ml. Exposure metrics and PK parameters at baseline and simulated prior RECIST evaluation were tested together with other covariates (i.e. age, sex, smoking, NLR, number of metastatic sites, line of treatment) as possible predictive markers of response or toxicity. None of the parameters related to Atezolizumab pharmacokinetics or exposure levels were associated with efficacy or toxicity, most likely because all patients had plasma levels well above pharmacologically active concentrations. First-line therapy was associated with better response on univariate analysis, but this effect was lost on multivariate analysis. Further simulations based on time required to fall below the efficacy threshold suggest that dosing intervals could be extended from Q7W to Q19W (mean: Q12W). Considering the annual budget for Atezolizumab at our institution, further simulations showed that the annual drug cost could thus be reduced from 2.5 M€ to 0.6 M€ while ensuring that all patients remain above active concentrations. **Conclusions:** Our study demonstrates in a real-world setting that standard Atezolizumab given as 1200 mg Q3W infusion leads to severe overexposure of the drug. This strong overexposure was not associated with more severe treatment-related toxicities. Finally, our study suggests that PK-guided dosing with Atezolizumab could help customizing the dosing interval while maintaining efficacious trough levels and that Q12W could be an alternate scheduling leading to significant cut in drug costs. Research Sponsor: None.

Contribution of the microbiome to differential drug efficacy and clinical trial outcomes between the US and Japan.

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Background: The gut microbiome is a source of patient variation that influences the efficacy of anticancer drugs (Spanogiannopoulos et al., 2022). The microbiome also varies at a population level (Pasolli et al., 2019).There is a limited understanding of the impact of this variation. We show for the first time that differences in drug-microbiome interactions may translate to differential clinical trial outcomes. For extensive-stage, small cell lung cancer (SCLC), irinotecan-cisplatin is a first-line treatment in Japan, based on data from Japan Clinical Oncology Group (JCOG) 9511 (Noda et al., 2002) demonstrating superior efficacy to etoposide-cisplatin (RR 87% vs 68%; PFS 12.8 vs 9.4 months). Despite employing an identical study design, the Southwest Oncology Group (SWOG) 0124 (Lara et al., 2009) failed to confirm this benefit for a US population. The reasons for this discrepancy are unclear. **Methods:** Microbiome analysis was performed using BioCorteX's industry-leading knowledge graph and integrated proprietary engines v20231108_220940. 56,171 stool microbiome samples from the US adult population and 3,558 stool samples from the Japanese adult population were included. A database built on existing literature was used to identify proteins produced by organisms in these samples. These microbial-derived proteins were analysed for sequence similarity to human proteins that interact with irinotecan, etoposide and cisplatin. Interactions were ranked by the abundance of microbial genera producing a given protein. This was normalised by interaction prevalence to produce a clinical impact metric denoted the "Numbers Needed to Interact" (NNI). **Results:** Our results show that the NNI for irinotecan is almost 5 times lower in the US (US: 6.2; Japan: 30.9). By contrast, the NNI for both cisplatin and etoposide (US: 2.3; Japan: 1.7) is similar between countries. A pooled analysis of anticancer drugs shows that a negative Spearman's rank correlation can be derived for NNI vs trial failure rate (ρ=-0.86, $p<0.01$). Analysis of the drug-microbiome interactions for irinotecan revealed 8 distinct, microbial-derived proteins with significant homology to proteins encoding human topoisomerases, including TOP1. All 8 of these molecular mimics were enriched in the US population. Only a single protein was found in Japanese stool samples. **Conclusions:** To our knowledge, this work represents the first demonstration that drug-microbiome interactions may contribute to the efficacy of anticancer drugs, as well as to differential trial outcomes between countries. Proteins produced by the microbiome that functionally mimic host proteins may interfere with the pharmacodynamics of cancer therapeutics, including irinotecan. This interaction is found 5 times more frequently in US stool samples than Japanese samples and may contribute to the observed differences in outcomes in JCOG9511 and SWOG0124. Research Sponsor: BioCorteX Inc.

An exploratory study on prediction of risk for abemaciclib-induced interstitial lung disease or hepatotoxicity by specific human leukocyte antigen alleles.

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Background: Interstitial lung disease (ILD) and hepatotoxicity have been observed in a small population of patients treated with abemaciclib. It has been reported that the antitumor effect of cyclin-dependent kinases 4 and 6 inhibitors including abemaciclib is contributed by not only inducing tumor cell cycle arrest but also promoting antitumor immunity. Based on our experience of higher incidence of severe toxicities in the clinical study of abemaciclib combined with nivolumab, we speculated that abemaciclib-related toxicity might also be mediated by immune system. This study sought to identify specific human leukocyte antigen (HLA)alleles associated with abemaciclib-induced ILD or hepatotoxicity. **Methods:** Of 236 abemaciclib-treated patients with advanced breast cancer in the previous observational study, 83 patients were enrolled by obtaining additional informed consent for collecting blood and pharmacogenetic investigation. Genomic DNA was extracted from peripheral whole blood, and *HLA-A*, *-B*, *-C*, *-DRB1*, *-DQA1*, *-DQB1*, and *-DPB1*were genotyped to four-digit resolution by next generation sequencing method. Exploratory marker identification evaluated the HLA alleles with frequency of ≥ 10% in cases. The significance level was adjusted by Bonferroni's correction for multiple testing. **Results:** One hundred seventeen alleles (*HLA-A*,13 alleles; *-B*, *26* alleles; *-C*, *16*alleles; *-DRB1*,*24* alleles; *-DQA1*, 14 alleles; *-DQB1*, 13 alleles; *-DPB1*, 11 alleles) were detected. Of 28 alleles with frequency of ≥ 10% in cases with development of ILD [significance level = .00178 (0.05 divided by 28)], there was no significant association between HLAallele carriages and development of ILD in 16 cases and 67 controls. Of 28 alleles with frequency of ≥ 10% in cases with grade ≥ 2 alanine aminotransferase (ALT) elevation [significance level = .00178 (0.05 divided by 28)], *HLA-DQA1*05:05* allele carriage was found to be significantly associated with ALT elevation in 13 cases with grade ≥ 2 and 47 controls with grade 0. *HLA-DQA1*05:05* was present in 30.8% of cases and in 0.0% of controls (*P*=.00147; odds ratio, 45.0; 95% CI, 2.23 to 907). Suggestive associations of ALT elevation were observed with *HLA-DPB1*05:01* allele carriage (*P*=.00930; odds ratio, 11.5; 95% CI, 1.38 to 95.7) and *HLA-A*31:01* allele carriage (*P*=.01522; odds ratio, 5.86; 95% CI, 1.46 to 23.4). **Conclusions:** Evaluated 28 HLA alleles were not associated with development of ILD. *HLA-DQA1*05:05* allele was identified as a promising marker candidate that can predict patients with a higher risk of abemaciclib-induced hepatotoxicity. Further study is necessary to confirm the association in an independent population for managing liver safety risk during abemaciclib treatment. This result also implicates an immune-mediated mechanism for abemaciclib-related hepatotoxicity. Clinical trial information: UMIN000046611. Research Sponsor: Eli Lilly Japan K.K.

Breaking from the paradigm of antibody-drug conjugates: Evaluation of clinical pharmacokinetics and safety of bicycle toxin conjugates (BTCs).

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Background: Bicycle toxin conjugates (BTCs) are chemically synthesized molecules comprising a small (~4.5 kDa) bicyclic peptide linked to a cytotoxin. BT8009 and BT5528 are BTCs linked to monomethyl auristatin E (MMAE) targeting nectin-4 and EphA2, respectively, and have shown preliminary activity. BTCs are a unique therapeutic class of small size, with corresponding pharmacokinetic (PK) properties distinct from antibody-drug conjugates (ADCs). MMAE-containing ADCs demonstrate anti-tumor efficacy but substantial safety issues attributable to the slow clearance of ADCs, which increases uptake into off-target tissues and exposure to plasma proteases (ie, payload release).To evaluate BTC PK and safety relative to ADCs, we present results of the ongoing Phase I/II trials for BT8009 (NCT04561362) and BT5528 (NCT04180371). **Methods:** Patients with advanced solid tumors receiving IV BT8009 (n=147) or BT5528 (n=109) monotherapy were evaluated. Doses were given as 2.5–10 mg/m^2 weekly (QW), every 2 weeks (Q2W), or 2 weeks on/1 week off for BT8009 and 2.2–10 mg/m^2 QW or Q2W for BT5528. Population PK (PPK) models for BT8009 and BT5528 were developed. PK exposures (Cycle 1 area under the concentration curve [AUC]) for BTCs, conjugated MMAE, and unconjugated MMAE were simulated for 5 mg/m^2 QW BT8009 and BT5528 and compared with those of an MMAE-containing ADC (approved regimen, using the PPK model in the literature). Treatment-related adverse events (TRAEs) were tabulated for BT8009 and BT5528. **Results:** BTCparent drugs were rapidly eliminated (half-life [$t_{1/2}$] <1 hour) while unconjugated MMAE exhibited persistent exposures and gradual elimination (MMAE $t_{1/2}$, 1.9 days [D] for both BT8009 and BT5528), in contrast with the ADC (parent drug $t_{1/2}$, 3.6 D; MMAE $t_{1/2}$, 2.6 D). Conjugated MMAE exposures for the ADC were higher than for BT8009 and BT5528 (75- and 73-fold, respectively). Unconjugated MMAE exposures for BT8009 and BT5528 were comparable to the ADC (25% and 8% higher, respectively). Among the BTC regimens most thoroughly evaluated (BT8009 5 mg/m^2 QW and BT5528 6.5 mg/m^2 Q2W), TRAEs of interest occurred with low frequency and severity (Table). **Conclusions:** Preliminary data show substantial differences between BTC and ADC PK, and a promising BTC safety profile, possibly resulting from the distinct PK and selectivity (and specificity) of Bicycle peptides. These data highlight the potential value of BTCs as a platform for developing therapies against advanced malignancies. Clinical trial information: NCT04561362 and NCT04180371. Research Sponsor: BicycleTx Ltd.

TRAEs of interest.

	BT8009 5 mg/m^2 QW N=113		BT5528 6.5 mg/m^2 Q2W N=74	
TRAE, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Peripheral neuropathy	25 (22)	1 (1)	14 (19)	0
Skin reactions	11 (10)	0	9 (12)	0
Neutropenia	10 (9)	6 (5)	6 (8)	2 (3)
Ocular disorders	6 (5)	0	2 (3)	0
Hyperglycemia	3 (3)	2 (2)	3 (4)	1 (1)

Q2W, every 2 weeks; QW, weekly; TRAE, treatment-related adverse event.

Prevalence of recreational and medical cannabis products in Veterans and their interactions with cancer directed pharmacological treatment.

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Background: There is proliferation of literature about the medical uses of cannabis products in patients with malignancies. However, research is lacking as to how cannabis use is affecting the efficacy and toxicity of anti-neoplastic regimens It is known that cannabis is metabolized by the cytochrome p450 pathway, the same as many anti-neoplastic agents and thus there are concerns for potential interactions. **Methods:** We report an observational study to identify cannabis users in veterans receiving anti-neoplastic therapy in the Memphis VA health system, and to then analyzed for potential interactions between cannabis product and the antineoplastic agent/s they were receiving. Data was collected via voluntary surveys. We then reviewed their charts, recorded the anti- neoplastic medications they were receiving, and evaluated for potential interactions with cannabis, based on a literature review of potential interactions. **Results:** In this study, 132 veterans agreed to participate. 50 of them acknowledged recent use of cannabis products within the last 90 days. Thus, the prevalence of cannabis use amongst those who participated is 37.87%. Demographically, 10% of the cannabis users were female, and 90% were male, with the majority aged 60-65 (range 46-85). Predominantly, patients inhaled cannabis once daily (38%) as opposed to using a different formulation. The patients who admitted cannabis use were primarily on chemotherapy (42%), while 38% were on immunotherapy, 24% were on targeted therapy and 20% were on endocrine therapy. Some were on multiple drugs. Based on this data and a literature search for interactions, we found that a significant number of the patients in our Veteran's oncology clinic have a potential increase in toxicity or decreased efficacy from their ant-neoplastic therapy due to CYP interactions with cannabis use. **Conclusions:** In this exploratory study, we discovered a notable prevalence of patients concurrently using cannabis products while on anti-neoplastic treatment. Given that many anti-neoplastic agents undergo metabolism via the CYP450 pathway, our data suggest that a moderate number of patients in our clinic risk less than optimal outcomes due to concurrent cannabis and anti-neoplastic therapy. To delve deeper, we intend to conduct a follow-up study, focusing on specific adverse effects, hospitalizations, and the subsequent need for 2nd and 3rd line treatments in patients using cannabis. A much larger multi-institutional study should be considered to provide statistically relevant data on true outcomes.
Research Sponsor: None.

Type of Therapy	Decreased Efficacy	Increased Toxicity	Potentiation	No Interaction
Immunotherapy	14	0	0	6
Chemotherapy	8	13	2	18
Targeted therapy	0	5	0	9
Endocrine therapy	7	1	1	1

Multi-ethnic genome-wide association study to identify a novel locus for susceptibility to immune-related adverse events from immune checkpoint inhibitors.

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Background: Immune-related adverse events (IrAEs) arising from immune checkpoint inhibitors (ICIs) can be unpredictable. As genomic variation underlies both disease susceptibility and drug responses, genomic markers may predict for the development of IrAEs. We perform a pioneering pharmacogenomic study across a multi-ethnic Asian patient population to uncover genomic biomarkers associated with IrAEs from ICIs. **Methods:** From March 2018 – July 2023, cancer patients treated with ICIs from the National University Cancer Institute Singapore and Tan Tock Seng Hospital were recruited. IrAEs were characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5. DNA was extracted and genotyped by Infinium Global Screening Array (700K markers). Statistical analyses were performed by SVS/HelixTree, PLINK and R. Genetic association was performed by logistic regression (additive model), accounting for all possible confounding factors. Bonferroni corrected $P < 1.28E-07$ (0.05/390,925 SNPs passed QC) was considered statistically significant. **Results:** Genome-wide association study (GWAS) was conducted amongst 507 patients of Asian Ancestry (Chinese, Malay, Indian and Others). Median age was 63. Majority were male (66.5%), Chinese (76.7%), ECOG PS 0-1 (40.1%) and had stage IV cancer at diagnosis (67.2%). Non-small cell lung cancer (37.1%), renal cell carcinoma (12.2%) and hepatocellular carcinoma (7.7%) were the three most common cancers. Top four ICIs used were pembrolizumab, nivolumab, durvalumab and atezolizumab, respectively (47.1%, 23.9%, 12.5%, 11.3%). 0.8% of patients received dual ICIs concurrently. Median duration of treatment was 142 days and median follow-up was 147 days. IrAEs were seen in 43.7% of patients. Skin (24.1%), endocrine (8.1%) and hepatotoxicity (6.1%) were the most common IrAEs. 4.9% of patients had grade ≥3 toxicity, of which skin (3.6%), hepatotoxicity (3.0%) and pulmonary toxicity (1.8%) were the most common. Multi-ethnic GWAS analysis identified one potential novel genetic locus associated with CTCAE grade ≥3 IrAEs. chr3:163402331 rs146525069; P = 7.29E-08, OR (95%CI) = 17.08 (5.40- 54.04); minor allele = A, 10.91% in Cases vs 0.71% in Controls. **Conclusions:** This pharmacogenomics GWAS uncovered a novel locus for susceptibility to serious immune-related adverse events from immune checkpoint inhibitors. Further pharmacogenomic discovery/replication and functional validation studies are currently ongoing. Our study provides a potential biological mechanism for IrAEs and a step towards more effective clinical translation of pharmacogenetic testing to personalize ICI use. Research Sponsor: National Medical Research Council Clinician-Scientist Individual Research Grant New Investigator Grant (CNIG23jan-0006); NUHS Seed Fund NUHSRO/2021/100/RO5+6/Seed-Sep/03.

Phase Ib portion of the ACTION-1 phase Ib/3 trial of RYZ101 in gastroenteropancreatic neuroendocrine tumors (GEP-NET) progressing after ^{177}Lu somatostatin analogue (SSA) therapy: Safety and efficacy findings.

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Background: RYZ101 (^{225}Ac-DOTATATE) is an alpha-emitting radiopharmaceutical in development for SSTR2+ solid tumors. Alpha-particles have a shorter path length/higher linear energy transfer than beta-particles, causing more frequent double-strand DNA breaks and potentially improved therapeutic index. ACTION-1 (NCT05477576) is a 2-part, global, randomized, controlled, open-label, phase 1b/3 trial of RYZ101 in advanced, well-differentiated SSTR+ GEP-NETs progressing after ^{177}Lu-SSA therapy. Herein, we report updated results from the phase Ib portion of the trial. **Methods:** The phase Ib portion of the trial had a dose de-escalation/Bayesian optimal interval design with boundaries based on a dose-limiting toxicity (DLT) rate of 25%. Patients received RYZ101 IV every 8 weeks for 4 cycles. Planned dose levels (n=6/level): Level 0 (starting dose) 120 kBq/kg; Level −1 90 kBq/kg; Level −2 60 kBq/kg. DLT was assessed for 56 days after the first RYZ101 dose. Treatment-emergent adverse events (TEAEs) were graded by NCI-CTCAE v5.0. Dose de-escalation decisions/safety data were overseen by a Data Review Committee. Tumor response was assessed locally by RECIST v1.1. **Results:** 17 patients have received at least one dose of RYZ101 at 120 kBq/kg (4 doses: 15 patients; 2 doses: 2 patients; median 8.3 MBq). Baseline characteristics: median age 63 years; male (n=11); ECOG PS 0/1 (n=10/7); primary tumor site GI/pancreas (n=12/5). As of 30 June 2023, the most frequent TEAEs were nausea (58.8%) and fatigue (52.9%). Serious adverse events (SAEs) were observed in 6 patients (none were treatment related); grade ≥3 AEs occurred in 9 patients (5 were treatment related). No AEs led to treatment discontinuation. 4 patients had TEAEs leading to dose modification, dose hold, and/or delays. The confirmed objective response rate was 29.4% (n=5; all partial responses); 1 patient had an unconfirmed partial response. 8 patients (47.1%) had stable disease and 3 patients (17.6%) had progressive disease. Updated safety and efficacy data, including duration of response and progression-free survival, will be presented. **Conclusions:** RYZ101 was well tolerated and a fixed dose of 10.2 MBq was declared the recommended phase 3 dose. Initial data suggest promising efficacy. Longer-term safety and efficacy data will be presented. Part 2 (phase 3) is enrolling and will compare RYZ101 at 10.2 MBq every 8 weeks for 4 cycles with standard of care in patients with advanced SSTR2+ GEP-NETs progressing following prior ^{177}Lu-labeled SSAs. Clinical trial information: NCT05477576. Research Sponsor: None.

Ipatasertib in patients with *AKT1/2/3* mutation-positive (*AKT*mut) tumors: TAPISTRY study.

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Background: *AKT1/2/3* point mutations are found in ~1% of all solid tumors, with varying prevalence across different tumor types. Ipatasertib is an inhibitor of the AKT kinase, but its antitumor activity as monotherapy in patients with *AKT*mut tumors is unknown. We present efficacy and safety data of ipatasertib in patients with advanced/metastatic *AKT*mut solid tumors from Cohort E of the TAPISTRY trial (NCT04589845). **Methods:** TAPISTRY is a phase II, global, open-label, multi-cohort trial evaluating the efficacy and safety of different therapies in patients with advanced/metastatic solid tumors. Patients in Cohort E were aged ≥12 years and had solid tumors harboring an *AKT1/2/3*mutation identified by next-generation sequencing and measurable disease by RECIST v1.1. Oral ipatasertib 400 mg was administered once daily. Tumor assessments were performed at screening, every eight weeks from Day 1/ Cycle 1 for one year, and every 12 weeks after that. The primary endpoint was objective response rate (ORR) by independent review committee (IRC). Key secondary endpoints included ORR by investigator, duration of response, progression-free survival, overall survival and safety. **Results:** At data cut-off (16 Jul 2023), 50 patients were safety evaluable and 48 were efficacy evaluable. In the safety-evaluable population, median age was 59 years (range, 30–79); 98% of patients (n/N = 49/50) had an *AKT1* mutation (*AKT1 E17K*, n=47) and 2% (n/N = 1/50) had an *AKT2 E17K* mutation; 41/50 patients (82%) had received ≥2 prior lines of treatment. Efficacy-evaluable patients had 10 different tumor types, the most common being breast cancer (n/N = 21/48; 44%). Key outcomes are summarized in the Table. After a median follow-up of 11.3 months, ORR by IRC in efficacy-evaluable patients was 31.3% (n/N = 15/48; 95% CI 18.7–46.3), driven by responses in three tumor types: breast (n/N = 7/21; 33%), endometrial (n/N = 7/7; 100%), and head and neck (n/N = 1/2; 50%). The most frequent adverse event was diarrhea (n/N = 39/50; 78%). Safety was consistent with the known profile of ipatasertib; no new safety signals were identified. **Conclusions:** Treatment with ipatasertib led to a marked and durable antitumor activity in some tumor types such as endometrial cancer, but not in the overall tumor-agnostic cohort. Further studies are needed to understand the relevance of AKT inhibition in these tumor types. Clinical trial information: NCT04589845. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy (by Independent Review Committee)	**N = 48**
Objective response rate, n (%) [95% CI]	15 (31.3) [18.7–46.3]
Complete / partial response	1 (2.1) / 14 (29.2)
Stable disease / progressive disease / missing	20 (41.7) / 10 (20.8) / 3 (6.3)
Median duration of response / progression-free survival, months (95% CI)	14.6 (7.1–20.3) / 4.8 (3.5–9.0)
Median overall survival, months (95% CI)	11.4 (9.3–25.7)
Safety, n (%)	**N = 50**
≥1 AE / Grade 3–5 AEs / serious AE	50 (100.0) / 31 (62.0) / 16 (32.0)
TRAEs / TRAEs leading to study withdrawal	46 (92.0) / 0
(TR)AE, treatment-related adverse event	

First-in-human study of TQB3617, a BET inhibitor in patients with relapsed/refractory hematologic malignancies.

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Background: TQB3617 is a first-in-class, oral, small molecular inhibitor of the bromodomain and extra terminal (BET) protein family. This is an open-label, Phase I study investigated TQB3617 monotherapy to treat advanced malignant tumors (NCT05110807). Here, we report the primary results of TQB3617 in patients with (pts/w) hematologic malignancies. **Methods:** This is a modified 3 + 3 design and dose escalation study. Aged ≥18 years old, ECOG PS score of 0~2, and pts/w advanced malignancy tumor who had failed standard treatment or were unable to receive standard treatment or had no effective treatment were enrolled. The doses of TQB3617 were 0.05mg, 0.1mg, 0.15mg, 0.2mg, 0.25mg and 0.3mg. TQB3617 was administered with a daily schedule in 28 day-cycles (28/28), or 14 days on drug/7 days off schedule in 21 day-cycles (14/21). The primary outcomes were the recommended Phase 2 dose (RP2D) or the maximum tolerated dose (MTD), secondary end points were pharmacokinetics (PK) and preliminary antitumor activity. **Results:** By November 9, 2023, 36 pts/w hematologic malignancies were enrolled, 32 lymphomas, 2 myelofibrosis (MF), 2 other hematologic malignancies. The median age was 53 years, 23 patients were male. The ECOG PS score of 28 patients was 1. Median number of prior therapies was 3 (IQR 1-7). The number of patients enrolled per dose level and schedule was one at 0.05 mg 28/28, eleven at 0.1 mg 28/28, eight at 0.15 mg 28/28, five at 0.15 mg 14/21, seven at 0.2 mg 14/21, four at 0.25 mg 14/21. The DLTs were experienced with by two patients, one at 0.1 mg 28/28 (grade 3 herpes zoster persists for more than 7 days), one at 0.25 mg 14/21 (grade 3 platelet count decrease with bleeding). 35 patients received TQB3617 at least once. The most common treatment-emergent adverse events (TEAEs) were platelet count decrease (74.3%), anemia (40%), hypertriglyceridemia (28.6%), hyperglycemia (25.7%), most of TEAEs was grade 1~2. Grade ≥3 TEAEs were reported in 16 (45.7%) patients, the most common were platelet count decrease (31.4%) and anemia (11.4%). There was no death happened. After dosing, the peak concentration reached at 2~3 h and AUC increased proportionally from 0.05mg to 0.15mg. The elimination of TQB3617 was slow with $t_{1/2}$ of 30~58 h. After 14 or 28 days of consecutive administration, there was 3~5 fold accumulations of exposure. The overall response rate (ORR) was 31.25% in pts/w lymphoma. The spleen volume of two pts/w MF decreased 6.57%, 20.99% at four weeks, respectively. On the basis of tolerability, PK and efficacy, 0.1mg was identified as RP2D, and the schedule is being explored. **Conclusions:** TQB3617 was generally safe, well-tolerated and demonstrated encouraging efficacy in pts/w lymphoma or MF. Meanwhile, a phase Ib/II study is ongoing, aiming to assess the efficacy and safety of rovadicitinib combined with TQB3617 in pts/w MF (NCT06122831). More studies are planned. Clinical trial information: NCT05110807. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

FCN-159, a MEK1/2 inhibitor, in patients with advanced melanoma harboring *NRAS* or *NF1*mutations: A phase 1B dose-expansion study.

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Background: In phase 1A dose-escalation study, preliminary anti-tumor activity of FCN-159 was observed in advanced melanoma patients harboring *NRAS* mutations (ORR: 19.0%, mPFS: 3.8 months) with tolerable safety profile, which was posted during AACR 2022 (No.: 22-LB-7398-AACR). Here, we report the results from phase 1B dose-expansion study in advanced *NRAS*- or *NF1*-mutant melanoma patients at RP2D predetermined at 12 mg. **Methods:** This open-label, dose-expansion, phase 1B study (NCT03932253) consists of two cohorts, which enrolled patients with unresectable stage III/IV melanoma harboring *NRAS* or *NF1* mutations, respectively. Patients received FCN-159 orally at 12 mg once daily (QD) continuously in 28-day cycles. The primary endpoint was anti-tumor activity. **Results:** As of July 17, 2023, 46 patients (32 patients with *NRAS*mutations in Cohort 1 and 14 patients with *NF1*mutations in Cohort 2) were enrolled and received 12 mg FCN-159 QD. The median follow-up time was 8.6 months. Among 25 patients who failed in previous anti-PD-1 therapy in Cohort 1, 6 had confirmed partial responses (ORR, 24.0%; 95% confidence interval [CI], 9.4–45.1). Median DOR was 6.5 months (95% CI, 2.7–NE). Median progression-free survival (mPFS) was 3.6 months (95% CI, 1.8–5.5). Among 14 patients in Cohort 2, 1 had PR (ORR, 7.1%; 95% CI, 0.2-33.9) and mPFS was 2.8 months (95% CI, 1.8-5.5) (Table). Grade≥3 FCN-159-related treatment-emergent adverse events (TEAEs) were reported in 10 (21.7%) patients in both cohorts; the most common was blood creatine phosphokinase increased (13.0%). FCN-159–related serious AEs (SAEs) were reported in 3 (6.5%) patients, which were edema lower limb, cellulitis and pneumonia. Two (4.3%) patients discontinued treatment due to FCN-159 related TEAEs, including serous retinal detachment and herpes zoster. No FCN-159-related TEAEs led to death. **Conclusions:** FCN-159 showed encouraging efficacy data with well tolerated safety profile in patients with *NRAS*-mutant advanced melanoma, especially those who failed in previous anti-PD-1 therapy. Clinical trial information: NCT03932253. Research Sponsor: None.

Confirmed best overall response.

	Cohort 1 NRAS-Mutant (n = 32)	Cohort 1 NRAS-Mutant and Failed in Previous Anti-PD-1 (n=25)	Cohort 2 NF1-Mutant (n = 14)	Total (N = 46)
Confirmed BOR, n (%)				
CR	0	0	0	0
PR	6 (18.8)	6 (24.0)	1 (7.1)	7 (15.2)
SD	14 (43.8)	9 (36.0)	6 (42.9)	20 (43.5)
PD	10 (31.3)	8 (32.0)	6 (42.9)	16 (34.8)
NE	2 (6.3)	2 (8.0)	1 (7.1)	3 (6.5)
ORR, n (%), 95% CI	6 (18.8), 7.2–36.4	6 (24.0), 9.4-45.1	1 (7.1), 0.2–33.9	7 (15.2), 6.3–28.9
CBR, n (%), 95% CI	20 (62.5), 43.7–78.9	15 (60.0) 38.7-78.9	7 (50.0), 23.0–77.0	27 (58.7), 43.2–73.0
Median DOR (95% CI), months	6.5 (2.7–NE)	6.5 (2.7-NE)	NR (NE–NE)	6.5 (2.7–NE)
Median PFS (95% CI), months	3.7 (1.8-5.5)	3.6 (1.8-5.5)	2.8 (1.8-5.5)	3.6 (1.9-3.8)
Median OS (95% CI), months	11.5 (8.2-NE)	12.7 (7.6-NE)	NR (4.1-NE)	12.7 (8.3-NE)

NE, not evaluable; NR, not reached.

Efficacy and safety of FCN-159, a MEK1/2 inhibitor in pediatric participants with neurofibromatosis type 1: Results from a phase 2 trial.

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Background: Neurofibromatosis type 1(NF1) is an autosomal dominant tumor predisposition syndrome characterized by NF1 gene variants, resulting in over-activation of the RAS pathway. Plexiform neurofibroma (PN) is benign tumors that arise from nerve tissue and are a hallmark feature of NF1. They typically grow along nerves and cause disfigurement, pain, and other complications depending on their location and size. FCN-159, a highly potent and selective inhibitor of MEK1/2 by targeting inhibition of the RAS pathway, holds promise as a therapeutic agent for treating NF1-related PN. **Methods:** A multi-center, open-label phase 1/2 clinical trial was conducted to assess the safety and efficacy in pediatric patients(pts) with NF1-related PN. Here, we reported the safety and efficacy outcomes observed during phase 2 in pediatric pts, who received FCN-159 at the 5 mg/m^2 dose once daily on a continuous basis in a 28-day cycle. Preliminary findings from the phase 1/2 trial were previously disclosed at ASCO 2023. **Results:** As of November 24, 2023,46 pts enrolled. The median age is 8.0 years (range 2-17). The most frequent PN related complications were disfigurement (69.6%) and pain (63.0%). Median volume of target neurofibroma were 37.7 cm^3 (range 2.2-1144.1). Efficacy outcomes are reported for 43 pts (modified intent-to-treat population). With the median follow-up of 15.1 months (range 14.1-16.4), the investigator and Blinded Independent Review Committee (BIRC) assessed ORR were 48.8% and 30.2%, respectively. The mDoR and median mPFS were not reached. Preliminary efficacy data are presented in the table. Among the 16 pediatric subjects with tumor pain at baseline (overall tumor pain NRS≥1) and at least one post-baseline assessment, pain scores decreased by at least 2 points in 81.3% (13/16) pts, and pain scores reduced to 0 points (indicating no pain sensation) in 81.3% (13/16) pts, signifying clinically meaningful improvement. 43 pts (93.5%) experienced TRAEs with grade ≥3 TRAEs occurred in 8 pts (17.4%), including dermatitis acneiform (4.3%), folliculitis (4.3%), pneumonia (2.2%), upper respiratory tract infection (2.2%), ejection fraction decreased (2.2%), and blood creatine phosphokinase increased (2.2%). 2 pts (4.3%) reported treatment-related serious adverse events (one case of dermatitis acneiform and pneumonia each). No TRAEs resulting in dose reduction, discontinuation or death. **Conclusions:** FCN-159 demonstrated good tolerability and exhibited notable anti-tumor activity in pediatric pts with NF1-related PN. Clinical trial information: NCT04954001. Research Sponsor: Fosun Pharma.

Summary of efficacy.

	Investigator	BIRC
Confirmed best overall response, n(%)		
CR	0	0
PR	21(48.8)	13 (30.2)
SD	22 (51.2)	30 (69.8)
PD	0	0
ORR, n (%)	21 (48.8)	13 (30.2)
95%CI	33.3-64.5	17.2-46.1
CBR, n (%)	42 (97.7)	43 (100)
95%CI	87.7-99.9	91.8-100.0
DCR, n (%)	43 (100)	43 (100)
95%CI	91.8-100.0	91.8-100.0
Time to response, months	4.1	4.1
95%CI	3.6-11.0	3.6-11.1

Phase II dose optimization with EZH2/EZH1 inhibitor tulmimetostat in patients (pts) with advanced solid tumors or hematologic malignancies.

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Background: Phase I dose-finding recommended a Phase II dose of 350 mg for the investigational oral, next-generation, dual EZH2/EZH1 inhibitor tulmimetostat (1), with preliminary Phase II results previously reported (2). To find an optimal dose, design of the ongoing Phase II part was later updated under the FDA's dose-optimization paradigm (NCT04104776). Here we report updated preliminary findings including dose expansions. **Methods:** Phase II is evaluating tulmimetostat ≤350 mg once daily (QD) in 28-day cycles in 6 disease-based cohorts. The dose-optimization design randomizes further pts with ovarian clear cell carcinoma (OCCC; M2)/endometrial carcinoma (EC; M3) to 200/300 mg tulmimetostat QD. Primary endpoint is objective response rate (complete response [CR]/partial response [PR]); secondary objectives include pharmacokinetics/pharmacodynamics and safety. **Results:** As of Oct 15, 2023, 117 pts received ≥1 dose (safety set); 111 had ≥1 post-baseline tumor assessment or discontinued prior to it (efficacy set). Median time since diagnosis was 2.8 years (0–19.6); 86.3% of pts had ≥2 prior lines of therapy. At cut-off, best responses of ≥1 CR/PR were seen in 5 cohorts (Table). 74.4% had dose modifications due to treatment-emergent adverse events (TEAEs), 41.9% had ≥1 serious TEAE, and 9.4% discontinued therapy due to TEAEs. Most frequent TEAEs (≥35% of pts; any grade/Grade ≥3) considered possibly related to treatment were diarrhea (49.6%/10.3%), thrombocytopenia (48.7%/24.8%), anemia (39.3%/16.2%), and nausea (35.9%/2.6%). Phase I/II data showed a direct correlation between increasing doses (50–375 mg) or exposure (area under the curve 0–24 hours or maximum concentration) and larger changes in gene expression, which plateau at higher doses (≥225–≤375 mg). **Conclusions:** The evolving Phase II data, including early data from lower doses, continue to show signs of antitumor activity/disease stabilization. The safety profile is consistent with EZH2 inhibition. These preliminary findings in heavily pretreated pts with multiple tumor types and evolving dose-optimization data support ongoing investigation of tulmimetostat. 1. Lakhani et al. ASCO 2021. 2. Drescher et al. ASCO 2023. Clinical trial information: NCT04104776. Research Sponsor: MorphoSys AG.

Best confirmed* responses.

Cohort	M1 Urothelial[†‡]		M2 OCCC[‡]		M3 EC[‡]			M4 Lymphoma[§]		M5 Mesothelioma[¶]	M6 Metastatic Castration-Resistant Prostate Cancer
	350 mg	200 mg	300 mg	350 mg	200 mg	300 mg	350 mg	300 mg	350 mg	350 mg	350 mg
Efficacy evaluable, N	12	5	7	14	3	1	11	6	13	29	10
Best response, n											
CR	0	0	0	0	0	0	0	2	2	0	0
PR	1	0	1	1	0	0	4	1	1	3	0
Stable disease	4	3	5	7	1	1	2	0	0	14	6
Progressive disease	5	1	0	6	1	0	4	1	6	7	3
Discontinued without response assessment	2	1	1	0	1	0	1	2	4	5	1

*Per RECIST 1.1 for M1–3, M5, M6; per 2014 Lugano criteria for M4, does not require confirmation.
[†]Or other advanced/metastatic solid tumors.
[‡]*ARID1A* mutant.
[§]1-stage enrollment; peripheral T-cell lymphoma (n=15) or diffuse large B-cell lymphoma (n=4).
[¶]*BAP1* loss.

Alectinib in pediatric patients with solid or CNS tumors harboring ALK-fusions: Emerging pharmacokinetic data from the iMATRIX alectinib phase I/II open-label, multi-center study.

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Background: Alectinib (a small orally administered CNS-penetrant molecule, inhibiting ALK-fusion proteins) is being evaluated within the iMATRIX Alectinib study (NCT04774718). The study consists of three parts (i.e., dose confirmation, initial expansion gated on response rate and additional expansion). Here we present the most recent pharmacokinetic (PK) results from all enrolled subjects within the ongoing study. **Methods:** Patients with ALK fusion-positive solid or CNS tumors for whom prior treatment has proven to be ineffective or for whom there is no satisfactory treatment available, less than 18 years of age, were enrolled in this study. Patients were recruited in Part 1, to confirm the Recommended Phase 2 Dose and to identify pediatric PK. PK sample analysis was expedited to provide an individualized dosing recommendation for each patient, and where necessary a dose adjustment. The pediatric starting doses within the dose confirmation phase are determined using population pharmacokinetic (popPK) analysis and simulations to match the exposures of 600 mg BID dose of alectinib in adults. Since body weight (BW) is a significant covariate influencing alectinib PK, the popPK model that accounts for BW was used as a strategy to match the PK exposures between the adult and pediatric populations. PK exposures after starting dose administration were evaluated during the first 28-day treatment cycle and doses were adjusted as needed for subsequent cycles. **Results:** A total of 16 patients were enrolled in the study (cut-off Jan 4th, 2024), of which 15 patients were considered PK-evaluable as they received at least one dose of alectinib and had at least one post-dose PK sample collected. Patients ranged from infants (lowest age enrolled 6 months / lowest BW 7 kg) to adolescents (highest age enrolled 17 years / highest BW 91 kg). None of the 11 pediatric subjects who were >2 years old at enrolment required any dose adjustment to match the Alectinib and its active metabolite, M4, target exposure ranges observed in adult patients. Doses for 3 out of 4 pediatric subjects < 2 years old at enrolment were below the target exposure ranges. Consequently, the administered doses were increased stepwise to bring these pediatric subjects' exposure within the target ranges. **Conclusions:** The BW based popPK model successfully predicted the starting doses of all 11 treated subjects > 2 years old, leading to target exposures within range. Since 3 out of 4 subjects < 2 years old had exposure below target, the starting dose for subjects <2 years needs to be increased while ensuring that the optimal benefit/risk ratio is maintained. Clinical trial information: NCT04774718. Research Sponsor: F. Hoffmann-La Roche Ltd.

Response to RAF/MEK/ERK inhibitors in patients with RAS altered and wild-type tumors.

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Background: The MAPK pathway is frequently activated in different cancers. Inhibitors of different molecules across this pathway have been developed and approved including BRAF, MEK, and ERK inhibitors. However, limited data are available regarding response in patients with upstream RAS alterations. The interplay between RAS and downstream RAF/MEK/ERK has been commonly noted; although distinct conclusions have been debated. In this study, we aimed to explore possible associations between RAS status and therapeutic outcomes to RAF/MEK/ERK inhibition in patients with advanced solid tumors. **Methods:** We used MD Anderson Cancer Center (MDACC) CHIMERA platform to extract data of patients with advanced solid tumors who were treated with investigational protocols including RAF, MEK, and/or ERK inhibitors in the department of investigational cancer therapeutics at MDACC as part of early phase-clinical trials. We included only patients who had molecular testing annotated by MD Anderson Precision Oncology Decision Support (PODSS) team. Patients who did not complete 30 days of therapy and those who were unevaluable for response were excluded from analysis. Treatment given at cycle 1 day 1 was manually checked to exclude patients who received other drugs in combination protocols that are not inclusive of RAF, MEK, and/or ERK inhibitors, patients who received non-selective RAF, MEK, and/or ERK inhibitors, and patients who received RAS inhibitors. **Results:** We included 219 patients (107 males and 112 females) who received treatment with investigational RAF, MEK, and/or ERK inhibitors. The majority of patients (58%, n=127) had RAS wild type status. Patients without RAS mutations had higher response rate compared to patients with RAS alterations (18.1% vs 2.2%, $p<0.001$) (Table). Disease control rate (PR or SD) was also higher in patients with RAS wild-type status compared to patients with RAS alterations (70.1% vs 52.2%, p=0.007). Additionally, progression-free survival (PFS), time to treatment failure (TTF), and overall survival (OS) were significantly longer in patients without RAS mutations (median PFS 18 weeks vs 9 weeks, $p<0.001$; median TTF 19 weeks vs 10 weeks, $p<0.001$; and median OS 58 weeks vs 42 weeks, p=0.027). **Conclusions:** RAS alterations are associated with lower efficacy of RAF/MEK/ERK inhibitors. This can be further validated while controlling for potential confounding factors in multivariable analysis. Additional studies are needed to investigate if RAS mutations might confer inherent resistance to treatment with RAF/MEK/ERK inhibition. Research Sponsor: None.

Best response for RAS-altered and RAS-wild type groups.

	RAS-Altered	RAS Wild Type
PR, n(%)	2 (2.2%)	23 (18.1%)
SD, n(%)	46 (50%)	66 (52%)
PD, n(%)	44 (47.8%)	38 (29.9%)
PFS, median (weeks)	9 (95% CI: 7-11)	18 (95% CI: 14-22)
TTF, median (weeks)	10 (95% CI: 8-12)	19 (95% CI: 16-22)
OS, median (weeks)	42 (95% CI: 27-57)	58 (95% CI: 47-69)

MyTACTIC: Activity of targeted therapy in patients (pts) with advanced solid tumors harboring specific biomarkers.

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Background: MyTACTIC (NCT04632992) is a tumor-agnostic, non-randomized, open-label phase II basket trial evaluating the activity of targeted therapies, alone or in combination, in pts with advanced solid tumors carrying potentially actionable molecular alterations. We report pt outcomes across all arms of the MyTACTIC trial. **Methods:** Eligible pts were ≥18 years old, had an ECOG PS ≤2, and measurable or evaluable lesions per RECIST v1.1 with one or more of these actionable oncogenic biomarkers: *ROS1*, *PIK3CA*, *ALK*, *AKT*, *PTEN*, TMB, MSI/dMMR, *ERBB2*,and *RET*. Alterations were identified prior to enrolment using local testing, typically by next-generation sequencing. Pts who had previously received the study drug or had symptomatic or active CNS metastases were excluded. Prior targeted therapy other than trial agents was allowed. Pts were assigned to 1 of 15 treatment arms to receive single-agent or combined targeted therapy according to positive biomarker results. The primary outcome was investigator-assessed confirmed objective response rate (cORR). Safety was assessed in all treated pts. **Results:** At data cut-off (Jan 12, 2024), 252 pts were enrolled into one of 14 arms; no pts were enrolled into arm A (entrectinib in *ROS1*fusion-positive tumors). Overall, pts had a median age of 65 years (range 34–90) and 93% of them had an ECOG PS ≤1. Median follow-up was 8.3 months (range 0.7–32.0). Responses were observed across 7 arms, with a cORR ranging from 11.5% to 66.7% (Table); no responses were seen in arms G, H, J, K, and L. Further efficacy outcomes including progression-free survival, duration of response, and disease control rate will be reported for each arm. The safety profile of each drug or drug combination was as expected based on prior reports. **Conclusions:** Targeted therapies yielded responses across tumor types in most treatment arms; testing for actionable molecular alterations is warranted for pts with limited treatment options. Clinical trial information: NCT04632992. Research Sponsor: Genentech, Inc.

Trial Arm	Biomarker Alteration	Treatment	cORR (95% CI)
B (n=26)	*PIK3CA*	Inavolisib	11.5% (2.4, 30.2)
C (n=5)	*ALK*	Alectinib	20% (0.5, 71.6)
D (n=26)	*AKT* / *PTEN*	Ipatasertib	11.5% (2.4, 30.2)
E (n=25)	TMB ≥10 / MSI-H / dMMR	Atezolizumab + chemotherapy	28% (12.1, 49.4)
F (n=25)	*ERBB2* - TMB ≥10 / MSI-H / dMMR	Trastuzumab emtansine + atezolizumab	12% (2.5, 31.2)
I (n=23)	*ERBB2* - TMB ≥10 / MSI-H / dMMR	Trastuzumab emtansine + tucatinib	13.0% (2.8, 33.6)
M (n=3)	*PI3KCA*+ *AKT*/ *PI3KCA* + *PTEN*	Ipatasertib + paclitaxel	66.7% (9.4, 99.2)

cORR was 0% in arms G (n=13; *ERBB2* - TMB ≥10 / MSI-H / dMMR; PH FDC SC), H (n=8; *ERBB2* - TMB ≥10 / MSI-H / dMMR; PH FDC SC + chemotherapy), J (n=19; *ERBB2* + TMB ≥10 / MSI-H / dMMR; trastuzumab emtansine + atezolizumab), K (n=28; *PIK3CA;*ipatasertib + atezolizumab) and L (n=25; *AKT*/ *PTEN*; ipatasertib + atezolizumab). Chemotherapy: paclitaxel, docetaxel, or capecitabine; PH FDC SC: fixed dose combination of trastuzumab and pertuzumab administered subcutaneously.

Safety, efficacy and pharmacokinetics of VC004, a highly selective next-generation pan-TRK inhibitor, in patients with locally advanced/metastatic solid tumors.

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Background: VC004 is a next-generation TRK tyrosine kinase inhibitor (TKI) developed to overcome acquired resistance to first-generation TRK TKIs in *NTRK* fusion-positive cancers for more durable response. It potently inhibited wildtype TRK A/B/C and mutants in tumor models. NCT04614740 is a first-in-human, multi-center, open-label, phase 1/2 clinical trial evaluating VC004 in locally advanced/metastatic solid tumors. **Methods:** The phase 1 study included two parts: dose escalation (Part 1) and dose expansion (Part 2). In Part 1, 4 dose levels (25, 50, 100, and 200 mg BID) of VC004 were tested using a "3+3" design in patients (pts) having failed or ineligible for standard therapy. In Part 2, *NTRK* fusion-positive pts were treated at 25, 50 and 75 mg BID. The primary endpoints were to evaluate safety and determine MTD/RP2D of VC004. Preliminary efficacy and PK were also assessed. **Results:** From Dec 4, 2020 to Dec 31, 2023, 51 pts were treated, 16 in Part 1 and 35 in Part 2. The mean (SD) age was 45.5 (16.4) years for Part 1 and 52.6 (13.6) years for Part 2. ECOG PS was 1 for all pts in Part 1 and 0-1 for 97.1% (34/35) of the pts in Part 2. Twelve (34.3%) of the pts in Part 2 had received ≥ 3 prior lines of therapy and 7 were TRK TKI-pretreated. Treatment-related adverse events (TRAEs) occurred in 98.0% (50/51) of the pts and most were grade 1-2. No fatal TRAEs occurred. Four (7.8%) pts reported treatment-related severe adverse events which were all recovered/resolved. TRAEs leading to dose reduction, interruption and permanent discontinuation occurred in 1 (2.0%), 12 (23.5%) and 1 (2.0%) pts, respectively. The most common TRAEs (≥20%) included dizziness, weight increased, hypertriglyceridemia, anemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypercholesterolemia, and hyperuricemia, consistent with the safety profile of first-generation TRK TKIs. At 50 mg BID, the selected RP2D, confirmed and confirmed + unconfirmed overall response rates were 65.4% (95% CI, 44.3 to 82.8) and 80.8% (95% CI, 60.6 to 93.4) in the TRK TKI-naïve pts (n=26) per RECIST v1.1. Target lesions disappeared in 1 pt. Two of the 3 pts who had progressed on TRK TKIs previously had tumor reduction, 1 of which achieved partial response (39.6%). Of the 8 pts with brain metastasis at baseline, intracranial lesions shrank by 48.4% and 25% for 2 pts, respectively, and non-target lesions disappeared in 2 pts after 4 months of treatment. Median duration of response (DoR) or progression-free survival has not been reached but 23.8% of the TRK TKI-naïve pts had maintained response for ≥ 12 months (DoR up to 27.6 months). The plasma exposure to VC004 increased in a dose proportional manner over the dose range examined in both parts. **Conclusions:** VC004 showed a manageable safety profile and promising efficacy against *NTRK* fusion-positive tumors. The phase 2 study has recently been initiated. Clinical trial information: NCT04614740. Research Sponsor: Jiangsu Vcare PharmaTech Co. Ltd.

Study update of the oral CDK9 inhibitor KB-0742 in relapsed or refractory transcriptionally addicted advanced solid tumors.

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Background: KB-0742 is a potent, and selective, oral inhibitor of CDK9 being evaluated in a phase I/II study in patients with transcriptionally addicted advanced solid tumors (NCT04718675). Interim data from the first 4 dose levels were presented previously noting manageable safety (MTD not reached), a 24-hour plasma half-life, linear PK, CDK9 target engagement in peripheral blood mononuclear cells (PBMCs), and anti-tumor activity in patients with transcription factor fusion (TFF) driven sarcomas. Here we present updated KB-0742 safety, pharmacokinetics (PK), pharmacodynamic data (PD) and anti-tumor activity for patients from the ongoing dose escalation through 5 dose levels and 60 mg expansion. **Methods:** Study objectives include evaluation of safety, tolerability, PK, PD, and identification of KB-0742 MTD and RP2D. KB-0742 is administered orally once daily for 3 consecutive days followed by 4 days off, weekly in 28-day cycles, until unacceptable toxicity or disease progression. Eligible patients were enrolled in 5 escalation cohorts (10, 20, 40, 60 and 80 mg) or 60 mg dose expansion. Eligibility criteria include age >18 years, relapsed or refractory solid tumors, and ECOG PS < 2. PD is assessed in (PBMCs) and tumor tissue from pre- and on-treatment biopsy samples. **Results:** As of January 4, 2024, 112 patients were enrolled, 42 in dose escalation and 70 in expansion. Patients received a median of 3 lines of prior therapy. The most common tumor types enrolled were soft tissue sarcoma (STS) (n=36; 18 TFF positive) and adenoid cystic carcinoma (ACC) (n=18). Treatment-emergent adverse events occurring in >15% of patients include nausea, vomiting, anemia, fatigue, diarrhea, and constipation; none assessed as grade 4 or 5. The most common reason for treatment discontinuation was disease progression (54.5%). Across 5 dose levels, PK remains linear with a terminal half-life of 24 hours. At 60 mg, evidence of target engagement was observed in post-treatment paired tumor tissue biopsies. Within STS, TFF positive patients displayed a trend towards improved outcomes vs. those without a TFF with a disease control rate (DCR) of 42.8% vs. 29.4%, and one partial response was observed in a patient with TFF positive myxoid liposarcoma at 60mg. The best observed response was durable stable disease (SD) yielding a DCR of 53.8% in ACC (n=18), and 83% in NSCLC (n=6). Two patients (MYCL1+ ovarian, NSCLC) with prolonged SD (>140 days) continue treatment on 60mg. **Conclusions:** KB-0742 treatment at 60 and 80 mg was well tolerated, with manageable toxicity. Achievement of long-term SD and some preliminary anti-tumor efficacy in highly pretreated patients motivates continued enrollment of patients with transcriptionally addicted tumors. Dose escalation and expansion in transcriptionally addicted (*MYC* amplification/overexpression) or TFF driven tumors continues. Clinical trial information: NCT04718675. Research Sponsor: Kronos Bio.

Phase Ib trial of tasurgratinib (E7090) with or without endocrine therapies for patients (pts) with ER+, HER2− recurrent/metastatic breast cancer (BC) after receiving a CDK4/6 inhibitor.

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Background: Previous preclinical study has shown the antitumor activity of E7090, a novel selective FGFR1–3 inhibitor (i), with endocrine therapy (ET) for ER+, HER2− BC with FGFR signaling dependency after CDK4/6i exposure. In Study 102, we evaluated E7090 with/without ET in pts with ER+, HER2− recurrent/metastatic BC following a CDK4/6i. **Methods:** Primary objectives were to evaluate the tolerability/safety of each cohort and determine a recommended dose (RD) for future study. Secondary objectives included evaluating ORR, disease control rate (DCR; complete response [CR] + partial response [PR] + stable disease [SD]), clinical benefit rate (CBR; CR + PR + SD for ≥23 wks), PFS, and OS. All pts had ER+, HER2− recurrent/metastatic BC and had received a CDK4/6i. In part 1, pts were treated with fulvestrant (FUL) 500 mg + E7090 (105 mg [Cohort 1] or 140 mg [Cohort 2]), or exemestane 25 mg + E7090 (105 mg [Cohort 3] or 140 mg [Cohort 4]). In part 2, pts with high FGFR1/2 protein expression by IHC were treated with E7090 140 mg monotherapy (Cohort 5). In part 3, pts were treated with the RD (Cohort 6) to evaluate preliminary efficacy and safety; these pts were not selected based on their level of FGFR expression. Pts were dosed in 28-day cycles (C). **Results:** 19 Pts were enrolled and treated in parts 1–2 (Cohort 1: n=3; Cohort 2: n=3, Cohort 3: n=3; Cohort 4: n=9); only 1 pt was enrolled to Cohort 5 as a correlation between efficacy and expression of FGFR1/2 protein was not seen in part 1. 2 Pts in Cohort 4 had dose-limiting toxicities during C1 (grade 2 serous retinal detachment and grade 3 hypertension/grade 2 hyperphosphatemia). A higher % of pts receiving E7090 140 mg had dose reduction (58.3% vs 16.7%) than E7090 105 mg. E7090 105 mg + FUL 500 mg was considered the RD. Of the 4 responders in part 1, 3 pts received E7090 for more than 2 years. As of the data cutoff date (August 21, 2023), 32 pts were treated with E7090 105 mg + FUL 500 mg in part 3; 10 pts (31.3%) received 2 lines of prior anticancer therapy for metastatic/locally advanced disease. The ORR was 21.9% (95% CI 9.3–40.0; Table). Median (m) PFS was 5.4 mos (95% CI 3.5–not estimable [NE]). All pts had a treatment-related adverse event (TRAE), most commonly hyperphosphatemia (n=32). 9 Pts (28.1%) had a grade ≥3 TRAE, most commonly neutrophil count decreased (n=3). No pts withdrew from treatment due to TRAEs. **Conclusions:** E7090 + FUL had a manageable safety profile. The combination showed promising preliminary antitumor activity in ER+ HER2− BC previously treated with a CDK4/6i; its ORR was 21.9%. Our results support the further development of this combination for HR+/HER2− advanced BC after a CDK4/6i. Clinical trial information: NCT04572295. Research Sponsor: Eisai Co., Ltd., Tokyo, Japan.

	E7090 105 mg + FUL 500 mg (Cohort 6; n=32)
ORR, n (%)	7 (21.9)
95% CI	9.3–40.0
DCR, n (%)	24 (75.0)
95% CI	56.6–88.5
CBR, n (%)	17 (53.1)
95% CI	34.7–70.9
mPFS, mos (95% CI)	5.4 (3.5–NE)
mOS, mos (95% CI)	NE (NE)
TRAEs, n (%)	32 (100)

Binimetinib and encorafenib for the treatment of advanced solid tumors with non-V600E BRAF mutations (mts): Final results of the investigator-initiated phase II BEAVER trial.

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Background: Oncogenic non-V600E BRAF mts are present in many cancer types. Pre-clinical data indicate that some BRAF non-V600E mts can be targeted with BRAF + MEK inhibitors. The BEAVER trial was designed to test the safety and efficacy of binimetinib and encorafenib (B+E) in patients (pts) with non-V600E BRAF mts. Safety data were previously presented [https://doi.org/10.1016/j.annonc.2021.08.1053]. Here, we present the final analysis of the efficacy and exploratory objectives. **Methods:** Key eligibility criteria were: pts with advanced solid tumors with non-V600E activating (Class 1 and 2) or inhibitory (Class 3) BRAF mts, and no prior BRAF/MEK inhibitors. Pts received binimetinib (45mg PO BID) and encorafenib (450mg PO daily) on a 28-day cycle until intolerable toxicity or progression. The primary objective is OR rate (ORR) as per RECIST 1.1. Secondary objectives included PFS. Log-rank test was used to assess PFS. Exploratory objectives included: development of patient derived xenograft (PDX) models, and genomic/transcriptomic profiling of tumors. Mice bearing PDXs were treated with inhibitors and tumors were measured by caliper measurement. Whole exome and RNAseq was performed on PDXs. **Results:** From June 2019 to Nov 2023, 27 pts were screened and 23 pts enrolled; 21 are evaluable for ORR. Tumor types were melanoma, colorectal and pancreaticobiliary (n=6 each), lung (n=2), and breast, uterine, and small bowel cancers (n=1 each).Median age was 59 yrs (range 40-73). Pts had Class 1 (n=1), Class 2 (n=9), and Class 3 (n=13) BRAF mts. Best ORR was 13% (3/23) with one confirmed PR in a pt with ampullary cancer (BRAF D594G) and unconfirmed PRs in 2 melanoma pts (BRAF G469S and K601E), 4 pts had SD as best response. The median PFS was 2.4 months (mo) in the entire cohort. BRAF mt Class was not associated with differences in PFS or ORR. TP53 was the most frequently co-mutated gene (9/23; 39%) and pts with TP53 mts experienced shorter PFS (1.8 vs. 4.0 mo, P=0.008). Pts with melanoma (4.0 mo) experienced longer PFS than pts with pancreaticobiliary (2.6 mo) colorectal (1.8 mo) or other tumor types (1.6 mo); P=0.006. PDX models were established from 9 pts, 8/9 PDXs expressed the same BRAF mt as corresponding pt tumor. Responses to B+E in BRAF mt PDX models correlated with pt tumor measurements (R=-0.63; P=0.046). RNAseq of PDXs identified PTPN11 (Shp2) and CDK4/6 as potential therapeutic targets in B+E-resistant PDXs. Combination therapies with a Shp2 inhibitor or a CDK4/6 inhibitor significantly enhanced B+E-induced tumor growth inhibition in multiple PDX models. **Conclusions:** B+E has only modest clinical activity in advanced cancers with non-V600E BRAF mts and resistance to B+E develops quickly. Alternative approaches incorporating Shp2 and CDK4/6 inhibitors warrant further investigation in this patient population. Clinical trial information: NCT03839342. Research Sponsor: Pfizer; Canadian Cancer Society; Conquer Cancer, the ASCO Foundation; Conquer Cancer, the ASCO Foundation; Jewish General Hospital.

Outcomes of larotrectinib compared with real-world data from non-TRK inhibitor therapies in patients with TRK fusion cancer: VICTORIA study.

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Background: *NTRK* gene fusions are oncogenic drivers identified in <1% of solid tumors. Larotrectinib (laro) is a highly selective TRK inhibitor (i) that was approved in patients (pts) with TRKfusion cancers based on data from single-arm trials. Here we report results from VICTORIA (NCT05192642), a protocol-driven, exact-matching study comparing the outcomes of pts with TRK fusion cancer treated with laro in clinical trials (NCT02122913, NCT02576431, NCT02637687) to pts treated with non-TRKi therapies in the real-world (RW) setting. **Methods:** Adult (≥18 years old) pts with non-small cell lung cancer, colorectal cancer, soft-tissue sarcoma, thyroid cancer, or salivary gland carcinoma were included. Deduplicated data from RW pts were from US and ex-US databases: American Association for Cancer Research GENIE, Cardinal, Flatiron, and ORIEN, as well as a global chart review. Pts in the laro cohort were exactly matched to RW pts based on tumor type and line of therapy to define index line and date for RW pts. A propensity score (weighting) model was used to balance key pt characteristics between cohorts. Pts were followed from index date to last activity, end of study period, or death, whichever occurred first. RW pts were censored at the start of any TRKi therapy or investigational agent, or censored at their last known alive date. Overall survival (OS) was the primary outcome. **Results:** In total,164 pts with TRK fusion cancer were matched (82 in each cohort). Balance in the baseline covariates was achieved after weighting. Matched RW pts received standard index treatments for their disease, which comprised chemotherapy (49%), non-TRKi small molecule targeted therapy (27%), chemotherapy + non-TRKi non-small-molecule targeted therapy (11%), or immune checkpoint inhibitor therapy (10%). Laro-treated pts had longer OS compared to RW pts (median not reached [NR] vs 37.2 months; hazard ratio [HR]: 0.44 [95% confidence interval {CI}: 0.23-0.83]) after weighting. In the weighted analysis, laro-treated pts had longer time to next therapy (TTNT; median NR vs 10.6 months; HR: 0.22 [95% CI: 0.13-0.38]), duration of therapy (DoT; median 30.8 vs 3.4 months; HR: 0.23 [95% CI: 0.15-0.33]), and progression-free survival (PFS; median 36.8 vs 5.2 months; HR: 0.29 [95% CI: 0.18-0.46] compared to RW pts. **Conclusions:** In adult pts with TRK fusion cancer, treatment with laro was associated with longer OS and all measured time-to-event endpoints (TTNT, DoT, and PFS), compared to exactly matched pts treated with standard non-TRKi therapies in the RW. These results furnish additional evidence illustrating the benefit of laro treatment in pts with TRK fusion cancer and support the data generated in the single-arm registrational trials. Clinical trial information: NCT05192642. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

Efficacy and safety of SY-5007, a highly potent and selective RET inhibitor, in Chinese patients with advanced *RET*-fusion positive non-small cell lung cancer (NSCLC): Results from a multicenter, single-arm, phase II study.

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Background: Lung cancer is the leading cause for all cancer-related death, with NSCLC accounting for 85% of all cases. The oncogenic *RET*-fusion is identified in 1-2% of NSCLC patients. Several RET inhibitors have been approved. This pivotal phase II study aimed to evaluate the efficacy and safety of SY-5007, a novel, highly selective RET inhibitor, in Chinese patients with advanced, positive *RET* NSCLC. **Methods:** This trial enrolled two cohorts of patients with *RET*-fusion positive NSCLC. Cohort 1 comprised treatment-naive patients, and cohort 2 included those previously treated with systemic therapy. Both cohorts received oral SY-5007 at 160 mg twice daily in a 28-day cycle. Primary endpoint was overall response rate (ORR) assessed by blinded independent central review (BICR) per RESICST v1.1. Secondary endpoints included ORR assessed by investigators, disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of the data cutoff date on January 16, 2024, the trial enrolled 105 patients, with a median follow-up of 4.57 months (95% confidence interval [CI] 0.2-10.3). The BICR-assessed overall ORR was 77.1% (95% CI 67.9-84.8) and DCR was 83.8% (95% CI 75.3-90.3). The investigator-assessed overall ORR was 77.1% (95% CI 67.9-84.8) and DCR was 90.5% (95% CI 83.2-95.3). In treatment-naive patients (cohort 1, n=56), SY-5007 showed an ORR of 83.9% (95% CI 71.4-92.4) and a DCR of 91.1% (95% CI 80.4-97.0). In pre-treated patients (cohort 2, n=49), SY-5007 exhibited an ORR of 69.4% (95% CI 54.6-81.7) and a DCR of 89.8% (95% CI 77.8-96.6). For 29 patients with baseline brain metastasis, the ORR and DCR were 69.0% (95% CI 49.2-84.7) and 86.2% (95% CI 68.3-96.1). Meanwhile, the ORR and DCR for 76 patients without baseline brain metastasis were 80.3% (95% CI 69.5-88.5) and 92.1% (95% CI 83.6-97.0). Among 10 patients with baseline intracranial target lesions, intracranial ORR and DCR were 80.0% (95% CI 44.4-97.5) and 100% (95% CI 47.8-100). Median PFS, DoR or OS were not reached. Treatment-related adverse events (TRAEs) were reported in 96.2% of patients, with common events ($\geq$ 30%) including increased AST, increased ALT, decreased neutrophil count, decreased white blood cell count and decreased platelet count. Grade $\geq$ 3 TRAEs and treatment-related serious adverse events were observed in 42.9% and 10.5% of patients. TRAE-induced dose interruption and dose reduction occurred in 39.0% and 23.8% of patients, respectively. TRAEs led to SY-5007 discontinuation in two patients (1.9%), with no deaths due to TRAE. **Conclusions:** SY-5007 demonstrated promising efficacy and safety for advanced NSCLC with positive *RET*. Clinical trial information: NCT05278364. Research Sponsor: Shouyao Holdings (Beijing) Co., Ltd, Beijing, China.

Interim analysis of ABM-1310, a blood-brain barrier-penetrant BRAF inhibitor, in patients with *BRAF V600*-mutated solid tumors.

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Background: ABM-1310 is a novel, small-molecule BRAF inhibitor with preclinical evidence of high blood-brain barrier penetration. Here we report interim results from a Phase 1 study of ABM-1310 in patients (pts) with *BRAF V600* mutations (NCT04190628). **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. Pts who failed previous BRAF ± MEK inhibitor treatment were eligible. In the dose-escalation (Part 1), pts received either ABM-1310 monotherapy (25–250 mg bid) continuously or ABM-1310 (100–200 mg bid) + cobimetinib (60 mg QD on d1–21) q28d. Escalation followed a "3+3 design" with dose-limiting toxicities assessed during Cycle 1. Part 2 was cohort expansion (ABM-1310 150–200 mg bid). Primary objectives were maximum tolerated dose (MTD) of ABM-1310 ± cobimetinib. Secondary objectives included safety, tolerability, pharmacokinetics, and anti-cancer activity. **Results:** As of 28 Nov 2023, 51 pts (36 male; median age 56 years; 38 pts refractory to BRAF ± MEK inhibitors) were enrolled. Of these, 74.5% (38/51) experienced treatment-related adverse events (TRAEs). The most frequent (≥10%) TRAEs were skin rash (n=15) and asymptomatic electrocardiogram QT prolongation (AQTP, n=18), most (97.4%) of which were grade (G) 1–2. Nine pts (17.6%) had G3 TRAEs including AQTP, rash, neutropenia, nausea, vomiting, lipase increased and myalgia. There were no treatment-related early discontinuations, G4 AEs, or treatment-related deaths. Among 28 efficacy-evaluable pts who received any dose of ABM-1310 monotherapy, the ORR was 21.4% and disease control rate (DCR) was 60.7%, including 6 partial responses (PR) (glioblastoma multiforme n=2, pleomorphic xanthoastrocytoma n=2, papillary thyroid carcinoma [PTC] n=1, and pancreatic cancer [PC] n=1). Eleven pts had stable disease (SD). Among 16 efficacy-evaluable pts treated with ABM-1310 + cobimetinib, the ORR was 12.5% and DCR was 68.8% including 2 PR (1 each with melanoma and PTC) and 9 SD. Among 10 pts with primary CNS tumors treated with ABM-1310 monotherapy, the ORR was 40% (4 PR, 4 SD), and the median PFS was 4.6 months. In 6 pts with PTC, the ORR was 33.3% (2 PR, 4 SD), and the median PFS was 6.0 months. In 4 pts with PC treated with ABM-1310 monotherapy, the ORR was 25% (1 PR for >6 months; pt remains on study treatment). The MTD for ABM-1310 either as monotherapy or in combination with cobimetinib was 200 mg bid. Preliminary assessment of ABM-1310 drug exposure vs. dose showed a linear dose-proportional relationship. **Conclusions:** ABM-1310, either alone or in combination with cobimetinib, was well tolerated without new or unexpected side effects or safety issues. Preliminary efficacy of ABM-1310 was seen in pts with *BRAF V600*-mutated solid tumors, including those who were refractory to prior BRAF ± MEK inhibitors. Clinical trial information: NCT04190628. Research Sponsor: None.

First-in-human phase 1/2a study of the first-in-class, next-generation CDK4-selective inhibitor PF-07220060 + endocrine therapy (ET): Updated safety data in patients with HR+/HER2− mBC.

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Background: PF-07220060 is a novel, highly selective CDK4 inhibitor with significant CDK6 sparing. Preliminary data have been reported for the monotherapy dose-escalation cohort (Part 1A) and ET combination dose-finding cohorts (Parts 1B-C) in the first-in-human study of PF-07220060 in patients (pts) with advanced solid tumors (1). Herein, we report updated safety data for PF-07220060 + ET in pts with HR+/HER2− advanced/metastatic breast cancer (mBC), including extended follow-up data for pts in dose-finding cohorts (Parts 1B-C) and first disclosure of data for pts in dose-expansion cohorts (Parts 2B-C). **Methods:** In Parts 1B and 1C of this Phase 1/2a study (NCT04557449),PF-07220060 + ET (letrozole [LET] or fulvestrant [FUL], respectively) was administered to pts with HR+/HER2− mBC as ≥2L therapy after prior CDK4/6 inhibitors (CDK4/6i). In dose-expansion cohort 2B, pts with HR+/HER2− mBC received 1L PF-07220060 + LET; in Part 2C, pts with progression after prior ET received PF-07220060 + FUL. Pts in Parts 2B-C were CDK4/6i-naïve. Primary objective was to evaluate safety and tolerability of PF-07220060 + ET. **Results:** At data cutoff (Nov 1, 2023), 33 pts received PF-07220060 (300 or 400 mg BID) + ET in Parts 1B-C; 34 pts in Part 2B and 36 pts in Part 2C received PF-07220060 (300 mg BID) with LET or FUL, respectively. Table summarizes patient characteristics in each cohort. In the pooled 1B-C cohort, the most common TEAEs were neutropenia (54.5% [18.2% G3]), diarrhea (42.4% [0% G3]), and nausea (42.4% [3.0% G3]). In Parts 2B-C, the most common TEAEs were neutropenia (61.8%/36.1% [23.5%/11.1% G3]), leukopenia (38.2%/33.3% [0%/13.9% G3]), and anemia (23.5%/27.8% [0%/2.8% G3]). No >G3 TEAEs were reported in Parts 1B-C or 2B-C. In Parts 1B-C, 2B, and 2C, TEAEs leading to discontinuation were reported in 3.0%, 5.9%, and 8.3% of pts, respectively; dose reductions due to AEs were reported in 12.1%, 5.9%, and 8.3% of pts, respectively. Median (range) relative dose intensity (RDI) of PF-07220060 was 98.3% (52.5–100) in Parts 1B-C, 99.8% (37.2–100) in Part 2B, and 99.7% (68.6–100) in Part 2C. **Conclusions:** PF-07220060 + ET was well tolerated in pts with HR+/HER2− mBC across post-CDK4/6i and CDK4/6i-naïve cohorts. Incidence of G3 neutropenia and other TEAEs was low, enabling high RDI and potential for continuous target coverage. 1. Yap, et al. *J Clin Oncol*. 2023;41(16_suppl):3009. Clinical trial information: NCT04557449. Research Sponsor: Pfizer Inc.

Baseline characteristics.

	Parts 1B-C (N=33)	Part 2B (N=34)	Part 2C (N=36)
Median age (range), y	62.0 (41–82)	59.0 (32–84)	55.0 (30–76)
ECOG PS 0/1, %	36.4/63.6	44.1/55.9	33.3/66.7
Prior anticancer surgery, %	81.8	55.9	77.8
Median prior systemic lines in advanced/metastatic setting, no. (range)	4.0 (1–11)	0.0 (0–0)	1.0 (0–3)
Prior CDK inhibitor, %	100	0	0
Prior fulvestrant, %	72.7	0	0
Prior chemotherapy, %	66.7	0	19.4

First-in-human study of simmitinib, a novel tyrosine kinase inhibitor targeting FGFR1-3, KDR and CSF-1R.

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Background: Simmitinib, a potent tyrosine kinase inhibitor targeting FGFR1-3, KDR and CSF-1R, was evaluated in a phase I study in patients with advanced solid tumors. **Methods:** The study included dose-escalation cohorts and dose-expansion cohorts. In the dose-escalation cohorts, patients received simmitinib at doses from 1 to 9 mg orally. The DLT observation period consisted of a single dose over 7 days and multiple doses over 28 consecutive days. Patients were assessed for safety, pharmacokinetics, and efficacy. **Results:** As of October 31, 2023, 98 patients with a median age of 60 years (range 27-70) were enrolled. 24 patients were enrolled in the dose-escalation cohorts and 74 in the dose-expansion cohorts. One DLT was reported in the 9 mg group (grade 3 hypertension lasted for more than 3 days). The maximum tolerated dose (MTD) was not achieved. Furthermore, 4 mg QD, 6 mg QD and 6 mg 3 weeks on 1 week off dosing regimens were employed for expansion. Treatment-related adverse events (TRAEs) were reported in 88 patients (89.8%); detailed TRAEs of any grade occurring in ≥ 10% patients are listed in the table below. The incidence of TRAEs in the 6 mg 3 weeks on 1 week off group was the lowest among all the dosing regimens, with TRAEs any grade and grade ≥ 3 reported in 18 patients (66.7%) and 4 patients (14.8%), respectively. Of 56 patients with pretreated esophageal squamous carcinoma, the ORR was 16.1% (95% CI, 7.6-28.3%) with DCR of 46.4% (95% CI, 33.0-60.3%) and median PFS of 5.7 months (95% CI, 3.5-6.7); the ORRs for 4 mg QD, 6 mg QD, 6 mg 3 weeks on 1 week off, and 9 mg QD groups were 0 (0/6), 13.6% (3/22, 95% CI, 2.9-34.9%), 19.2% (5/26, 95% CI, 6.6-39.4%) and 50.0% (1/2, 95% CI, 1.3-98.7%), respectively. Based on the results of safety and efficacy, 6 mg 3 weeks on 1 week off was selected as recommended phase II dose (RP2D). Statistical analysis using a power model for ln-transformed exposures (C_{max} and $AUC_{0-\infty}$) suggested dose proportionality from 1 to 9 mg (95% CI of the slope estimate included the value of 1). Higher copy numbers of FGF3, FGF4, or FGF19 appeared to be associated with durable disease control in preliminary biomarker analysis, and further exploration is ongoing. **Conclusions:** Simmitinib showed manageable toxicity in the study and encouraging activity in esophageal squamous carcinoma. Accordingly, 6 mg 3 weeks on 1 week off was recommended for phase II trials. Clinical trial information: NCT04058587. Research Sponsor: CSPC ZhongQi Pharmaceutical Technology Co., Ltd.

TRAEs, n (%)	Any Grade (N = 98)	Grade ≥ 3 (N = 98)
Proteinuria	50 (51.0)	6 (6.1)
Hypertension	42 (42.9)	27 (27.6)
Decreased platelet count	20 (20.4)	2 (2.0)
Elevated ALT	17 (17.3)	2 (2.0)
Decreased white blood cell	16 (16.3)	1 (1.0)
Hypoalbuminemia	15 (15.3)	0
Fatigue	15 (15.3)	1 (1.0)
Elevated AST	14 (14.3)	2 (2.0)
Decreased neutrophil count	12 (12.2)	2 (2.0)
Hyperuricemia	12 (12.2)	0
Anemia	11 (11.2)	1 (1.0)
Weight loss	10 (10.2)	0

Dabrafenib and trametinib in patients with tumors with *BRAF V600E/k* mutations: Updated results from NCI-MATCH arm H.

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Background: The NCI-MATCH precision medicine trial assigns patients (pts) with solid tumors, lymphomas or multiple myeloma to a targeted therapy based on genetic alterations identified in pretreatment biopsies. Arm H (EAY131-H) evaluated the combination of the BRAF inhibitor (inh) dabrafenib (DAB), and the MEK inh, trametinib (TRM), in pts with *BRAF V600E/K* mutations. Thirty-five pts in the primary cohort (PC) were enrolled from Jan 2016-Feb 2018, with 30 patients included in the primary efficacy analysis (1). The trial reactivated for an expansion cohort (EC) in October 2020. **Methods:** Pts could enroll based on molecular results from approved local CLIA labs; central confirmation was required to be included in primary efficacy analyses. Pts with melanoma, thyroid, or colorectal cancer were excluded. Pts with NSCLC were excluded after the US Food and Drug Administration (FDA) approved DAB/TRM in 2017. Pts received DAB 150 mg po BID and TRM 2 mg PO daily on 28-day cycles until disease progression or intolerable toxicity, with restaging every 2 cycles. The primary endpoint was objective response rate (ORR); secondary endpoints included progression-free survival (PFS), 6-month (mo) PFS, and overall survival (OS). **Results:** An additional 9 pts were accrued to the EC; 6 pts were eligible, started treatment and molecularly confirmed. One pt never started therapy and 2 pts had inadequate tissue for central molecular confirmation, resulting in a combined cohort (CC) population of 36 pts. The trial closed to accrual in Jan 2023. In the CC, 17 different histologies were represented. In the EC, 38% of pts were female, with a median age of 60; > 50% had received at least 3 lines of prior therapy. In the 6 pts with central assay results, 1 pt with a pilocytic astrocytoma had a CR, with a PFS >18 mo and 1 pt with GBM had a PR, with a PFS of >12 mo. The 2 pts without central assay results had PRs, both were alive and free of progression for >7 mo. Median OS in the EC is 19.8 mo. For the CC, the confirmed ORR is 36.1% (90% CI 22.9-51.2%); the estimated 6 mo PFS is 67.6% (90% CI 54.5-80.8%). Median OS for the CC is 28.6 mo. At the time of data cutoff (Nov 2023) 2 pts in the PC and 1 pt in the EC are still on therapy. Adverse events were comparable to previously reported profiles of DAB/TRM. **Conclusions:** In this pretreated cohort of $BRAF^{V600}$ mutated solid tumors, the combination of DAB/TRM showed clinically meaningful activity with durable responses seen in pts across multiple histologies, further supporting the disease agnostic approval by the FDA for this regimen. 1. *J Clin Oncol*. 2020;38[33]. Clinical trial information: NCT04439292. Research Sponsor: ECOG-ACRIN; NCI; U10CA180820, U10CA180794, UG1CA233253, UG1CA189954, UG1CA233198, UG1CA233341, UG1CA233302, UG1CA233180.

Characterization of BTX-9341, a bifunctional degrader of CDK4 and CDK6 for HR+/HER2- breast cancer and glioblastoma multiforme.

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Background: CDK4/6 inhibitors (CDK4/6i) are used to treat HR+/HER2- breast cancer, but patients develop resistance via many mechanisms, many of which involve on the upregulation of the cyclin D-CDK4/6 or cyclin E-CDK2 signaling nodes. This has been shown to limit the effectiveness of CDK4/6i in HR+ breast cancer with up to 20% patients exhibiting innate resistance and up to 70% patients developing acquired resistance after 3 years on therapy (doi: 10.3390/ijms222212292). Glioblastoma multiforme (GBM) is an aggressive form of brain cancer with a high frequency of dysregulated CDKN2A-cyclin D-CDK4/CDK6 signaling, however CDK4/6i have shown limited efficacy in GBM due to poor brain exposure. **Methods:** We utilized our PRODEGY platform of Cereblon (CRBN) binders to synthesize CRBN mediated CDK4/6 bifunctional degraders and identified BTX-9341 as a development candidate. We examined retinoblastoma (RB) phosphorylation by in-cell western, E2F target gene expression by western and qPCR, cell cycle progression by flow cytometry, and cell proliferation by colony formation assay (CFA). **Results:** Breast cancer cell lines treated with BTX-9341 showed up to 85% degradation of CDK4 and CDK6 with DC_{50}s <1nM. CDK4/6 phosphorylates RB which releases the transcription factor E2F, inducing the expression of genes including CDK2 and Cyclin E which promote cell cycle progression. BTX-9341 displayed phospho-RB IC_{50}s <30nM, E2F target gene downregulation and G_0/G_1 cell cycle arrest at concentrations as low as 10nM. These downstream effects including inhibition of CDK2 and Cyclin E transcription were sustained up to 72 hours with BTX-9341 treatment but recovered at 24 hours with palbociclib treatment. BTX-9341 inhibited cell proliferation with CFA IC_{50}s of 20-50nM while CDK4/6i had CFA IC_{50}s of 50-1000nM. In a palbociclib-resistant HR+/HER2- cell line model BTX-9341 maintained a low CFA IC_{50} (<150nM). In HR+ breast cancer cells, BTX-9341 in combination with fulvestrant had a synergistic anti-proliferation effect. BTX-9341 has good oral bioavailability and high brain to plasma ratios which allowed for oral dosing and the assessment of BTX-9341 in both breast cancer and GBM *in vivo* models. In several breast cancer xenograft models, BTX-9341 showed dose-dependent tumor growth inhibition, tumor regression at higher dose levels, and was effective with multiple alternate dosing regimens. BTX-9341 inhibited tumor growth and promoted survival in both intracranial and subcutaneous GBM efficacy models. **Conclusions:** BTX-9341, a degrader of CDK4 and CDK6 and inhibitor of CDK2 and Cyclin E transcription, displayed enhanced activity compared to CDK4/6i in breast cancer and GBM *in vitro* and *in vivo*. This indicates that a degrader approach to targeting this pathway in breast cancer may be more effective than current therapies, and that BTX-9341 may also be a promising candidate for brain metastases and GBM. Research Sponsor: None.

A phase 2 clinical trial of first-in-class fascin inhibitor NP-G2-044 as monotherapy and in combination therapy with anti-PD-1 immunotherapy in patients with advanced solid tumor malignancies.

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Background: Fascin is the main actin cross-linker in filopodia and its elevated levels are correlated with increased risk of cancer metastasis, disease progression and mortality. Preclinical evidence shows that deletion of the fascin gene (FSCN1) delays tumor development, slows tumor growth, reduces metastatic colonization and increases overall survival. NP-G2-044 is a novel, small molecule antagonist of fascin that blocks tumor metastasis, inhibits cancer growth and increases antigen uptake by intra-tumoral dendritic cells. In a previously presented phase 1 clinical trial, the drug was well tolerated and demonstrated signals of anti-tumor and anti-metastatic activity. **Methods:** This open-label study was designed to establish the recommended phase 2 dose (RP2D) of orally administered NP-G2-044 administered as both monotherapy (MT) and in combination (CT) with anti-PD-1 immunotherapy (IO). Efficacy was assessed by RECIST 1.1 and iRECIST [CT patients (pts.) only]. Following MT-RP2D identification, additional treatment-refractory pts. with advanced/metastatic gynecologic (GYN) malignancies were evaluated at the MT-RP2D. The CT-RP2D was established by a 3+3 design followed by an expansion cohort in pts. experiencing stable disease (SD) or progressive disease (PD) on prior anti-PD(L)-1 therapy. **Results:** MT-RP2D of 2100mg QD was selected based on a 16-pt. comparative review of PK, safety, and efficacy between two highest doses previously identified in phase 1. No DLTs or drug-related SAEs were observed among MT-RP2D pts. Median PFS for 12 GYN pts. receiving the MT-RP2D was 20 weeks and greater than 70% of these pts did not develop new metastases while on study. One pt. (treatment-refractory ovarian cancer) continues on study with SD exceeding 24 months. A CT-RP2D of 1600 mg. QD was selected and enrollment is ongoing. Among 29 enrolled CT pts. evaluated to-date, no DLTs were observed. Multiple tumor bulk reductions were observed among CT pts. incl one confirmed RECIST PR (53% reduction in tumor bulk) for a pt. with cutaneous squamous cell cancer who progressed on prior anti-PD(L)-1 therapy. Most common TEAEs observed for CT were diarrhea, fatigue and nausea with the safety monitoring is ongoing. **Conclusions:** The first-in-class fascin inhibitor, NP-G2-044, appears safe and well tolerated administered both as MT and in CT with IO. Signals of anti-cancer and anti-metastatic activity were observed with both mono and combination therapy. A phase 3 randomized clinical trial evaluating NP-G2-044 in combination with chemo in pts. with platinum-resistant ovarian cancer is in development with enrollment anticipated to start later this year. Additionally, a phase 2 study to further evaluate NP-G2-044 in combination with anti-PD-1 therapy in IO-naïve pts is planned. Clinical trial information: NCT05023486. Research Sponsor: Novita Pharmaceuticals, Inc.

Targeting rare variants of a pan-cancer target: The landscape of *BRAF* non-v600 mutations and *BRAF*fusions from 172,005 adult patients with cancer.

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Background: BRAF is a recognized pan-cancer target, with dabrafenib in combination with trametinib receiving FDA accelerated approval for unresectable metastatic solid tumors with *BRAF* V600E mutation. *BRAF* fusions and mutations at codons aside from V600 (non-V600) activate the MAP kinase/ERK-signaling pathway, however the spectrum of these alterations is not yet well-defined. Preclinical data suggests that *BRAF* non-v600 mutations are diverse, with evidence of alternate signaling, requiring dimerization to function, while *BRAF*V600E tumors activate the pathway as monomers. We include a comprehensive analysis of non-*BRAF* V600 mutations and *BRAF* fusions in pan-cancer adult malignancies. **Methods:** 198,041 samples from 172,005 patients available from AACR Project GENIE v.15 (1) database were analyzed for the prevalence of non-V600 BRAF mutations, fusions and copy number alterations in a range of cancer types. **Results:** A total of 6374 separate non-V600 *BRAF* alterations were identified in 5876 samples (2.97%), including 1176 fusions (18.4%), 4435 missense mutations (69.6%), 299 truncating mutations (4.7%), and 245 in-frame mutations (3.8%), splice variants (3.4%). Most frequent tumors included lung (19%), melanoma (14%), colorectal (9.7%) glioma (5%), thyroid (1.4%). *BRAF* fusions were observed in 0.7% of tumor samples, most identified in glioma, prostate, lung, thyroid, and colorectal cancer (20%, 7.3%, 6.1%; 4%, 4% of identified *BRAF* fusions, respectively). Mostfusions were considered driver events (1123, 95.5%); frequent fusion gene partners included *KIAA1549*, intragenic fusions, *SND1*, *AGK*, *MKRN1* (39.9%, 15%, 4%, 3.3%, 2.4% of 1176 samples respectively). Of 4435 missense mutations identified, most were considered driver events (2734, 62%); 1701 missense mutations were variants of uncertain significance (VUS) using OncoKB database (38%). Missense mutations occurred across codons, most frequently involving codon 469 (n=584, 13.2%, G469A/V/R/E/S/L/K/I), 466 (n=310, 10.5%, G466V/E/A/R), 594 (n=506, 11.4%, D594G/N/A/E/H/Y/V/F), 601 (n=279, 6.3%, K601E/N/I/T/__S602delinsNT), 581 (n=231, 5.2%, N581S/I/Y/H/T/D/K) 597 (n=118; 2.7%, L597R/Q/S/V/P/H/I). *BRAF* amplification occurred in 0.14% of samples. **Conclusions:** While *BRAF* fusions are rare events across cancers, non-v600 *BRAF* alterations occur in 3% of malignancies. Atypical non-V600 *BRAF*alterations and BRAF fusions represent a distinct molecular cohort across cancers. Most *BRAF* fusion events and non-V600 missense mutations are characterized as oncogenic, underlining the spectrum of BRAF inhibition, and the urgent need to expand agents beyond the current *BRAF*V600 indications. Functional characterization of atypical *BRAF* variants is therefore crucial, together with enrolling patients with these rare alterations on rationally designed clinical trials. 1. Cancer Discov. 2017. Research Sponsor: None.

The microtubule-destabilizing agent AUS_001 as a candidate for glioblastoma therapy.

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Background: The development of novel drugs targeting glioblastoma (GBM) is crucial due to the aggressive nature of this brain cancer, which often resists current treatments. Microtubules are a well-established target for cancer treatment, however there is a need to identify microtubule targeting agents (MTAs) with decreased toxicity and the ability to also retain efficacy in drug-resistant tumors. The novel MTA, AUS_001 has been shown to impede the growth of 15 established glioma cell lines with a half-maximal inhibitory concentration in the range of 0.04-0.246uM. The goal of the current study was to explore its potential in GBM treatment. **Methods:** Co-cultures of primary Human brain endothelial cells, pericytes and astrocytes layered in an insert were applied for the assessment of Blood Brain Barrier (BBB) permeability. AUS_001 efficacy against GBM was studied *in vitro* and in an *ex vivo* platform of advanced 3D cell culture systems. Differences in drug response were investigated between a Temozolomide (TMZ)-resistant human GBM cell line and parental cells. The ability of AUS_001 to overcome taxane-associated drug resistance was explored in P-glycoprotein (P-gp) and βIII-tubulin over-expression models of drug resistance. A microelectrode array system was used to assess the electrical activity and functionality of human Pluripotent Stem Cell (hPSC)-derived midbrain and cortical neurons, upon dose escalation drug treatments followed by a full media change to allow the recovery period. **Results:** By employing a 3D Human BBB Model, we demonstrated that AUS_001 is a good BBB permeability substrate. AUS_001 prevents the growth of Parental Primary Patient-Derived GBM and Patient-Derived Glioma Lines enriched in Cancer Stem cells under 2D culturing conditions with high potency. To this end, we evaluated the effect of AUS_001 in 3D spheroids originating from primary GBM patient-derived tumors that include all cells present in each patient's primary tumor. AUS_001 efficiently prevented the growth of these tumors, including cases where the standard of care, TMZ was not effective. Notably, 2D GBM cultures with acquired TMZ resistance retained sensitivity to the cytotoxic effects of AUS_001. We also found that AUS_001 is less prone to mechanisms of resistance to currently approved MTAs, including increased expression of the βIII-isotype of tubulin or the P-gp drug efflux pump. An *in vitro* neurotoxicity model revealed that functional damage caused by AUS_001 was reversible, while paclitaxel-treated neurons suffered sustained neurotoxicity. **Conclusions:** Collectively, we show that AUS_001 has the potential to circumvent significant limitations of clinically approved MTAs, including brain penetration, drug resistance and peripheral neuropathy, making it a promising approach for the treatment of GBM. Research Sponsor: None.

Preclinical characterization of HBW-012-E, a novel, potent, selective, safe, and orally active KRAS G12D inhibitor with superior pharmacokinetic (PK) properties and anti-tumor efficacy.

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Background: HBW-012-E is a newly identified KRAS G12D small molecule inhibitor with improved oral bioavailability than MRTX1133, the more advanced clinical candidate with poor bioavailability. **Methods:** Small molecules were designed through our medicinal chemistry efforts, aiming to discover KRAS G12D inhibitors that are of good oral bioavailability. The compounds were screened via pERK and cell viability (CTG) assays in multiple cell types. The optimized compounds were further evaluated based on their PK properties and toxicity. The anti-tumor efficacy of the leads was confirmed in a mouse GP2D (with KRAS G12D) colon cancer model. **Results:** As shown in the table, HBW-012-E has better potency and PK characteristics than MRTX1133. In the GP2D model, comparing head-to-head with the same vehicle and protocol (50 mg/kg, BID, PO), HBW-012-E can not only inhibit tumor growth completely but also further regress tumor size by ~40%, whereas MRTX1133 can hardly inhibit tumor growth. HBW-012-E demonstrated anti-tumor efficacy in a dose-dependent manner; at a dose as low as 10 mg/kg, it achieved ~80 % tumor inhibition rate (TGI). Preliminary toxicity tests showed that HBW-012-E is safe: weak inhibition of CYP450 enzymes, negative mini-Ames test, excellent kinase selectivity, and no obvious abnormalities in the 14-day rat or mouse toxicity test. **Conclusions:** A new KRAS G12D inhibitor, HBW-012-E, was identified. Its preclinical profile, including potency, efficacy, and PK properties, are all superior to MRTX1133, and its safety meets the criteria of clinical development. It can potentially be used to treat intractable tumors mediated by KRAS G12D mutations, such as pancreatic cancer that still lacks effective treatments. Research Sponsor: Chengdu Hyperway Pharmaceuticals.

IC50 (nM)	MRTX1133	HBW-012-D	HBW-012-E
AGS (stomach, pERK)	~1	0.8	0.46
GP2D (colon, 3D CTG)	1.38	0.67	0.69
PANC-1 (pancreas, 3D CTG)	2.32	0.88	0.63
Rat pharmacokinetic @ 100 mpk oral			
Cmax (ng/mL)	9	82	1444
AUC0~t (mg.h/mL)	20	258	5724

Efficacy and safety of olaparib in patients with tumors harboring alterations in homologous recombination repair pathway associated genes: Results from the Drug Rediscovery Protocol.

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Background: *BRCA1/2*are crucial genes in the homologous recombination repair (HRR) pathway, and loss-of-function mutations in these genes are associated with response to PARP-inhibitors (PARPi). However, it remains unclear to which extent patients with alterations in other HRR-pathway associated genes may benefit from PARPi. In the Drug Rediscovery Protocol (DRUP, NCT02925234), patients receive off-label drugs based on their tumor molecular profile. Here, we present the results from two separate DRUP-cohorts to evaluate the efficacy and safety of olaparib in patients with tumors harboring mutations in *ATM*, *CKD12*, *PPP2R2A*, *CHEK1/2* or *RAD51B*. **Methods:** Adult patients with progressive, treatment-refractory tumors with loss-of-function mutations in *ATM* (cohort A) or other HRR-pathway associated genes as described above (cohort B), and measurable disease according to RECISTv1.1 were eligible for inclusion. Patients received olaparib (300mg) twice daily, until disease progression (assessments every 8 weeks) or unmanageable toxicity. The primary endpoints of DRUP are clinical benefit (CB: defined as confirmed objective response (OR) or stable disease (SD) ≥16 weeks) and safety. Per protocol, patients were enrolled using a Simon-like two-stage model. Whole genome sequencing (WGS) was performed on pre-treatment biopsies to identify potential biomarkers for CB. **Results:** A total of 25 evaluable patients with 10 different tumor types (n = 10 prostate cancer; n = 5 colorectal cancer; n = 2 non-small cell lung cancer; n = 2 adenoid cystic carcinoma; n = 6 other) were enrolled in cohort A. CB was observed in 8/25 patients (32%; 95% CI 14.9%-53%); one patient achieved an OR (4%). Median progression-free (PFS) and overall survival (OS) were 3.4 months (95% CI 1.8-5.3) and 9.2 months (95% CI 5.2-21.3), respectively. In cohort B, 24 evaluable patients with 4 different tumor types (n = 18 prostate cancer; n = 3 ovarian cancer; n = 2 pancreatic; n = 1 breast cancer) were included. These patients harbored loss-of-function mutations in *CDK12* (n = 9), *PPP2R2A* (n = 6), *CHEK1/2* (n = 5), and *RAD51B* (n = 4). CB was observed in 10/24 patients (41.7%; 95% CI 22.1%-63.4%), with loss-of-function mutations in *CDK12* (n = 7), *RAD51B* (n = 2) and *CHEK2* (n = 1). Median PFS and OS were 3.5 months (95% CI 3.4-6.6) and 8.1 months (95% CI 6.6-14.2), respectively. Overall, no unexpected toxicities were observed. Biomarker analysis (HR-deficiency core, loss of heterozygosity, telomeric allelic imbalance and large-scale transitions) is currently ongoing. **Conclusions:** Olaparib has clinical benefit in patients with progressive, treatment-refractory tumors harboring mutations in *ATM*, *CDK12*, *CHEK2* or *RAD51B*. The ongoing biomarker analysis aims to identify potential biomarkers that can help refining patient selection and thereby improving clinical benefit rate. Clinical trial information: NCT02925234. Research Sponsor: Dutch Cancer Society; 14809; Lilly; Novartis; Pfizer; Roche; Stelvio for Live Foundation; Hartwig Medical Foundation; Amgen; AstraZeneca; Bristol-Myers Squibb; Eisai; GlaxoSmithKline; Janssen.

Open-label, dose-escalation phase 1a study of SPH5030, a tyrosine kinase inhibitor (TKI) targeting HER2, in patients with HER2 positive advanced solid tumors.

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Background: Although existing HER2-targeted agents have driven treatment strategies of HER2-overexpressed advanced solid tumor, unmet need still occurred in clinical setting. SPH5030, is a novel tyrosine kinase inhibitor targeting HER2, with a modified structure from tucatinib and pyrotinib. It has advantages such as target selectivity of tucatinib and the irreversible inhibitory effect of pyrotinib. **Methods:** This Phase Ia, open-label, multi-center study was conducted to evaluate the safety, pharmacokinetics and preliminary activity of SPH5030 in patients (pts) with HER2-positive advanced solid tumor. A 3+3 dose-escalation was conducted with six dose levels of SPH5030 (50,100,200,300,400,600 mg) administered orally once every day (QD) to evaluate dose limiting toxicity (DLT). Adverse events were assessed using CTCAE V5.0; tumor response per RECIST 1.1 every 6 weeks. **Results:** As of Feb 2, 2024, 30 pts were enrolled with a median age of 51 years, including 28 (93.3%) pts with breast cancer (BC) and 2 (6.7%) pts with colorectal cancer (CRC). All pts were heavily treated with a median of 4 (range, 1-9) prior lines of therapy. All the 28 BC pts received previous anti-HER2 therapy, and 23 of them received anti-HER2-TKI therapy. Treatment-emerged adverse events (TEAEs) and ≥grade (G) 3 TEAEs occurred in 30 pts (100.0%) and 10 pts (33.3%), respectively. Treatment-related adverse events (TRAEs) and ≥G3 TRAEs occurred in 28 pts (93.3%) and 8 pts (26.7%), respectively; the most common TRAEs (≥20%) were diarrhea (66.7%, 16.7% ≥ G3), creatinine increased (30.0%, 0% ≥ G3), hypokalemia (23.3%, 3.3% ≥ G3), fatigue (23.3%, 3.3% ≥ G3), AST increased (20.0%, 0% ≥ G3), and bilirubin increased (20.0%, 0% ≥ G3). One in 6 pts receiving 600 mg dose experienced a DLT (diarrhea, G3). SPH5030 plasma exposures from single-dose and steady-state showed a proportional dose increase, but absorption of SPH5030 was found to reach a plateau from 400 to 600mg. Of the 28 evaluable pts for efficacy (BC = 26, CRC = 2),6 pts (21.4%) achieved partial response (PR, BC = 5, CRC = 1), while 16 pts (57.1%) achieved stable disease (4 pts SD≥ 24 weeks,14.3%). Objective response rate (ORR) was 21.4%, disease control rate was 78.6%, and clinical benefit rate was 35.7%. Three pts in the 600 mg dose group achieved PR, with ORR of 50.0%. **Conclusions:** This study demonstrated that SPH5030 was well tolerated at doses ranging from 50 to 600mg. A dose of 600 mg QD regimen could be considered for further clinical trials. Clinical trial information: NCT05245058. Research Sponsor: Shanghai Pharmaceuticals Holding Co. Ltd., China.

3119 Poster Session

Efficacy of erdafitinib in adults with advanced solid tumors and non-prespecified fibroblast growth factor receptor mutations in the phase 2 RAGNAR trial: Exploratory cohort.

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Background: Erdafitinib is an oral selective pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor approved in the US for adult patients (pts) with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations, as determined by an FDA-approved companion diagnostic test, whose disease has progressed on or after ≥1 line of prior systemic therapy. Primary analysis of the RAGNAR study Broad Panel Cohort (BPC) demonstrated tumor agnostic efficacy with an objective response rate (ORR) of 30% in pts with solid tumors harboring predefined susceptible *FGFR* mutations (*FGFR*mut) or fusions (Pant 2023). Here we report on efficacy results in the RAGNAR exploratory cohort investigating erdafitinib in pts with other *FGFR*mut that were not predefined as potentially susceptible *FGFR*mut. **Methods:** Pts with advanced non-urothelial solid tumors harboring non-predefined *FGFR*mut, who had disease progression after ≥1 line of systemic therapy and who exhausted standard therapy options received oral erdafitinib 8 mg daily with optional up-titration until disease progression or intolerable toxicity. Eligible pts had *FGFR*mut that were not predefined as potentially susceptible. Objective was to evaluate efficacy of erdafitinib based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1) objective response rate (ORR), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS). **Results:** At data cutoff, 53 pts received erdafitinib. Median age was 62 years (range 24-80). Most common histologies were cholangiocarcinoma (n=10), breast cancer (n=7), endometrial cancer (n=6), squamous cell head and neck cancer (n=5), ovarian cancer (n=4), soft tissue sarcoma (n=4); 94% of patients had visceral metastases. Pts had a median of 3 prior lines of systemic therapy. Pts had mutations in *FGFR1* (17%), *FGFR2* (17%), *FGFR3* (30%), and *FGFR4* (38%). ORR was 4%; DCR 45%; and CBR 17%. Median PFS was 0.94 months (95% CI 0.49, not evaluable); median OS was 1.79 months (95% CI 0.92, not evaluable). Most common adverse events (AE) were hyperphosphatemia (79%), diarrhea (53%), dry mouth (45%), stomatitis (42%), decreased appetite (38%), fatigue (32%), and increased alanine transaminase levels (32%). 49% of pts had serious treatment-emergent AEs. No treatment-related deaths were observed. **Conclusions:** In contrast to tumor-agnostic efficacy of erdafitinib reported in pts with predefined *FGFR* alterations (mutations or fusions), clinical activity was limited in tumors with *FGFR*mut not predefined as potentially susceptible. These findings further validate the predictive *FGFR*biomarker panel, studied in the RAGNAR BPC in pts with advanced solid tumors and highlight the importance of careful *FGFR*mut selection for targeted *FGFR* inhibition. Clinical trial information: NCT04083976. Research Sponsor: Janssen Research & Development, LLC.

Results of a phase 1, dose-finding study of Debio 0123 as monotherapy in adult patients with advanced solid tumors: Safety, pharmacokinetic, and preliminary antitumor activity data.

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Background: Debio 0123 is an oral, brain-penetrant, highly selective WEE1 inhibitor. WEE1 inhibition leads to S phase and G2/M cell cycle checkpoint abrogation, permitting mitosis without DNA repair, leading to mitotic catastrophe and subsequent cell death. Debio 0123 has demonstrated significant growth inhibition in vitro in a broad range of cancer cell lines and antitumor activity in vivo in human xenograft tumor models. **Methods:** Debio 0123-102 (NCT05109975) is a phase 1 dose-escalation study evaluating the safety, tolerability, pharmacokinetics (PKs) and preliminary antitumor activity of Debio 0123 in patients (pts) with advanced solid tumors who have recurred or progressed following prior therapy and/or for whom no standard therapy is available. Debio 0123 is given as monotherapy, once daily, over a 21-day cycle, using a Bayesian Logistic Regression Model-guided dose escalation. The primary objective of this study is to determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D). **Results:** As of October 24, 2023, 27 pts were treated with 2 pts ongoing (67% female, mean age 63 years; most common primary tumors: ovarian [33%], colon [18%]). Debio 0123 was escalated from 30 mg to 350 mg. Three pts had dose limiting toxicities (DLTs) [Grade (Gr) 3 fatigue and Gr3 Fridericia-corrected QT (QTcF) prolongation at 350 mg, and Gr3 rash at 260 mg]. The MTD was determined at 260 mg. The most frequent treatment related adverse events (TRAEs) (≥20%) were blood creatinine increased (37%), QTcF prolongation (37%), nausea (33%), vomiting (26%), dysgeusia (22%) and fatigue (22%). The most common TRAEs Gr≥ 3 were QTcF prolongation (n = 3, 11%) and fatigue (n = 2, 7%). Retalted adverse events led to dose interruptions, reductions, or discontinuations in 6 (22%), 4 (15%) and 2 (7%) pts, respectively. Debio 0123 plasma exposure increased proportionally with dose from 150 to 350 mg, with steady state achieved after 15-21 days. Target engagement, assessed by reduction of phosphorylated CDC2 levels in skin biopsies, was observed consistently from a dose of 200 mg. Median duration of treatment was 6 weeks (3-30 weeks). Of the 25 pts with post-baseline tumor assessment, 8 (32%) pts had stable disease as best response of ≥5 weeks duration. Two ovarian pts achieved 17% and 20% reduction in the target lesions as per RECIST 1.1, despite requiring dose reductions from 350mg during the 1st cycle. One of these pts had CA-125 response. Based on cumulative safety, exposure-response data, and additional PK modeling, 260 mg once daily of Debio 0123 was selected as RP2D. **Conclusions:** Continuous dosing of Debio 0123 as monotherapy has a manageable safety profile and linear pharmacokinetics. A multi cohort expansion, including biomarker-selected and unselected cohorts, will further evaluate the safety and antitumor activity of Debio 0123. Clinical trial information: NCT05109975. Research Sponsor: Debiopharm International.

Safety, tolerability, pharmacokinetics and clinical activity of AST-3424, an AKR1C3-activated bis-alkylating moiety prodrug, in subjects with advanced solid tumors in China: A phase I dose-escalation study.

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Background: Aldo-keto reductase family 1 member C3 (AKR1C3) modulates cellular differentiation and proliferation through indirect regulation of ligand access to hormone and nuclear receptor signaling. AKR1C3 is expressed at high levels in various human cancers, including hepatocellular carcinoma (HCC). AST-3424 is an AKR1C3-activated prodrug and releases a toxic bis-alkylating moiety (AST-2660) in the presence of AKR1C3, which forms intra- and inter-strand DNA crosslinks resulting in cell death. Here we report the results of a phase I dose escalation study of AST-3424 in patients with advanced solid tumors (NCT06239155). **Methods:** Patients with histologically and/or cytologically confirmed advanced solid tumors who failed standard treatment or no standard treatment, or not suitable for standard treatment were enrolled to receive AST-3424 intravenously (i.v.) at doses of 1, 2, 4, 6, 8 mg/m^2 on Day 1 and Day 8 every 21 days. A parallel and accelerated titration for 1 and 2 mg/m^2, and 3+3 dose escalation design for other cohorts were used to guide dose escalation and maximum tolerable dose (MTD) determination. **Results:** 21 subjects were enrolled and received at least one treatment (HCC=4, colorectal cancer=6, gastric cancer=4, pancreatic carcinoma=2, breast cancer=2, intrahepatic cholangiocarcinoma=1, prostate cancer=1, salivary gland cancer=1). 4 dose-limiting toxicities (DLTs) were observed (3 grade 4 platelet count decreased; 1 grade 2 gamma-glutamyltransferase increased, DLT reported due to dosing delayed more than 14 days). Safety Review Committee confirmed 6.0 mg/m^2 as the MTD and recommended Phase 2 dose (RP2D). Grade≥3 adverse events (AEs) were observed in in 10 patients (47.6%). 8 patients (38.1%) had grade≥3 treatment-related AEs (TRAEs), being anemia (33.3%), platelet count decreased (19.0%), white blood cell count decreased (9.5%) and neutrophil count decreased (9.5%). Most of the grade≥3 AEs were observed in the 8.0 mg/m^2 cohort. No patient had a fatal TRAE. 15 subjects with baseline target lesions had at least one post baseline assessment. 9 subjects (42.9%) had stable disease (SD); 1 subject (4.8%) had non-complete remission/non-disease progression (Non-CR/Non-PD); 5 subjects (23.8%) had progressive disease (PD). AST-3424 showed linear pharmacokinetic characteristics in the range of 1.0-8.0 mg/m^2 with a half-life of 0.16-0.40 hours. AST-2660 showed linear pharmacokinetic characteristics in the range of 4.0-8.0 mg/m^2 with a half-life of 1.59-2.08 hours. **Conclusions:** AST-3424 showed a tolerable safety profile and preliminary anti-tumor activity in advanced solid tumors. The phase II dose expansion phase of AST-3424 monotherapy is ongoing in subjects diagnosed as advanced HCC and with high AKR1C3 expression. Clinical trial information: NCT06239155. Research Sponsor: Ascentawits Pharmaceuticals, LTD.

A phase Ib/IIa study of DX1002, a novel drug in patients with pretreated advanced hepatocellular carcinoma: Efficacy and safety analysis.

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Background: Advanced hepatocellular carcinoma (HCC) is a lethal malignancy with limited treatment options. DX1002 is a novel, specific, small-molecule, tubulin inhibitors, that targets the beta subunit of tubulin in tumor vascular endothelial cells. It has been designed to destroy tumor blood vessels which has been demonstrated in preclinical efficacy models. The objectives of this trial were to assess safety, tolerability and preliminary efficacy of DX1002 in patients (pts) with pre-treated advanced HCC or gastric cancer. Here, we present the results from the HCC subpart. **Methods:** This is a prospective, single-arm open-label multi-center phase Ib/IIa trial (CTR2400080296) to investigate DX1002 in patients with pre-treated advanced HCC or gastric cancer. Patients received DX1002 600 mg orally once daily, continuously in 28-day cycles until progressive disease or intolerable toxicity. Primary endpoints were safety and objective response rate (ORR); other endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), pharmacokinetics and safety. **Results:** From Jun-2021 to Jan-2024, 40 patients with advanced HCC were enrolled. The median age was 54 (36-71) years. As of 31-Jan-2024, of the 40 pts, 4 pts (10.0%) showed PR and 15 (37.5%) had SD. ORR was 21.1% and DCR was 47.5%. The median PFS was 3.55 (95% CI 2.89-8.31) months and median OS was 13.4 (95% CI 11.0-NA) months. Any-grade TRAEs occurred in 75% pts (30/40), with 22.5% Grade 3 (9/40). The most common TRAEs were Aspartate aminotransferase increased (22.5%), total bilirubin increased (20%), albuminuria (20%), Hypoalbuminemia (15%) and gamma-glutamyl transferase increased (15%). Four patients (10%) discontinued DX1002 due to TRAEs. No death-related cases occurred. **Conclusions:** Initial data shows DX1002 demonstrated manageable safety profile and promising anti-tumor potential in pre-treated advanced hepatocellular carcinoma. Further exploration of DX1002 in HCC is warranted. Clinical trial information: ChiCTR2400080296. Research Sponsor: None.

BY101921: Restoring interferon signaling and anti-tumor immunity through PARP7 inhibition.

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Background: PARP7(*TIPARP*), a member of monoPARP family, catalyzes ADP-ribose transfer to specific amino acids within itself and other substrate proteins, utilizing nicotinamide adenine dinucleotide (NAD^+) as substrate. It plays a vital role in various biological processes such as gene expression, protein degradation, and cellular stress response. PARP7 amplification has been observed in various cancers, including squamous cell carcinoma, ovarian cancer, breast cancer, and pancreatic ductal adenocarcinoma. Over expression of PARP7 correlates with reduced survival in squamous cell carcinoma. PARP7's MARylation of α-tubulin induces microtubule instability, promoting proliferation and migration of ovarian cancer cells. As a negative regulator of tumor cell nucleic acid sensing, PARP7 inhibits TBK1 through. This, in turn, hampers the cGAS-STING signal pathway and downregulates the type I interferon expression. BY101921, developed by Chengdu Baiyu Pharmaceutical, is a highly selective PARP7 inhibitor demonstrating significant anti-tumor effect *in vitro* and *in vivo,* both alone and in combination with anti-PD-1. **Methods:** Enzymatic evaluation was conducted on BY101921 to assess its selectivity among major PARP family members. PK studies were investigated in both mouse and dog species. The anti-tumor activity of BY101921, both as a monotherapy and in combo with anti-PD-1, was investigated in NCI-H1373 and CT26 tumor-bearing mice, respectively. In terms of anti-tumor mechanism, pSTAT1, IFN-β and CXCL10 levels were analyzed in RAW264.7 cells and CT26 tumor-bearing tissues. In addition, the effect of BY101921 on the type I interferon signaling pathway was systematically evaluated. **Results:** BY101921 demonstrated outstanding selectivity as a PARP7 inhibitor, displaying limited off-target effects on PARP1/2, reducing the risk of systemic toxicity, especially hematologic effects. In mice and dogs, BY101921 revealed favorable PK characteristics following oral administration. In vivo, BY101921 exhibited potent inhibition of tumor growth as a monotherapy, and its combination with anti-PD-1 further enhanced its anti-tumor efficacy, with excellent tolerability in animals. Mechanism of action studies showed that BY101921 generated an anti-tumor immune response by upregulating pSTAT1 levels and promoting the secretion of IFN-β and CXCL10, thereby restoring the type I interferon signaling pathway. **Conclusions:** BY101921, a potent and selective PARP7 inhibitor, demonstrates significant anti-tumor efficacy both as a monotherapy and in combo with anti-PD-1, while maintaining excellent tolerability in animal models. With favorable drug-like properties and a promising safety profile, BY101921 holds potential as an enhanced therapeutic option for cancer patients. At present, clinical studies investigating BY101921 as a single agent and in combo with anti-PD-1 are in the recruitment phase. Research Sponsor: Chengdu Baiyu Pharmaceutical Co., Ltd.

Updated study results of novel FAK/ALK/ROS1 inhibitor APG-2449 in patients (pts) with non-small-cell lung cancer (NSCLC) resistant to second-generation ALK inhibitors.

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Background: ALK inhibitors increase FAK pathway gene expression in ALK$^+$ NSCLC cell lines, with the highest induced expression in drug-tolerant persister cells. This suggests that FAK pathway activation is involved in ALK inhibitor-induced early adaptive tolerance in ALK$^+$ NSCLC. Investigational APG-2449 is a novel, orally active FAK inhibitor and a third-generation (3G) ALK/ROS1 tyrosine kinase inhibitor (TKI) with potent activity in preclinical models. APG-2449 is well tolerated at the recommended phase 2 dose (RP2D) and showed preliminary efficacy in pts resistant to 2G ALK TKIs. Here, we provide further safety and efficacy results and demonstrate associations between this therapy and FAK signaling pathways. **Methods:** After the RP2D was determined as 1,200 mg daily (QD), pts with NSCLC were enrolled into 2 dose expansion cohorts. Cohort 1 included pts who were resistant to 2G ALK TKIs. Cohort 2 included those who were ALK or ROS1 TKI naïve. **Results:** As of December 9, 2023, 144 pts (median [range] age, 53 [21–78] years; 53.5% female) with NSCLC, mesothelioma, or ovarian cancer were treated with APG-2449 at doses of 150 to 1,500 mg. A total of 129 (89.6%) pts had treatment-related adverse events (TRAEs), the most frequent of which were elevated serum creatinine (49.3%), ALT (42.4%), and AST (36.1%); nausea (28.5%); vomiting (23.6%); diarrhea (22.9%); and decreased leukocyte count (22.2%). In all, 20 (13.9%) TRAEs were grade ≥ 3. Of pts with TKI-naïve NSCLC (n = 36) treated at the RP2D, the overall response (ORR) and disease control rates (DCR = CR + PR + SD) were 68.2% (15/22) and 90.1% (20/22) in ROS1 TKI-naïve pts; and 78.6% (11/14) and 100% (14/14) in ALK TKI-naïve pts. Median progression-free survival (mPFS) in ALK TKI-naïve pts was not reached. Of 22 pts with NSCLC resistant to 2G ALK inhibitors and without targetable bypass gene mutations (e.g., *KRAS G12C, BRAF V600E*), 9 had PRs (9/22; 40.9%) and the mPFS during APG-2449 treatment at RP2D was 11.86 months. Nine of 12 pts in the RP2D group achieved intracranial PR, resulting in an intracranial ORR of 75.0%. Before APG-2449 administration, 17 tumor tissue samples were collected from pts with NSCLC resistant to 2G ALK inhibitors (in the RP2D group), and IHC was used to assess protein levels of phosphorylated FAK (pFAK). The PFS of pts treated with APG-2449 correlated with pFAK levels in baseline tumor tissue, and pts with higher pFAK levels were more likely to benefit from APG-2449 treatment. **Conclusions:** APG-2449 demonstrated preliminary efficacy in pts with NSCLC whose disease was TKI naïve and resistant to 2G ALK inhibitors, especially in brain metastases. High pFAK expression levels in baseline tumor tissue correlated with improved APG-2449 treatment responses in pts with NSCLC resistant to 2G ALK inhibitors. Internal study identifier: APG2449XC101. Clinical trial information: NCT03917043. Research Sponsor: None.

A phase 1 study evaluating the safety, pharmacokinetics, and efficacy of fadraciclib, an oral CDK2/9 inhibitor, in patients with advanced solid tumors and lymphoma.

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Background: Fadraciclib (formerly CYC065)is a highly selective inhibitor of CDK2 (IC_{50}= 5 nM) and CDK9 (IC_{50}=26 nM) causing mitotic catastrophe and apoptotic death of cancer cells at sub-micromolar concentrations. In a previous Phase 1 study of intravenous fadraciclib monotherapy, a heavily pretreated endometrial cancer patient with CDNK2A, CDKN2B and PRMT5 loss achieved confirmed CR. This is the first study to evaluate oral fadraciclib monotherapy. **Methods:** A global Phase 1/2, open-label, dose-escalation study in subjects with advanced solid tumors or lymphoma (NCT04983810). The Phase 1 portion is exploring both schedule and dose of oral fadraciclib monotherapy in 28-day cycles to identify MTD and/or RP2D using a standard 3+3 design. **Results:** As of January 31, 2024, 45 subjects have received fadraciclib at 8 dose levels (DL1-6a: 50-150 mg, bid given 3-5 days per week for 3-4 out of 4 weeks or DL6b: 125 mg, daily for 4/4 weeks). Heavily pretreated patients with breast, colorectal, gynecological cancers, and T cell lymphoma with ECOG PS 0:1 (9:36) were enrolled. Fadraciclib was well tolerated at dose levels 1 to 5 (up to 100 mg bid). Adverse events reported were nausea (n=31), vomiting (n=23), thrombocytopenia (n=6). Grade 3 DLT of hyperglycemia (1/2 DL6 and 2/6 DL6a) and nausea (1/2 DL6) was observed at doses above 125mg bid M-F, 4/4 weeks. Hyperglycemia was controlled after dose interruption and blood glucose levels returned to normal range after treatment. Preliminary PK analysis suggests dose dependent exposure. At DL5 and above, plasma concentration was above target concentration from CDK2 and CDK9 target engagement studies. Preliminary PD analysis of treated patient samples showed suppression of expression in multiple target genes, including MYC, MCL1, CCNE/cyclin E, CDKN2A, CDKN2B, and PRMT5. Preliminary efficacy data are available for 31 evaluable patients. Two PRs after the first cycle were observed in one patient with CTCL and one with angioimmunoblastic T-Cell Lymphoma (AITL). Twenty patients showed SD. Tumor size reduction was observed in 10 patients. A squamous NSCLC patient harboring a CDK2NB loss of function mutation and prior chemo- and immunotherapy achieved reduction of 22% in the sum of all target lesions after 1 cycle of treatment. **Conclusions:** Based on data from the CYC065-101 study, fadraciclib appears well tolerated from DL1 to 5. The MTD for the bid dosing schedule is 100mg bid, M-F, 4/4 weeks. The trial is ongoing with evaluation of a daily dosing schedule. Clinical trial information: NCT04983810. Research Sponsor: None.

PAS-004: A novel macrocyclic MEK inhibitor to inhibit cancer cell growth in vitro and tumor growth in mouse xenograft studies.

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Background: Three MEK inhibitors have been approved to date to treat melanomas driven by RAS pathway mutations and a 4th compound (selumetinib) is approved to treat Neurofibromatosis type 1 (NF1) in pediatric patients. PAS-004 is the first macrocyclic MEK inhibitor in development for solid tumors and NF1. **Methods:** Ten NRAS mutant cancer cell lines were cultured for 48 hrs in the presence of the MEK inhibitor PAS-004, trametinib, binimetinib (bini) and selumetinib (selu) and cell proliferation was assayed using a Cell Titer Glo luminescence assay. The anti-tumor activity of PAS-004 was compared with selu and bini in two mouse xenograft studies using NRAS mutant human hepatocellular carcinoma (HCC) and lung carcinoma cell lines. Dose response was assessed with treatment initiated when the tumor reached a volume of 150 mm^3 and mice treated for 20 days. Body weights and tumor volumes were measured twice weekly. Tumors were excised at the end of the study and pERK inhibition was assessed by Western blot. Terminal plasma was collected for PK analysis. **Results:** PAS-004 strongly inhibited 5/10 NRAS mutant cancer lines with IC_{50} values ranging from 0.024 to 0.306 μM. Maximal growth inhibition of $>$50% was achieved by PAS-004 in 8 cell lines and PAS-004 achieved greater maximal inhibition in 7/10 lines vs selu and bini. PAS-004 inhibition was comparable to trametinib in 5/10 cell lines tested. However, in contrast to trametinib PAS-004 did not reach a plateau at the highest dose tested in three of these lines. In the HCC xenograft study the highest dose of PAS-004 completely prevented tumor growth and the same dose caused a 69% reduction in tumor volume in the lung carcinoma xenograft study. The anti-tumor efficacy of PAS-004, when taken at equivalent doses, was shown to be superior to that of bini and selu. Specifically, PAS-004 at dose levels of 10 mg/kg and 5 mg/kg, once daily, exhibited higher efficacy compared to bini and selu at dose levels of 5 mg/kg and 2.5 mg/kg, when administered twice daily, respectively. No significant differences in body weight loss were seen between the compounds. **Conclusions:** The novel macrocyclic MEK inhibitorPAS-004 inhibited NRAS mutant tumor growth in mouse xenograft studies with similar activity as the approved MEK inhibitors selu and bini. In vitro, PAS-004 provided greater maximal growth inhibition of NRAS lines than selu and bini. These results support investigating PAS-004 further and a clinical trial in patients with advanced solid tumors carrying RAS pathway mutations, including NRAS variants, is ongoing. Research Sponsor: Pasithea Therapeutics Corp.

On the right TRACK: Providing comprehensive genomic profiling (CGP) and molecular tumor board (MTB) for patients (pts) with rare cancers.

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Background: Patients (pts) with rare cancers are under-represented in precision medicine trials despite making up ~22% of cancer incidence. We created the TCF-001 TRACK (Target RAre Cancer Knowledge, NCT04504604) study to provide a home-based, patient-centered trial utilizing comprehensive genomic profiling (CGP) at enrollment and progression with review by a molecular tumor board (MTB). **Methods:** Pts with rare cancers (incidence<6/100,000) were enrolled and consented remotely (WCG IRB 1287011). Liquid (blood via mobile phlebotomy) and tissue biopsy samples were sent for CGP at Foundation Medicine. A fully remote MTB was convened following availability of each test. MTB notes and therapy recommendations were returned to patients and local physicians. **Results:** TRACK activated on 1 Oct 2020. The MTB included medical/surgical oncologists, genomics experts, molecular pathologists, a basic scientist, a pharmacist, a genetic counselor, regulatory staff, a scribe, an oncology fellow ("mentern"), and a medication acquisition specialist. MTB members were from 8 states. 132 eligible pts with evaluable results were enrolled from 41 states. Tissue and liquid biopsy results were available in 89 pts; tissue only in 5; liquid only in 38. 128 pts had an MTB before the 30 June2023 cut-off date (mean age 54.1 y; female 61.7%). There were >40 rare/ultra-rare cancers, including cholangiocarcinoma (62) and soft tissue tumors (24). No pts had identical molecular alterations. The median number of pathogenic alterations per tissue sample was 3 (range: 0-14) and blood was 2 (range: 0-40). 3 patients had no pathogenic alterations on tissue or liquid CGP. The most commonly altered genes found by tissue biopsy CGP on study (n=68) were *TP53*(33.8%), *CDKN2A* (25.0%), *KRAS* (23.5%), *CDKN2B* (17.6%), *IDH1* (17.6%), and *MTAP* (14.7%); by liquid biopsy (n=126), they were *TP53* (31.7%), *KRAS* (11.9%), and *IDH1* (8.7%), as well as genes often associated with clonal hematopoiesis: *DNMT3A* (22.2%), *ATM* (12.7%), and *CHEK2* (8.7%). The sensitivity of liquid biopsy for pathogenic alterations found in tissue was 89.3% for pts with ctDNA tumor fraction (TF) ≥1% and 28.1% for TF <1%. 1 pt had microsatellite instability. Median tumor mutational burden (TMB) by tissue was 2.5 mutations/megabase and by blood was 1.3. 3 pts had TMB≥10. Liquid biopsy results were available more quickly than tissue (median processing time, 9.1 vs 13.3 days); time from submission to processing was shorter for blood than tissue (2.4 vs 4.9 weeks). TRACK staff encountered 0.94 queries/sample. MTB recommendations based on CGP were generated for 87.5% of the 128 pts presented. **Conclusions:** A fully remote, advocacy driven, national precision genomics trial is feasible for managing rare cancers. CGP with expert MTB review can identify potentially targetable alterations and inform therapeutic options. Clinical trial information: NCT04504604. Research Sponsor: TargetCancer Foundation; Foundation Medicine, Inc.

The genomic, transcriptomic, and immunologic landscape of TEM8 (*ANTXR1*) in small-cell lung cancer (SCLC).

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Background: The TEM8 receptor (coded by *ANTXR1*) plays several roles in oncogenesis. Novel oncolytic therapies, such as the SVV-01 virus, uniquely bind this protein in tumor histologies such as small-cell lung cancer (SCLC). Emerging pre-clinical data suggest that TEM8-targeting therapies may convert immunologically "cold" tumor microenvironments (TME) into "hot" milieu with greater responses to immune checkpoint inhibitors (ICIs). **Methods:** NextGen sequencing of DNA (592 genes or whole exome)/RNA (whole transcriptome) was performed on SCLC (N=1404) submitted to Caris Life Sciences (Phoenix, AZ). Mutations were defined as pathogenic SNVs/indels. *ANTXR1*^{H} and *ANTXR1*^{L} samples included those with $>75^{th}$ and $<25^{th}$ percentile expression, respectively. PD-L1 expression (22c3; Positive (+):TPS ^{3}1%) was assessed by IHC. High tumor mutational burden (TMB-H) was defined as ≥10 mutations per MB. Cell infiltration in the TME was estimated by QuantiSEQ. Gene expression profiles were analyzed for transcriptional signatures predictive of response to immunotherapy (T cell-inflamed) and MAPK pathway activation score (MPAS). Real-world median overall survival (mOS) was assessed from insurance claims data, and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients. Mann-Whitney U and X^2/Fisher-Exact tests were applied where appropriate, with P-values adjusted for multiple comparisons ($p<0.05$). **Results:** No pathogenic mutations were significantly associated with *ANTXR1*^{H} vs ^{L} tumors ($p>0.05$ for all), along with no differences in the prevalence of TMB-H (28.6% vs 36.3%, p=1) or PDL1+ (45.0%: vs 35.0%, p=1). However, a greater proportion of B cells (6.53 % vs 5.12%, $p<0.001$), M1 (1.63% vs 0.37%, $p<0.001$) and M2 macrophages (3.40% vs 1.50%, $p<0.001$) were observed in ANTXR1^{H} TME, which were more frequently classified as T cell-inflamed compared to *ANTXR1*^{L} TME (23% vs 5%, $p<0.001$). *ANTXR1*^{H} tumors also had higher MPAS compared to *ANTXR1*^{L} (1.36 vs -1.86 arbitrary units, $p<0.001$). There was no significant difference in mOS between *ANTXR1*^{H} vs ^{L} tumors (12.2 vs 10.5 months, HR: 0.95, p=0.678). **Conclusions:** Increased B cell, M1 and M2 macrophage infiltrates, and increased prevalence of T-cell inflamed tumors in ANTXR1^{H} TME suggest that these patients with SCLC may respond preferentially to ICI. A Phase 1 trial incorporating SVV-01 along with ICI is underway. Prospective investigation of molecular associations and clinical outcomes related to *ANTXR1* expression in SCLC is warranted. Research Sponsor: None.

Characterization of diverse targetable *ERBB2* alterations in 512,993 patients with solid tumors.

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Background: Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) that has demonstrated activity against a range of HER2-expressing and HER2-mutant (mut) solid tumors. We present an extensive landscape of *ERBB2* alterations (alt) that may predict sensitivity to HER2-targeted therapies in development with a focus on mutations and cancer types without approved indications. **Methods:** We queried institutional databases (MSKCC and Foundation Medicine, Inc.) of comprehensive genomic profiling (CGP) performed on solid tumor tissue samples using either MSK-IMPACT (N=83,332; MSK) or FoundationOne/FoundationOne CDx (N=429,661; FMI) and on patient-matched liquid biopsies using FoundationOne Liquid CDx (N=1,922). ctDNA tumor fraction (ctDNA TF) on FoundationOne Liquid CDx was estimated using a composite algorithm. Clinicopathological characteristics and treatment outcomes were annotated for MSK-IMPACT samples. **Results:** *ERBB2* activating alt were detected in 6.6% (n=28,508) and 5.0% (n=4,133) of tumors in the FMI and MSK cohorts, respectively. In FMI tissue samples, *ERBB2* alt were most prevalent in gastroesophageal (GEC; 18.1%), bladder (18.0%), salivary gland (14.1%), breast (12.7%), and uterine (12.1%) cancers. The cancer types with the largest number of *ERBB2*mut tumors, specifically, included NSCLC (n=1,618, 1.9%), breast (n=1,565, 3.5%), colorectal (CRC; n=1,221, 2.3%), bladder (n=855, 8.8%), and GEC (n=660, 3.4%). Across these 5 cancers, *ERBB2* mut were most commonly located in the kinase domain (KD; 58%), followed by the extracellular domain (ECD; 28%) and transmembrane domain (TMD; 2%). Rare splice site mut and in-frame deletions resulting in exon 16 loss (Ex16Alt) were also observed (n=76, $<$0.1%). *ERBB2* mut were found to be mutually exclusive with other RTK/MAPK driver oncogenes including: *EGFR*, *KRAS*, *ALK*, *MET*, *BRAF*, and *RET* in NSCLC; *FGFR1* in breast cancer; *BRAF* in CRC; and *FGFR3* in bladder cancer. In patient-matched liquid biopsy samples, sensitivity for detecting *ERBB2* amplifications (amp; 33.3%, 43/129) was lower than for detecting *ERBB2* mut (72.3%, 47/65) across select cancers. However, sensitivity for detection of both alts was improved in liquid samples with elevated ctDNA TF ($\geq$1%), increasing to 52.6% (40/76) for amp and 97.3% (36/37) for mut. In the MSK cohort, 110 of 986 (11.2%) patients with *ERBB2* mut non-NSCLC tumors received one or more HER2-targeted therapies, including ADCs. Clinical responses to HER2-targeted therapies were observed in patients harboring KD mut (n=10), ECD mut (n=6), TMD mut (V659E, n=1), and in 1 patient with a V697L mut. **Conclusions:** CGP detects diverse *ERBB2*activating alt at a high incidence in solid tumor types beyond NSCLC. These represent patient populations who may benefit from HER2-directed therapies. Trials of novel HER2-targeted agents are necessary to refine our understanding of the biological dependency of HER2 alterations. Research Sponsor: None.

Nivolumab plus ipilimumab (N+I) in patients (pts) with solid tumors with high tumor mutational burden (HTMB): 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 alterations. Results in a cohort of pts with advanced solid tumors with HTMB treated with N+I are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options or prior immune checkpoint inhibitor tx. PD-L1 expression testing was not required. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. HTMB was defined *a priori*as ≥9 mutations/megabase (Muts/Mb) via a qualifying test for TAPUR or approved by the Molecular Tumor Board. Pts received I at 3 mg/kg every 3 weeks (wks) for 4 doses with N at 1 mg/kg IV every 3 wks for 4 doses. N alone was then continued at 240 mg every 2 wks or 480 mg every 4 wks until disease progression. Low accruing histology-specific cohorts with HTMB were collapsed into 1 cohort for analysis. 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+). The hypothesized null DC rate of 15% was evaluated by a 1-sided exact binomial test (α= 0.10; 86% power based on alternative DC rate of 35%). Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response (OR), duration of response (DOR), duration of SD, and safety. DOR is time from documented OR to progressive disease (PD); duration of SD is time from tx start to PD. **Results:** 26 pts with 13 tumor types with HTMB were enrolled. Table shows demographics and outcomes. Tissue tumor mutational burden (TMB) ranged from 8 to 374 Muts/Mb (median= 16). 1 CR (small intestine; TMB= 48 Muts/Mb; DOR= 36 wks), 7 PR (biliary tract, site unspecified [3], soft tissue sarcoma, uterus, vagina; median TMB= 17 Muts/Mb; median DOR= 20 wks [range, 5-231]) and 1 SD16+ (pancreas; TMB= 26 Muts/Mb; duration of SD= 26 wks) were observed for a DC rate of 35% (1-sided 90% CI: 22 to 100) and OR rate of 31% (95% CI: 14 to 52). The null hypothesis was rejected (p=0.011). Notably, 1 pt (uterus, 374 Muts/Mb) is still on tx with an ongoing 66-wk PR as of Jan 2024. Most pts, including 8/9 with DC, were microsatellite stable. 10 pts had ≥1 grade 3 tx-related adverse event (AE) or serious AE. **Conclusions:** N+Ishowed antitumor activity in pts with advanced solid tumors with HTMB. Additional study is warranted to confirm the efficacy of N+I in pts with HTMB. Clinical trial information: NCT02693535. Research Sponsor: Bristol Myers Squibb; AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Genentech, Merck, Pfizer, Seagen, Taiho Oncology.

Demographics and efficacy outcomes (N=26).

Median Age, yrs (range)		**63 (37-86)**
ECOG PS, %	0	11 (42)
	1	14 (54)
	2	1 (4)
Prior systemic regimens, %	0-2	17 (65)
	≥3	9 (35)
DC rate, % (OR and SD16+) (1-sided 90% CI)		35 (22, 100)
OR rate, % (95% CI)		31 (14, 52)
Median PFS, wks (95% CI)		9 (8, 18)
Median OS, wks (95% CI)		53 (18, 127)

3131 Poster Session

Afatinib in patients (pts) with solid tumors with neuregulin 1 (*NRG1*) fusions: 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 alterations. Results in a small cohort of pts with advanced solid tumors with *NRG1* fusions treated with afatinib are reported. **Methods:** Eligible pts had measurable, advanced disease, *NRG1*fusion, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Pts with non-small cell lung cancer (NSCLC) were eligible if they had no pathogenic mutations in *ALK*, *BRAF*, *EGFR* or *ROS1*. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts received 40 mg of afatinib daily 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+). Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response (OR), duration of response, duration of SD, and safety. This cohort was closed after 2 years before completing stage 1 enrollment (n = 10) of the Simon's 2-stage design used in TAPUR according to a prespecified cohort closure rule. **Results:** 4 pts with 3 tumor types with *NRG1* fusion were enrolled between February 2020 and July 2021. 1 pt had NSCLC with a *CD74-NRG1* fusion and achieved a PR that lasted 24 weeks (wks). This pt was a 58-year-old White, non-Hispanic female with ECOG PS 0, 2 prior systemic therapies and progressed after 32 wks on study tx. Co-alterations included *CCNE1* amplification (amp), *GATA* amp, *TP53* R65fs*58, and an *ALK* G1121D variant of unknown significance. 2 pts achieved SD16+: 1 was a 47-year-old White, Hispanic female with colorectal cancer (CRC) with a *MATN2-NRG1* fusion, ECOG PS 1, 3 prior systemic therapies and co-alterations in *APC*, *DDX11*, *FBXW7*, *FGFR1* and *TP53*; the other pt was a 49-year-old Black, non-Hispanic male with pancreatic cancer with a *NRG1* exon 2 fusion, ECOG PS 1, 5 prior systemic therapies, a comutation in *ARID1A*. The durations of SD for these 2 pts were 136 and 64 wks, respectively. The pt with CRC underwent resection of a remaining target lesion and is still alive off study drug at 198 wks after the baseline visit as of Dec 2023. 1 pt was a 70-year-old White, non-Hispanic female with CRC with a *CD74-NRG1* fusion, ECOG PS 0, 1 prior systemic therapy, and a best response of progressive disease. This pt had comutations in *ARID1A*, *PBRM1* and *TP53*and progressed at 8 wks. Median OS was 81 wks. No grade 3-5 tx-related adverse events (AE) or serious AEs were reported. **Conclusions:** Though a small sample size, afatinib demonstrated promising activity in pts with advanced solid tumors with *NRG1* fusion, including very durable DC. Additional study in a larger group of pts is warranted to confirm the efficacy of afatinib in pts with *NRG1* fusion. Clinical trial information: NCT02693535. Research Sponsor: Boehringer Ingelheim; AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly and Company, Genentech, Merck, Pfizer, Seagen, Taiho Oncology.

Ex vivo assessment of cellular mass response for personalized therapy selection of hyperthermic intraperitoneal chemotherapy (HIPEC) agents.

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Background: Despite progress in the development of HIPEC protocols for the treatment of peritoneal carcinomatosis, agent selection remains largely empiric with few biomarkers for guiding treatment. *Ex vivo* assessment of drug response using single-cell mass measurements offers a promising option for therapy selection. Previously, we have shown that mass response testing (MRT) is a malignancy- and drug-agnostic means of assessing drug response (1) and can predict a patient's clinical response to therapy in a range of solid and hematological malignancies (2). **Methods:** Tissue specimens were collected from patients with peritoneal carcinomatosis as part of an ancillary study for a HIPEC clinical trial (NCT04847063) to explore the feasibility of performing MRT with these specimen types. Briefly, after overnight shipment of viable tumor tissue, tumor cells were isolated and treated with various therapies *ex vivo. S*ingle-cell mass distributions of vehicle and drug-treated populations were compared to determine the functional activity of each agent. **Results:** MRT was attempted for 60 patients with metastatic disease, 10 of whom had peritoneal carcinomatosis and ultimately received HIPEC. The HIPEC cases included histologies such as peritoneal mesothelioma (n=4), colorectal cancer (n=3), ovarian cancer (n=2), and small bowel adenocarcinoma (n=1). In total, 8 out of 10 peritoneal specimens had a sufficiently high tumor cell count, viability, and purity to perform MRT. These specimens displayed clear and statistically distinguishable mass response patterns of response and non-response to several different agents commonly used for HIPEC treatment such as cisplatin, oxaliplatin, doxorubicin, and mitomycin C. Study design:These feasibility results serve as the foundational data for launching a single-site phase II interventional study at the NCI's Center for Cancer Research. The study will evaluate the potential benefit of personalized treatment regimens determined by MRT for patients with peritoneal carcinomatosis, particularly mesothelioma, a context where therapeutic options have relative equipoise in clinical efficacy. Tumor biopsies will be obtained via laparoscopy prior to HIPEC and submitted to a CLIA-certified lab for MRT to assess the responses of various clinically acceptable agents. The HIPEC regimen will be selected based on these MRT results returned within two days of sample collection. Enrolled patients will then undergo cytoreduction and HIPEC, and progression-free and overall survival will be monitored. As a single-arm, non-randomized trial, patient responses will be compared with a matched synthetic control to assess the impact of MRT on efficacy of HIPEC regimens. **Conclusions:** MRT is feasible for peritoneal carcinomatosis tissues, with future studies focusing on its role in guiding HIPEC treatment. 1. *Nat Comm Bio,*2022. 2. *JCO PO*, 2024. Clinical trial information: NCT04847063. Research Sponsor: None.

Diversity in B7-H3/CD276 expression across cancer types: Exploring a dynamic novel immune checkpoint.

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Background: The resistance encountered in immune checkpoint blockade has persistently impaired the achievement of robust, durable antitumor immune responses in most cancer patients, prompting the search for additional immune targets. B7 homolog 3 (B7-H3)/CD276 is an emerging immune biomarker whose contrasting immune functions challenge conventional immune marker classifications, making it a compelling target. The present study aimed to characterize the expression of B7-H3/CD276 in a pan-cancer setting, analyze its co-expression patterns with potentially co-targetable immune checkpoints, and discuss implications for ongoing clinical trials. **Methods:** We conducted a focused analysis of B7-H3/CD276 expression in 514 cancer patients with diverse tumor histologies evaluated under the PREDICT protocol at the University of California San Diego. RNA sequencing of tissue specimens was performed, and results were used to characterize the RNA expression levels of B7-H3/CD276 and its correlation with key cancer immunity markers including PD-1, PD-L1, PD-L2, CTLA4, LAG3, BTLA, TIM3, VISTA, ADORA2A and IDO1. **Results:** Elevated expression levels of B7-H3/CD276 were observed in 41.6% [214/514] of the 514 tumor samples analyzed. When stratified by cancer type, the highest rates of elevated expression were found in sarcomas (58.30%, 14/24), followed by pancreatic (58.20%, 32/55) and liver and bile duct cancers (52.60%, 10/19). The independent association with pancreatic cancers was statistically significant on multivariate analysis (odds ratio 2.20, 95% confidence interval 1.09 – 4.45, p = 0.027). Ninety-three unique patterns of immune co-expression were observed among the 214 patients with high B7-H3/CD276 expression levels. Among them, the most commonly observed pattern was high expression of B7-H3/CD276 alone (26.2%, 56/214) followed by co-expression with high VISTA (7.0%, [15/214]) and high ADORA2A (5.6%, [12/214]). Of note, there was significant heterogeneity observed in the patterns of co-expression in cancer immunity markers, with 72.04% (67/93) in the cohort being unique to one patient. **Conclusions:** We have observed immunomic diversity in our analysis of B7-H3/CD276 expression levels across varied tumor types as well as in its co-expression patterns with other immune markers. Our findings suggest that leveraging immune profiling to build customized therapeutic regimens may be pertinent to optimizing response rates and minimizing toxicity to B7-H3/CD276 targeting therapies. Research Sponsor: LabCorp (OmniSeq).

Phase II study to evaluate safety and efficacy of neratinib, an irreversible pan-HER tyrosine kinase inhibitor, and trastuzumab biosimilar in patients with HER2 mutated advanced solid tumors (KCSG AL20-17).

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Background: Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, has single agent clinical activity in HER2 mutated cancer. This open-label single arm phase 2 trial investigated the efficacy and safety of the dual anti-HER2 therapy, neratinib plus trastuzumab in heavily pretreated patients with HER2 mutated solid tumors excluding HER2 amplifications. **Methods:** Neratinib was administered 240mg p.o. daily with trastuzumab biosimilar (Herzuma) every 3 weeks. The primary endpoint was objective response rate (ORR) by RECIST v1.1. Secondary endpoints were duration of response (DoR), progression free survival (PFS), and safety. An exploratory biomarker study was also conducted. **Results:** Forty patients were enrolled with a median follow-up of 11.08 months (range, 0.39-21.63 months) and a median of 3 (range 1-9) lines of prior systemic therapy. Tumor types included lung (42.5%), colorectal (20%) biliary (12.5%), and breast (7.5%). Sixty percent (60%) of patients (n=24) had HER2 mutation in the kinase domain. Among evaluable patients (n=39), the ORR was 23.1% (CR=0, PR=9) with a median DoR of 11.18 months (95% CI 0-22.63). Median PFS was 3.42 months (95% CI 1.57-5.27) and median overall survival was 9.47 months (95% CI 2.93-16.01). Grade ≥3 adverse events (AEs) occurred in 47.5% of patients (n=19) and diarrhea was the most frequently reported AE (n=10; 25%) followed by bilirubin elevation (n=2; 5%), and anemia (n=2; 5%). **Conclusions:** In heavily pretreated patients with HER2 mutated solid tumors, neratinib plus trastuzumab showed a moderate response rate, with a durable duration of response. Most AEs were manageable, highlighting the need for prophylactic diarrhea management. Exploratory biomarker results will be presented at the upcoming meeting. Clinical trial information: NCT06083662. Research Sponsor: Ministry of Health & Welfare, Republic of Korea; HI17C2206.

Artificial intelligence (AI) -powered H&E whole-slide image (WSI) analysis of tertiary lymphoid structure (TLS) to predict response to immunotherapy in non-small cell lung cancer (NSCLC).

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Background: Recent data indicate that immune cells present in the TLS within the tumor microenvironment (TME) could potentially serve as a favorable predictor for immune checkpoint inhibitor (ICI) therapy. To examine this further, AI model was created to provide an assessment of TLS in H&E WSI, and to determine its correlation with survival outcomes of NSCLC patients treated with ICI. **Methods:** We collected H&E-stained WSI of primary and metastatic tumors and clinical data in a retrospective study of advanced-stage NSCLC patients treated with ICI (with or without chemotherapy) at Northwestern University from May 2015 to November 2022. When evaluating the TLS status in the biopsy specimen collected from the lymph nodes (LNs), TLSs were only considered if they were admixed with tumor cells and located distant from the residual parenchyma, ensuring the exclusion of innate lymphoid follicles. Following the assessment of the presence of TLS by a pathologist, the identical WSIs were evaluated by the AI-powered H&E WSI analyzer. We used Lunit SCOPE IO, an AI-powered H&E WSI analyzer developed using 21,096 H&E stained WSIs, which can segment various classes of tissue area including TLS within the TME. Survival analysis was performed using Kaplan-Meier curves, and differences in survival outcomes among TLS groups were evaluated using the log-rank test. **Results:** In this analysis, out of a total of 73 patients, 24 (33%) cases were identified as containing TLS (TLS +) by the AI analyzer. In contrast, the pathologist classified 17 (23%) cases as TLS+. The AI model demonstrated an accuracy of 84.9% (with a sensitivity of 88.2% and specificity of 83.9%) in identifying the presence of TLS compared to the pathologist's interpretation. The median value of the proportion of TLS area within TME (TLSP) in samples containing TLS was 0.418% (Q1: 0.228%, Q3: 1.311%). TLSP was not found to be correlated with survival outcomes. The number of clusters of TLS was not found to be correlated with survival outcomes. **Conclusions:** AI-powered TLS analysis can be potentially utilized as a predictive biomarker of survival outcomes of NSCLC patients treated with ICI. Research Sponsor: None.

		PFS		OS	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Pathologist	TLS - (n = 56)	Reference	0.016	Reference	0.012
	TLS + (n = 17)	0.309 (0.119-0.804)		0.334 (0.141-0.788)	
AI analyzer	TLS - (n = 49)	Reference	0.009	Reference	0.030
	TLS + (n = 24)	0.328 (0.142-0.756)		0.472 (0.240-0.928)	
Pathologist + AI analyzer	Pathologist TLS +, AI TLS + (n = 47)	Reference		Reference	
	Pathologist TLS +, AI TLS - (n = 2)	0.490 (0.066-3.632)	0.485	0.497 (0.068-3.638)	0.491
	Pathologist TLS -, AI TLS + (n = 9)	0.479 (0.145-1.583)	0.227	0.808 (0.340-1.922)	0.629
	Pathologist TLS +, AI TLS + (n = 15)	0.251 (0.087-0.724)	0.011	0.302 (0.118-0.772)	0.012

Cold-inducible RNA-binding protein as a context-specific functional mediator of breast cancer metastasis.

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Background: Cold-inducible RNA-binding protein (CIRBP) is a stress-induced mRNA-binding protein associated with clinical outcomes in a variety of human disease states. CIRBP's role as a prognostic biomarker in breast cancer (BC) has yet to be established. **Methods:** We describe a clinically annotated tissue micro-array cohort of 1406 hormone receptor positive (HR+) and 281 triple negative primary breast cancers (TNBC) stained by immunohistochemistry (IHC) for CIRBP. Statistical analyses were performed with the Kaplan-Meier estimator, as well as univariate and multivariate Cox proportional-hazards models. Multivariate models incorporated tumor size, lymph node status, grade and CIRBP expression levels. Co-primary endpoints were overall survival (OS) and progression-free survival (PFS). MDA-MB-231 TNBC cells and MDA-MB-361 HR+ cells were used for CIRBP knockout (KO) by CRISPR/Cas9, and subsequent mammary fat pad injections were performed in immunocompromised mice. **Results:** In N=281 primary TNBCs, high levels of CIRBP expression by IHC was associated with poor prognosis in multivariate analysis (OS: adjusted hazard ratio (aHR) 2.05, 95% confidence interval (CI) 1.24-3.41, P=0.005. PFS: aHR 2.46, 95% CI 1.33-4.57, P=0.004). However, in N=1406 HR+ primary BC, CIRBP expression was correlated with favorable prognosis (OS: aHR 0.927, 95% CI 0.88-0.98, P=0.05. PFS: aHR 0.904, 95% CI 0.85-0.96, P=0.002). CIRBP KO had minimal impact on mammary fat pad primary tumor growth in both MDA-MB-231 and MDA-MB-361 cell models. However, CIRBP KO resulted in the inhibition of efficient spontaneous metastasis to the liver and lungs in TNBC MDA-MB-231 cells but not HR+ MDA-MB-361 cells. **Conclusions:** CIRBP expression is associated with poor prognosis in TNBC but not HR+ BC patients, a finding validated with CRISPR/Cas9 KO in representative model systems. This finding highlights the prognostic significance of CIRBP in TNBC and suggests differential underlying mRNA targets bound and modulated by CIRBP in TNBC and HR+ BC, respectively. Research Sponsor: Quebec Breast Cancer Foundation; RRCancer.

Molecularly matched therapies identified by comprehensive genomic profiling before the first-line setting to provide alternative treatment outcomes in patients with solid tumors: 1-year follow-up of the prospective FIRST-Dx study.

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Background: Comprehensive genomic profiling (CGP) test by next-generation sequencing has been reimbursed in Japan since 2019. However, only 9.4% of patients (pts) had received molecularly-matched treatment because CGP test in Japan is only indicated after standard of care (SoC). To determine the clinical utility of a CGP test (FoundationOne CDx) in the first-line setting for pts with advanced solid tumors, we previously reported the results of the FIRST-Dx study, in which the molecular tumor board identified molecular-based recommended therapy (MBRT) for 61% of pts (105/172) (Matsubara J, et al. JAMA Netw Open 2023). In this 1-year follow-up of the FIRST-Dx study, we investigated the clinical benefits provided by the upfront CGP test. **Methods:** The FIRST-Dx study was a multi-institutional, prospective study in 6 hospitals in Japan. Chemotherapy-naïve adult pts with advanced solid tumor (GI, Lung, Breast, GYN, Melanoma) and ECOG performance status of 0-1 were enrolled. This follow-up study was planned for 3 years and an interim analysis was prespecified at 1 year after the final patient enrollment in the FIRST-Dx study. Primary endpoint was overall survival (OS). Secondary endpoints were the proportion of pts who received MBRT, overall response rate, progression-free survival (PFS), and a PFS ratio (PFS on MBRT/PFS on prior therapy). **Results:** Data from 172 pts with a median follow-up of 15.1 months were available. Median OS was not reached (95% CI: 18.4 months to not reached). Thirty-nine pts (22.7%) had received MBRT. The total number of pts treated with MBRT were 21 in 1^{st}-line, 20 in 2^{nd}-line, 4 in 3^{rd}-line, and 1 in 4^{th}-line, respectively. Overall response rate was 56.3% [95% CI: 29.9-80.2%] in 1st-line MBRT group vs 42.3% [95% CI: 33.9-51.1%] in 1st-line SoC (N=137), and 26.3% [95% CI: 9.1-51.2%] in 2nd-line MBRT group vs 17.1% [95% CI: 9.7-27.0%] in 2nd-line SoC (N=82), respectively. Median PFS was 12.9 months [95% CI: 7.4 months to not reached] in 1st-line MBRT group vs 11.3 months [95% CI: 8.6-14.1 months] in 1st-line SoC, and 6.9 months [95% CI: 2.8 months to not reached] in 2nd-line MBRT group vs 5.7 months [95% CI: 3.7-7.4 months] in 2nd-line SoC, respectively. Regarding the PFS ratio of 2nd-line MBRT (N=15) (PFS on MBRT in 2nd-line/PFS on 1st-line therapy), median PFS ratio was 1.0 (range: 0.1-14.6) and 4 pts (27%) had the PFS ratio of >1.3, indicating that MBRT might be effective in changing the clinical outcome (Von Hoff DD, et al. J Clin Oncol 2010). **Conclusions:** We showed that MBRT identified by CGP test before the first-line setting provides better treatment outcomes than SoC in pts with solid tumors early in their disease course. Our data suggested that the timing of CGP test in Japan for pts with advanced solid tumors should be indicated before starting SoC. Clinical trial information: jRCT1050220041. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

The pathway alteration load as a pan-cancer determinant of outcome of targeted therapies: Results from the Drug Rediscovery Protocol (DRUP).

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Background: Although targeted treatment (TT) has improved outcomes for many patients with cancer, the emergence of primary or secondary resistance remains a common challenge. A frequently suggested contributing mechanism to this resistance is the existence of parallel activated oncogenic signaling pathways that remain untargeted and support tumor survival. Therefore, we hypothesized that an increased number of altered oncogenic signaling pathways (Pathway Alteration Load, PAL) predicts reduced benefit of TT which targets only one altered pathway. **Methods:** The Drug Rediscovery Protocol (DRUP) is a prospective, pan-cancer, non-randomized clinical trial (NCT02925234) in which patients with treatment-refractory metastatic cancer with an actionable molecular profile are treated with matched approved targeted- and immunotherapies outside their registered indication. All patients treated with TT for whom clinical outcome and whole genome sequencing results of a pre-treatment biopsy were available were included. The PAL was determined by counting the number of proliferation pathways impacted by somatic driver alterations, using an established pathway classification scheme (Sanchez-Vega et al., *Cell*, 2018). Influence of PAL on clinical benefit rate (CBR, defined as objective response or stable disease $\geq$ 16 weeks according to RECIST v1.1 or RANO), progression-free survival (PFS) and overall survival (OS) was evaluated. Cox proportional-hazards models, stratified by tumor type, were used to adjust outcomes for drug, performance status, previous treatment lines, tumor mutational burden and cancer cell ploidy. Results were validated using the independent Hartwig database of metastatic cancers. **Results:** In all 154 patients treated with single pathway-directed TT, PAL was 0 in 3, 1 in 20, 2 in 37, 3 in 56, 4 in 31, 5 in 6 and 6 in 1 patient(s). Patients with a PAL below the median of 3 (N= 60) demonstrated a higher CBR (41.7% vs 25.5%, odds ratio [OR] 0.48, P = 0.051), longer PFS (median 4.7 vs 2.9 months, adjusted hazard ratio [aHR] 1.70, P = 0.020) and OS (median 13.7 vs 5.6 months, aHR 3.80, $P<$ 0.001), compared to those with PAL $\geq$3. Results were consistent across different PAL cut-offs and when applying PAL continuously (aHR for PFS 1.41, P = <0.001; aHR for OS 1.77, P = <0.001). In the independent Hartwig cohort, 258 patients treated with single pathway-directed TT were identified and similar results were found for CBR (54.2% vs 36.7%, OR 2.04, P = 0.009) and PFS (7.0 vs 4.2 months, aHR 1.55, P = 0.009), but not for OS (14.7 vs 8.2 months, aHR 1.37, P = 0.111). **Conclusions:** In our population, PAL emerged as a pan-cancer predictor of resistance to TT. Our findings provide support for more refined patient selection for TT and highlight the rationale for combinatorial treatment strategies, especially in patients with multiple affected pathways. Clinical trial information: NCT02925234. Research Sponsor: Hartwig Medical Foundation; KWF (Dutch Cancer Society); Stelvio For Life Foundation; Amgen; AstraZeneca; Bristol-Myers Squibb; Clovis Oncology; Eisai; Merck Sharp & Dohme; Novartis; Pfizer; Roche.

Single cell characterization of persistent cells upon immunotherapy treatment in colorectal and endometrial tumors: The SERPENTINE trial.

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Background: Immune checkpoint inhibitor (ICI) therapy has proved efficacy in MSI colorectal (CRC) and endometrial cancer (EC), but its use in MSS tumors remains a challenge. As the mechanisms of action of CTLA-4 and PD-1 are non-redundant, targeting both pathways may have additive or synergistic activity in comparison with single PD-1/PD-L1 inhibition in MSS and MSI CRC and EC tumors, while single cell characterization of persistent cells upon treatment would enable to describe cell populations and build a detailed single-cell map of the immune, tumor and stromal cell composition. A single dose of tremelimumab (Trem) 300mg, while maintaining a similar overall exposure, has 3- to 4-fold higher Cmax compared to 4 doses of Trem 1 mg/kg, which may have the potential for better anti-tumor activity while potentially avoiding cumulative toxicity. Here we present the results of patients (pts) with refractory ICI-naïve MSS EC and CRC treated with Dur plus Trem and the characterization of immune and persistent cells with longitudinal single-cell analyses. **Methods:** Pts with advanced MSS/pMMR CRC and EC that have progressed during or after standard therapy with measurable disease per RECIST 1.1, ECOG ≤1, were treated with Dur 1500mg plus Trem 300mg at Week 0, followed by Dur 1500 mg Q4W. Response rate was correlated with transcriptome and T cell repertoire dynamics measured at single-cell level from freshly processed biopsies at three different timepoints: baseline, upon treatment and at progression. **Results:** 24 samples for single-cell analysis were obtained (4 MSS CRC and 4 MSS EC). The response rate (RR) was 0%, while disease control rate was 12.5%. Despite the lack of response, we found a massive shift in the immune tumor microenvironments of all patients. Following treatment, immune cell composition shifted to increased frequency of effector-memory, proliferating $CD8^+$ cells and $CD4^+$ cells, surprisingly, with enriched T helper phenotypes. Both lineages showed strong signals of exhaustion. The integration of matched T cell receptor (TCR) data pointed to an infiltration of new clonotypes, rather than the expansion of pre-existing tumor-resident T cells, with distinct degrees of dysfunctional phenotypes between the clones. Intriguingly, expanded clonotypes could be detected and monitored in peripheral blood cells using ultra-deep TCR sequencing. **Conclusions:** Dual treatment with Dur and Trem does not result in an improved RR in patients with refractory MSS/pMMR CRC and EC, despite profound dynamics in the tumor infiltrating immune cells landscape. The infiltration of $CD4^+$ T helper cells provides mechanistic insights of immune evasion, a potential avenue to treat MSS/pMMR tumors. Clinical trial information: 2021-004061-13. Research Sponsor: None.

Evaluation of a predictive biomarker for antibody drug conjugates (ADCs).

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Background: Several ADCs are FDA-approved for patients with advanced solid tumors; dozens more are in trials. Predictive biomarkers are lacking, with ADC target expression alone performing poorly across ADCs/tumor types. We previously described the development of ADC Treatment Response Scores (ADC-TRS)—a tissue-based multivariate gene-expression test combining individual ADC target expression with proliferation and adhesion—with high correlation of per-ADC/tumor type biomarker frequency (TRS-High) with corresponding clinical trial ORRs for 9 ADCs (PO1-14-04; SABCS 2023). Here we evaluated ADC-TRS in two cohorts of patients treated with approved ADCs. **Methods:** Adults with advanced solid tumors from an observational trial (NCT03061305) treated with an ADC with TRS results from FFPE tissue (collected prior to 1st ADC treatment) were eligible; HER2+ patients previously treated with trastuzumab or with hormonal therapy treatment between sample collection/first ADC treatment were excluded. Kaiser Permanente Northern California (KPNC; limited to breast [BR] and bladder [BL] cancer) patients and non-KPNC patient (pan-solid tumor) cohorts were analyzed separately. We evaluated whether treatment-matched ADC-TRS status (High or Low) was significantly associated with overall survival (OS) after ADC treatment initiation by Cox proportional hazards models (adjusting for age, indication, and years since tissue collection). Additional analyses in the non-KPNC cohort evaluated whether proliferation/adhesion-related gene expression provided information on outcomes beyond ADC target expression only and predictive/prognostic effect. **Results:** Patients treated with an approved ADC were included in the non-KPNC (n=72; 5 ADCs/9 tumor types); most frequent sacituzumab govitecan/BR [43%]) and KPNC (n=127; 3 ADCs/two tumor types; most frequent enfortumab vedotin/BL[50%]) cohorts, respectively. In both cohorts, ADC TRS status was significantly associated with OS (High vs. Low, median OS 22.8 vs. 8.7 months [mo.], aHR 0.15, p=0.005, and median OS 15.3 vs. 8.3 mo., aHR 0.58, p=0.011, respectively). In the non-KP cohort, ADC-TRS significantly improved model fit for OS beyond target gene expression alone (likelihood ratio test [LRT] p=0.0008). A predictive biomarker effect was confirmed by lack of ADC-TRS status association with OS from systemic chemotherapy start in indication-matched patients not treated with an ADC (n=126, aHR 0.43-2.79, p=0.11-1.0 for the 9 individual TRS). In a 15,108 patient pan-tumor cohort (regardless of treatment), 26.7% were ADC-TRS High for at least 1 approved ADC outside approved indications. **Conclusions:** Results support ADC-TRS as a multivariate gene-expression-based biomarker that predicts ADC OS across tumor types and targets. More than 25% of all patients with advanced solid tumors have a greater likelihood of being responsive to one or more approved ADCs outside of approved indications. Research Sponsor: Strata Oncology.

Role of dynamic ctDNA monitoring in cervical and anal epidermoid carcinomas under curative chemoradiation.

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Background: Cervical and anal canal squamous cell carcinoma (SSC) are a significant health problem in underdevelopment countries. Definitive chemoradiation (CRT) is the standard-of-care (SOC) approach for curative treatment in locally advanced disease. Due to the common substantial local inflammation during CRT, the conventional clinical image cannot identify non-responders early. In this scenario, the evaluation of circulating tumor DNA (ctDNA) is a promising tool for real-time tumor response monitoring. **Methods:** We performed a prospective multicentric cohort study of patients treated between 2020 and 2023 in tertiary oncologic centers in Brazil to evaluate the role of ctDNA dynamic monitoring in epidermoid cervical (CC) and anal cancer (AC) T1-4, N0-1, M0 by AJCC 8th edition and candidates to complete curative CRT. The cDNA was assessed by Signatera test at D1, D29, immediately post-treatment, 8 weeks (w) post-CRT, 24w post-CRT, every 6 months (m) in the first 1-2 years(y), and yearly at 3-5y of follow-up (FUP). The primary endpoint was to estimate the correlation of ctDNA with a tumoral response assessed by conventional routine image and clinical evaluation at 8w. Secondary endpoints included a correlation between ctDNA results at different time points with progression-free survival (PFS) and overall survival (OS). The predictive potential of the biomarker was evaluated using receiving operating characteristic (ROC) curve analysis. **Results:** We included 33 patients, and 27 were evaluable with ctDNA, with a median FUP of 10m. The majority were female (n=23, 85.1%), and 3 (11%) were HIV-positive(+). Most patients presented with positive nodes and stage III disease (n=18, 66.6%). In the AC group (n=15), the majority received CRT with capecitabine and cisplatin (n=12, 55.5%); in the CC group (n=12), all pts received cisplatin. All pts tested expressed ctDNA+ before treatment. At 8w, images had a sensitivity of 42.8% and specificity of 100% for disease progression (area under the curve [AUC] 0.714), while ctDNA yielded a sensitivity of 85.7% and specificity of 89.4% (AUC 0.875). The ctDNA+ immediately after CRT ended (32%) was consistent with ctDNA+ at 8w (30.7%) and 24w (30%). Pts with ctDNA+ immediately post CRT have a higher risk of disease progression with PFS of 8.2m in ctDNA+ and not reached in ctDNA- group (HR:17.5; IC95%:1.9-157.3; p=0.01). Data are immature for OS analysis. **Conclusions:** CtDNA immediately post-CRT has a high predictive value in patients with anal and cervical tumors in early access CRT non-responders, who are at a high risk of disease progression. This biomarker should be considered for tailoring strategies of treatment escalation in this population. Research Sponsor: None.

Pertuzumab plus trastuzumab (P+T) in patients (pts) with solid tumors with *ERBB2*or *ERBB3*amplification (amp) or mutations (mut): 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 alterations. Results in a cohort of pts with advanced solid tumors with *ERBB2/3*amp or mut 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. Dosing of P was 840 mg IV over 60 minutes (m), then 420 mg IV over 30-60 m Q3 weeks (wks); T was 8 mg/kg IV over 90 m, then 6 mg/kg IV over 30-60 m Q3 wks until disease progression. Low accruing histology-specific cohorts with *ERBB2/3*amp and/or mut were collapsed into 1 cohort for analysis. 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+). The hypothesized null DC rate of 15% was evaluated by a 1-sided exact binomial test (α= 0.10; 82% power based on alternative DC rate of 35%). Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response (OR), duration of response (DOR), duration of SD, and safety. DOR is time from documented OR to progressive disease (PD); duration of SD is time from tx start to PD. **Results:** 28 pts with 11 tumor types with *ERBB2/3*amp +/- mut (25) or mut only (3) were enrolled. The table shows demographics and outcomes. 2 CR (vagina, *ERBB2*amp, DOR= 151 wks; sweat gland, *ERBB2*amp, DOR= 48 wks), 6 PR (esophagus [2], small intestine, urothelial carcinoma [UC], site unspecified [SU], vagina; all with *ERBB2*amp) and 8 SD16+ (cervix [3], small intestine [2], UC, SU, testis; 6/8 pts had *ERBB2* amp only, 1 had *ERBB2*mut only, 1 had *ERBB3*amp only) were observed for a DC rate of 57% (1-sided 90% CI: 43 to 100) and OR rate of 29% (95% CI: 13 to 49). The null hypothesis was rejected ($p<0.001$). Median duration of PR was 30 wks (range, 15-116, n=6). Median duration of SD for 8 pts with SD16+ was 28 wks (range, 18-84). 4/19 pts with *KRAS*testing performed had *KRAS*alterations. 5 pts had ≥1 grade 3 tx-related adverse event (AE) or grade 2-5 serious AE: anemia, cardiac arrest resulting in death, diarrhea, ejection fraction decrease, pleural effusion, supraventricular tachycardia and vomiting. **Conclusions:** P+T showed antitumor activity in pts with advanced solid tumors with *ERBB2/3*amp. Additional study is warranted to confirm the efficacy of P+T in this population. Clinical trial information: NCT02693535. Research Sponsor: Genentech; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck & Co., Pfizer, Seagen and Taiho Oncology.

Demographics and efficacy outcomes (N=28).

Median age, yrs (range)		**64**	**(29-88)**
ECOG PS, %	0	7	(25)
	1	14	(50)
	2	7	(25)
Prior systemic regimens, %	1-2	14	(50)
	≥3	14	(50)
DC rate, % (OR and SD16+) (1-sided 90% CI)		57	(43, 100)
OR rate, % (95% CI)		29	(13, 49)
Median PFS, wks (95% CI)		21	(9, 28)
Median OS, wks (95% CI)		62	(29, 83)

Identification of a patient tissue-based phosphorylation site as a biomarker for epidermal growth factor receptor (EGFR) activity in non-small cell lung cancer.

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Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related deaths globally. EGFR tyrosine kinase inhibitors (TKIs) have shown promise in treating NSCLC, yet resistance to these agents is common and current biomarkers rely on genetic data alone. Therefore, identifying reliable biomarkers to more comprehensively monitor EGFR activity and predict therapeutic responses is paramount. Here, we report an uncharacterized threonine phosphorylation site within core regulator of the EGFR pathway SHP2, that is strongly predictive of EGFR activity as defined by genetic mutation status that shows potential as a clinically relevant biomarker. **Methods:** Using DIA mass spectrometry phosphoproteomics, we could quantify >20,000 phosphosites from patient normal adjacent tumor (NAT) and primary tumor tissue. We further characterized these tissues using whole genome sequencing allowing us to define the mutational status of the EGFR. Statistical analysis was undertaken across all phospho-sites that identified a single uncharacterized phospho-site as a strong predictor of EGFR kinase activity. Finally, we generated monoclonal antibodies against the phosphopeptide and tested these in patient FFPE primary tumor tissue using immunohistochemistry to correlate phosphorylation levels with EGFR activation status. **Results:** Our results highlight how an individual phosphosite on SHP2 closely correlates with EGFR activity as defined by genetic mutation status in patient tissue. Interestingly, we further identify a group of patients who carry wild type EGFR yet have a phospho-signal potentially indicative of high EGFR activation without genetic aberration. These results were corroborated by a phospho-site specific antibody in FFPE tissue IHC, with strong signals observed in patients with an activating EGFR mutation (n=5), and complete absence of signal in patients harboring a wild type EGFR and no detectable mass spec signal (n=5). **Conclusions:** Our findings suggest that this uncharacterised SHP2 phosphosite may serve as a potent biomarker for EGFR activity in NSCLC. Further validation of the monoclonal antibodies as tools for this clinically relevant biomarker is required in larger patient cohorts to elucidate the role of the phosphosite in therapy response. This novel biomarker has the potential to guide therapeutic decision-making and contribute to personalized medicine strategies for NSCLC patients. Research Sponsor: None.

Expression of metabolic genes associated with changes in brain structure across the lifespan affects patients (pts) outcomes in metastatic colorectal cancer (mCRC): Data from CALGB/SWOG 80405 (Alliance).

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Background: Longitudinal brain structure changes across the lifespan are associated with neurodegenerative disorders. We previously showed that genetic variants in dopamine and Parkinson's disease genes are predictive and prognostic in mCRC. Indeed, the brain-gut axis is emerging as a critical player in CRC biology. Hence, we investigated whether the tumor gene expression of 3 metabolic genes involved in brain development and aging could affect treatment response in patients enrolled in the CALGB/SWOG 80405 trial. **Methods:** 433 mCRC pts treated with either bevacizumab (bev, n = 226) or cetuximab (cet, n = 207) in combination with first-line chemotherapy were included in the analysis. RNA was isolated from FFPE tumor samples and sequenced on the HiSeq 2500 (Illumina). Overall survival (OS) and progression-free survival (PFS) were compared between groups of pts categorized by tertiles of expression of 3 genes: *APOE*, *DACH1*, and *GPR139*. Likelihood ratio tests, hazard ratios and 95% confidence intervals were computed from multivariate Cox proportional hazards models, adjusting for age, sex, ethnicity, ECOG PS, tumor location, number of metastatic sites, *KRAS*, MSI status, and treatment. Logrank *P*-values describe differences without adjustment for patient characteristics. **Results:** Both *APOE* and *DACH1* (but not *GPR139*) met the 0.05 false discovery rate threshold for association with both PFS (P = .00085, P = .015) and OS (P = .021, P = .021, respectively) in the full Cox models. In cet-treated pts, *APOE*-high (H) showed significantly shorter PFS (median 9.2 vs 11.8 vs 13.0 months (mo), high vs low (as reference) logrank P = .0021) and OS (median 21.9 vs 35.8 vs 34.6 mo; logrank P = .0017) compared to *APOE*-median and -low, respectively. Opposite results were observed for *DACH1*, where *DACH1*-H tumors had longer PFS (median 14.5 vs 10.6 vs 8.07 mo; logrank P = .0011) and OS (median 39.4 vs 30.9 vs 21.5 mo; logrank P = .0021) when treated with cet. In bev-treated pts, similar results were observed with *APOE*-H showing shorter OS (median 25.8 vs 26.3 vs 37.5 mo; logrank P = .0016) and *DACH1*-H longer OS (median 36.5 vs 28.3 vs 22.4 mo; logrank P = .0017). No significant gene-treatment interaction was observed for either gene for PFS and OS. **Conclusions:** The tumor expression of metabolic genes associated with changes in the brain structure was prognostic in mCRC pts treated with first-line therapy. Notably, *APOE* and *DACH1* have been recently reported to play a role in CRC where *APOE* overexpression has been associated with aggressive biological behavior whereas *DACH1* has been shown to suppress CRC cell growth and invasion. Our results support this evidence and suggest that further investigation into the role of *APOE* and *DACH1* in CRC biology and into their potential as targets for drug development is warranted. Trial Identifier: NCT00265850. Research Sponsor: P30CA014089, U10CA180821, U10CA180882, U10CA180820 (ECOG-ACRIN); U10CA180888 (SWOG); Pfizer, Genentech; https://acknowledgments.alliancefound.org.

Clinical and molecular characterization of *AXL* in colorectal cancer: CALGB (Alliance)/SWOG 80405 and real-world data.

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Background: Dysregulation of AXL signaling is linked with chemotherapy and targeted therapy resistance. However, it remains unclear which patients may benefit from therapies targeting *AXL*, given its role in both tumor cell intrinsic resistance and immune microenvironmental reprogramming. Here, we present a clinical and molecular characterization of *AXL* in colorectal cancer (CRC). **Methods:** 24,257 CRC samples tested at Caris Life Sciences (Phoenix, AZ) with WTS (Illumina NovaSeq), NextGen DNA sequencing (NextSeq, 592 genes and NovaSEQ, WES), and PD-L1 expression (22C3 clone; TPS $\geq$ 1%) were analyzed. RNA deconvolution analysis with QuantiSEQ estimated cell infiltration in the tumor microenvironment (TME). In this cohort, *AXL* expression was categorized as high (H) or low (L) using median cutoff: overall survival (OS) was evaluated from treatment initiation using insurance claims data. Data from the phase III CALGB/SWOG 80405 trial on 433 metastatic CRC (mCRC) patients treated with bevacizumab (Bev, n = 226) or cetuximab (Cet, n = 207) in combination with first-line chemotherapy were also evaluated. RNA isolated from FFPE tumor samples were sequenced with HiSeq 2500 (Illumina). OS and progression-free survival (PFS) were compared using categorical gene expression tertiles (high (T3), medium (T2), and low (T1)) adjusting for age, demographics, ECOG, and tumor/treatment characteristics. **Results:** *BRAF* and *RNF43* mutations were more prevalent in AXL-H, but *APC*, *NRAS*, *KRAS*, and *PIK3CA* correlated with *AXL*-L (all $q < .001$). *AXL*-H had increased B cells, M1/M2 macrophages, T-regs, and NK cells in the TME while increased neutrophils and dendritic cells were associated with *AXL*-L (all $q < .001$). *AXL*-H had increased PD-L1 positivity (5.1 vs 2.6%) and pathway activation of epithelial-mesenchymal transition (EMT), inflammatory/IFN-G response, and TNF-a signaling (all $q < .005$). *AXL*-H demonstrated worse OS in FOLFOX/FOLFIRI treated CRC (H: 35.7 vs L: 38.7 months [mo], $P = .003$; HR 1.08, 95% CI [1.03-1.14]). The effect persisted within *KRAS* wildtype (wt) CRC (45.4 vs 40.1 mo, $P = .005$; HR 1.12 [1.04-1.22]) but not *KRAS*mutant (mt). In 80405,higher *AXL*expression was associated with worse PFS and OS (P_{linear} = 2E-04 and 2.2E-05, respectively). *AXL*-T3 showed significantly shorter PFS (T3: 9.2 vs T2: 11.7 vs T1: 12.9 mo, T3 vs T1 (reference) adjusted HR 1.53 [1.19-1.97]) and OS (24.2 vs 34.0 vs 34.7 mo, adjusted HR 1.73 [1.33-2.25]). No significant interaction between *AXL* expression and treatment was observed for PFS and OS (likelihood ratio test). **Conclusions:** Our results indicate increased *AXL* expression is associated with immune cell infiltration, EMT, and inflammatory signaling. *AXL*-H confers worse OS/PFS on first-line chemotherapy, with a more pronounced effect in KRASwt CRC. This data supports evaluation of *AXL* as a prognostic marker and potential therapeutic target in CRC. Trial Identifier: NCT00265850. Research Sponsor: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org. P30CA014089, UG1CA180830 [HJL]; UG1CA180830 and U10CA180888 (SWOG); Genentech.

Comprehensive molecular profiling of newly diagnosed advanced, high-grade ovarian cancer: Unveiling *BRCA1/2* mutations and genomic instability scores to advocate for public insurance coverage of genetic testing—Insights from the Hellenic Society of Medical Oncology (HeSMO) national program.

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Background: Homologous recombination deficiency (HRD) in ovarian cancer, indicative of impaired DNA repair, contributes to genomic instability (GIS). Beyond mutations in BRCA1/2 genes, GIS is particularly significant for identifying patients who may benefit from PARP inhibitors. Equivalence between Myriad Genetics' myChoice CDx and the standard diagnostic tests OncoScan and Amoy Diagnostics has been published, prompting HeSMO to launch a national program addressing GIS and BRCA 1/2 mutations in newly diagnosed advanced high grade ovarian cancer patients, with the utilization of these more economically advantageous tests, in order to guide effective therapeutic strategies, since official reimbursement is not yet applicable in our country. **Methods:** Patients with locally advanced or metastatic high-grade stage III/IV ovarian cancer were eligible for the HeSMO program, submitting an FFPE tissue tumor sample. The evaluation focused on HRD detection (positive or negative) and GIS assessment (high or low), combining results from OncoScan and Amoy Diagnostics. **Results:** Between August 2022 and December 2023, 511 patients from Greece underwent testing. 48.14% (n=246) tested HRD positive, 46.58% (n=238) HRD negative. High GIS score was observed in 44.81% (n=229), low GIS in 49.71% (n=254). Potential pathogenic mutations in BRCA1/2 genes were found in 19.96% (n=102). BRCA1 mutations (13.70%, n=70) included key mutations: c.190T>C p.(Cys64Arg), c.3700_3704delGTAAA p.(Val1234GlnfsTer8), c.4065_4068del p.(Asn1355LysfsTer10). BRCA2 mutations (6.26%, n=32) comprised of c.1129G>T p.(Glu377-Ter), c.3650_3659del p.(Arg1217IlefsTer8), c.7150C>T p.(Gln2384Ter). In 27 samples (5.28%) no result was produced. **Conclusions:** HRD and GIS are vital genomic instability biomarkers in high-grade ovarian cancer. These metrics provide valuable insights into tumor aggressiveness, guiding therapeutic decisions, including the use of PARP inhibitors. In this study of 511 patients from 50 centers across Greece, 48.14% tested positive for HRD, emphasizing PARP inhibitors' significance and suggesting hereditary implications. Our commitment to enhance patient access to reliable diagnostic biomarker testing in Greece is unquestionable. Furthermore, we believe, our results will strengthen our efforts towards official state reimbursement, paving the way for local HRD testing solutions. Research Sponsor: AstraZeneca.

HGOC HeSMO Program	No of Patients	Percentage Among the 511 Patients
HRD positive	246	48.14%
HRD negative	238	46.58%
High GIS score	229	44.81%
Low GIS score	254	49.71%
BRCA1 mutations	70	13.70%
BRCA2 mutations	32	6.26%
Failed samples	27	5.28%

The immunological milieu of oropharyngeal squamous cell carcinoma (OPC) according to HPV and smoking status and its influence on prognosis.

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Background: OPC exhibits distinct epidemiological, genetic, and clinical characteristics, significantly influenced by the presence of HPV. Despite multidisciplinary therapy, approximately 40% of OPC patients (pts) experience recurrence, and those who achieve cure often endure late and morbid sequelae of treatment. In this study, we comprehensively explored the composition and functional status of the tumor immune microenvironment (TIME) in a cohort of OPC pts treated with curative intent and investigated TIME differences based on HPV infection, smoking status, and clinical outcomes. **Methods:** Two tissue microarrays with baseline OPC tissues were stained with a previously validated panel containing 33 metal-tagged markers. Imaging mass cytometry was performed with the Fluidigm Helios CyTOF instrument, and analysis performed with Visiopharm software. HPV status was determined by p16 IHC and/or DNA testing. Comparison of cell types and markers densities among subgroups (HPV positive vs negative) were analyzed with Wilcoxon signed-rank test and its association with clinical outcomes (recurrence vs no-recurrence) with log-rank and Cox Proportional Hazards. Multiple comparisons were corrected by Benjamini Hochberg procedure. **Results:** A total of 99 samples from 61 pts from a single institution were included in this study. The majority of pts were male (N=47, 77%) and heavy smokers (N=55, 90%); 72% were HPV-negative. The median age was 61 years (range, 39 – 87 years), and 52% of cases were diagnosed with stages III-IVB (AJCC 8th edition). Most pts (57%) was treated with surgery (±RT). Thirty-three pts (54%) experienced recurrent disease. Smoking, stage III-IVB, and HPV-negative tumors were associated with higher recurrence rates ($p < 0.01$). Regarding the OPC TIME, the most prevalent cell populations in the stroma were fibroblasts (22%), followed by T-cells (17%) and endothelial cells (10%). The stroma of HPV+ tumors exhibited higher densities of memory T cells (FDR < 0.01), B cells (FDR = 0.02), and T cells (FDR = 0.02) compared to HPV negative counterparts, which displayed an increased density of neutrophils (FDR = 0.04). The density of cancer stem cells was directly associated with smoking history (FDR<0.001), and an increased density of intra-tumoral B-cells was found in non-smokers (FDR=0.01). Higher intra-tumoral neutrophil density was linked to recurrent disease (FDR < 0.001). Conversely, higher densities of memory CD8+ T cells and non-M2 macrophages in the TIME were associated with a lower chance of recurrence (FDR < 0.1). **Conclusions:** The intricate analysis of the OPC TIME revealed significant differences according to HPV and smoking status and highlighted the prognostic role of neutrophils, memory CD8+ T cells, and non-M2 macrophages. These findings may guide the development of personalized therapeutic strategies for OPC. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Comprehensive characterization of *ERBB2* genomic alterations inlung cancer.

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Background: *ERBB2*mutations () occur in 1-4% of non-small cell lung cancers (NSCLC). Trastuzumab-deruxtecan is FDA-approved for the treatment of metastatic *ERBB2*-mutant NSCLC based mostly on data from NSCLCs harboring tyrosine kinase domain (TKD) *ERBB2*mut. The genomic and clinical characteristics of NSCLC with *ERBB2* mut beyond the TKD remain largely unexplored. **Methods:** Patients (pts) with NSCLCs with oncogenic *ERBB2* mut and genomic tumor profiling data from the AACR Project GENIE database were included. The cohort was divided into pts with tumors harboring TKD, extracellular (ECD), or transmembrane (TMD) and juxtamembrane domain (JMD) *ERBB2*mut. Clinico-genomic characteristics were compared between the groups. The Kaplan-Meier method was used to estimate progression-free survival (PFS) with first-line systemic therapy, and log-rank tests were used for comparisons. **Results:** Of 483 pts with *ERBB2*-mutant NSCLC, 64% were female, 81% were White, and 13% were Asian. TKD, ECD, and TMD/JMD *ERBB2* mut were identified in 362 (75%), 88 (18%), and 33 (7%) cases, respectively. Pts with ECD vs. TKD *ERBB2*mut tumors were more likely to be males (47% vs. 33%, p=0.03) and have tumors with squamous histology (7% vs. 1%, p<0.0001). Among pts with (n=39), those with ECD vs. TKD *ERBB2* mut tumors were more likely to have a history of smoking (100% vs. 42%, p = 0.02). The most common TKD, ECD, and TMD/JMD *ERBB2* mut were in-frame ex20ins Y772_A775dup (n=224/362, 62%), missense S310F/Y (n=45/88, 51%), and missense V659E/D (n=10/33, 30%) mut, respectively. ECD vs. TKD *ERBB2*-mutant tumors harbored a distinct genomic phenotype with significantly higher median tumor mutational burden (11.1 vs. 5.2 mut/Mb, p<0.003), median fraction of genome altered (0.2 vs. 0.1, p = 0.02), and rate of co-mut in *EGFR* (32% vs. 3.6%, p<0.0001), *KRAS* (17% vs. 2.5%, p<0.0001), *STK11* (23% vs. 4.3%, p<0.0001), *KEAP1* (23% vs 5%, p<0.0001) and *SMARCA4* (19% vs 4.5%, p<0.0001). Of 343 cases with *ERBB2* copy number profiling, 32 (9.3%) harbored *ERBB2* amplification. *ERBB2*-mutant NSCLCs with vs. without *ERBB2*amplifications had a higher frequency of *TP53* co-mut (84% vs. 48%, p <0.001). Of 39 pts with available clinical data, most had ECD (n=6) *ERBB2* mut tumors and received first-line platinum-based chemotherapy (n=31). The presence of a co-mut in *STK11* (HR 3.5, 0.4–27.4, p=0.03) and *KEAP1* (HR 3.9, 0.7–20.6, p=0.002) conferred shorter PFS on first-line systemic therapy. Pts with ECD vs. TKD *ERBB2* mut tumors had shorter PFS (HR 2.4, 95% CI 0.7–8.2, p=0.04). **Conclusions:** NSCLC tumors harboring ECD *ERBB2* mut are associated with a distinct clinical and molecular phenotype and inferior outcomes with chemotherapy compared to pts with tumors harboring TKD mut. These findings enhance our understanding of disease heterogeneity in *ERBB2*-mutant NSCLC and may aid in optimizing treatment strategies for this unique population. Research Sponsor: None.

Biomarker discordance after neoadjuvant systemic therapy and associated patterns of recurrence.

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Background: Understanding and addressing intratumor heterogeneity in breast cancer (BC) is crucial for advancing research and improving patient outcomes. The identification of biomarkers for targeted therapies is complex when dealing with heterogeneous tumors, and this heterogeneity complicates cancer outcomes since it affects treatment response, and the development of resistance. **Methods:** A single institution retrospective review of patients with BC who received neoadjuvant systemic therapy (NAST) followed by definitive surgical resection from 2008 to 2022 was performed. Initial tumor biopsies were tested for hormone receptors (HR) [estrogen receptor (ER) and progesterone receptor (PR)], and HER2 status and repeated on the residual tumor tissue after NAST. HER2 status was categorized into HER2-negative, HER2-low, and HER2-positive and HR status was categorized into ER and/or PR positive or negative based on the 2023 ASCO-CAP guidelines. HER2 and HR concordance and discordance rates were obtained and patients who had disease recurrence were identified and analyzed using descriptive statistics and Fisher's exact test. **Results:** 480 patients with BC received NAST, and 143 patients with residual disease had pre and post treatment biomarker data available for analysis with a median post-surgery follow up of 15.2 months. Discordance in either HER2 or HR status was identified in 50% (72/143) of samples. Out of 143 patients, 44 patients had disease recurrence in which 50% (22/44) of tumors exhibited biomarker discordance. Among the changes in biomarker status, a shift in PR expression occurred most frequently in 27% of tumors (12/44). A change from HER2-low to HER2-negative status, as well as changes in ER expression occurred in 11% of tumors (5/44). 14% (6/44) of tumors had changes in both HER2 and HR. In patients who did not have recurrence, 51% (50/99) of tumors exhibited biomarker discordance. A HER2-low to HER2-negative status occurred most frequently in 18% (18/99). A change in ER expression occurred second most frequently, in 14% (14/99) of tumors. There was no statistical significance of discordance rates in the recurrence group and non-recurrence group (p-value=0.96). **Conclusions:** Tumor heterogeneity plays a role in shaping the distinct tumor biology of each patient. While the rates of biomarker discordance were comparable between samples with and without recurrence, the importance of HR discordance in this group requires extensive long-term monitoring. Our research highlights the importance of biomarker changes in a curative setting. Considering the implications for treatment, further investigation into additional biological and tumor-related factors associated with recurrence is warranted.
Research Sponsor: None.

	Tumor Recurrence (n=44)	No Recurrence (n=99)	All Patients (n=143)
Any Biomarker Discordance	22	50	72
HR Discordance	17	27	43
HER2 Discordance	15	37	52
HR Receptor and HER2 Discordance	6	7	13

Selpercatinib in non-MTC, RET-mutated tumors: Efficacy in MEN-associated and other tumors.

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Background: Selpercatinib, a first-in-class highly selective and potent RET kinase inhibitor with CNS activity, is approved in multiple countries for the treatment of *RET*-activated cancers. Current indications for RET mutant disease are limited to MTC. This analysis examined if selpercatinib was effective in non-MTC, RET mutation positive tumors and whether certain RET mutations demonstrated better activity (n=23; data cut-off: 13Jan2023). **Methods:** The phase 1/2 LIBRETTO-001 trial (NCT03157128) enrolled pts with locally advanced/metastatic *RET*-altered solid tumors, including pts with RET mutations in tumors other than MTC. Mutations must be known to be activating based on activity in MTC or other published evidence. Primary endpoint was objective response rate (ORR) by independent review committee (IRC). Secondary endpoints included ORR by investigator (INV), duration of response (DoR), progression-free survival (PFS), and safety. **Results:** Fourteen different tumor types were identified among the 23 pts with non-MTC RET-mutated tumors. This included 8 tumors from the Multiple Endocrine Neoplasia (MEN) syndrome spectrum; adrenal (pheochromocytoma; n=5), paraganglioma (n=2), neuroendocrine (n=1) (Table). Most of the mutations were located in extracellular cysteine-rich domain (CRD) and in the tyrosine kinase domain (TKD) of RET. In 23 efficacy-evaluable pts, confirmed ORR by IRC was 21.7% (5/23, 95% CI: 7.5, 43.7). ORR by IRC for pts with MEN-associated tumors (n=8) was 37.5% while five of these pts (62.5%) had stable disease lasting at least 16 weeks (SD16+). ORR by IRC for the sub-population with pheochromocytoma (n=5) was 40.0% and for pts with tumors manifesting RET extracellular cysteine mutations (n=5) was 60.0%. Of the 15 pts with non-MEN-associated tumors, 2 pts (8.7%; mutation in TKD) had a partial response (both with NSCLC adenocarcinoma, of which one had co-existent MTC). For the overall pts, the median DoR was 12.2 months (95% CI: 3.8, NE) and median PFS was 5.5 months (95% CI: 1.8, 19.4). No new safety signals were identified compared to previous reports. One grade 5 AE, general physical health deterioration, was observed and deemed by INV as not related to selpercatinib. **Conclusions:** This study suggests that RET-mutated, MEN-associated cancers (adrenal, paraganglioma, neuroendocrine) may benefit from selpercatinib treatment, which could be mediated through mutations in the extracellular CRD. The non-MTC RET-mutated tumor types appear not to derive benefit from selpercatinib. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

Tumor Type	n (%)	BOR by IRC
MEN-associated tumors	**8 (34.8)**	**PR=3**
Pheochromocytoma	5 (21.7)	PR=2
Paraganglioma	2 (8.7)	SD16+=2
Neuroendocrine	1 (4.3)	PR
Non-MEN-associated tumors	**15 (65.2)**	**PR=2**

Clinical update related to the first-in-human trial of SYS6002 (CRB-701), a next-generation nectin-4 targeting antibody drug conjugate.

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Background: SYS6002 (CRB-701) is a novel, nectin-4 targeting antibody drug conjugate (ADC) that take advantage of a third generation, site-specific cleavable linker with novel conjugation chemistry. This technology is designed to establish a stable linker across antibody and payload, to produce an ADC with a homogenous drug antibody ratio of 2.0, with the additional aim to reduce the concentration of free-MMAE and thereby improve known payload related toxicities. SYS6002 (CRB-701) also contains a novel monoclonal antibody with a prolonged half-life that can support Q3W dosing. **Methods:** This is a multicenter, open-label, single-arm, phase I study using Bayesian optimal interval design. Eligible patients were aged ≥18 years with histologically confirmed Nectin-4 positive solid tumors (no Nectin-4 testing was required for urothelial carcinoma [UC]) who had failed or were intolerant to standard of care options. In the dose escalation, patients were given SYS6002 (dose level 0.2, 0.6, 1.2, 1.8, 2.7, 3.6, and 4.5 mg/kg) administered Q3W by intravenous infusion. The primary endpoints were safety, tolerability, and the recommended phase 2 dose. **Results:** As of January 2024, SYS6002 (CRB-701) has established a differentiated safety profile across a broad dose range (0.2-3.6 mg/kg) with no dose limiting toxicities and the majority of adverse events representing grade 1 or 2. No low-grade peripheral neuropathy, skin rash or fatigue, known toxicities that rate limit the usage of enfortumab vedotin (EV) have occurred. Herein, we report the anti-tumor activity of SYS6002 (CRB-701) in patients with nectin-4 positive solid tumors with a median of 4 prior therapies. The first confirmed stable disease was observed at 0.6 mg/kg and the first confirmed partial response was at 1.2 mg/kg. Anti-tumor activity in nectin-4 positive patients at doses ≥ 2.7 mg/kg (n=6) would suggest an overall unconfirmed objective response rate of 50%, and among them, the ORR of patients with UC was 50% (1/2), and that of patients with cervical cancer reached 67% (2/3). Across this group of patients, 4/6 had moderate to high nectin-4 expression (H-score ≥ 150) and 3 achieved a partial response, suggesting SYS6002 (CRB-701) could achieve a highly differentiated ORR of 75% in patients with moderate to high Nectin-4 expression. After single IV infusion of SYS6002 0.2-3.6 mg/kg, the exposure of TAb, ADC and MMAE generally increased in a dose proportional manner. The half-lives of TAb, ADC and MMAE were 4-6 days, 4-5 days and 5-10 days, respectively. SYS6002 (CRB-701) exhibited a longer ADC half-life and lower free-MMAE exposures relative to EV at comparable dose levels. **Conclusions:** SYS6002 (CRB-701) demonstrates promising anti-tumor activity with a well-tolerated safety profile in patients with advanced nectin-4 positive solid tumors. Dose escalation at 4.5 mg/kg Q3W and dose expansion at 3.6 mg/kg Q3W are ongoing. Clinical trial information: ChiCTR2200066256. Research Sponsor: CSPC Megalith Biopharmaceutical Co., Ltd.

A phase I study of TAK-659 and paclitaxel in patients with taxane-refractory advanced solid tumors.

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Background: Paclitaxel resistance in patients is a clinical challenge that limits the durability of clinical benefit in patients with taxane-responsive advanced solid tumors. One proposed mechanism for this resistance is overexpression of spleen tyrosine kinase (SYK); which can be inhibited with new molecules including TAK-659. In this phase I study, we have investigated the combination of TAK-659 and paclitaxel in patients with taxane-refractory advanced solid tumors; hypothesizing that use of TAK-659 would help to overcome resistance to prior taxane-based therapy. **Methods:** We included patients with advanced solid tumors who received and progressed on prior taxane-based therapy. Patients received treatment with intravenous paclitaxel on day 1,8, and 15 in addition of daily TAK-659 in 28-day cycles. Six cohorts were treated during dose escalation at different dose levels followed by a dose expansion phase in patients with advanced ovarian cancer. We used the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for evaluation of toxicity and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for assessment of preliminary efficacy. **Results:** We included 49 patients with advanced solid tumors. The maximum tolerated dose was not reached in this study; and no patients experienced treatment-related deaths. Most adverse events were either grade 1 or 2. Grade 3 or more adverse events were reported in 47% of patients (n=23). The most common grade $\geq$3 adverse events were decreased neutrophil count (n=7; 14%), elevated lipase (n=6; 12%), anemia (n=5; 10%), increased amylase (n=4; 8%), and decreased white blood cell counts (n=4; 8%). In 44 patients with taxane-refractory tumors who were evaluable for efficacy, 9% (n=4) had RECIST partial response and 27% (n=12) had RECIST stable disease, including 3 patients with prolonged stable disease for at least 6 months. **Conclusions:** The combination of paclitaxel and TAK-659 was well tolerated and showed preliminary modest efficacy which could be possibly overcoming resistance to taxane-based therapy in patients with advanced solid tumors. Clinical trial information: NCT03756818. Research Sponsor: Takeda Pharmaceuticals; Cancer Center Support Grant (CCSG); Clinical and Translational Sciences Award (CTSA).

Results of IMPACT 2, a randomized study evaluating molecular profiling and targeted agents in metastatic cancer at MD Anderson Cancer Center.

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Background: To address the limitations of exploratory studies, we conducted IMPACT2. The primary endpoint was to compare the progression-free survival (PFS) between patients treated with matched targeted therapies (MTT) selected on the basis of tumor molecular alterations and those whose treatment was not selected on the basis of alteration analysis (non-targeted therapy, NTT). **Methods:** Patients with metastatic cancer and targetable alterations were randomized between the 2 arms when eligibility criteria were met (Part A, 5/2014-4/2017; sponsor, Foundation Medicine). In Part B (3/2019-9/2023; sponsor, Tempus), patients who declined randomization selected the treatment arm (NCT02152254). PFS/OS analysis (Kaplan Meier, Cox model; reference group, comparison, NTT). All cases were presented at weekly Molecular Tumor Board meetings; initial plan, to randomize 300 of 1,362 enrolled patients. **Results:** Overall, 829 patients (Parts A, 391; B, 438); were enrolled (med. age 59.5 yrs, range 18-84; men 50%; med. No. of prior therapies 3, range 0-17; most common cancers: gastrointestinal 34%, head/neck 13.5%, gynecologic 10%, sarcoma 9.53%; most common genomic alterations RAS 38%, PI3K 31%, FGFR 28%). In Part A, 69 were randomized (MTT, n=35; NTT, n=34); Part B (MTT, n=11, NTT=13; Selected arm: n=16: MTT, n=13; NTT, n=3). Results are shown (Table). MTT group: median PFS by therapy type: FDA approved/off-label, 4.7 months (95% CI, 2.93, 7.1); investigational, 2.6 months (95% CI, 2.27,4.87), combined FDA approved/investigational, 1.7 months (1.7, NR) (p=0.22). **Conclusions:** Considering the challenges to randomize patients (doi: 10.1038/s41698-022-00317-0), and that the study was underpowered for its original goal, no differences in response, PFS (primary endpoint), or OS was noted between the 2 arms, possibly because of the advanced stage disease and the complexity of tumor biology that cannot be addressed by randomization. Clinical trial information: NCT02152254. Research Sponsor: Foundation Medicine, Inc; Tempus; Steven McKenzie's Endowment and donor funds; Katherine Russell Dixie Distinguished Endowed Professor; Jamie's Hope; NIH National Cancer Institute award number P30 CA016672 (to The University of Texas MD Anderson Cancer Center).

	N	Rx arm	N	Clinical benefit (CR/PR/ SD>= 4 months), N/evaluable for response	P	PFS, median (95% CI)	P	HR, 95% CI	OS, median (95% CI)	P	HR, 95% CI
Part A	69	NTT	34	11/21, 52% (1/1/9)	1.00	3.27 (2.76, 4.87)	0.82	1.06 (0.65,1.72)	9.52 (7.79,28.14)	0.4	1.23 (0.76,2)
		MTT	35	12/23, 52% (1/2/9)		3.29 (2.33, 4.9)			8.58 (6.48,20.15)		
Part B, Randomized arms	24	NTT	13	3/8, 38% (0/0/3)	0.62	2.53 (1.78, NR)	0.65	0.82 (0.36,1.88)	6.67 (6.05, NR)	0.88	0.94 (0.39,2.24)
		MTT	11	2/9, 22% (0/0/2)		2.73 (2.3, NR)			5.62 (3.65, NR)		
Part B, Patients selected treatment arm	16	NTT	3	1/3 (0/1/0)	0.52	5.36 (1.41, NR)	0.47	1.75 (0.38,8.03)	13.71 (5.75, NR)	0.6	1.5 (0.33,6.87)
		MTT	13	6/9,67% (0/2/4)		4.83 (1.68, NR)			11.64 (5.56, NR)		
Total, Parts A+B	109	NTT	50	15/32, 47% (1/2/12)	1.00	3.02 (2.56, 4.57)	0.78	1.06 (0.72,1.56)	9.09 (6.67,19.46)	0.58	1.12 (0.75,1.65)
		MTT	59	20/41, 49% (1/4/15)		3.16 (2.47, 4.83)			8.68 (6.48,12.46)		

Abbr. CR complete response, PR partial response, SD stable disease, NR not reached.

A phase 1 study of HRS-1167 (M9466), a highly selective PARP1 inhibitor, in patients (pts) with advanced solid tumors.

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Background: The use of first-generation dual PARP1/2 inhibitors is limited due to their hematological toxicities and inevitable drug resistance. Given that loss of PARP1 is the primary driver of synthetic lethality in homologous recombination repair (HRR) deficient tumors, and PARP2 is largely associated with hematological toxicities, development of next-generation PARPi with selectivity for PARP1 is warranted. Here, we present results of the dose escalation (D-ESC) and dose expansion (D-EXP) parts of a first-in-human study of HRS-1167 (M9466), a highly selective PARP-1 inhibitor, in pts with advanced solid tumors. **Methods:** Pts were eligible for the D-ESC part if they had advanced solid tumors that had progressed on standard therapies or for which no standard therapies were available. The D-ESC part began with accelerated titration (30 mg; QD) and then switched to the BOIN design (50, 100, 200, and 300 mg; QD). In the D-EXP part, previously treated pts harboring germline or somatic *BRCA1/2*, *PALB2*, or *RAD51C/D* mutations received HRS-1167 at 50, 100, and 200 mg QD. Prior PARPi was allowed. The primary objectives were to assess the safety and tolerability of HRS-1167. **Results:** As of Nov 20, 2023, 40 pts were enrolled (median lines of prior treatment, 2 [range, 1–5]; prior PARPi, 15.0%). No dose-limiting toxicities occurred, and the maximum tolerated dose was not reached. Grade ≥3 treatment-related adverse events occurred in 12 (30.0%) pts, with the most common being anemia (6 [15.0%]), decreased neutrophil count (5 [12.5%]), and decreased WBC count (5 [12.5%]). Of the 24 pts with HRR mutations who had at least one post-baseline assessment for tumor response, 10 (41.7%) pts had objective responses (8 ovarian cancer, 1 prostate cancer, and 1 pancreatic cancer). PK exposures were approximately dose-proportional. The median T_{max} was 1.0–1.5 h, and the mean $t_{1/2}$ was 10.5–15.0 h following a single dose of HRS-1167 at 30–300 mg. No obvious drug accumulation was observed (Rac, 1.08–1.30 for C_{max}; 1.29–1.62 for AUC_{0-24}). **Conclusions:** HRS-1167 was well-tolerated and exhibited favorable safety and PK profiles in pts with advanced solid tumors, and demonstrated promising anti-tumor activity in pretreated pts with HRR mutations. Clinical trial information: NCT05473624. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

A randomized, double-blind, study to evaluate the efficacy, pharmacodynamics, safety and immunogenicity of FKS518 proposed biosimilar to denosumab with the originator in postmenopausal women with osteoporosis (LUMIADE-3 study).

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Background: Biosimilars can increase patient access to treatment. FKS518 is a candidate biosimilar of denosumab, a RANKL inhibitor used in patients with bone metastases from certain solid tumors and in multiple myeloma. To establish biosimilarity, comparative studies are conducted in the most sensitive patient population to detect if there are clinically meaningful differences. LUMIADE-3 was designed to assess the safety and efficacy of FKS518 compared to the originator in postmenopausal women with osteoporosis (PMO). **Methods:** A randomized, double-blind, multicenter, 2-arm study recruited female patients aged 55 to 85 years with confirmed postmenopausal status and lumbar spine bone mineral density (LS-BMD) T-score $\leq$ -2.5 and $\geq$ -4.0, as measured by central dual-energy X-ray absorptiometry (DXA) assessment. Subjects with prior osteoporosis treatment that could add risk for cumulative effect or affect the interpretation of results were excluded. Patients were randomized and received three 60 mg administrations. At week 52, patients receiving denosumab originator were re-randomized to continue their treatment or switch to FKS518 for the third dose. Those receiving FKS518 continued receiving FKS518. The primary efficacy endpoint was the percent change from baseline in LS-BMD DXA at week 52. An analysis of the covariance model was used to compare the two treatments and two separate one-sided tests at alpha=0.05 were performed to assess equivalence. Secondary efficacy endpoints included the percent change from baseline in BMD at the femoral neck and total hip. **Results:** A total of 553 patients were randomized to FKS518 (n=276) or the originator (n=277). Clinically relevant increases in LS-BMD were evident at week 52 in both the FKS518 and originator product groups. The results demonstrated therapeutic equivalence: the lower bound of the 90% CI for non-inferiority (-0.05) was above -1.45, and the upper bound of the 90% CI for non-superiority (1.20) was below 1.45. All secondary objectives were met. At week 52, a similar percent change from baseline in BMD at the femoral neck and total hip was observed between the two groups. 374 patients (67.6%) experienced treatment-emergent adverse events: 185 (66.8%) in the FKS518 group and 189 (68.5%) in the originator product group. Safety evaluation did not point to notable differences between FKS518 and the originator product groups. **Conclusions:** We demonstrated the therapeutic equivalence of FKS518 and originator product. The safety data showed similar safety profiles for the FKS518 and the originator product groups. Results from this study add to the totality of evidence supporting the similarity of FKS518 as a proposed biosimilar to denosumab originator product, a RANKL inhibitor used in patients with bone metastases from solid tumors. Clinical trial information: NCT04934072. Research Sponsor: Fresenius Kabi.

Total toxicity burden as a practical tool to quantify the overall severity of multiple adverse events in clinical trials.

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Background: Phase I clinical trials (CT) report adverse events (AEs) using the Common Terminology Criteria for AEs (CTCAE) version 5.0. If multiple qualitatively AEs are recorded in a trial, this results into manifold AE counts. Total toxicity burden (TTB) is defined for each patient as the sum of the highest grade of each AE divided by the number of AEs recorded [Thall, 2003]. We computed the TTBs for five groups of drugs studied in phase I trials. **Methods:** Pts treated from 2016 to 2022 in the phase I CT unit at MD Anderson Cancer Center were included. Clinical baseline prognostic factors [ECOG, age, Carlson comorbidity index (CCI)] were included and analyzed. AEs according to the CTCAE v5.0 were collected and simplified into 21 categories per trial and patient. Treatments were divided into: Cytotoxic agents (Chemo), Targeted Therapy (TT), Immune checkpoint inhibitors (ICI), Chimeric antigen receptor T cells (CART), or Cytokines (CYT). Using regimen-related AEs for evaluable patients, mean (SD) TTB for each treatment group was computed using each patent's worst grade as the severity weight for each type of AE. **Results:** A total of 1322 evaluable pts from an initial sample of 2,350 were collected. Median age was 61 years (range, 19-92), 75.6% ECOG PS 1, median CCI was 8, and all pts were treated in a phase I/II CT. A total of 1782 AEs were treatment related and 3071 AEs were not treatment related. 715 evaluable pts (54.1%) had at least one treatment-related AE, and 902 patients (68.2%) had at least one treatment unrelated AE. A total of 265 (20.0%) grade 1 (G1) treatment-related AEs, 231 (17.5%) G2, 184 (13.9%) % G3, and 29 (2.2%) G4, and one G5 was reported. The most frequent G≥3 AEs overall were Neutropenia (N=54), Anemia (N=52), and low platelets (N=35). The most frequent G≥3 AEs per treatment group were Neutropenia (10%), Anemia (15%), and increased AST/ALT (13%) in group Chemo, Neutropenia (8%), Low platelets (9%), and Anemia (9%) in group TT, Increased AST/ALT (10%), Anemia (5%), and Pain (5%) in group ICI, Neutropenia (10%), Anemia (10%), and Low platelets (5%) in group CART, and Nausea/Vomit (3%), Pneumonitis (1%), and Infection (1%) in group CYT. Mean TTBs for the five treatment groups were 2.7 (SD=3.3) for Chemo, 2.9 (SD=3.6) for TT, 1.7 (SD=1.9) for IO, 5.9 (SD=5.1) for CART, and 0.8 (SD=1.8) for CYT. Corresponding G≥3 treatment-related AE rates were 21.7%, 21.0%, 12.2%, 52.4%, and 6.4% in the five treatment groups. It appears that CART is the most toxic treatment group based on TTBs and conventional analysis based on G>3. These results suggest that propensity score-based comparisons of mean TTB to correct for selection bias using prognostic variables are warranted. **Conclusions:** TTB is a useful tool to quantify the mean severity of qualitatively different types of adverse events experienced by patients in a clinical trial, and mean TTB may be compared between treatment groups. Research Sponsor: None.

Genomics to select treatment for patients (pts) with metastatic cancer: Final analysis of Molecular Tumor Board (MTB) evaluations in the ROME trial.

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Background: The ROME trial (NCT04591431) investigates the efficacy of a tailored treatment (TT), driven by extensive genomic tests and Molecular Tumor Board (MTB) evaluation, compared to standard treatment (SoC) in patients (pts) with refractory metastatic cancer. Here we report the prevalence of actionable variants identified and the personalized treatment received by the patients enrolled. **Methods:** A centralized extensive NGS test (FoundationOne CDx and Liquid CDx) was performed on both tissue and blood samples. Pts with at least one potentially targetable alteration matched to the available drugs were discussed at the MTB. MTB evaluation criteria were: genomic variant type, tumor mutational burden (TMB), VAF, availability of preclinical or clinical data of efficacy and patients' clinical characteristics. COSMIC, ClinVar, OncoKB and VarSome datasets were used to evaluate the clinical actionability of genomic alterations. MTB indications were: randomization to TT vs SoC, screening failure (SF), or indication to other trial/access to the drug. **Results:** From November 2020 to August 2023, 1794 pts were screened. A total of 127 weekly MTB meetings were conducted and 899 cases were discussed (7 cases/meeting on average). After MTB discussion, a targetable genomic alteration was identified in 425 pts, who received an indication to be randomized. MTB assigned ICIs to 190 pts (155 to ipilimumab plus nivolumab; 8 to nivolumab) due to high (≥10 mut/mb) TMB. 234 pts had indications to target therapy: 86 pts (37%) to PI3K/AKT/mTOR inhibitors(i), 59 (25%) anti-HER2 agents, 34 (15%) FGFRi, 31 (13%) BRAF/MEKi, 7 (3%) PARPi, 5 (2%) CDK4/6i, 4 (2%) ALKi, 2 (>1%) NTRKi, 2 (>1%) RETi, 2 (>1%) Hedgehog-i, 1 (>1%) JAKi, 1 (>1%) MEKi. 27 pts had indication to ICIs plus target therapy combinations. Additionally, 150 pts with potentially hereditary variants were addressed to genetic counselling and germline testing. Finally, according to the genomic evaluation, 63 pts were referred by MTB to other clinical trial even if considered SF for the ROME trial, 34 patients received from the MTB a modification of the initially proposed standard therapy and 4 had both suggestions. Overall, 652 pts (36%) received an indication following NGS test and MTB evaluation. **Conclusions:** Our study provides evidence that MTB discussion of comprehensive genomic profiling data identifies a personalized treatment in a large (36%) fraction of patients, thus outperforming the traditional histological approach. Clinical trial information: NCT04591431. Research Sponsor: None.

Phase II study of the combination of lenvatinib (L) and eribulin (E) in advanced solid tumors.

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Background: Tumor angiogenesis remains a focal point in cancer therapeutics, necessitating innovative strategies to counter resistance mechanisms. Lenvatinib, a multitargeted tyrosine kinase inhibitor, and eribulin, a microtubule inhibitor, exhibit promise in disrupting tumor vasculature. Understanding their efficacy and safety in combination therapy is crucial, especially in heavily pretreated patients with advanced solid tumors. **Methods:** A single-center phase II study (NCT02640508) enrolled patients with stage IV breast carcinoma, lung carcinoma, and sarcoma, evaluating the safety and efficacy of lenvatinib and eribulin combination therapy. Eribulin was given on day 1 and day 8 at 1.4 mg/m^2 and lenvatinib at a dose of 20 mg starting on day 2 of a 21-day cycle. Immunohistochemistry assessed biomarkers CD31, e-cadherin, CA-9, and vimentin. Statistical analyses included multivariate modeling and Kaplan-Meier curves. The primary endpoint of the study was the overall response rate (ORR), defined per RECIST 1.1 as assessed by investigator imaging review. Secondary endpoints included safety, progression free survival (PFS) and overall survival (OS). **Results:** Among 29 patients enrolled, median age was 58 years, majority were female and had at least ≥3 prior lines of chemotherapy. Treatment with lenvatinib and eribulin resulted in an ORR of 24%, as seen in the table. Median PFS was 7.4 months and OS was 8.2 months. Toxicities were manageable with grade ≥3 neutropenia seen in 34.5%, febrile neutropenia in 17.2%, and hypertension in 13.8% of patients. Treatment-related adverse events leading to study-drug discontinuation occurred in 6.8% of patients. Vimentin-negative patients exhibited significantly increased OS (fold change 4.374, $p<0.001$) and PFS (fold change 3.395, $p<0.001$) after adjusting for age, CD31, and CA9. **Conclusions:** Lenvatinib combined with eribulin showcased promising anti-tumor activity in heavily pretreated patients with metastatic breast carcinoma, lung carcinoma, and sarcoma. Although manageable, neutropenia emerged as a notable adverse effect. These findings underscore the potential of this combination as a therapeutic strategy for advanced solid tumors, warranting further clinical investigation. The observed significant survival benefits in Vimentin-negative patients align with the biological role of Vimentin in tumor invasiveness and metastatic potential, supporting the plausibility of these results biologically. Acknowledgement: This clinical trial was supported by Eisai. Clinical trial information: NCT02640508. Research Sponsor: Eisai Inc.

Summary of response by tumor types.

Tumor types (n)	PR, n (%)	SD, n (%)	PD, n (%)	Not Evaluable, n (%)*	Median PFS, months	Median OS, months
Mammary carcinoma (n=17)	5 (29.4%)	6 (35.3%)	2 (11.8%)	4 (23.5%)	7.4	8.2
Lung carcinoma (n=6)	2 (33.3%)	4 (66.6%)	0	0	8.6	12.2
Sarcoma (n=6)	0	3 (50%)	1 (16.7%)	2 (33.3%)	3.5	6.8
Overall cohort (n=29)*	7 (24.1%)	13 (44.8%)	3 (10.3%)	6 (20.7%)	7.4	8.2

Clinicopathologic and genomic characteristics of patients with advanced ovarian, breast, and prostate cancer treated with poly (ADP-ribose) polymerase inhibitors (PARPi) in a real-world setting.

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Background: PARPis induce synthetic lethality in tumors that have homologous repair deficiencies (HRD). Due to relative rarity of HRD-related genomic and germline alterations across solid malignancies, it remains unclear which patients (pts) may derive most benefit from PARPis across different tumor types. **Methods:** We analyzed clinicopathologic and genomic characteristics of pts with advanced ovarian (OC, n=33), prostate (PC, n=28) and breast cancer (BC, n=13) treated with PARPi monotherapy at our institution. Only pts with HRD-related pathogenic alterations detected via next-generation sequencing of tumor tissue, with or without genetic susceptibility testing, were included. **Results:** Forty-one (55%) pts had a confirmed germline HRD-related gene alteration, of which 33 had BRCA1/2 and 8 had non-BRCA1/2 gene alterations. Average age of pts with BC was 54 years, OC 62 years, and PC 68 years. Median number of prior lines of therapy in the advanced setting was 1 (1-4) for OC and BC (0-7) and 3 (1-6) for PC. Median time to progression (TTP) in pts with OC was 8.3 months, BC 4.9 months and PC 3.6 months, likely due to i) majority of pts with OC received maintenance PARPi following favorable response to first-line chemotherapy, ii) pts with PC were older, and iii) more pts with PC had somatic rather than germline HRD-related mutations. Pts with germline vs somatic HRD mutation had longer median TTP in PC (5.0 vs 3.3 months) and BC (6.1 vs 4.0 months), but the opposite was true for OC (7.9 vs 10.8 months). Pathogenic *TP53* mutations were identified in all but one pt with OC (32/33), 10/13 pts with BC, and 6/28 PCs. [table] Average *TP53*gene variant allele fraction (VAF) was similar in OC and BC (49.8% and 51.1%, respectively) but significantly lower in PC (26.4%), suggesting that *TP53* mutations in PC were subclonal. No specific *TP53* VAF or *HRD*-to-*TP53* VAF ratio cut-off was associated with TTP or overall survival in any of the 3 cancer types. In addition, 7/28 (25%) of pts with PC had *PTEN* loss associated with modified response to PARPis, whereas none of the pts with BC had *PTEN* loss and only 3/13 had alterations of the *PTEN/PI3K/AKT*pathway. **Conclusions:** Double-strand DNA breaks caused by synergistic effects of aberrant *TP53* and HRD-related genes can possibly explain the more favorable response of pts with OC and BC to PARPi, compared to those with PC. Co-alterations in other signaling pathways, epigenetic factors and/or tumor microenvironment likely play a role in the degree of response to PARPis, rather than *TP53* clonality alone. In the era of expansion of genomic testing and new indications for PARPi larger genomic studies are needed to identify biomarkers of response to PARPi beyond HRD. Research Sponsor: None.

	GERMLINE		SOMATIC	
	TP53m	TP53wt	TP53m	TP53wt
OVARIAN	21 (95%)	1 (5%)	11 (100%)	0 (0%)
BREAST	7 (78%)	2 (22%)	3 (75%)	1 (25%)
PROSTATE	3 (30%)	7 (70%)	3 (17%)	15 (83%)

TPS3160 **Poster Session**

An open-label phase 1 study to investigate SGNCEACAM5C/SAR445953 in adults with advanced solid tumors (SGNCEA5C-001).

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Background: Patients (pts) with recurrent or metastatic solid tumors, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), colorectal cancer (CRC), gastric adenocarcinoma (GC), and pancreatic ductal adenocarcinoma (PDAC), have limited treatment options with short PFS and OS despite recent advances (1-3). Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is highly expressed across multiple solid tumors, such as CRC, GC, PDAC, and NSCLC. Restricted normal tissue expression and efficient lysosomal trafficking of CEACAM5 highlight its potential as an anticancer target. SGN-CEACAM5C is a novel investigational antibody-drug conjugate (ADC) directed to CEACAM5 composed of the humanized immunoglobulin G (IgG1) anti-CEACAM5 monoclonal antibody tusamitamab chemically conjugated to 8 molecules of the topoisomerase 1 inhibitor 7-aminomethyl-10,11-methylenedioxycamptothecin (AMDCPT). SGN-CEACAM5C selectively binds to CEACAM5 present on the cell surface and is internalized via the endo-lysosomal pathway, with subsequent release of the payload through enzymatic cleavage. Release of the cytotoxic payload induces DNA damage, cell cycle arrest in S phase, and apoptosis in tumor cells. In vitro bystander activity was observed against tumor cells without CEACAM5 surface expression. SGN-CEACAM5C is highly active in multiple patient-derived xenograft models, including CRC, GC, and NSCLC, across various levels of CEACAM5 expression (4,5). These preclinical findings justify evaluation of SGN-CEACAM5C in a clinical trial setting. **Methods:** SGNCEA5C-001 (NCT06131840) is a phase 1, open-label, multicenter study designed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of SGN-CEACAM5C in adults with select advanced solid tumors. This study consists of dose escalation (Part A), dose and schedule optimization (Part B), and dose expansion (Part C). Eligible pts are adults ≥18 years of age with confirmed metastatic or unresectable solid tumor malignancy, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, an ECOG PS of 0-1, and 1 of the following tumor types: CRC, GC/gastroesophageal junction adenocarcinoma (GEJ), PDAC, NSCLC (squamous/non-squamous), or SCLC. Primary endpoints include incidence of AEs, laboratory abnormalities, dose modifications due to AEs, dose-limiting toxicities, and cumulative safety. Secondary endpoints include estimates of PK parameters, incidence of antidrug antibodies, objective response rate and best response per RECIST v1.1 by investigator, duration of response, PFS, and OS. Safety and antitumor activity endpoints will be summarized using descriptive statistics. Recruitment is ongoing for Part A in North America. 1. Bordry 2021. 2. Chakrabarti 2022. 3. Merle 2022. 4. Baudat 2023. 5. Baudat 2024. Clinical trial information: NCT06131840. Research Sponsor: This study is sponsored by Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec 2023, in collaboration with Sanofi.

TPS3161 **Poster Session**

A multi-center, open-label phase 1/1b dose finding, safety, and pharmacokinetic study of MBRC-101, an Anth-EphA5 monomethyl auristatin (MMAE) antibody drug conjugate, in advanced refractory solid tumors.

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Background: EphA5 receptor is a member of the Ephrin receptor tyrosine kinase family. Several lines of compelling nonclinical evidence indicate EphA5 is a novel and selective target for solid tumor-directed therapy. Expressed only minimally in normal tissues, it is highly expressed in non-small cell lung carcinoma (NSCLC), head and neck squamous cell carcinoma (HNSCC), and breast, colorectal, pancreatic, gastric, and hepatic malignancies. MBRC-101 is a novel antibody drug conjugate (ADC) composed of an anti-EphA5 antibody conjugated to an MMAE payload (drug-to-antibody ratio of 4) through a valine citrulline cleavable linker. In pre-clinical toxicology studies and testing against a variety of cell-derived (CDX) and patient-derived (PDX) xenograft solid tumor models expressing EphA5—including NSCLC, triple negative breast cancer (TNBC), and HNSCC—MBRC-101 demonstrated favorable safety profiles and robust anti-tumor activity. **Methods:** This first-in-human, Phase 1/1b, multicenter, open-label study is examining the safety and efficacy of MBRC-101 in patients with advanced metastatic solid tumors refractory to standard treatment. Phase 1 will identify potential optimal biologically relevant doses (OBRD) and the maximum tolerated dose (MTD) of MBRC-101 at one or more dosing regimens. Phase 1b will evaluate the safety and preliminary clinical activity of MBRC-101 at potential OBRDs. Phase 1 will enroll patients ($n \approx 30$) with advanced or metastatic solid tumors. EphA5 expression will not be required for enrollment into Phase 1 but will be assessed retrospectively. A modified toxicity probability interval (mTPI-2) method will guide dose escalation using a pre-specified decision matrix. The primary endpoints are MTD, dose limiting toxicities (DLTs), treatment emergent adverse events (TEAEs), and clinical laboratory tests. Phase 1b ($n \approx 60$ patients) will include 3 expansion cohorts ($n \approx 20$ patients per cohort): Cohort A, NSCLC; Cohort B, triple negative or HR+/HER2- breast cancer; and Cohort C, solid tumors irrespective of histologic tissue type (i.e., tumor agnostic) excluding NSCLC and breast cancer. Expression of EphA5 in primary or metastatic tumor tissue will not be required for enrollment into cohorts A and B but will be required for Cohort C. The primary endpoints are TEAEs, clinical laboratory tests, and investigator-assessed objective response rate (ORR) by RECIST v1.1 and clinical evaluation. Secondary endpoints for Ph1 and 1b include PK analytes and EphA5 expression as determined by immunohistochemistry (IHC). A Safety Review Committee will monitor safety at each dose escalation in Phase 1 and at regular intervals throughout Phase 1b. Clinical trial information: NCT06014658. Research Sponsor: MBrace Therapeutics.

TPS3162 **Poster Session**

Phase 1b study evaluating the efficacy and safety of ABBV-400, a c-Met–targeting antibody-drug conjugate, in select advanced solid tumor indications.

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Background: c-Met (MET protein) is commonly overexpressed in a number of tumors, including hepatocellular carcinoma (HCC), pancreatic ductal adenocarcinoma (PDAC), biliary tract cancers (BTC), esophageal squamous cell carcinoma (ESCC), breast cancer (BC), and head and neck squamous cell carcinoma (HNSCC). Patients with c-Met–overexpressing tumors represent an underserved population, with the need for more effective c-Met–targeting therapies to become available. ABBV-400 is an antibody-drug conjugate, consisting of the c-Met–targeting antibody telisotuzumab conjugated to a potent topoisomerase 1 inhibitor payload. Initial results from the ongoing first-in-human study (NCT05029882) of ABBV-400 in patients with advanced solid tumors indicate a tolerable safety profile, with a maximum tolerated dose of 3 mg/kg once every 3 weeks (Q3W), and promising antitumor activity, with an overall response rate of 24.4% (1). Herein, we describe a signal-seeking study evaluating ABBV-400 treatment in patients with select solid tumors. **Methods:** Multicenter, open-label, phase 1 signal-seeking study(NCT06084481). Eligible patients (≥18 years) have confirmed locally advanced/metastatic disease measurable per RECIST v1.1 and Eastern Cooperative Oncology Group performance status ≤1. Approximately 220 patients are planned for enrollment across 7 cohorts (HCC, n=40; PDAC, n=40; BTC, n=20; ESCC, n=40; triple-negative BC, n=20; hormone receptor-positive/HER2-negative BC, n=20; HNSCC, n=40). The primary objectives are to assess efficacy and safety/tolerability of ABBV-400 in each tumor indication. Secondary objectives include the evaluation of pharmacokinetics (PK) and immunogenicity of ABBV-400. Pharmacodynamic (PD) and biomarker analyses are exploratory endpoints. Patients receive intravenous ABBV-400 at 3 mg/kg Q3W until disease progression, intolerable toxicity, or any other per-protocol discontinuation criteria. c-Met expression will be assessed retrospectively by immunohistochemistry. The maximum treatment duration is 2 years. Tumor assessments are performed at screening and every 6 weeks from the first dose of study drug, with objective response rate as primary efficacy endpoint and duration of response, clinical benefit rate, progression-free survival, and overall survival as secondary efficacy endpoints. Safety evaluations include adverse events monitoring (graded according to the NCI CTCAE, v5.0), physical examinations, vital sign measurements, ECG variables, and clinical laboratory testing. Blood samples for PK, PD, and biomarker analysis are collected at designated time points throughout the study. Enrollment started in November 2023. As of 19 January 2024, 24 patients have been enrolled. 1. Sharma et al. JCO 2023;41[16 suppl]:3015. Clinical trial information: NCT06084481. Research Sponsor: AbbVie; n/a.

TPS3163 **Poster Session**

CLARITY-PanTumor01: A phase 2 trial of the claudin 18.2-specific antibody-drug conjugate AZD0901 (CMG901) in patients with CLDN18.2-expressing advanced solid tumors.

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Background: Gastric/gastroesophageal junction (G/GEJ) and pancreatic cancer are associated with poor outcomes and high unmet need. Claudin 18.2 (CLDN18.2) is highly expressed in gastric, esophageal, and pancreatic ductal adenocarcinoma (PDAC), and is a clinically validated target. AZD0901 is a potential first-in-class antibody-drug conjugate (ADC) comprising a humanized anti-CLDN18.2 IgG1 antibody conjugated via a protease-cleavable linker to monomethyl auristatin E (MMAE), a cytotoxic microtubule-disrupting agent. Interim results from the ongoing, first-in-human, Phase 1 trial of AZD0901 monotherapy in patients with G/GEJ cancer (NCT04805307) who were refractory to and/or intolerant of standard therapies demonstrated promising efficacy and a manageable safety profile. Here we describe an ongoing, Phase 2 study of AZD0901 in patients with CLDN18.2-expressing advanced solid tumors, including G/GEJ cancer and PDAC. **Methods:** This open-label, multicenter study (NCT06219941) comprises multiple substudies. Substudy 1 is recruiting patients with human epidermal growth factor receptor 2 (HER2)-negative, CLDN18.2-expressing G/GEJ cancer with ≤2 prior lines of therapy for unresectable or metastatic disease, who are randomized 1:1 to receive AZD0901 1.8 or 2.2 mg/kg intravenous (IV) every 3 weeks (Q3W). Substudy 2 is recruiting patients with previously untreated CLDN18.2-expressing metastatic PDAC to receive AZD0901 (up to 2.2 mg/kg IV Q3W) and either a combination of 5-fluorouracil 2400 mg/m^2 IV on Days 1 and 2 Q2W, leucovorin 400 mg/m^2 or l-leucovorin 200 mg/m^2 IV on Days 1 and 2 Q2W, and irinotecan 150 or 180 mg/m^2 or nanoliposomal irinotecan 50 mg/m^2 IV on Day 1 Q2W (Arm 1), or gemcitabine 1000 mg/m^2 IV on Days 1 and 8 Q3W (Arm 2), per investigator's choice. Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent. Eligible patients are aged ≥18 years with histologically confirmed, unresectable or metastatic disease, ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, and Eastern Cooperative Oncology Group performance status 0–1. Key exclusion criteria include unstable and/or active peptic ulcer disease or digestive tract bleeding, ascites requiring drainage, central nervous system metastases, and prior exposure to an MMAE-based ADC or CLDN-18.2-targeted agents other than an anti-CLDN18.2 targeted monoclonal antibody. Primary endpoints include safety, tolerability, and objective response rate per RECIST v1.1. Secondary endpoints include overall survival, progression-free survival, duration of response, disease control rate, best change in target lesion size, pharmacokinetics, immunogenicity, and pharmacodynamics. Recruitment began in December 2023, and sites across Australia, Asia, Europe, and North America will enroll patients. Clinical trial information: NCT06219941. Research Sponsor: AstraZeneca.

TPS3164 **Poster Session**

HERTHENA-PanTumor01: A global, multicohort, phase 2 trial of HER3-DXd in relapsed/refractory metastatic solid tumors.

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Background: Human epidermal growth factor receptor 3 (HER3) is a member of the HER/EGFR family of receptor tyrosine kinases. HER3 is expressed in numerous solid tumors, including melanoma, head and neck squamous cell cancer (HNSCC), and gastric cancer, and high levels of HER3 expression in multiple tumor types are associated with poor clinical outcomes. HER3-DXd is a potential first-in-class HER3-directed antibody-drug conjugate (ADC) composed of a fully human anti-HER3 monoclonal antibody (patritumab) covalently linked to a potent topoisomerase I inhibitor payload via a tumor-selective cleavable linker. HER3-DXd has shown antitumor activity and a manageable safety profile in previously treated *EGFR*-mutated metastatic NSCLC and metastatic breast cancer. Based on clinical data and exposure-response analyses, HER3-DXd 5.6 mg/kg IV every 3 weeks (Q3W) was selected as the monotherapy dose for investigation in new indications. HERTHENA-PanTumor01 (NCT06172478) is a global, multicohort, open-label, single-arm, phase 2 trial evaluating the efficacy and safety of HER3-DXd in previously treated patients (pts) with cutaneous melanoma, HER2-negative gastric cancer, or HNSCC. **Methods:** Each cohort of HERTHENA-PanTumor01 will enroll 40 pts. Study sites are in Australia, Belgium, France, Japan, South Korea, Spain, Taiwan, the UK, and the US. Key inclusion criteria for melanoma include cutaneous or acral subtype, *BRAF*–wild-type or -mutant status, and progression on or after ≥1 anti–PD-(L)1 therapy. Key inclusion criteria for HNSCC include HPV+ or negative status and progression after platinum-based chemotherapy (PBC) ± anti–PD-(L)1 therapy; pts with nasopharyngeal cancer are excluded. Key inclusion criteria for gastric or gastroesophageal junction cancer include confirmed HER2-negative tumor status (immunohistochemistry [IHC] 0/1+ or IHC 2+/in situ hybridization negative) and progression after PBC ± anti–PD-(L)1 therapy; pts with HER2+ cancer are excluded. Other key exclusion criteria for all cohorts include any history of, suspected, or current interstitial lung disease; active brain metastases (treated/asymptomatic brain metastases are allowed); or prior treatment with an anti-HER3 antibody and/or ADC containing an exatecan derivative. A fresh biopsy or pretreatment archival biopsy performed since progression on or after treatment with the most recent cancer therapy is required for all cohorts. Pts will be treated with HER3-DXd 5.6 mg/kg IV Q3W; tumor assessments will occur every 6 wks for the first 48 wks, then every 12 wks until disease progression, adverse events, or other discontinuation criteria are met. The primary endpoint for each cohort is ORR by investigator per RECIST version 1.1. Secondary endpoints include safety and tolerability, DOR, DCR, PFS, overall survival, pharmacokinetics, and the correlation between HER3 IHC protein expression and efficacy. Clinical trial information: NCT06172478. Research Sponsor: Daiichi Sankyo, Inc.

TPS3165 **Poster Session**

A phase 1/2, first-in-human study of DS-3939a in patients with advanced solid tumors: A new DXd ADC targeting TA-MUC1.

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Background: Mucin 1 (MUC1), a single-transmembrane glycoprotein, is expressed on the apical membrane of the epithelial surface. In normal tissues, it is highly glycosylated and protects the underlying epithelia. In cancer cells, however, MUC1 is hypoglycosylated due to changes in the expression patterns of some sialyltransferases, and exposes new epitopes on MUC1 in tumors, referred to as tumor-associated MUC1 (TA-MUC1). TA-MUC1 loses cell polarity and is redistributed over the cell surface and within the cytoplasm. Overexpression of TA-MUC1 in several malignancies is associated with poor prognosis and development of metastasis, thus making it an attractive therapeutic target. DS-3939a is a novel antibody-drug conjugate in development for the treatment of malignant tumors composed of a humanized anti-TA-MUC1 antibody, a peptide-based cleavable linker, and a potent topoisomerase I inhibitor (DXd). This study will assess the safety, tolerability, and efficacy of DS-3939a in patients with advanced solid tumors.
Methods: This phase 1/2, first-in-human, open-label, multicenter, 2-part, dose-escalation, and dose-expansion study (NCT05875168) is active and plans to enroll up to 430 adult patients. Part 1 (dose-escalation) is accruing patients with locally advanced, metastatic, or unresectable urothelial, non-small cell lung, breast, ovarian, biliary tract, or pancreatic cancers, and Part 2 (dose-expansion) will enroll patients with various advanced solid TA-MUC1-expressing tumors. In Parts 1 and 2, DS-3939a will be administered intravenously on Day 1 of a 21-day cycle. The primary endpoints in Parts 1 and 2 include safety and tolerability of DS-3939a as assessed by the number of patients with dose-limiting toxicities (Part 1 only), treatment-emergent adverse events, and other safety parameters. Part 2 will also evaluate efficacy by objective tumor response rate per RECIST version 1.1 as a primary endpoint. Secondary endpoints include the disease control rate, duration of response, time to response, progression-free survival, overall survival, TA-MUC1 expression (detected by immunohistochemistry), the pharmacokinetic profile of DS-3939a, and the number of patients with anti-drug antibodies against DS-3939a. Clinical trial information: NCT05875168. Research Sponsor: Daiichi Sankyo, Inc.

TPS3166 **Poster Session**

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

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Background: Cadherin-6 (CDH6) is a transmembrane glycoprotein involved in cancer metastasis and invasion expressed in various tumor types including ovarian cancer (OC), renal cell carcinoma (RCC), papillary thyroid cancer, cholangiocarcinoma, hepatocellular cancer, glioma, uterine serous carcinoma and non-small cell lung cancer. CUSP06 is an antibody-drug conjugate composed of a human IgG1 monoclonal antibody against CDH6 conjugated with a protease-cleavable linker, T1000, to exatecan, a topoisomerase I inhibitor payload. In preclinical studies, CUSP06 showed CDH6-dependent cell growth inhibition in ovarian cancer cell lines. High CDH6-expressing ovarian and renal CDX and PDX models demonstrated tumor regression after treatment with CUSP06, as did low CDH6-expressing PDX models of other solid tumors. **Methods:** This is a Phase 1a/1b, open-label, multicenter dose escalation and expansion study to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), recommended Phase 2 dose (RP2D), and preliminary efficacy of CUSP06 in patients with platinum-refractory/resistant ovarian cancer (PRROC), advanced RCC and other advanced CDH6-positive solid tumors. Patients with advanced solid tumors previously treated with standard of care systemic therapy, or for whom no standard therapy is available are eligible for enrollment. Prescreening for CDH6 expression will be required for those patients with solid tumors other than PRROC or RCC. CUSP06 will be administered intravenously every 21 days. Phase 1a will follow a standard 3+3 dose escalation design. Phase 1a also includes up to 3 dose enrichment cohorts at doses that have demonstrated safety, each with a maximum of 18 patients, to generate additional safety, PK, PD, and preliminary efficacy data to support an optimized dose for expansion. Phase 1b consists of several dose expansion cohorts including PRROC, RCC, and other CDH6-positive solid tumors, to be enrolled according to Simon's 2-stage design. Mandatory pre- and on-study biopsies in dose expansion cohorts will support a robust exploratory biomarker plan that may include correlation of CDH6 levels with response, and other RNA and protein markers of sensitivity and resistance. The study is currently enrolling in Phase 1a dose-escalation. Clinical trial information: NCT06234423. Research Sponsor: OnCusp Therapeutics.

TPS3167 Poster Session

An open-label, multicenter phase 1 study to characterize safety, tolerability, preliminary antitumor activity, pharmacokinetics, and pharmacodynamics of VIP943 monotherapy in patients with advanced CD123+ hematologic malignancies.

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Background: VIP943 is an anti-CD123 antibody-drug conjugate (ADC) with a unique linker cleaved only by legumain and a novel kinesin spindle protein inhibitor payload. The linker-payload was engineered to increase the therapeutic index thereby improving efficacy and reducing severe toxicities compared with current ADCs. In an in vivo MOLM-13 model, VIP943 had statistically significant ($p < 0.001$) improvement in tumor growth inhibition compared with the only ADC approved for the treatment of acute myeloid leukemia (AML), gemtuzumab ozogamicin (GO). In a nonhuman primate (NHP) single dose toxicology study, VIP943 (20 mg/kg) showed no signs of toxicity as measured by hematology, serum chemistry and survival. In contrast, NHP treated with a single dose of GO (3 mg/kg) had significant toxicity including death and mandatory euthanasia. The single-dose toxicity of GO was ameliorated by substituting the VIP943 proprietary linker and payload on an anti-CD33 antibody (3 mg/kg) as measured by hematology, serum chemistry and survival. (1,2). **Methods:** This trial in progress (NCT06034275) is an open-label, multicenter, Phase 1, first-in-human (FIH), dose-escalation and dose-optimization study of VIP943 in subjects with relapsed or refractory CD123+ hematologic malignancies including AML, myelodysplastic syndrome, and B-cell acute lymphoblastic leukemia. A cycle of VIP943 treatment is 28 days of once weekly intravenous infusions with no pause between cycles. The dose-escalation portion of this study follows a standard 3+3 design. Dose escalation decisions will be made by the safety review committee, and decisions will be based on the incidence of dose-limiting toxicities (DLTs). Based on FDA guidance, a dose-optimization portion of this study will randomize subjects into ≥ 2 dose cohorts to derive a recommended dose range for Phase 2. The study will also characterize the pharmacokinetics of VIP943 and its components and explore potential biologic activity by assessing pharmacodynamic/exploratory biomarkers, and antitumor activity using standard response criteria. As this is a FIH study, only subjects with CD123+ hematologic malignancies who have exhausted all available therapies or are not fit for standard of care can be enrolled. The results from this study will form the basis for decisions for future studies. Enrollment for cohorts 1 (no DLTs) and 2 (safety review ongoing) has completed. 1. Stelte-Ludwig et al ASH 2022. 2. Stelte-Ludwig et al ASH 2023. Clinical trial information: NCT06034275. Research Sponsor: Vincerx Pharma.

TPS3168 **Poster Session**

An open-label, multicenter phase 1 study to characterize safety, tolerability, preliminary antitumor activity, and pharmacokinetics of VIP236 monotherapy in patients with advanced cancer.

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Background: VIP236, a first-in-class SMDC, consists of an αvβ3 integrin small molecule binder, a peptide linker cleaved by neutrophil elastase (NE) in the tumor microenvironment (TME), and a camptothecin (CPT) payload VIP126 which was optimized for high permeability and low efflux. The overall drug design strategy for VIP236 is targeted delivery to the TME and tumors expressing $\alpha_V\beta_3$ integrin on their cell surface with release of the optimized CPT derivative by NE also present in the TME. VIP126, when delivered as a component of VIP236, is anticipated to kill tumor cells while reducing effects to normal tissue. VIP236 exhibits convincing single agent in vivo antitumor efficacy and acceptable tolerability in multiple human tumor cell line- and patient- derived xenograft models in mice, including breast, colorectal, small cell lung, gastric, metastatic breast and metastatic colon cancer. In three gastric cancer xenograft models, VIP236 caused statistically significant tumor growth inhibition across the models independent of HER2 status. VIP236 outperformed an anti-HER2 ADC, trastuzumab deruxtecan, in all three models. **Methods:** This trial in progress is an open-label, global, multicenter Phase 1 study to characterize safety, tolerability, preliminary antitumor activity and pharmacokinetics of VIP236 monotherapy in subjects with advanced cancer. Enrollment includes all comer patients with histologically confirmed advanced or metastatic solid tumors that are relapsed or refractory to standard of care. Subjects must have exhausted all available standard therapies or be deemed ineligible for potential available therapies. Frequency, severity, and relationship to study drug of any treatment-emergent adverse events or abnormalities of laboratory tests will be studied. Tumor response will be assessed using RECIST 1.1 criteria. The following dose schedules are being evaluated: 1) Cohorts 1, 2a, and 3a: A cycle is 21 days 1-hour intravenous (IV) infusions on a 2 days on/5 days off schedule with no pause between cycles. 2) Cohorts 2b, 3b, 4b, 5b, 6b, 7b, and 8b: A cycle is 21 days of VIP236 given as a 1-hour IV infusion once every three weeks (Q3W) with no pause between cycles. 3) Cohorts 1, 2a, 3a, 2b, 3b and 4b have been completed. Enrollment continues in the Q3W cohorts. Clinical trial information: NTC05371054. Research Sponsor: Vincerx Pharma.

TPS3169 **Poster Session**

Dose-expansion part of a phase 1b global study of E7386 in combination with lenvatinib (LEN) in patients (pts) with hepatocellular carcinoma (HCC) and other solid tumors including endometrial cancer (EC).

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Background: E7386, a first-in-class anticancer agent, inhibits protein-protein interaction between β-catenin and the CREB-binding protein, thus modulating Wnt/β-catenin signaling. E7386 is being tested in combination with LEN in the open-label global phase 1b Study 102. The dose-escalation part of Study 102 determined the recommended dose of E7386 + LEN in pts with HCC and other solid tumors. Here we describe the ongoing dose-expansion part in pts with HCC or EC. **Methods:** Eligible pts ≥18 years old should have an ECOG PS of 0-1 and a confirmed diagnosis of advanced, unresectable, or recurrent solid tumor. Pts with HCC will have a Child-Pugh score of A and a categorization of BCLC Stage B (not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment) or Stage C. Pts with HCC should also have received 1 prior immuno-oncology (IO)-based regimen and have progressed on/after prior treatment with IO therapy. If ineligible for IO therapy, pts should not have received prior systemic therapy; pts who previously received LEN are ineligible. In the EC subpart, pts should have disease progression after receiving prior platinum-based chemotherapy (PBT) and an IO-based therapy for EC. Pts may have received 1 additional line of PBT if given in the neoadjuvant/adjuvant setting, but not exceeding 3 lines of therapies. Pts with EC who are ineligible for IO therapy may have received only 1 prior systemic therapy including PBT. Pts who have received prior LEN therapy will be eligible if they meet protocol-specified criteria. Pts with HCC (n≈60) will be randomized in a 2:1 ratio into 1 of 2 treatment arms and will receive either the combination E7386 + LEN or LEN monotherapy in 28-day cycles. E7386 will be administered at 100 mg BID in the combination arm and LEN will be administered QD at 8 mg (if body weight <60 kg) or 12 mg (if body weight ≥60 kg) in both arms. Pts with HCC will be stratified by geographical region (Western Europe and North America vs Japan vs other countries). Pts with EC (n≈30) will receive only the combination E7386 120 mg BID + LEN 14 mg QD. The expansion part of Study 102 aims to assess safety and tolerability (primary endpoints), and pharmacokinetics and preliminary efficacy (secondary endpoints), of E7386 in combination with LEN for pts with HCC and EC. Efficacy of LEN monotherapy will be assessed for HCC (secondary endpoint). Tumors will be assessed by investigator per RECIST v1.1 every 8 weeks from the date of the first dose. Adverse events will be monitored and recorded for up to 30 days after the last dose or until initiation of a new anticancer therapy, whichever occurs first. Study sites will include the United States, France, Republic of Korea, Japan, and Taiwan. As of February 5, 2024, 46 pts with HCC and 16 pts with EC have enrolled. Clinical trial information: NCT04008797. Research Sponsor: Eisai Inc., Nutley, NJ, USA.

TPS3170 **Poster Session**

A modular, open-label, phase I/IIa study to evaluate the safety, tolerability, pharmacokinetics (PKs) and anti-tumour activity of a first-in-class (FIC) specific dUTPase inhibitor CV6-168 combined with anti-cancer treatments in patients (pts) with advanced malignancies.

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Background: CV6-168 is a FIC DNA uracilation agent targeting the enzyme dUTPase with high specificity. CV6-168 induces misincorporation of uracil into DNA when combined with thymidylate synthase (TS) inhibitors resulting in significantly increased DNA damage and lethality in cancer cells and activation of immune stimulatory mechanisms. CV6-168 does not inhibit dihydropyrimidine dehydrogenase, the rate-limiting enzyme responsible for 5-FU catabolism avoiding fluoropyrimidine drug-drug interactions and complex dose modifications. This is a first-in-human, modular study initially investigating PK and safety of CV6-168 with bolus/infusional 5-fluorouracil (5-FU) and folinic acid (FA). **Methods:** Primary objective: characterise safety and tolerability of CV6-168 with 5-FU and FA. Secondary objectives: establish PK profile of CV6-168 and 5-FU alone and in combination and evaluate anti-tumour activity of the combination. Exploratory objectives: investigate multiple surrogate, tumour and circulating pharmacodynamic assays related to mechanism of action and predictive biomarkers for CV6-168 and 5-FU. Each module of this study investigates a different hypothesis, driven by emerging data. Module 1, investigating CV6-168/5-FU/FA, consists of Part A (dose escalation in up to 51 pts) where the maximum tolerated/feasible dose will be identified to guide dose optimisation; Part B, proof of concept [PoC] expansions and identification of the recommended Phase 2 dose/schedule; and optional Parts C (dose optimisation cohorts) and D (basket cohort expansions). Part A is a "3 + 3" dose escalation design in pts with incurable advanced solid tumours and Part B expansions, powered to compare response rates to historical data, will include 3 cohorts of different tumour types. Part C is a randomised comparison of 2 doses/schedules to be selected based on Part A and B data, with pt populations selected based on emerging data. Further Modules may explore: Combination of CV6-168/5-FU/FA with a PD-(L)1 inhibitor; Combinations with other standard of care treatments; Food effects on CV6-168 bioavailability; and Different CV6-168 formulations. This trial design 1) Allows one protocol responsive to emerging data for a compound with multiple hypotheses, supporting studies in multiple combinations, reducing time from emerging data to 'first subject in study" compared with multiple individual studies; 2) Has the potential to reduce the number of pts unnecessarily exposed to a novel agent; and 3) Allows investigators to pre-empt emerging data and changes to the treatment landscape. These challenges in oncology drug development emphasize the need for flexible designs as the landscape of drug development continually evolves. Clinical trial information: ISRCTN12434145. Research Sponsor: CV6 Therapeutics (NI) Ltd.

TPS3171 **Poster Session**

A phase 1, first-in-human, open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of TT125-802 in patients with advanced solid tumors.

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Background: TT125-802 is a selective, potent, orally bioavailable small molecule inhibitor of the bromodomain of CBP and p300, two highly homologues lysine acetyltransferases. CBP/p300 act as transcriptional co-activators with multiple domains and functions, including well-documented roles in cell cycle regulation and several critical tumorigenic pathways (1-3). TT125-802 has shown mono-therapy efficacy in preclinical models of castration-resistant prostate cancer, KRAS-mutated colorectal and non-small cell lung cancer (4,5). Furthermore, TT125-802 is capable to interfere with transcriptional resistance mechanisms limiting targeted therapies (6) which will be explored clinically upon determination of a safe, well-tolerated, and biologically active single-agent dose. **Methods:** This study aims to establish the safety, tolerability, and pharmacokinetic profile of TT125-802. The maximum tolerated dose/recommended dose for expansion (MTD/RDE) of repeat daily dosing for TT125-802 monotherapy will be determined in subjects with advanced solid tumors in a sequential escalating cohorts design, (1 cycle = 21 days) using the Bayesian Logistics Regression Model (BLRM) with sentinel patients (2-day window for first patient enrolled in each cohort). Cohorts will consist of 3 to 6 subjects who will be followed over a dose-limiting toxicity (DLT) period of at least 21 days. TT125-802 will be administered orally once daily; additional schedules may be evaluated. Dose escalation is planned to follow two-fold increments. It may be adapted upon dose level revision and guided by pharmacokinetic analysis. Additional subjects (up to 6) may be enrolled in at least two monotherapy cohorts deemed safe and tolerable to optimize the recommended phase 2 dose (RP2D). Up to a total of 20 additional subjects may be enrolled. Translational/pharmacodynamic endpoints: Exploratory endpoints will provide proof-of-principle and early biomarker data for CBP/p300 inhibition. These analyses will include: 1. Single-cell gene expression evaluation of peripheral blood mononuclear cells (PBMCs) at multiple time points, 2. anagen hair bulb bulk RNAseq analysis, and 3. paired tumor biopsies will be analyzed with single-cell RNA sequencing. Together, these investigations are expected to support optimal dose determination. Additionally, circulating tumor DNA might be evaluated to define molecular responses. Outlook: The recommended phase 2 dose will be used further to explore the efficacy of TT125-802 as monotherapy. TT125-802 will be evaluated with targeted therapies (for example, KRASG12C/D, BRAF, EGFR, etc., inhibitors) to exploit the blocking of transcriptional escape mechanisms driven by CBP/p300. 1. Iyer, 2007. 2. Dutta, 2016. 3. Attar, 2017. 4. AACR2023 posters #6268. 5. AACR poster #3907. 6. AACR2023 poster #3907. Clinical trial information: 2022-500849-24-00. Research Sponsor: TOLREMO therapeutics AG.

TPS3172 **Poster Session**

A phase 1 trial evaluating the safety, tolerability, PK, and preliminary efficacy of QTX3034, an oral G12D-preferring multi-KRAS inhibitor, in patients with solid tumors with *KRAS^{G12D}* mutation.

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Background: *KRAS* is one of the most mutated driver oncogenes across solid tumors, and *KRAS^{G12D}* missense mutations have high prevalence in pancreatic, colorectal (CRC), and endometrial cancers. QTX3034 is a highly-selective, non-covalent, orally bioavailable, multi-KRAS inhibitor with potent activity across several KRAS variants, particularly G12D. QTX3034 binds to GDP-bound forms of mutant and wild-type KRAS with (sub)nanomolar affinities, allosterically inhibiting its conversion to the active state. QTX3034 inhibits KRAS signaling in in vitro studies and displays synergy with EGFR inhibitors. In vivo evaluation of QTX3034 resulted in significant tumor growth inhibition across various tumor models, with tumor regressions observed in 100% of animals in both HPAC pancreatic and GP2D colorectal *KRAS^{G12D}* xenograft models. QTX3034 exhibits brain penetration in preclinical studies, including an orthotopic model of intracranial efficacy. This clinical trial is now enrolling patients with advanced solid tumors harboring a *KRAS^{G12D}* mutation. **Methods:** This is a first-in-human, multicenter, open-label phase 1 study in adult patients with advanced solid tumors with *KRAS^{G12D}* mutations, without prior direct KRAS inhibitor treatment (NCT06227377). The primary objectives are to evaluate the safety and tolerability and to determine maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of QTX3034 alone, and in combination with cetuximab. Secondary objectives are characterization of the PK profile and preliminary antitumor activity. Part 1 consists of two dose-escalation arms: QTX3034 monotherapy (advanced solid tumors) and QTX3034 plus cetuximab (CRC) and will enroll 3-4 subjects per cohort in a Bayesian Logistic Regression Model (BLRM) design. QTX3034 will be administered orally in 21-day cycles until disease progression, intolerable toxicity, or withdrawal from treatment. Exploratory paired biopsies will be collected in Cycle 2 in a group of patients in the dose-escalation phase. Serial ctDNA will be collected in all patients. Following identification of a RP2D, QTX3034 will be evaluated in dose-expansion cohorts of up to 30 patients with various *KRAS^{G12D}* mutated tumor types to determine preliminary activity: pancreatic cancer, CRC, non-small cell lung cancer and endometrial cancer. To further optimize the recommended dose, patients will be randomized between two dose levels in the pancreatic cancer cohort. QTX3034 plus cetuximab will be explored following identification of a recommended combination dose in patients with CRC. Clinical trial information: NCT06227377. Research Sponsor: None.

TPS3173 **Poster Session**

Study of ELU001, a C'Dot drug conjugate (CDC) targeting folate receptor α (FRα) overexpressing solid tumors.

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Background: ELU001, pasifolate exatecan, is an ultra-small nanoparticle drug conjugate, known as a CDC (~6 nm), designed to target and penetrate into solid tumors. Due to its size, ELU001 exhibits rapid renal elimination which is expected to reduce or eliminate the toxicities associated with many antibody drug conjugates. ELU001 has ~13 folic acid targeting moieties and ~21 cathepsin-B cleavable exatecan topoisomerase-1 inhibitor payloads covalently bound to short polyethylene glycol chains surrounding a silica core, the C'Dot. ELU001 binds to cancer cells expressing FRα and is internalized into the lysosome where it releases the exatecan payload. ELU001's dose escalation study reported at ESMO Congress 2023 (1), examined weekly, bi-weekly (Q2W), and tri-weekly schedules over a range of doses in 42 patients. The study revealed that ELU001 could be administered safely and identified a dose level and schedule for the Expansion Studies described below. 22 of the patients with ovarian or endometrial cancers had >1 post-baseline scan(s), of these 2 had a PR and 19 had SD by RECIST v1.1 criteria. ELU001 demonstrated activity against tumors across a range of FRα expression levels, from low to high, retrospectively assessed using the VENTANA FOLR1 RxDx assay and the PS2+ scoring system. **Methods:** The current multicenter, Tumor Group Expansion open-label phase 1/2 clinical trial investigates ELU001 in patients with ovarian and endometrial cancers and is enrolling three cohorts; 1) ovarian cancer with high FRα expression, 2) ovarian cancer with moderate and low expression and 3) endometrial cancer with low to high expression with assessments based upon the PS2+ scoring system (high = ≥ 75%, moderate = ≥ 50% to < 75%, low = 25% to < 50%, negative = <25% of tumor cells with 2+ or 3+ staining intensity). An initial exploratory dose of 2.0 mg/m^2 Q2W was employed in all three cohorts and a second dose of 1.7 mg/m^2 Q2W will be studied in the ovarian cancer cohorts. Patients will ultimately be randomized to one of two or more doses to optimize dosing for registration. Primary endpoint: Objective Response Rate (ORR); secondary endpoints include DOR, PFS, TFST, PFS2, OS, adverse events, PK, and ADA assessments. Approximately 20 patients per tumor group will be recruited in the U.S. 1. Ann. Oncol. (2023) 34 (suppl_2): S458-S497. Clinical trial information: NCT05001282. Research Sponsor: None.

TPS3174 **Poster Session**

First-in-human, phase 1/2 study of GSK4524101, an oral DNApolymerase theta inhibitor (POLQi), alone or combined with the poly(ADP-ribose) polymerase (PARP) inhibitor (PARPi) niraparib in adults with solid tumors.

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Background: Double-stranded DNA breaks (DSBs) in human cells are typically repaired via nonhomologous end joining (NHEJ) or homologous recombination (HR). Deficiency of HR-mediated DNA repair plays a role in the initiation and progression of many tumor types. In tumors with HR deficiency, PARP inhibition leads to generation of DSBs that cannot be effectively repaired because of the HR defect, resulting in synthetic lethality. This finding has led to the clinical development and approval of several PARPi for the treatment of various tumors including certain ovarian, breast, prostate, and pancreatic cancers that are prone to display HR deficiency (HRd). DNA polymerase theta (encoded by *POLQ*) mediates an alternative DNA repair mechanism, microhomology-mediated end joining (MMEJ). DNA polymerase theta is generally not detectable in normal tissues but is upregulated in many tumor types. In preclinical studies, POLQi plus PARPi treatment demonstrated superior efficacy to PARPi alone in preventing the growth of HRd tumors. To evaluate the clinical potential of combining POLQi and PARPi, this first-in-human study investigates treatment with GSK4524101, an investigational POLQi, with or without the PARPi niraparib, in patients with solid tumors. **Methods:** This open-label, multicenter, phase 1/2 study (NCT06077877) opened in October 2023 and comprises dose-finding (part 1, including a food-effect cohort) and dose-expansion (part 2) parts. This trial aims to assess the maximum-tolerated dose, pharmacokinetics, safety, and preliminary antitumor activity of oral GSK4524101 with or without niraparib. The primary endpoints are safety (part 1) and confirmed objective response rate (part 2). Secondary endpoints include pharmacokinetics, safety, progression-free survival (part 2), and response duration (part 2). Up to 135 patients may be enrolled. To be eligible, patients must be aged ≥18 years; have an advanced or metastatic solid tumor, an Eastern Cooperative Oncology Group performance status score of 0–2, and a life expectancy of ≥3 months; and have exhausted all standard treatment options. Individuals are ineligible if they have not recovered from chemotherapy-associated adverse events or have symptomatic uncontrolled brain or leptomeningeal metastases, a history of myelodysplastic syndrome or acute myeloid leukemia, uncontrolled hypertension, or a second malignancy that has progressed or required active treatment in the previous 2 years. The study is actively recruiting in the US and Canada; as of January 1, 2024, 1 patient has been dosed. Patients enrolled in part 1 will receive GSK4524101 alone or GSK4524101 plus niraparib; patients enrolled in part 2 will be randomized to either GSK4524101 plus niraparib or niraparib alone. Part 1 of this study is expected to complete in 2025. Data presented on behalf of the original authors with their permission. Presented at the American Association for Cancer Research (AACR) Annual Meeting 2024; April 5-10, 2024; San Diego, CA. Final publication number: 9686. Reused with permission. Clinical trial information: NCT06077877. Research Sponsor: GSK.

TPS3175 **Poster Session**

A first-in-human, phase 1/2 trial of FOG-001, a β-catenin:TCF antagonist, in patients with locally advanced or metastatic solid tumors.

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Background: The Wnt/β-catenin pathway is a frequently activated oncogenic pathway and a well-described driver of many cancers. FOG-001 is designed to be a first-in-class direct inhibitor of β-catenin that blocks β-catenin's interaction with the T-cell factor (TCF) family of transcription factors. Preclinical studies have indicated FOG-001 can cause tumor growth inhibition and regression by disrupting β-catenin-dependent signaling. FOG-001 is unique from previously reported Wnt/β-catenin pathway modulators as it is designed to directly inhibit TCF transcription factor and β-catenin interaction, the most downstream node in the Wnt pathway. It is hypothesized FOG-001 will abrogate the hyperactivation of the Wnt pathway that is driven by most known pathway mutations. **Methods:** This first-in-human, Phase 1/2, multicenter, open-label, dose escalation (Parts 1a and 1b) and dose-expansion (Part 2) study is evaluating the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of FOG-001 in patients with advanced or metastatic solid tumors. Patients with the following tumor types are eligible: microsatellite stable (MSS) colorectal cancer (CRC) or any solid tumor with documented Wnt pathway activating mutation (WPAM) (Part 1a), MSS CRC only (Part 1b) and MSS CRC, gastric/gastroesophageal (GEJ) cancer, non-small cell lung cancer (NSCLC), and any solid tumors with documented WPAM in Part 2. Patients must have received ≥1 prior systemic anticancer therapy(ies) and be ineligible for curative surgery or curative chemoradiation. In Part 1, FOG-001 is administered at escalating doses via intravenous (IV) infusion on Days 1, 8, 15, and 22 of each 4-week cycle; additional dosing regimens may be explored. After selection of the preliminary recommended Phase 2 dose(s) (pRP2D) and regimen(s) in Part 1, the following cohorts will be enrolled to receive FOG-001 at the pRP2D in Part 2: (2a) MSS CRC; (2b) NSCLC with documented WPAM in adenomatous polyposis coli (APC) or β-catenin; (2c) gastric/GEJ cancer with documented WPAM in APC or β-catenin; and (2d) solid tumors with ≥1 documented WPAM in any predefined Wnt pathway genes. The primary endpoints are safety/tolerability (Parts 1 and 2), and also preliminary antitumor activity (objective response rate) (Part 2). Secondary endpoints are PK, PD, and additional antitumor activity assessments. Enrollment in Part 1 is ongoing. Clinical trial information: NCT05919264. Research Sponsor: Fog Pharmaceuticals Inc.

TPS3176 **Poster Session**

A first-in-human, phase 1 study evaluating oral TACC3 inhibitor, AO-252, in advanced solid tumors.

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Background: TACC3 is the most oncogenic member of the transforming acidic coiled-coil domain-containing protein (TACC) family, which have important roles in microtubule and centrosome-related processes. TACC3 is overexpressed in multiple cancers with centrosome amplification caused by genomic aberrations such as *TP53* mutations, leading to chromosome instability and worse prognosis. AO-252 is a computationally designed, small molecule inhibitor of TACC3 protein-protein interactions. Binding assays and kinome screening suggested the specificity of AO-252 to TACC3. AO-252 targets the interactions of TACC3 with Clathrin/KIFC1, BRDA1 and MBD2/HAT complexes regulating mitosis, DNA damage response and epigenetic functions and was confirmed using co-immunoprecipitation (co-IP) assays. Gene expression analysis in multiple cell lines further confirmed the various TACC3 pathways affected by AO-252. *In vitro*, AO-252 showed low nanomolar potency in >200 cell line panel covering multiple different cancer indications and spared the normal cells. *In vivo*, AO-252 demonstrated strong tumor growth inhibition or regression in multiple xenograft models including triple-negative breast (TNBC), high-grade serous ovarian (HGSOC) and endometrial cancer with *TP53* mutation/loss with a good therapeutic index. **Methods:** This first-in-human, multicenter, open-label phase I dose escalation and expansion study evaluates the safety, tolerability, maximum tolerated dose, and recommended phase 2 dose (RP2D) of AO-252 in solid tumors (NCT06136884). Patients with unresectable or metastatic TNBC, platinum-resistant HGSOC, primary peritoneal, fallopian-tube and serous endometrial cancers with documented *TP53* mutation/loss, who have failed on at least 1 prior line of systemic therapy in advanced/metastatic setting (maximum 4 for TNBC and endometrial carcinoma) are eligible for enrollment. Part 1 follows an accelerated titration dose-escalation for cohort 1 and 2 and a traditional 3+3 study design from cohort 3. A maximum of 54 patients will be treated in the dose escalation, patients receiving AO-252 orally once or twice daily in a 28-day cycle. Part 2 consists of dose-expansion of a maximum of 30 patients into 2 RP2D levels of AO-252. Primary objectives are to evaluate the safety and tolerability as noted by dose-limiting toxicities, adverse events, serious adverse events, laboratory test results, electrocardiograms, vital signs, physical exams, and ECOG performance status. Secondary objectives are to determine the antitumor activity assessed by objective response rate per RECIST1.1, duration of response and disease control rate and to determine the pharmacokinetics of single and repeated doses of AO-252. Potential biomarkers relating to treatment outcome will be evaluated as exploratory endpoints. Enrollment in Cohort 1 is completed and enrollment to Cohort 2 will begin in February 2024. Clinical trial information: NCT06136884. Research Sponsor: A2A Pharmaceuticals, Inc.

TPS3177 **Poster Session**

^{177}Lu-edotreotide versus everolimus in patients with advanced neuroendocrine tumors of lung or thymic origin: The phase 3 randomized LEVEL, GETNE-T2217 trial.

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Background: Everolimus is the only approved drug for the treatment of patients with neuroendocrine tumors (NETs) of lung and thymic origin, showing a median progression-free survival (PFS) of 11 months. Retrospective data for peptide receptor radionuclide therapy (PRRT) have demonstrated promising activity in somatostatin receptor (SSTR)-positive lung NETs. This study aims to compare the efficacy, safety, and patient-reported outcomes of ^{177}Lu-edotreotide versus the standard of care everolimus in patients with advanced lung and thymic NETs. **Methods:** The LEVEL trial is a randomized, open-label, phase 3 international trial of ^{177}Lu-edotreotide versus everolimus in patients with progressive, advanced, and well/moderately differentiated NETs of lung (typical/atypical) or thymic origin. Patients could be treatment naïve or have progressed (PD) on somatostatin analogues or ≤2 additional systemic treatments. Prior PRRT or mTOR inhibitors are not permitted. Eligible patients are randomly assigned 3:2 to 6 cycles of ^{177}Lu-edotreotide (7.5±0.7 GBq / cycle) or to oral everolimus 10 mg once daily until PD or unacceptable toxicity. Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans are performed every 12 weeks until PD. Blood samples are analyzed at baseline, at 1st tumor assessment, and at PD for pharmacodynamic endpoints. Archival tumor tissue samples will be analyzed for ancillary studies. The primary endpoint is PFS according to RECIST v1.1. Secondary endpoints include overall response rate, duration of response, overall survival, safety, and quality of life (assessed through EORTC QLQ-C30). The expected sample size is 120 patients using a two-sided group sequential Lan-DeMets with O'Brien-Fleming-like boundaries test to demonstrate statistically significant risk reduction of 46.4% (HR= 0.536) in PFS between arms (α=0.05, β=0.2). The study has received institutional review board/ethics committee approval. Recruitment started in Oct 2023. Thirteen patients are already included. Clinical trial information: NCT05918302. Research Sponsor: GETNE through industry collaborator ITM Oncologics GmbH.

TPS3178 **Poster Session**

An open-label study to assess the safety and efficacy of naporafenib (ERAS-254) administered with trametinib in previously treated patients with locally advanced unresectable or metastatic solid tumor malignancies with RAS Q61X mutations (SEACRAFT-1).

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Background: The rat sarcoma viral oncogene (RAS)/mitogen-activated protein kinase (MAPK) pathway is a key signaling cascade that drives cell proliferation, differentiation, and survival. Inappropriate activation of this pathway drives tumorigenesis in a subset of solid tumors. There are 3 isoforms of RAS (KRAS, NRAS, and HRAS) with the most commonly mutated codons being 12, 13, and 61. While these codon mutations map to the active site of RAS, they appear to have differential impacts on pathway activation. Mutations at codon 61 (RAS Q61X) are generally thought to be the most MAPK pathway-activating relative to mutations at codons 12 and 13 and are therefore thought to be the most oncogenic. Naporafenib is a pan-RAF inhibitor that is being evaluated in combination with trametinib, which inhibits MEK, a downstream node of the RAS/MAPK pathway. Clinical proof of concept (PoC) in patients with NRASm melanoma (of which 80 to 90% have Q61X mutations) and preliminary PoC for patients with RAS Q61X NSCLC have been established for the combination. Preclinical data across tumor types suggest that RAS Q61X is a potential predictive biomarker for the combination of naporafenib with trametinib, a hypothesis being tested in this trial. **Methods:** SEACRAFT-1 (NCT05907304) is a Phase 1b, open-label study evaluating the clinical activity and safety of the combination of naporafenib and trametinib in pts with locally advanced, unresectable, or metastatic solid tumor malignancies that are not responsive to standard therapies or for which there are no standard therapies. Eligible pts must be ≥18 years (or ≥12 and <18 years in an adolescent substudy) with documented RAS Q61X mutation by an analytically validated assay. Pts must also have ≥1 measurable lesion per RECIST (Response Evaluation Criteria in Solid Tumors, v1.1) and Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2 (or Karnofsky/Lansky Performance Status ≥70 for adolescent pts). Exclusion criteria include prior therapy with an ERK, MEK, RAF, or RAS inhibitor, QTcF >450 ms at baseline, and left ventricular ejection fraction (LVEF) <50% at baseline. A total of up to 115 pts will be enrolled to receive naporafenib 200 mg BID and trametinib 1 mg QD continuous in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint is ORR; secondary endpoints include assessment of PFS, DOR, safety, and tolerability. Clinical trial information: NCT05907304. Research Sponsor: None.

TPS3179 **Poster Session**

PRIMROSE: A modular phase 1/2a study of AZD3470, an MTA-cooperative PRMT5 inhibitor, in patients with MTAP deficient advanced solid tumors.

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Background: Protein arginine methyltransferase 5 (PRMT5) is an epigenetic enzyme that catalyzes symmetric dimethylation of arginine substrates, regulating multiple cell processes. Deletion of the methylthioadenosine phosphorylase gene *MTAP* in tumor cells results in accumulation of the metabolite methylthioadenosine (MTA), a partial inhibitor of PRMT5, potentially rendering tumor cells susceptible to further PRMT5 targeting. Clinical activity of first-generation, non-selective PRMT5 inhibitors (PRMT5i) is limited by bone marrow toxicity due to lack of selectivity between normal cells and MTAP-deficient tumor cells. Second-generation PRMT5i, including AZD3470, should selectively target MTAP-deficient tumor cells whilst sparing normal cells. AZD3470 preferentially binds PRMT5 in the presence of MTA in MTAP-deficient tumor cells, inhibiting PRMT5 methylation activity, and is less effective in MTAP-proficient cells. PRIMROSE (NCT06130553) is a first-in-human, Phase 1/2a, open-label, multicenter study of AZD3470 as monotherapy and in combination with anti-cancer agents in patients with MTAP-deficient advanced / metastatic solid tumors. **Methods:** Eligible patients are aged ≥18 years with MTAP-deficient advanced or refractory solid tumors, ≥1 prior line of treatment in the recurrent / metastatic setting, ≥1 measurable lesion per RECIST v1.1, ECOG performance status 0/1, adequate organ and bone marrow function, and no prior treatment with PRMT5i. Module 1 will evaluate AZD3470 monotherapy. Part A (dose escalation) will enroll up to ~54 patients and follow a modified toxicity probability interval-2 (mTPI-2) design with once-daily dosing in 21-day cycles. Treatment will be given until progression or discontinuation criteria are met. Part B (dose optimization and expansion) will expand specific patient populations and / or tumor types, with up to ~30 patients per cohort; dosing will be based on safety and tolerability data from Part A. Further modules for combination treatments may be added based on emerging supportive data. The primary objectives are to assess safety and tolerability, including dose-limiting toxicities, and to determine the recommended phase 2 dose of AZD3470. The secondary objective is evaluation of efficacy, including objective response rate, duration of response, disease control rate, change in tumor size, progression-free survival, and overall survival. An additional secondary objective in Module 1 is to assess pharmacokinetics. The study is planned to take place in ~20 centers across eight countries. The study was opened to enrollment in December 2023. Clinical trial information: NCT06130553. Research Sponsor: AstraZeneca.

TPS3180 **Poster Session**

A phase 1, open-label, dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of PF-07799544 (ARRY-134) as a single agent and in combination with PF-07799933 BRAF dimer inhibitor, in participants 16 years and older with advanced solid tumors.

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Background: The MAPK pathway plays a role in several key signaling and phosphorylation events that contribute to tumorigenesis. Inhibition of MEK, along with RAF kinases, has proven to be a successful transformative strategy for melanoma and other MAPK pathway-altered tumors. However, the duration of clinical benefit is limited by a narrow therapeutic index, de novo and acquired resistance and poor brain penetration. PF-07799544 is a next-generation, fully brain penetrant MEK inhibitor. PF-07799933 is an oral selective ATP-competitive small-molecule RAF kinase inhibitor that suppresses BRAF signaling in BRAF V600-mutant and non-V600-BRAF mutant tumors. It displays significantly less paradoxical activation than approved BRAFi and is not "pan RAF" as it spares non-BRAF mutated-containing RAF dimers. We describe here the design of the Phase 1 study of PF-07799544 as Monotherapy or in Combination with a next generation BRAF dimer inhibitor PF-07799933 in participants with BRAF mutated (BRAFm) advanced solid tumors. **Methods:** The purpose of this first-in-human study is to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and potential clinical benefits of PF-07799544 administered as a single agent in participants with advanced solid tumors (Phase 1a) and in combination with PF-07799933 in participants with BRAF Class 1, 2 and 3 mutated solid tumors with or without brain involvement (Phase 1b). Phase 1a will enroll participants with advanced solid tumors who have progressed on standard of care. The primary objective is to determine monotherapy MTD/RDE of PF-07799544. Once PK measurements indicate the potential for significant WT MEK mutation target coverage, participants with untreated and symptomatic brain metastases (bm) will be allowed to enroll. Phase 1b is comprised of multiple sub-studies, all of which evaluate PF-07799544 in combination with PF-07799933 in participants with BRAFm solid tumors who have progressed on standard of care therapies, including Class 1 BRAFi where indicated. Sub-study B: BRAFm melanoma (V600 and non-V600) will determine the MTDc/RDEc of the combination (Part 1 primary objective), followed by dose expansion cohorts (Part 2) (~80 participants): Cohort 1: BRAF V600 melanoma (asymptomatic and untreated bm permitted), Cohort 2: BRAF V600 melanoma (symptomatic bm), Cohort 3 BRAFm Class 2/3 melanoma (asymptomatic and untreated bm permitted); Sub-study C: BRAFm Class 2 or 3 advanced solid tumor Cohort 1 (asymptomatic and untreated bm permitted and Cohort 2 (symptomatic bm) (~20 each cohort). The main objectives of the dose expansion cohorts in all substudies, will be to evaluate antitumor activity, safety, PK and PD. Clinical trial information: NCT05538130. Research Sponsor: Pfizer.

TPS3181 **Poster Session**

A phase I/II, first-in-human study of VLS-1488, an oral KIF18A inhibitor, in patients with advanced cancer.

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Background: Chromosomal instability (CIN) is a hallmark of cancer characterized by high rates of chromosomal segregation errors during mitosis. This creates structural and numerical changes to chromosomes, driving genetic heterogeneity and cancer evolution. KIF18A is a mitotic kinesin protein shown to be important for successful division of cancer cells with CIN but not required for mitosis in normal diploid cells. Pre-clinical studies demonstrated that treatment of chromosomally unstable cancer cells in vitro and in xenograft models (HCC15 and OVCAR-3) with a KIF18A inhibitor resulted in failure of chromosomal congression, mitotic arrest, cell death and dose-dependent inhibition of tumor growth. VLS-1488 is an oral small molecule inhibitor of KIF18A that is being examined in an open-label, phase I/II, first-in-human study evaluating the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumor activity in advanced solid tumors with high prevalence of CIN. **Methods:** Key eligibility criteria include specific histologically confirmed metastatic or advanced tumor types with at least one site of measurable disease per RECIST 1.1, adequate organ function, and mismatch repair proficient/microsatellite stable.Eligible tumor types include high grade serous ovarian/fallopian tube/primary peritoneal cancer, squamous non-small cell lung cancer, triple negative breast cancer, gastric adenocarcinoma, gastroesophageal cancer, esophageal cancer, colorectal adenocarcinoma, transitional cell carcinoma of bladder, head and neck squamous cell carcinoma, ovarian or uterine carcinosarcoma, and uterine serous carcinoma. Subjects will receive VLS-1488 monotherapy continuously for 28-day cycles once daily. The study consists of two parts, Dose Escalation and Dose Expansion. Utilizing a Bayesian Optimal Interval (BOIN) design, Dose Escalation will examine the safety and tolerability of VLS-1488 at various dose levels (DLs) to identify the Maximum Tolerated Dose (MTD) and to select DLs for Dose Expansion. Dose Expansion may commence after the MTD or DLs of interest are identified. Dose Expansion will examine the safety, tolerability, preliminary efficacy and preliminary drug-drug interaction (DDI) and food effect risk of VLS-1488 in selected tumor types. Subjects enrolled to specific tumor type cohorts may be randomized to DLs of interest. Enrollment to Dose Escalation began in September 2023 and is ongoing. Clinical trial information: NCT05902988. Research Sponsor: Volastra Therapeutics, Inc.

TPS3182 **Poster Session**

A phase 1 study of the BET inhibitor ZEN003694 in combination with the MEK1/2 inhibitor binimetinib in solid tumors with RAS pathway alterations and triple-negative breast cancer (NCI number 10449).

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Background: Bromodomain and extra-terminal (BET) proteins serve as epigenetic readers and regulate transcription by binding acetylated lysines in histones. BET inhibitors target this epigenetic machinery modifying the expression of oncogenes and have the potential to overcome drug resistance in different settings. Resistance to mitogen-activated extracellular kinase (MEK) inhibition appears to rely upon changes in gene expression, a process that can be potentially inhibited via BET blockade. Preclinical data have demonstrated synergistic efficacy of dual MEK and BET inhibition in MAPK-altered solid tumors. Triple negative breast cancer (TNBC) is a disease frequently found to have gene amplifications in BRAF, NF1 mutations, and upstream regulators of the MAPK pathway and preclinical work has shown efficacy with dual inhibition of MEK and BET. **Methods:** This phase 1, open-label, multicenter study was designed to evaluate the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the BET inhibitor ZEN003694 in combination with the MEK inhibitor binimetinib in solid tumors with RAS pathway alterations and TNBC. The study has two parts: dose escalation (part 1) which plans to recruit a maximum of 30 patients and dose expansion (part 2), which will comprise 12 patients. The primary objective of part 1 is to determine the MTD and recommended Phase 2 dose (RP2D), whereas the primary objective of dose expansion is to evaluate safety and toxicity. Secondary objectives include tolerability, pharmacokinetics (PK), and antitumor activity. Additional analyses will explore epigenetic changes such as ChIPseq to determine levels of H3K27ac and ATACseq to determine treatment-induced changes in open chromatin regions. ZEN003694 is given orally daily, and binimetinib is administered orally twice daily in 28-day cycles. Dose escalation is being conducted using a standard 3+3 cohort design to determine the MTD. Part 1 requires evaluable or measurable disease, whereas Part 2 requires measurable disease as per RECIST v1.1. Patients must have an ECOG performance status of ≤2. Included tumors are TNBC (estrogen receptor ≤1%, progesterone receptor ≤1%, human epidermal growth factor receptor 2 (HER2) 0–1+ or non-amplified) or any other solid tumor with actionable MAPK alterations (e.g. KRAS, NRAS, HRAS, or BRAF activating mutations, inactivating NF1 mutations, or BRAF fusions). Patients with any PI3K pathway activating genomic alterations are excluded. Prior therapy with BET, RAF, MEK, or ERK inhibitor is not permitted. This study is currently ongoing in dose escalation. Clinical trial information: NCI number 10449. Research Sponsor: None.

TPS3183 **Poster Session**

Phase II study of enasidenib in IDH2-mutated malignant sinonasal and skull base tumors.

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Background: Advanced sinonasal malignancies are rare and heterogeneous cancers with limited therapeutic options. Tumor types include olfactory neuroblastoma (ONB), sinonasal undifferentiated carcinoma (SNUC) and large cell neuroendocrine carcinoma (LCNEC), chondrosarcoma, and sinonasal adenocarcinoma (SNAC). Pathogenic driver mutations in isocitrate dehydrogenases 1 and 2 (*IDH1* and *IDH2*) were identified first in glioma and myeloid malignancies. IDH1/2 enzymatic activity catalyzes conversion of isocitrate and $NADP^+$ to α-ketoglutarate (α-KG) and NAPDH, which are critical for cellular metabolism and for α-KG-dependent dioxygenases; mutant IDH1/2 catalyze conversion of α-KG to the oncometabolite 2-hydroxyglutarate (2-HG), a competitive antagonist of α-KG in regulating dioxygenases activity, with subsequent impact on DNA histone methylation and cellular differentiation. R172S or R172T $IDH2^{mut}$ have been detected in up to 80% of SNUCs and in a minority of ONB, chondrosarcoma, LCNEC and SNAC. Enasidenib is an oral small molecule inhibitor of the mutant IDH2 protein which prevents 2-HG accumulation and releases cancer cells from the differentiation block. It is currently approved for relapsed/refractory $IDH2^{mut}$ myeloid malignancies with proven clinical efficacy. **Methods:** This is a phase 2, single arm clinical trial conducted at the Center for Cancer Research (CCR) of the National Cancer Institute. The trial investigates the activity of enasidenib in adult patients with histologically or cytologically confirmed locally advanced or metastatic $IDH2^{mut}$ sinonasal cancers (SNUC, ONB, LCNEC, chondrosarcoma, SNAC). Participants must have RECIST 1.1 measurable disease and must have progressed following at least one prior systemic treatment line administered in the recurrent/metastatic setting; those with locally advanced disease must not be amenable to potentially curative approaches. Participants must also have ECOG performance status ≤ 2, be 18 years old or higher, and have adequate organ function. Participants with active, either new or progressive brain metastases or leptomeningeal disease are excluded. Enasidenib will be given continuously at a fixed dose of 100 mg orally daily in a 28-day cycle, until disease progression, unacceptable toxicity, or consent withdrawal. Imaging will be performed every 8 weeks. Baseline and on-treatment research biopsies will be mandatory, where clinically feasible. The trial aims to accrue a total of 25 participants. The primary end point is progression free survival. Secondary outcomes include safety, overall survival, and clinical benefit rate, defined as complete response, partial response and stable disease (per RECIST 1.1) lasting above 4 months. Correlative studies include evaluating changes in 2-HG plasma levels during treatment, and transcriptomic profiling. The study has just started enrolling in the CCR. Clinical trial registry: NCT06176989. Clinical trial information: NCT06176989. Research Sponsor: None.

TPS3184 Poster Session

Phase 1/2 study of FMC-376 an oral KRAS G12C dual inhibitor in participants with locally advanced unresectable or metastatic solid tumors (PROSPER).

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Background: FMC-376 is a highly selective, orally bioavailable, dual (ON/OFF) irreversible covalent inhibitor that rapidly and effectively blocks signaling via ON (GTP-bound) mutant KRAS G12C and prevents OFF (GDP-bound) KRAS G12C from being activated. This prevents downstream KRAS G12C signaling without affecting wild-type KRAS protein. Nonclinical pharmacology studies demonstrate that FMC-376 inhibits tumor cell growth and viability in cells harbouring KRAS G12C mutation and results in tumor regression in multiple mouse models including PDX models of NSCLC, PDAC and CRC. FMC-376 demonstrated the ability to overcome mechanisms associated with innate and acquired resistance to the first generation KRASG12C (off) only inhibitors. [1]. **Methods:** This clinical study is global and is designed to evaluate the safety, tolerability, PK/PD and anti-tumor activity of FMC-376. Phase 1A (Dose Escalation) may enroll ~83 participants, Phase 1B (Dose Expansion) in tumor specific cohorts may enroll ~120 participants to optimize dosing and Phase 2 (Cohort Expansion) may enroll multiple tumor specific cohorts. Phase 1A includes participants who have progressed on or are ineligible for available standard approved therapies including KRAS G12C inhibitors. Participants will be enrolled into 1 of 5 escalating dose levels. BOIN design will be employed with a single Cohort, accelerated titration. Key eligibility criteria include histologically or cytologically confirmed locally advanced/unresectable or metastatic solid tumors with KRAS G12C mutations, ECOG 0-1 and adequate hematologic, hepatic and renal function. Participants with stable treated brain metastases may be eligible, but participants with leptomeningeal disease or carcinomatous meningitis are not eligible. FMC-376 will be administered PO QD for 21-day cycles until PD. Key objectives include establishing doses, based on incidence of DLTs, identifying SAEs/AEs and changes in ECG parameters, characterizing the PK profile and evaluating the clinical activity of FMC-376 via RECIST v1.1. In addition, FMC-376 target engagement and changes in expression of RAS pathway genes will be evaluated. A dose escalation and safety committee will be established to oversee the dose escalation portion of the study. The study is open to enrollment as of February 2024, NCT06244771. 1. AACR 2023 Annual Meeting Discovery of FMC-376 a novel orally bioavailable inhibitor of activated $KRAS^{G12C}$ Kevin Webster, April 16, 2023. Clinical trial information: NCT06244771. Research Sponsor: Frontier Medicines.

TPS3185 **Poster Session**

A first-in-human study of IK-595, an oral MEK/RAF molecular glue, in patients with RAS- or RAF-altered advanced solid tumors.

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Background: Alterations in the RAS/RAF/MEK/ERK pathway are the most common drivers of oncogenesis. MEK is a clinically validated cancer target and despite FDA approval of several MEK inhibitors, their clinical utility has been limited to BRAF V600 mutant cancers and NF1 mutant neurofibromas mostly due to early emergence of resistance and low therapeutic indices. IK-595, a potent novel MEK-RAF molecular glue, is being developed to overcome these limitations. IK-595 traps MEK in an inactive complex with all RAF isoforms and blocks RAF-dependent MEK phosphorylation, thereby alleviating CRAF-mediated MEK reactivation that hinders the efficacy of approved MEK inhibitors in RAS/RAF-driven tumors, in addition to kinase independent CRAF activity. IK-595 exhibits potent single agent activity in a wide range of *in vivo* cancer models harboring various RAS/RAF alterations, including, but not limited to, lung, pancreatic, colorectal cancer (CRC), melanoma, and AML. The preclinical pharmacokinetic profile of IK-595 also enables flexible dosing schedules resulting in a broader therapeutic window. **Methods:** This is a phase 1, first-in-human, open-label, multicenter study to evaluate IK-595 as monotherapy in patients with RAS- or RAF-altered advanced solid tumors for whom there are no other further treatment options known to confer clinical benefit. Dose escalation uses a Bayesian Optimal Interval Design (BOIN) in patients with advanced and unresectable, or metastatic solid tumors with confirmed RAS/RAF gene alterations. Backfilling of cleared dose levels with key target indications will initiate upon achievement of efficacious plasma exposures. Dose expansion will occur in genetically defined cohorts, for example NRAS-mutant CRC and malignant melanoma, as well as BRAF non-V600 and KRAS mutant tumors using a Simon 2-stage adaptive design. IK-595 will initially be administered on an intermittent dosing schedule in 30-day cycles. Additional dosing schedules may be explored. Primary objectives of the study are to evaluate safety and tolerability of IK-595 and to determine the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD). Secondary objectives include evaluation of preliminary antitumor activity by RECIST 1.1, pharmacokinetic (PK) parameters, and pharmacodynamic effects of IK-595 on pERK in paired tumor biopsies. Key exploratory endpoints include changes in pERK in peripheral blood cells, changes in pERK target genes in tumor biopsies, and assessment of candidate baseline response biomarkers. The study began in December 2023 and enrollment in Cohort 1 was completed with no DLTs; dose escalation continues to enroll. Clinical trial information: NCT. Research Sponsor: Ikena Oncology.

TPS3186 **Poster Session**

IAM1363-01: A phase 1/1b study of a selective and brain-penetrant HER2 inhibitor for HER2-driven solid tumors.

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Background: HER2 activation promotes carcinogenesis, prompting the development of HER2-directed therapies in cancers with HER2 alterations. There is a critical need for novel agents to treat HER2-driven cancers, as current inhibitors display significant toxicity and lack efficacy against certain mutations. IAM1363 (formerly IAM-H1 and ENT-H1) is an irreversible and brain-penetrant small molecule inhibitor targeting both wildtype HER2 and oncogenic HER2 mutants, including the recalcitrant exon 20 mutations. IAM1363, discovered through Iambic Therapeutics' AI-driven discovery platform, represents the only example of a Type II HER2 inhibitor. It was designed to avoid off-target toxicities from EGFR inhibition thus expanding the therapeutic index over existing HER2 inhibitors. In preclinical studies, IAM1363 shows preferential tumor enrichment, a unique feature observed across tumor types and anatomic sites. The promising target specificity and pharmacokinetic profile of IAM1363 offers the potential to bridge gaps left by current standard of care HER2 targeted treatments. **Methods:** IAM1363-01 is a first-in-human, multicenter, open-label, Phase 1/1b dose escalation and expansion trial evaluating IAM1363 as monotherapy and in combination with trastuzumab. The study will enroll patients with relapsed/refractory malignancies that have documented HER2 gene alterations (amplification or tyrosine kinase domain mutations) or protein over-expression. Prior treatment with HER2 directed therapies is allowed after a washout period. Part 1, dose escalation, will enroll patients with any tumor type. Part 2 will optimize IAM1363 dosing as monotherapy and in combination with trastuzumab. Part 3 consists of a Simon 2-Stage evaluation of IAM1363 as monotherapy in patients with colorectal, non-small cell lung, and bladder cancer with or without brain metastases and in combination with trastuzumab in breast cancer patients with brain metastases. Key objectives are to establish the safety and tolerability of IAM1363, characterize PK/PD, and determine the recommended Phase 2 dose. Exploratory analysis will correlate HER2 expression level/mutation status with tumor response and tolerability. IAM1363 will be given orally once daily at a starting dose of 120 mg/day in up to 4 planned dose levels. Dose escalation employs an accelerated titration design that transitions to a standard 3 + 3 design based on protocol-specific criteria. Up to 287 patients will be enrolled at approximately 20 sites and treated until disease progression or unacceptable toxicity. The trial is designed to establish the safety profile of IAM1363 as a single agent and in combination with trastuzumab and to provide initial proof of antitumor activity in malignancies with HER2 overexpression, gene amplification, or tyrosine kinase mutations, including in patients with brain metastases. Clinical trial information: NCT06253871. Research Sponsor: None.

TPS3187 **Poster Session**

Pilot study of CBX-12 pharmacodynamics in patients with advanced solid tumors.

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Background: Topoisomerase 1 (TOP1) inhibitors effectively kill a diverse range of tumor cells but have limited clinical utility due to severe off-target toxicities. Targeted therapeutic strategies have been developed to circumvent these limitations, although there remains an unmet need for antigen-agnostic tumor targeting. CBX-12 is a peptide conjugate that uses a novel pH-low insertion peptide (pHLIP) linked to TOP1 inhibitor exatecan to selectively target the low-pH tumor microenvironment and deliver the payload intracellularly. Recently published results of the first-in-human study of CBX-12 (NCT04902872) demonstrated single-agent activity in 4 patients, including a complete response in a patient with ovarian cancer. The predominant reported toxicity was myelosuppression with the most common grade 3/4 treatment-related adverse event being neutropenia in 28.6% of patients. Here we report our new pharmacodynamic (PD) biomarker-driven pilot study of CBX-12 in patients with advanced solid tumors. The primary objective of this study is to assess the effects of CBX-12 on biomarkers of DNA damage response (DDR) in biopsy specimen to establish the degree and duration of CBX-12 target engagement. The secondary objectives are to assess the effects of CBX-12 on TOP1 molecular response; determine any association between tumor TOP1 levels, DDR modulation, and plasma exatecan levels; evaluate the effect of CBX-12 on CD8+ T cell infiltration and activation in the tumor microenvironment; assess the objective response rate using RECIST v 1.1; and assess safety and tolerability of CBX-12. The planned PD endpoints aim to confirm and further enrich knowledge of the mechanisms underlying response or resistance to CBX-12 treatment, and guide future complementary treatment combination strategies. The study results may also help identify future patient populations likely to benefit from CBX-12 treatment. **Methods:** CBX-12 will be administered intravenously once weekly in 28-day cycles at the recommended phase 2 dose. Mandatory biopsies will be collected at baseline, 24-36 hours post first dose, and on cycle 3 day 1 to assess both short- and long-term effects of CBX-12 on the tumor. Mandatory research blood samples will be collected at specified timepoints for pharmacokinetic, circulating tumor cell, and cell-free DNA analyses. Clinical trial information: NCT05691517. Research Sponsor: None.

TPS3188 **Poster Session**

A pan-tumor prospective translational, Irish study, investigating the association of gut microbiome (GM) diversity with pathological complete response (pCR) after neoadjuvant treatment in early stage breast, rectal, and esophageal cancers.

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Background: The gut microbiome (GM) is thought to influence host immunity by modulating multiple immunologic pathways. Studies have suggested that dysbiosis of the GM confers a predisposition to certain malignancies and influences response to immune checkpoint inhibitors. However, little is known about how the GM diversity influences complete pathological response to neo-adjuvant therapy in gastrointestinal (GI) and breast tumors. We hypothesize that a more diverse GM constitution at baseline will lead to improved pathological response at the time of definitive surgery. **Methods:** This is a cross institutional multi-centre Irish translational study investigating the impact of the GM diversity on the efficacy of neo-adjuvant therapy in GI and breast cancers by assessing its association with pathological response. The study population includes pts with early-stage breast, rectal or esophageal cancers commencing neo-adjuvant therapy (including chemotherapy, immunotherapy and chemo-radiation) and planned for definitive surgery. Exclusion criteria include prior allogenic tissue/solid organ transplantation and prior receipt of anti-cancer therapy. The study assessments will include fecal sampling of the GM prior to neo-adjuvant therapy, upon completion and again six months post completion of therapy. Fecal samples will be analysed by 16S RNA sequencing. Pathological response will be examined at time of surgery and patients will be classified as responders (complete pathological response) or non-responders. The primary endpoint of the study is to examine the association between the GM diversity and pathological response. Exploratory analysis will include the assessment of the association between cf-DNA and the GM diversity as well as an assessment of the association between cf-DNA at baseline and pCR. 120 patients will be recruited over 18 months. Species richness (Alpha Diversity) will be analysed using the Shannon diversity index and Jaccard similarity index will be used to calculate beta diversity. Following planned study recruitment, classification and clustering analysis will be performed with Principal Component Analysis (PCA) and Random Forest analysis. To assess the primary endpoint the association between GM and complete pathological response will be examined using logistic regression analysis adjusting for potential confounding factors in the final statistical analysis. Adjusted odds ratios (OR) and 95% confidence intervals will be presented. This is expected to read out in early 2025. Recruitment is ongoing, with 14 pts recruited to date. We demonstrate that it is feasible to accrue to translational studies in Ireland and we have streamlined screening and recruitment pathways to improve our methodology and recruitment numbers. Research Sponsor: Science Foundation Ireland (18/SP/3522) and Breakthrough Cancer Research, under the Precision Oncology Ireland research program.

TPS3189 **Poster Session**

Phase I/II study of pegylated arginine deiminase (ADI-PEG 20) in combination with gemcitabine and docetaxel in non-small cell and small cell lung cancers.

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Background: Arginine is essential to neoplastic growth and development, yet many cancer cells do not express argininosuccinate synthetase (ASS1), an enzyme necessary to produce arginine. ADI-PEG 20 is a microbial enzyme that degrades arginine causing arginine auxotrophy in cancer cells that are ASS1 negative. Preclinical data suggests that ADI-PEG 20 in combination with docetaxel (D), resulted in increased expression of hENT, the transporter for gemcitabine (G) as well upregulation of dCK to trap G inside of cancer cells. A phase II trial of ADI-PEG 20, G and D was shown to be a safe and efficacious combination in soft tissue sarcoma (STS). We are conducting a phase I/II trial examining the safety, tolerability, to determine the recommended phase II dose (R2PD) and evaluate the efficacy of this combination in patients with previously treated metastatic non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) with an alternative dosing regimen than that used in STS based on the mechanism of action. **Methods:** Eligible pts include previously treated metastatic NSCLC and SCLC with performance status 0-1 with adequate organ function. Pts are excluded if previously treated with G; however, prior use of docetaxel is permitted. Up to 12 patients will be enrolled in an open-label phase I trial with a 3 + 3 dose escalation design with ADI-PEG 20 in combination with G and D. Primary objectives of the phase I portion are to determine the safety, tolerability and recommend phase II dose (RP2D) of combination ADI-PEG 20, G and D. Pts will be treated with ADI-PEG 20 intramuscularly at 36mg/m^2 on day -7 of cycle 1 and then on days 1, 8, and 15 of each subsequent cycle with dose-escalated G (600, 750, 900 mg/m^2) on day 2 and D (60, 75, 75 mg/m^2) on day 1 of each 21-day cycle for up to 8 cycles then will continue with combination therapy at provider discretion for up to 34 cycles. The phase II will consist of two cohorts (NSCLC and SCLC) receiving the triplet treatments at the RP2D determined during phase I. Primary objective of the phase II portion is to determine the objective response rate (ORR) in each cohort. Phase II uses a Simon optimal two-stage design per cohort for ORR with a minimum of 12 patients and a maximum of 36 patients per cohort. In the phase I, patient accrual at the maximum tolerated dose level is nearing completion and ADI-PEG in combination with G and D will be further evaluated in the phase II with separate cohorts for NSCLC and SCLC. Clinical trial information: NCT05616624. Research Sponsor: Polaris.

TPS3190 **Poster Session**

A phase 1/1b first-in-human (FIH) study of JZP898 as monotherapy and in combination with pembrolizumab in adult patients with advanced or metastatic solid tumors.

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Background: JZP898 is a conditionally activated prodrug of interferon alpha (IFNα) that can preferentially deliver IFNα to the tumor microenvironment while potentially minimizing systemic IFNα therapy-associated toxicity. Antitumor activity of IFNα is well-established, but concerns regarding systemic toxicity restrict its use in clinical practice. JZP898, in combination with a checkpoint inhibitor such as pembrolizumab, may provide lasting and potent antitumor activity with minimal additive toxicity attributed to conventional or pegylated IFNα. This phase 1 FIH study will determine a maximum tolerated dose (MTD)/recommended dose (RD) and investigate safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary antitumor activity of JZP898 monotherapy and JZP898 combined with pembrolizumab in adult patients with advanced or metastatic solid tumors. **Methods:** This phase 1, FIH, open-label, multicenter study (NCT06108050) is investigating JZP898 intravenous infusion in adult patients (≥18 years old) with histological or cytological diagnosis of advanced or metastatic solid tumors, European Cooperative Oncology Group performance status ≤1, and measurable disease per RECIST v1.1 criteria. The study consists of a dose finding phase (JZP898 as monotherapy and in combination with pembrolizumab; Part A) and a combination dose expansion phase (JZP898 in combination with pembrolizumab; Part B). In Part A (dose finding), the JZP898 MTD and/or monotherapy RD will be determined using Bayesian optimal interval (BOIN) design based on the incidence of dose-limiting toxicities (DLTs) and all available safety and PK data; the combination recommended phase 2 dose (RP2D) will be determined using BOIN criteria and all available safety, PK/PD, immunogenicity, and preliminary signal of antitumor activity data. Patients will be treated until disease progression, death, unacceptable toxicity, or withdrawal from the study. All patients will be followed for survival until 18 months after the last patient starts study intervention. Primary endpoints include: the incidence and nature of DLTs (Part A); investigator-assessed objective response rate (ORR) per RECIST v1.1 (Part B); the incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events; changes in laboratory values or vital signs; and the incidence of dose modifications or discontinuations due to TEAEs. Secondary endpoints include: PK parameters; incidence of antidrug antibodies; investigator-assessed duration of response; progression-free survival; disease control rate; investigator-assessed ORR (Part A); and overall survival (Part B). The study is actively enrolling patients with a planned enrollment of up to 177 patients. Clinical trial information: NCT06108050. Research Sponsor: Jazz Pharmaceuticals.

TPS3191 Poster Session

A first-in-human (FIH), phase 1/2, dose-escalation, dose-optimization, and dose-expansion study of PARP1-selective inhibitor IMP1734 in participants with advanced solid tumors.

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Background: PARP inhibitors (PARPi) selectively kill tumor cells harboring genetic mutations in critical DNA repair genes (e.g., BRCA1/2). While several approved nonselective PARPi have provided robust anti-tumor activity, they are associated with significant hematologic toxicities that limit dose intensity and clinical benefit. Drugs that selectively inhibit PARP1 but spare PARP2 may improve the risk-benefit profile for this class of therapies by retaining anti-tumor activity while avoiding PARP2-related toxicities. IMP1734 (EIK1003) is a potent PARP1-selective inhibitor that inhibits tumor growth in nonclinical models and may widen the therapeutic index in tumors where non-selective PARPi have demonstrated efficacy. **Methods:** Study EIK1003-001 (IMP1734-101) is a global, multi-center, Phase 1/2 study evaluating the safety and potential antitumor activity of IMP1734 in participants with advanced solid tumors. The study has 3 parts: Part 1 (FIH; Dose Escalation), Part 2 (Dose Optimization), and Part 3 (Dose Expansion at the recommended dose for expansion [RDE]). Part 1 of this study is currently enrolling and consists of dose escalation of IMP1734 in study participants with advanced/recurrent/metastatic ovarian, breast, or prostate cancer with suspected deleterious/deleterious mutations in a pre-specified panel of homologous recombination repair (HRR) genes (n = 70). Eligible participants must be $\geq$ 18 years of age, have histologically or cytologically confirmed tumors as indicated in each study part, and at least 1 RECIST v1.1-measurable lesion and/or pre-specified serum tumor-specific marker. All participants must have a deleterious or suspected deleterious mutation in select HRR genes. Primary endpoints include safety and tolerability (evaluation of dose-limiting toxicities and determining the maximum tolerated dose, maximum achievable dose, and RDE). Secondary endpoints include evaluation of the pharmacokinetic parameters of IMP1734 and measures of efficacy, including overall response rate, duration of response, progression-free survival, and overall survival. Exploratory endpoints include analysis of pharmacodynamic biomarkers, serial ctDNA measurements, and patient quality-of-life measures. This study opened on 11 Dec 2023. Clinical trial information: NCT06253130. Research Sponsor: Eikon Therapeutics, Inc.