Lete-cel in patients with synovial sarcoma or myxoid/round cell liposarcoma: Planned interim analysis of the pivotal IGNYTE-ESO trial.

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Background: Letetresgene autoleucel (lete-cel) is an autologous engineered T cell receptor therapy targeting the NY-ESO-1 cancer testis antigen highly expressed in synovial sarcoma (SyS) and myxoid/round cell liposarcoma (MRCLS). Lete-cel pilots showed promising efficacy in patients (pts) with NY-ESO-1–expressing SyS or MRCLS. We report the planned interim analysis (IA) of IGNYTE-ESO substudy 2 (SS2). **Methods:** IGNYTE-ESO is an ongoing, international, open-label Phase 2 trial (NCT03967223). SS2 planned enrollment/apheresis of ~87 human leukocyte antigen (HLA)-A*02:01, *02:05, or *02:06-positive pts aged ≥10 years with NY-ESO-1–expressing (≥30% staining at 2+/3+ per IHC) metastatic or unresectable SyS or MRCLS, with a 0–1 ECOG PS. Pts must: have started/received anthracycline based chemotherapy before apheresis, have progression on their last prior line of therapy (bridging therapy excluded) and measurable disease per RECIST v1.1 before lymphodepletion (LD). LD (fludarabine 120 mg/m^2, cyclophosphamide 2700–3600 mg/m^2, cumulative) was dose reduced for predefined risk factors. Dose range: (1–15)×10^9 transduced cells. Primary endpoint: overall response rate (ORR) per RECIST v1.1 by central independent review. IA efficacy population: the 1st 45 evaluable pts who had ≥6 months follow-up. Safety population: pts who had received lete-cel at time of the IA. Pre-defined success criterion at IA: 14 responders of 45 evaluable pts with ≥6 months follow-up. Primary analysis occurs when the 60th dosed pt has 12 months follow-up. **Results:** As of the March 2, 2023 IA, 98 pts were apheresed, 73 pts received lete-cel (safety) and 45 pts were evaluable for efficacy. Median age was 46.0 years (range 18–68), 23 (51%) had SyS. Median transduced cell dose was 6.40×10^9 cells (range 2.1–11). ORR: 18 of 45 (40%, multiplicity-adjusted 99.6% CI: 20.3%, 62.3%) pts by independent review (2 CR, 16 PR); 9 of 23 (39%) for pts with SyS, 9 of 22 (41%) for pts with MRCLS. Median duration of response: 10.6 months (95% CI: 3.3, NE; data are immature with 12 of 18 pts censored). Adverse events (AEs) were consistent with those previously observed with lete-cel. Most common AEs (all grades) were cytokine release syndrome (CRS) in 65 (89%), neutropenia in 53 (73%), thrombocytopenia in 46 (63%), rash in 39 (53%), anemia in 38 (52%) and leukopenia in 36 (49%) pts. Grade ≥3 cytopenias occurred in 63 (86%) pts, including grade 5 neutropenia in 1 (1%) pt. 9 (12%) pts had grade 3 CRS and 17 (23%) pts had grade 3 rash (no grade 4 or 5 in either). Immune effector cell-associated neurotoxicity (ICANS) occurred in 3 (4%) pts; all grade 1. **Conclusions:** IGNYTE-ESO SS2 met the primary endpoint success criterion at this planned IA, with a 40% ORR consistent across SyS and MRCLS, and a known safety profile of hematologic toxicity and CRS. This supports the potential of lete-cel as a novel therapy for pts with advanced or metastatic SyS and MRCLS. Clinical trial information: NCT03967223. Research Sponsor: GlaxoSmithKline and Adaptimmune.

Claudin18.2-targeted chimeric antigen receptor T cell-therapy for patients with gastrointestinal cancers: Final results of CT041-CG4006 phase 1 trial.

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Background: Autologous anti-claudin18.2 (CLDN18.2) CAR T cell, satricabtagene autoleucel (satri-cel)/CT041, was investigated in gastrointestinal cancers in clinical trials. The interim results of CT041-CG4006 trial (NCT03874897) were published in June 2022 [1]. Herein, we present the final results of this trial. **Methods:** This single-arm, open-label, phase 1 trial evaluated the safety and efficacy of CT041 in patients (pts) with CLDN18.2-positive advanced gastrointestinal (GI) cancers. The trial consisted of a dose-escalation (250×10^6, 375×10^6, 500×10^6 or 1000×10^6cells) using modified '3+3' design and dose expansion of CT041 in 4 cohorts (Cohort 1: CT041 in pretreated pts with advanced GI cancers, Cohort 2: CT041 plus anti-PD-1 therapy in pretreated pts with advanced GI cancers, Cohort 3: CT041 sequential treatment following first-line therapy in gastric cancer (GC) and Cohort 4: CT041 in pts with prior failure to anti-CLDN18.2 antibody). The primary endpoint was safety; secondary endpoints were efficacy using RECIST v1.1, pharmacokinetics, and immunogenicity. **Results:** From 26 March 2019 to 26 January 2024, a total of 98 pts received CT041 infusion, including GC (n=73), pancreatic cancer (n=10), biliary tract cancer (n=4), intestinal cancer (n=8) and other tumors (n=3). A total of 89 pts were dosed with 250×10^6, 6 pts with 375×10^6, and 3 pts with 500×10^6 cells, with a median follow-up of 29.7 (range: 1.2, 35.5) months. 250×10^6 was selected for the dose-expansion stage based on the dose-escalation results. The most commonly reported treatment-emergent adverse events of grade 3 or higher were hematologic toxicity related to lymphodepletion. No dose-limiting toxicities, treatment-related deaths, or immune effector cell-associated neurotoxicity syndrome were reported. Cytokine release syndrome occurred in 96.9% of pts, all classified as grade 1-2. Gastric mucosal injuries were identified in 8 (8.2%) pts, including 7 cases of grade 1-2 and 1 case of grade 3 gastritis erosive which recovered. For all pts (N=98), the ORR and DCR reached 37.8% and 75.5%, respectively. The median PFS and median OS were 4.4 (95% CI: 4.0, 6.0) months and 8.4 (95% CI: 7.0, 10.0) months for all pts. Among efficacy evaluable GC pts who received CT041 monotherapy, the ORR and DCR in those with measurable disease (n=47) reached 57.4% and 83.0%, respectively, and the median PFS and median OS in all efficacy evaluable GC pts (n=55) were 5.8 (95% CI: 4.2, 8.4) months and 9.7 (95% CI: 7.1, 14.4) months, respectively. **Conclusions:** Satri-cel/CT041 demonstrated a promising safety profile and highly encouraging efficacy in heavily pretreated patients with CLDN18.2-positive advanced GI cancers. Clinical trial information: NCT03874897. Research Sponsor: CARsgen Therapeutics Co., Ltd.

A potential best-in-class BCMA-CD19 bispecific CART with advanced safety by self-inhibiting IFNG signaling during CRS.

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Background: CART cells have demonstrated remarkable clinical efficacy in treating hematological cancers. However, CRS remains as a major challenge in clinical application, with multiple cytokines significantly elevated. IL6 signaling blockade by Tocilizumab has become a standard treatment to relieve CRS in patients. Our previous studies suggested that CAR T secreting IL6 antagonist could effectively maintain IL6 at very low levels during CRS. Furthermore, we observed that a huge quantity of tumor cells in one patient was significantly reduced after CART infusion, but a low level of IFNG with only grade 2 CRS was present. Therefore, we hypothesized that high level of IFNG might not be necessary to CART clinical efficacy and direct blockade of IFNG signaling by CART secreting an IFNG antagonist (designated as SAFET) serves an interesting approach to effectively reduce CRS toxicity. Although IFNG is usually thought important in T cell cytotoxicity, our results indicated that IFNG KO or autonomous secretion of IFNG antagonist did not affect the killing activity of CART cells. **Methods:** This pilot phase 1 study of SAFET BCMA/CD19 BiCART self-inhibiting IFNG signaling is a single arm study conducted in China, enrolling refractory/relapsed multiple myeloma patients. The patients had received more than 3 lines of prior therapies including at least a proteasome inhibitor and an immunomodulatory agent and were refractory to the last line of treatment. Lymphodepletion was performed with fludarabine and cyclophosphamide prior to the CART infusion. Following 2-14 days of rest, patients received a single infusion of SAFET BCMA/CD19 BiCART, at the dose of $0.4\text{-}1.0 \times 10^8$ CAR+ T cells/patient. The primary objectives of this study were to evaluate the safety and efficacy of SAFET BCMA/CD19 BiCART. The pharmacokinetics of SAFET BCMA/CD19 BiCART was investigated by quantitative PCR based detection of CAR vector copies in peripheral blood. Minimal residual disease (MRD) negativity was assessed by standardized multicolor flow cytometry analysis of bone marrow aspirate. **Results:** 10/11 R/R MM patients achieved CR and 1 achieved VGPR. Among the 10 CR patients, 7 remained CR after treatment with a median PFS 858 days; 1 patient showed relapse at Days 215; 2 patients showed MRD positive relapse at Days 637 and 733, and then received KRd and/or Kd treatment to achieve SD and MRD negative CR. Interestingly, the remarkable short and long term remission suggested that CART self-inhibiting IFNG signaling did not impair the CART clinical efficacy. Notably, minimal CRS was observed, including 6 grade 0, 2 grade 1, 2 grade 2, and 1 grade 3 who displayed mild transient hypotension for only 1 day while there were 79.5% blast tumor cells in the bone marrow before CART therapy. **Conclusions:** These results suggest BCMA-CD19 bispecific CART self-inhibiting IFNG signaling is promising in translation to a best-in-class treatment for MM. Clinical trial information: ChiCTR2000032124. Research Sponsor: None.

2503 Oral Abstract Session

A phase 1/2 study of REGN7075 in combination with cemiplimab (cemi) in patients (pts) with advanced solid tumors: Efficacy and safety results.

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Background: REGN7075, a first-in-class costimulatory bispecific antibody (bsAb), aims to restore immune sensitivity in traditionally non-immunoresponsive tumors by bridging CD28+ T cells with EGFR-expressing tumor cells (unlike other bsAbs that target CD3), facilitating T-cell activation through endogenous tumor antigens. A first-in-human, open-label, Phase 1/2 study (NCT04626635) of REGN7075 (EGFR×CD28) ± cemi (anti–PD-1) in pts with advanced solid tumors was conducted, consisting of a dose escalation (Part 1) and dose expansion (Part 2) phase. This is the first report of efficacy data (Part 1) for this costimulatory bsAb EGFR×CD28 with a novel mechanism of action. **Methods:** In Part 1, pts with metastatic/locally advanced solid tumors who had exhausted standard treatment options received REGN7075 QW/Q3W + cemi Q3W, including a 3-week REGN7075 monotherapy QW lead-in. Primary objective: assess safety and tolerability of REGN7075 ± cemi; secondary objectives: PK characterization (REGN7075 ± cemi), preliminary efficacy (REGN7075 + cemi), and immunogenicity of REGN7075 and cemi. Biomarkers were also evaluated. **Results:** At Part 1 data cutoff (Oct 13, 2023), 94 pts (median age, 55.0 years; 48.9% female) were treated with REGN7075 up to the 900 mg IV dose. Most pts (65%) had microsatellite stable colorectal cancer (MSS CRC). Of the 15 pts with MSS CRC without liver metastases treated with active REGN7075 doses (≥100 mg), ORR was 20% and disease control rate was 80% (CR, n=1; PR, n=2; SD, n=9). After data cutoff, 1 additional pt with liver metastases achieved PR. No dose-limiting toxicities (DLTs) were reported; maximum tolerated dose was not reached. Most TRAEs were Grade 1–2; >95% of infusion-related reactions (IRRs) were Grade 1–2. IRRs were manageable with premedication and split/step-up dosing. One pt experienced cytokine release syndrome (CRS; Grade 1 fever). No treatment-related deaths were reported. REGN7075 concentration in serum increased more than dose-proportionally at the dose range studied (0.03–900 mg).T-cell activation-associated IFN-γ was observed with monotherapy lead-in and combination dosing. **Conclusions:** MSS CRC is historically unresponsive to immunotherapy. REGN7075 is one of the first immune therapies to demonstrate clinical activity in pts with MSS CRC (including a pt with liver metastases), and dose escalation was completed through 900 mg with an acceptable safety profile and no DLTs. One pt experienced Grade 1 CRS, demonstrating differentiation from CD28 superagonists and CD3-targeting bsAbs. IRRs were mitigated with premedication and split/step-up dosing. Efficacy data in non-immunoresponsive tumors, along with encouraging pharmacodynamic evidence, suggest that REGN7075 can enhance immune response and anti-tumor immunity. Initiation of dose expansion (Part 2) in select tumor cohorts with different EGFR levels is planned. Clinical trial information: NCT04626635. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Efficacy and safety of LM-108, an anti-CCR8 monoclonal antibody, in combination with an anti-PD-1 antibody in patients with gastric cancer: Results from phase 1/2 studies.

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Background: Targeting tumor-infiltrating regulatory T cells (Tregs) is a potential approach to overcome immunotherapy resistance in the treatment of cancers. LM-108 is a novel Fc-optimized, anti-CCR8 monoclonal antibody that selectively depletes tumor-infiltrating Tregs. Here we report a pooled analysis of results from 3 phase 1/2 studies (NCT05199753; NCT05255484; NCT05518045) to evaluate the efficacy and safety of LM-108 in combination with anti-PD-1 therapy in patients with gastric cancer. **Methods:** Eligible patients with gastric cancer treated with LM-108 in combination with an anti-PD-1 antibody were included in the analysis. Patients received intravenous LM-108 at dose levels of 3 mg/kg Q2W, 6 mg/kg Q3W, or 10 mg/kg Q3W plus an anti-PD-1 antibody (intravenous pembrolizumab 200 mg Q3W or 400 mg Q6W or toripalimab 240 mg Q3W). The primary endpoint was investigator-assessed ORR per RECIST v1.1. The secondary endpoints included safety, other efficacy outcomes, and biomarkers analysis. Data cutoff date for the pooled analysis was December 25, 2023. **Results:** Forty-eight patients with gastric cancer (median age: 60.5 years; male: 72.9%) from China, USA, and Australia were treated ≥ 1 dose of LM-108 in combination with pembrolizumab or toripalimab. Most (n = 47, 97.9%) patients had received at least 1 prior anticancer treatment, and 43 (89.6%) had received prior anti-PD-1 therapy. Treatment-related adverse events (TRAEs) occurred in 39 (81.3%) patients, in which the most common events (≥15%) were alanine transaminase increased (25.0%), aspartate transaminase increased (22.9%), white blood cell decreased (22.9%), anemia (16.7%). Grade ≥ 3 TRAEs occurred in 18 (37.5%) patients, the most common events (≥ 4%) were anemia (8.3%), lipase increased (4.2%), rash (4.2%), and lymphocyte count decreased (4.2%). Among 36 efficacy-evaluable patients across all regimens, ORR was 36.1% (95% CI 20.8%–53.8%) and DCR was 72.2% (95% CI 54.8%–85.8%). The median PFS was 6.53 months (95% CI 2.96–NA). Among 11 patients whose disease had progressed on first-line treatment, ORR was 63.6% (95% CI 30.8%–89.1%) and DCR was 81.8% (95% CI 48.2%–97.7%). Of the 11 patients who progressed on first-line treatment, 8 had high CCR8 expression. Among these 8 patients, ORR was 87.5% and DCR was 100%, with 1 CR, 6 PR, and 1 SD observed. **Conclusions:** LM-108 in combination with an anti-PD-1 antibody showed promising antitumor activity in patients with gastric cancer that was resistance to anti-PD-1 therapy. The combination therapy was well tolerated. These results support further evaluation of LM-108 in CCR8 positive gastric cancer. Clinical trial information: NCT05199753; NCT05255484; NCT05518045. Research Sponsor: LaNova Medicines Limited.

2505 Oral Abstract Session

First-in-human study (FIH) of FS222, a next-generation tetravalent PD-L1/CD137 bispecific antibody: Safety, pharmacodynamics (PD), and antitumor activity in patients (pts) with advanced solid tumors including PD-1 refractory melanoma.

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Background: Most pts receiving immune checkpoint inhibitors do not respond to treatment or relapse. FS222 is a novel affinity optimized, tetravalent bispecific PD-L1/CD137 antibody. FS222's structure allows for potent, PD-L1-dependent, CD137 activation across a wide range of dose levels, and is designed to provide selective CD137 agonism in the tumor. We present data from the ongoing, FIH, open-label, phase I trial of FS222 in advanced solid tumors. **Methods:** Pts with pretreated advanced solid tumors received increasing doses of FS222 in an accelerated dose titration and 3+3 design intravenously every 3 or 4 weeks (Q4W) until disease progression or unacceptable toxicity. The primary endpoint was safety. Secondary and exploratory endpoints included pharmacokinetics, PD and antitumor activity (by Response Evaluation Criteria in Solid Tumors [RECIST] 1.1). **Results:** As of data cut off (DCO) on 05Dec2023, a total of 104 pts had been treated across a range of doses and schedules in the FIH study (NCT04740424). We report interim results from the Q4W cohorts (N=90). Patients had a median age of 61 years (31-88 years) and had received a median of 2 (1-7) regimens of prior treatments. The median duration of exposure to FS222 was 82.5 days (24 – 529 days). The most common treatment-related AEs (TRAEs; >20% of pts) were increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), pyrexia, thrombocytopenia, asthenia, and neutropenia. The most common TRAEs grade ≥3 (≥10% of pts) were increased AST (13.3%) and ALT (11.1%). The most common treatment related serious AEs (≥3 pts) were febrile neutropenia (5 pts, 5.6%); and pyrexia, cytokine release syndrome, increased ALT, increased AST (all in 3 pts, 3.3%). On-target FS222 pharmacology was confirmed by the presence of dose-dependent target engagement, significant peripheral $CD8^+$ T cell modulation and increased tumor $CD3^+$ $CD8^+$ T cells at multiple dose levels. At the DCO, 20 (22.2%) pts remained on treatment. Objective responses (CR, PR) were observed in pts with melanoma, NSCLC, ovarian cancer, TNBC, liposarcoma and colon cancer, for an ORR of 15.7% with evidence of further enrichment by dose. In post-PD-1 treated metastatic/advanced cutaneous melanoma the ORR was 60% (9/15, all PRs - 7 confirmed) and the disease control rate was 86.7% (13/15). **Conclusions:** The novel PD-L1/CD137 bispecific antibody FS222 demonstrated PD activity across a broad range of doses. The safety profile was acceptable and manageable. Encouraging anti-tumor activity was observed, including in patients with PD-1 refractory cutaneous melanoma. Next steps include further dose optimization and further evaluation of FS222 in patients with melanoma and other tumor types. Clinical trial information: NCT04740424. Research Sponsor: Invox Pharma.

Phase 1/2 study of the TGF-β-trap-enhanced oncolytic adenovirus, AdAPT-001, plus an immune checkpoint inhibitor for patients with immune refractory cancers.

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Background: The benefit of immune checkpoint inhibition is limited to 20-40% of patients. Moreover, acquired resistance often arises. Also, certain tumor types like breast are more CI-refractory. Therefore, the focus is on new combination strategies to increase clinical benefit. This multicenter phase 2 trial evaluated AdAPT-001, an oncolytic adenovirus armed with a "TGF-β trap" that neutralizes the immunosuppressive cytokine, TGF-β, +/- a checkpoint inhibitor (CI) in resistant patients some of whom previously failed a CI. **Methods:** Eligible patients with refractory tumors, many of them sarcomas, received 1 or more intratumoral injections of AdAPT-001 at dose level 1×10^{12} viral particles every 2 weeks +/- a CI at Investigator discretion. The CI was administered every 2^{nd}-3^{rd} week. Adverse events were recorded and managed. The primary endpoints of this combination therapy were objective response rate (ORR) and progression free survival (PFS). **Results:** 36 patients (22 males and 14 females) enrolled with a median age of 60.8 years (range 23-86) from Feb 2023-Dec 2023. 24/36 enrolled patients received AdAPT-001 with a CI and 12 patients received AdAPT-001 single agent. The most common treatment related adverse events (TRAE) were transient flu-like symptoms (fever, chills, vomiting, fatigue) 10/36 (27.7%), and injection related events 10/36 (27.7%). Notably, only 1 patient, 1/24 (4.0%), developed an immune-related AE, hypophysitis. All other related AEs were Grade 1/2. 33/36 patients were evaluable for response analysis; monotherapy produced 2/9 (22.2%) favorable responses (complete response (CR): eccrine carcinoma; confirmed partial response (cPR): acral melanoma); and produced a 4/9 (44.4%) clinical benefit rate defined as CR/PR/SD greater than 12 weeks. The combination of AdAPT-001 plus a CI produced 7/24 (29.1%) favorable responses (1 clinical CR: angiosarcoma; 6 cPRs: 3 sarcoma, 1 triple negative breast cancer, 1 head and neck cancer, 1 squamous cell carcinoma; and a 15/24 (62.5%) clinical benefit rate defined as CR/PR/SD greater than 12 weeks. 21/33 failed a CI before enrollment (16/24 before AdAPT-001 + CI). The PFS was 3.5 months (95% CI: 1.8-NA months). **Conclusions:** Combination therapy of AdAPT-001 with a CI is well tolerated and demonstrates a high ORR including 1 patient with a CR per RECIST 1.1, 1 patient with a clinical CR and 6 PRs. In several cutaneous sarcomas treated with AdAPT-001 plus a CI, radiologic SD belied how much better they looked visually—not only smaller, but less irregular and more circumscribed. Clinical trial information: NCT04673942. Research Sponsor: None.

Overall response rate and clinical benefit rates for AdAPT-001 monotherapy and combination with CI.

	AdAPT Monotherapy	Combination CI
Overall Response Rate	2/9 (22.2%)	7/24 (29.1%)
Clinical Benefit Rate	4/9 (44.4%)	15/24 (62.5%)
% of CI-refractory Responders	–	5/16 (31.2%)

2507 Oral Abstract Session

Phase 1 study (DRAGON) of SRK-181 (linavonkibart), a latent TGFβ1 inhibitor, combined with pembrolizumab in patients with anti-PD1 resistant advanced solid tumors: Updated results of expansion part.

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Background: Linavonkibart (LKT), also known as SRK-181, a fully human IgG4 monoclonal antibody, selectively inhibits latent transforming growth factor-beta isoform 1 (TGFβ1). TGFβ1 drives tumor immune escape by promoting an immunosuppressive pro-tumor microenvironment, including reducing antigen presentation, impairing T-cell infiltration, and tumor-killing activity. Previously, results from the dose escalation phase (3+3 design) of the ongoing open-label, phase 1 DRAGON study (NCT04291079) have showed antitumor activity with LKT + pembrolizumab (P). The combination was well tolerated with no dose limiting toxicity and the recommended dose for LKT is 1500mg q3W. **Methods:** In the Part B (expansion phase), LKT (1500mg q3w) + P were administered in melanoma (MEL), urothelial carcinoma (UC), and non-small cell lung cancer (NSCLC) pts, who were non-responders to prior anti-PD-1; and in ccRCC and HNSCC pts, with disease progression on the most recent prior anti-PD-1.Biomarker analyses include immunohistochemistry and flow cytometry. **Results:** As of 12 Jan 2024, 72 pts (29% females, median age of 65 years) were enrolled in Part B. All pts received at least one anti-PD-1 therapy with median prior lines of therapies of 3 (range 1-9). All ccRCC and all but 2 HNSCC pts had a best response of SD or PD on prior anti-PD-1. All these patients had progressed on the most recent anti-PD-1. None of the MEL, UC and NSCLC pts had a response to prior anti-PD-1. The most common treatment-related AEs (TRAE, ≥10%) of any grade were rash (23.6%), pruritus (20.8%), fatigue (19.4%) and diarrhea (12.5%). Grade 3 TRAE (≥5%) were rash (8.3%). Only 1 grade 4 TRAE (dermatitis exfoliative generalised) occurred. No grade 5 TRAE and no treatment-related SAE (≥2% [1 pt]) was observed. Efficacy results are presented in the table below. Tumor assessments were based on RECIST 1.1 criteria by PI assessment. Biomarker results showed decreased circulatory myeloid derived suppressor cell levels and increased CD8+ infiltration into tumors across multiple tumor types, indicating enhanced proinflammatory microenvironment. **Conclusions:** Combination treatment with LKT+P is associated with enhanced proinflammatory microenvironment with promising efficacy in anti-PD-1 resistant pts across multiple tumor types with manageable safety profile. The result supports LKT as a potential treatment to overcome immune checkpoint inhibitor-associated resistance. Clinical trial information: NCT04291079. Research Sponsor: Scholar Rock, Inc.

Enrolled pts (n)	ccRCC (N=30)	HNSCC (N=9)	MEL (N=11)	UC (N=11)	NSCLC (N=11)
Efficacy Evaluable pts[1] (n)	30	6	10	11	11
ORR	20%	33.3%	20%	9.1%	0%
PR (n)	6	2	2	1	0
Tumor Reduction	38.8% -98.2%	35.9% -48%	41% -56.3%	39%	–
DoR[2] (months)	0.7+~17.9+	0.1~1.4+	3.8+~7.1+	13.2+	–
SD (n)	11	1	5	4	3

[1]Ongoing pts are pending first post-treatment radiographic evaluation are not efficacy evaluable.
[2]DoR: duration of response.

LBA2509 **Clinical Science Symposium**

Atezolizumab in patients (pts) with tumor mutational burden (TMB)—high tumors from the TAPISTRY trial.

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Prognostic and predictive value of ultrasensitive ctDNA monitoring in a metastatic pan-cancer cohort treated with immune checkpoint inhibitors in the context of phase 1 clinical trials.

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Background: Determining which patients will achieve clinical benefit from immune checkpoint inhibition (ICI) therapy remains an open question. Liquid biopsy tests to assess baseline and early dynamics of circulating tumor DNA (ctDNA) may allow clinicians to track response more granularly and predict ICI response or resistance prior to imaging. However, lack of sensitivity may hinder accurate detection of low ctDNA levels in tumors with low shedding rates or during substantial drops and clearance in response. **Methods:** This study represents a cohort of 175 patients with refractory metastatic tumors from 18 different cancer types, who received 1-3 successive lines of ICI treatment in the context of phase-1 clinical trials. Thus far, 609 plasma samples from 90 stage-IV cancer patients receiving immune checkpoint inhibitor (ICI) treatment have been processed. ctDNA was profiled using the NeXT Personal assay, a liquid biopsy platform that leverages whole-genome sequencing of tumor and normal samples to create custom, patient-specific panels that include up to 1,800 somatic variants. This enables the detection of molecular residual disease (MRD) down to a detection threshold of 1 part per million (PPM) of ctDNA. **Results:** NeXT Personal assay detected positive levels of ctDNA in 99% (81/82) of plasma baseline samples, with a wide dynamic range, extending from 4.2 PPM (~0.00042% TF) to ~640,000 PPM (~64% TF) (median limit of detection = 2 PPM, 0.0002% TF). Lower ctDNA values at baseline were correlated with increased duration of PFS (log-rank p=0.017, HR=0.57, 95% CI 0.36-0.91) and extended OS (log-rank p=0.002, HR=0.46, 95% CI 0.28-0.75). Early reduction in ctDNA level from baseline to treatment cycle 3 was associated with significant increases in PFS (log-rank p=0.001, HR=0.36, 95% CI 0.19-0.67) and OS (log-rank p=0.015, HR=0.44, 95% CI 0.22-0.87), representing a >3-fold increase in both median PFS and OS. ctDNA clearance resulted in significant improvement in both PFS and OS (PFS: log-rank p=0.002, HR=0.24, 95% CI 0.09-0.62; OS: log-rank p=0.01, HR=0.29, 95% CI 0.1-0.8). All plasma timepoints from periods of durable complete response (CR) assessed via RECIST 1.1 were ctDNA-negative, with a molecular clearance lead time of 277 days over radiographically confirmed CR. **Conclusions:** We demonstrate that early ctDNA dynamics are predictive of long-term ICI response in the advanced, pan-cancer ECT setting. Even in this refractory advanced cancer cohort, an ultra-sensitive assay was required for accurate MRD status determination, with low ctDNA detections down to 4.2 PPM that might otherwise have been missed. Taken together, these findings suggest a high sensitivity ctDNA assay is crucial for accurate monitoring of ICI response, providing information for more accurate patient management. Research Sponsor: None.

CD8 radiomics signature to assess inter-lesion spatial heterogeneity and cold liver lesions in advanced non-small cell lung cancers treated with durvalumab.

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Background: The objective of this study was to assess whether a validated CD8 radiomics signature may help to evaluate patient inter-lesion heterogeneity and to predict the clinical outcome of advanced non-small cell lung cancers (NSCLC) patients treated with durvalumab in Study 1108 phase I/II trial (NCT01693562). **Methods:** Clinical data and imaging data from patients with naïve and pretreated advanced NSCLC who received durvalumab monotherapy were used. Radiomic features were extracted on contrast-enhanced CT scans and a validated CD8 radiomics signature was applied. A progressive lesion was defined by an increase in lesion longest diameter of 20% at 8 weeks. Dispersion metrics of the radiomics signature were estimated to evaluate the impact of inter-lesion heterogeneity on patient's response. **Results:** A total of 188 patients were included in this study, accounting for a total of 1137 lesions (median [IQR] = 4 [3 - 9] lesions per patient) evaluated at baseline using a radiomics approach. A low CD8 radiomics score at baseline was associated with a significantly higher risk of progression at the lesion-level (AUC=0.59, P-value$<$0.0001), and was especially performant for liver lesions (AUC=0.66, P-value=0.0002). At the patient level, the least infiltrated lesion of a patient according to the radiomics score of CD8 T-cells was positively associated with OS (HR=0.70, P-value=0.029) and PFS (HR=0.68, P-value=0.014), the highest values being associated with the best outcomes. 55 patients had liver lesions, with worse prognosis than patients without liver lesion (HR=2 for OS and PFS, P-value = 0.00012 and 0.00022 respectively). In these patients, the CD8 radiomic score enabled the stratification of patients according to hot and cold liver metastasis (HR=0.6, P-value=0.072 and HR=0.54, P-value=0.038 for OS and PFS respectively). A 4-class stratification of the whole cohort based on the least infiltrated (cold/hot) and liver or non-liver lesion was independently associated with clinical outcomes. These radiomics approaches have shown independent prognostic values when adjusting for PD-L1 status in multivariate analyses (Table). **Conclusions:** These results confirm the predictive value at a lesion level and the patient level of the biologically inspired CD8 radiomics score for advanced NSCLC patients treated with durvalumab. It has shown interesting results in discriminating outcomes of patients with liver lesions by identifying hot and cold lesions. Research Sponsor: Astrazeneca; ESR-17-13385; National Research Agency (ANR); ANR-21-RHUS-0005; Fondation pour la recherche médicale; DIC20161236437; Fondation ARC pour la recherche contre le cancer; SIGN'IT20181007805; SIRIC-SOCRATE 2.0; grant INCa-DGOS-INSERM_12551; Amazon AWS; Fondation BETTENCOURT-SCHUELLER; Ecole de l'INSERM.

	OS (HR [95%CI])	p	PFS (HR [95%CI])	p
PD-L1 expression: ≥25%	0.64 [0.45, 0.92]	0.015	0.58 [0.41, 0.82]	0.0020
Patient stratification by Liver-based CD8 RScore (vs Cold liver lesion)				
- Hot liver lesion	0.44 [0.22, 0.9]	0.024	0.40 [0.2, 0.79]	0.0084
- Cold non liver lesion	0.40 [0.23, 0.69]	0.0011	0.42 [0.24, 0.72]	0.0018
- Hot non liver lesion	0.40 [0.23, 0.68]	0.00084	0.35 [0.2, 0.61]	0.0002

2512 Clinical Science Symposium

High-dimensional longitudinal immune profiling uncovers a dual role of the CXCL9/CXCR3, CXCL13/CXCR5, and CCL11/CCL3 axis in the coupling of immune-related adverse events to immune checkpoint inhibitor response.

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Background: Additional characterization is required to understand the immune network signatures and immunophenotypes that link immune-related adverse events (irAEs) to immune checkpoint inhibitor (ICI) therapy responses in cancer patients. **Methods:** A comprehensive immune profiling analysis was conducted on whole blood and peripheral blood mononuclear cells (PBMC) from 165 oncology patients with various irAEs, including colitis (n=64), myocarditis (n=19), pneumonitis (n=25), arthritis (n=24), and cytokine release syndrome CRS (n=33), and compared to a cohort of 219 cancer patients prior to ICI treatment. **Results:** Following ICI therapy on cycle 2 day 1 (C2D1), we observed significant increases in IL-6, CCL2, CXCL9, CXCL10, and CXCL13 levels preceding irAEs. CXCL9 was specifically upregulated during the development of colitis, arthritis, CRS, and myocarditis, while CXCL13 increased only in CRS, and CCL3 only in myocarditis and CRS, with no CCL11 upregulation in any irAE. High levels of CXCL9, high CCL11 and low CXCL13 strongly correlated with improved oncologic outcomes in different irAEs. Compared to other cluster, in the high CXCL9 cluster, 5-year overall survival (OS) was significantly improved (HR = 10.26 [95% CI, 1.27-82.82], p = 0.029) in colitis (n=20), in CRS (n=21) (HR = 6.45 [95% CI, 1.60-25.99], p = 0.009), and in arthritis. In the high CCL11 cluster, 5-year OS was significantly improved in pneumonitis (n=15), (HR = 4.04 [95% CI, 1.05-15.46]). Conversely, in myocarditis, the high CXCL13 cluster (n=9) was associated with decreased 2-year OS (HR = 6.05 [95% CI, 1.03-35.48], p = 0.046). It is important to note that the CXCL9-driven immunophenotypes were characterized by low IL-6. Notable observations include CD38 upregulation and large-scale activation of CD8 memory subsets during ICI therapy, concomitant with increased circulation of immature neutrophils at the onset of irAEs diagnosis. This event may increase the migration of TCR$\gamma\delta$, NK, DC, and CD8 cells to tumor sites through CXCR3/CXCL9 interactions. **Conclusions:** This study unravels intricate connections between immune activation and tumor response. CXCL9, CCL11, and CXCL13 emerge as pivotal biomarkers bridging the gap between ICI therapy effectiveness and distinct irAEs-associated immunophenotypes. Research Sponsor: None.

Effects of neutralization of tumor-derived immunosuppressant GDF-15 on anti-PD-1 activity in anti-PD-(L)1 relapsed/refractory non-squamous NSCLC, urothelial, and hepatocellular cancer.

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Background: Growth and Differentiation Factor 15 (GDF-15) plays a critical role as potent, local immunosuppressant during pregnancy. Here we report for the first time data identifying GDF-15 as immunosuppressant in non-sq NSCLC, urothelial (UC) and hepatocellular (HCC) cancer and provide clinical evidence that GDF-15 blockade with visugromab can restore anti-PD1 activity in last-line, anti-PD1-(L)1 r/r patients with these tumors. **Methods:** A large translational research program, analyzing > 11.000 tumors in The Cancer Genome Atlas (TCGA) and paired serum/tumor samples for GDF-15 impact on the tumor microenvironment was conducted. In the GDFather ph2a first-in-human visugromab trial, subjects with advanced-stage, anti-PD1/PD-L1 relapsed/refractory (r/r) last-line solid tumors received the GDF-15 neutralizing antibody visugromab (CTL-002) at 10 mg/kg Q2W in combination with nivolumab 240 mg Q2W om three defined expansion cohorts (NSCLC:n=5 2, UC :n=34, HCC: n=16). All patients were either (1) primary refractory to or (2) relapsed on continued checkpoint inhibitor (CPI) therapy after initial response, with all patients having received minimum of 12 weeks of continuous prior anti-PD-1/-L1 exposure. Primary endpoint was ORR. **Results:** In in-silico TCGA analyses, an inverse correlation between GDF-15 mRNA expression and key immune-related signatures revealed potent immunosuppression of several solid tumors including non-sq NSCLC and UC by GDF-15. In addition, in newly diagnosed, early-line UC patient samples, correlation of GDF-15 serum levels with reduced density of CD8+ T cells and immune cell proliferation (CD45+ki67+) was demonstrated. In the ph2a trial, visugromab + nivolumab showed excellent overall tolerability in heavily pre-treated patients, with just 6.9% of patients experiencing CTCAE Grade ≥ 3 treatment-related adverse events across these three indications. The observed ORR as per RECIST v1.1 criteria was 13.5% (5/37, 4PR, 1CR) in non-sq NSCLC, and 0% (0/15) in sq-NSCLC, in line with the translational research data. In UC, ORR was 17.6% (6/34, 5 PR, 1CR), and in HCC 18.8% (3/16, 2PR, 1CR); with 25 pts continuing on treatment, respectively. Duration of response (DoR) is surpassing 12 months for non-sq and UC lead cohort patients (N = 27 each) already, and 10/14 responses are ongoing. **Conclusions:** These analyses presented identify GDF-15 as novel, potent immunosuppressant in the tumor microenvironment of non-sq NSCLC, UC and HCC and identify it as potential key cause for CPI resistance. In heavily pretreated, by strict criteria anti-PD-1/-L1 r/r, late/last-line patients with NSCLC, UC and HCC, neutralization of GDF-15 by visugromab in combination with nivolumab resulted in an ORR of 16.1% (14/87; 11 PR and 3 CR) across these indications and long durability. Clinical trial information: NCT04725474. Research Sponsor: Catalym GmbH.

Evaluation of mixed response in tumor size and survival in patients with rare cancers treated with dual checkpoint inhibitor therapy (DART SWOG S1609).

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Background: RECIST criteria evaluate changes in tumor burden and have been utilized in cancer research for decades. Changes in the sum of maximum diameters of "target" lesions are used to designate patients into response categories, including complete response, partial response, stable disease, and progressive disease. However, not much is known about the implications of mixed response, where lesions within a patient show contrasting responses to systemic treatment. Here we evaluate the data from the Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609 to investigate the association between mixed response and survival among patients treated with dual checkpoint inhibitor therapy. **Methods:** A total of 796 patients were enrolled on the S1609 DART trial, a basket trial evaluating ipilimumab plus nivolumab across solid rare tumor subtypes. All patients had RECIST-measurable disease at the study entry. Patients were excluded from the analyses due to: ineligibility, n=47; not receiving any protocol therapy, n=23; death before day 65 (landmark for analysis based on first scan), n=86; 1 target lesion, n=153. Thus, 487 patients were analyzed. A 5mm cut-off for increase/decrease in lesions was used to define a mixed response. Cox regression models were used to evaluate associations between survival (landmarked at day 65, stratified by basket) and response category (reference of Stable Disease). **Results:** 6 groups were identified among the 487 patients: no lesions changed more than 5 mm (n = 105), all lesions increased more than 5mm (n = 69), all lesions decreased more than 5mm (n = 39), one+ lesion increased more than 5mm and one+ lesion decreased more than 5 mm (n = 24), one+ lesion increased more than 5mm and one+ lesion did not change more than 5 mm (either direction) (n =155), one+ lesion decreased more than 5mm and one+ lesion did not change more than 5 mm (either direction) (n =95). Hazard ratios and median survival (mOS) are shown (Table). **Conclusions:** This is the first evaluation of the association between mixed response and survival outcomes among patients with various tumors receiving dual checkpoint therapy. Our results suggest that survival outcomes are driven by the "worst" performing lesion; in other words, having an increase in any lesion is associated with worse outcomes, even if not all lesions increase. Research Sponsor: None.

Group	N (%)	HR (95% CI)	P-value	mOS
No lesions changed > 5 mm (stable disease)	105 (22)	-	-	24mo
All lesions decreased > 5 mm	39 (8)	0.71 (0.44, 1.16)	0.17	36mo
One+ lesion decreased > 5 mm One+ lesion did not change > 5 mm (either direction)	95 (20)	1.23 (0.88, 1.71)	0.23	18mo
One+ lesion increased > 5 mm and one+ lesion decreased > 5 mm	24 (5)	2.83 (1.74, 4.6)	<0.001	6mo
One+ lesion increased > 5 mm and one+ lesion did not change > 5 mm (either direction)	155 (32)	2.25 (1.68, 3.02)	<0.001	9mo
All lesions increased > 5 mm	69 (14)	3.72 (2.59, 5.35)	<0.001	6mo

2515 Rapid Oral Abstract Session

Pan-tumor harmonization of pathologic response assessment for standardized data collection in neoadjuvant IO trials (PATHdata): Final analysis of a multi-institutional reproducibility study.

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Background: Immunotherapeutic agents are now being investigated for treating earlier-stage cancers. Radiographic assessment by RECIST, widely used to assess treatment response in clinical trials for advanced cancers, has limitations in the neoadjuvant setting; and pathologic response assessment is increasingly being used as a primary and/or secondary endpoint. To that end, a pan-tumor scoring system for assessing pathologic response was developed (1,2). This scoring system allows for the quantitative assessment of residual viable tumor (RVT) in multiple locations: i.e. primary and lymph node (LN) or distant metastases, akin to RECIST. %RVT scored using this system been associated with patient outcomes after treatment with anti-PD-1-based therapies. Additionally, %RVT in LN has been shown to have additive value to %RVT in the primary tumor when predicting patient survival (3). As a result, pathologists are now being asked to score pathologic response in the primary tumor and LN as a part of ongoing clinical trials and routine clinical care. Here, we evaluated the reproducibility of %RVT scoring using pan-tumor immune-related pathologic response criteria (irPRC). **Methods:** A multi-institutional, international study led by the Society for Immunotherapy of Cancer was initiated to assess the concordance of pathologic response assessment in resection specimens from patients treated with anti-PD-1-based therapies. Online lecture-based modules for irPRC scoring were developed, and 14 pathologists from multiple institutions, including academic and industry partners, were trained to score H&E-stained slides. The pathologists have scored n=37 pathology cases from resection specimens and on-treatment biopsies from >10 different tumor types, in part derived from phase II/III clinical trials. %RVT in the primary tumor and LN from patient specimens were scored separately (total of n=374 slides scored by each pathologist). **Results:** At the first interim analysis, scoring of pathologic response using irPRC was shown to be highly reproducible, irrespective of disease location (i.e. primary tumor vs lymph node metastasis). The second half of the study is nearing completion, and these reproducibility numbers will be finalized and presented in the final abstract. Extended analyses will also be presented that include subset analyses by tumor type. **Conclusions:** The results will be interpreted and presented in the context of the larger field for pathologic response assessment. A post-study survey completed by the participating pathologists will be used to refine irPRC training materials prior to dissemination to the wider immuno-oncology community. 1. Cottrell et al. *Ann Oncol*2018. 2. Stein et al. *Clin Can Res* 2020. 3. Deutsch, et al. *Nat Med* 2023. Research Sponsor: Society for Immunotherapy of Cancer; Bristol Myers Squibb; AstraZeneca; Merck.

2516 Rapid Oral Abstract Session

HLA associations with immunotherapy related endocrine toxicity.

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Background: Endocrine immune related adverse events (irAEs), including thyroid dysfunction (ICI-T), diabetes mellitus (ICI-DM) and hypophysitis (ICI-HP), caused by treatment with immune checkpoint inhibitors (ICIs) are largely irreversible and pose a burden to cancer patients. Variation in HLA predisposes to many autoimmune conditions, but data associating endocrine irAEs to HLA types is limited. **Methods:** We included 6300 patients from multiple centers across the United States, Canada, Europe and Australia who were treated with ICIs for multiple cancer types. The most common endocrine irAE in these patients was ICI-T (806 cases), followed by ICI-HP (163 cases) and ICI-DM (75 cases). Cases of ICI induced adrenal insufficiency were considered to be ICI-HP unless the patient had an elevated ACTH. Patients without the specific irAE were considered controls. Genotyping and HLA imputation were completed at each institution independently. Associations between HLA types and ICI-T, ICI-DM, and ICI-HP were tested in patients of European ancestry after adjustment for type of immunotherapy (PD-1/PD-L1 monotherapy, anti-CTLA-4 monotherapy, and combination), cancer type, sex, age and 5 principal components, at each center. The results were then meta-analyzed using fixed-effects inverse-variance weighted approach. False discovery rate (FDR) adjusted p-value of 0.05 was considered significant whereas those between 0.05 and 0.1 were considered nominally significant. **Results:** In the ICI-DM group, we identified 1 significant association with HLA DRB1*04:01 (OR=2.45, FDR=0.002) which is known to increase risk for type 1 DM (T1DM) in European ancestry. There were 5 additional nominal associations including DRB1*0301 (OR=2.16, FDR=0.07), a known HLA for T1DM in European ancestry. For ICI-HP, there were 7 significantly associated HLA types. Of particular interest are DRB1*14:01 (OR=3.98, FDR=0.02), DRB1*07:01 (OR=1.86, FDR=0.02) and C*07:02 haplotype (OR=1.79, FDR=0.02). While DR7 and DR14 are novel associations, C*07:02 is in linkage disequilibrium with DR15 and DQB1*06:02, both of which have previously been associated with ICI-HP. For ICI-T, there were no associated HLA types. **Conclusions:** In our study, we report HLA types associated with endocrine irAEs. In particular, we see HLA associations for ICI-DM that are known to be associated with T1DM. This suggests a potential shared mechanism between these forms of autoimmune DM. Additionally we found novel HLA associations with ICI-HP. These findings may have an impact on the clinical care of patients treated with ICI. However, further work is warranted to determine if HLA typing prior to ICI initiation should be considered for irAE risk prediction, irAE surveillance, irAE prevention, and possibly cancer treatment decisions. Research Sponsor: None.

Effect of fecal transplantation on patient reported outcomes after immune checkpoint inhibitor colitis.

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Background: The use of fecal microbiota transplantation (FMT) has traditionally been reserved for the treatment of recurrent Clostridioides difficile infections (CDI). As the gut microbiome has been increasingly acknowledged to play a role in a variety of bodily processes, FMT has seen its application extended to other gastrointestinal disorders. Immune-mediated colitis (IMC) is a similar entity to inflammatory bowel disease and arises as a side effect of immune checkpoint inhibitor therapy to stimulate the immune response. Treatment of IMC is mostly limited to immunosuppressants e.g. corticosteroids, infliximab, and vedolizumab. Cases refractory to such medications pose a significant challenge. FMT has been shown to be a successful treatment in refractory IMC in small case series, further large studies are needed to determine its efficacy. **Methods:** We measured the efficacy of FMT for refractory IMC among 37 patients via chart review and clinical assessment and patients' reported outcome (PRO) via established MD Anderson Symptom Inventory (MDASI). Among them, 9 patients had concurrent CDI as well at the time of diagnosis. **Results:** Fifty-nine patients were included in our study. Most patients had a peak diarrhea grade ≥ 3 (94.9%) and colitis grade ≥ 2 (91.5%). Ulcerous (26, 44.1%) and non-ulcerous (21, 35.6%) inflammation were the predominant endoscopic findings. Fifty-seven (96.6%) patients received corticosteroids, and 54 patients (91.5%) received add-on infliximab or vedolizumab. IMC symptom response was 84.7% after FMT with median time to response of 4 days. The transient complication rate is 30.5% at 7 days and 18.6% at 30 days. Response rate among the 50 patients without concurrent CDI was 86.0%. Fifty (84.7%) patients demonstrated clinical remission by the end of the study period, and 11 (18.6%) were able to resume ICI treatment, and among them, 9 patients remained in remission. A total of 10 patients (16.9%) in our cohort developed recurrent colitis after FMT requiring immunosuppression; 3 of these recurrent cases were triggered by ICI resumption. On the PRO analysis, we observed a favorable trend of significant patient-reported symptom reduction on diarrhea (61% to 11%, $p<0.01$) and abdominal bloating (36% to 7%, $p<0.05$) during 12 weeks after FMT. There was a 49.4% reduction of moderate to severe symptoms with only 44% of patients reporting such symptoms after 12 weeks (down from 89%, $p<0.01$). **Conclusions:** FMT may serve as a potential treatment option in IMC refractory to standard treatment to avoid long-term steroid dependency and immunosuppression. It is effective to maintain IMC remission with a low complication rate. The role of the gut microbiome in cancer and the implications for FMT remain uncertain and need further elucidation. Clinical trial information: NCT03819296. Research Sponsor: Gateway, Moonshot.

Phase I study of GUCY2C CAR-T therapy IM96 in patients with metastatic colorectal cancer.

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Background: The clinical outcomes of metastatic colorectal cancer (mCRC) therapies are limited, especially for liver metastasis. Guanylyl cyclase 2C (GUCY2C) is ectopically expressed in all stages of CRC and intestinally restricted. GUCY2C-targeted CAR-T (IM96) was developed and phase I study was conducted to evaluate the safety and efficacy (NCT05287165). **Methods:** In this open-label, 3+3 dose-escalation study, IM96 was evaluated in GUCY2C-positive mCRC patients (pts) failed to ≥3 lines of therapies. Pts were pre-treated with fludarabine and cyclophosphamide, and received a single infusion of IM96 at the dose of 3×10^8 (DL1), 6×10^8 (DL2), 12×10^8 (DL3), or 20×10^8 (DL4) CAR-T cells. Dose-expansion study was performed at DL3. The primary objectives were safety and toxicity, and the secondary objectives were efficacy and pharmacokinetic profile. **Results:** As of December 2023, 20 pts were enrolled and infused with IM96. The follow-up time was 7-19 months for all pts. The median age was 52.5, and 11/20 cases were male. Liver metastasis was found in 11/20 cases (55%), proficient mismatch repair (pMMR) in 20/20 pts (100%), *KRAS* mutation in 12/20 pts (60.0%), *NRAS* mutation in 1/20 pts (5.0%), and *BRAF* mutation in 3/20 pts (15.0%). Bridging therapies were used in 19 pts. Only 1/20 pt (5.0%) showed neurotoxicity and ≥grade 3 cytokine release syndromes (CRS). Grade 1-2 CRS occurred in 16/20 pts (80.0%) with dramatic increase of interleukin-6. Grade 1-3 rash was observed in 14/20 pts (70.0%). Grade 3 diarrhea occurred in 11/20 pts (55.0%), and grade 1-3 oral mucositis appeared in 7/20 pts (35.0%), only in DL2, DL3 and DL4 groups. Dose-limiting toxicity and maximum tolerated dose were not achieved. Among 19 evaluable pts, the disease control rate (DCR) was 73.7%, and the objective response rate (ORR) was 26.3%. In DL3 group, pts showed an ORR of 40.0%, nevertheless of liver metastasis or not. The median progression-free survival time was 7 months, and the median duration of response was 10 months in DL3 group. No responding pts showed disease progression within 6 months. Tumor responses were correlated with significant decreases in carcinoembryonic antigen levels among all pts. **Conclusions:** This study demonstrated that IM96 has durable efficacy with acceptable safety profile in pMMR mCRC pts, in particularly, showing high therapeutic potential in liver metastasis pts. Clinical trial information: NCT05287165. Research Sponsor: None.

2519 Rapid Oral Abstract Session

Safety and preliminary efficacy results of IBI389, an anti-CLDN18.2/CD3 bispecific antibody, in patients with solid tumors and gastric or gastro-esophageal tumors: A phase 1 dose escalation and expansion study.

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Background: CLDN18.2 expression has been observed in various solid tumors especially in gastric cancer, indicating its potential as a novel target for anti-tumor therapy. IBI389 is an anti-CLDN18.2/CD3 bispecific antibody that induces immune synapse formations by linking CD3 molecules in T-cell receptor complexes and CLDN18.2 antigens on the membrane of tumor cells. Herein, we report preliminary results from a phase I study to evaluate safety and efficacy of IBI389 in patients (pts) with advanced solid tumors. **Methods:** Eligible pts with advanced solid tumors who failed or were intolerant to standard treatments were enrolled. The dose escalation of IBI389 monotherapy used intra-patient dose escalation with accelerated titration and the classic 3+3 design (0.003 μg/kg to 600 μg/kg). Selected dose levels were expanded in pts with advanced gastric/gastroesophageal junction cancer (G/GEJ C) and pancreatic ductal adenocarcinoma (PDAC). The primary objective was safety. Secondary objective was efficacy assessed by investigator per RECIST v1.1 including objective response rate (ORR) and disease control rate (DCR). **Results:** As of January 9, 2024, a total of 114 pts were enrolled (males: 67.5%, median age: 60.0 years, G/GEJ C: 32.5%, PDAC: 57.9%, stage IV: 81.6%). No dose-limiting toxicity (DLT) was observed during dose escalation. The MTD was not reached. In all pts, treatment-emergent adverse events (TEAEs) occurred in 112 (98.2%) pts including 76 (66.7%) pts with grade ≥3 TEAEs. Treatment-related adverse events (TRAEs) occurred in 111 (97.4%) pts including 63 (55.3%) pts with grade ≥3 TRAEs. The most common grade ≥3 TRAEs (≥ 4%) were gamma-glutamyl transferase increased (21.9%), lymphocyte count decreased (13.2%) and nausea (4.4%). Cytokine release syndrome (CRS) related adverse events occurred in 65 (57.0%) pts including 1 (0.9%) pts with grade 3 CRS and no grade 4 or 5 CRS. TEAEs leading to dose interruption and treatment discontinuation occurred in 44 (38.6%) and 8 (7.0%) pts. Preliminary efficacy of IBI389 was observed in pts with CLDN18.2 expression ≥10% (immunohistochemistry 2+/3+). In G/GEJ C pts with previous treatments ≥2 lines receiving IBI389 at various dose levels ranging from 10μg/kg to 600 μg/kg (n=26), 8 pts had partial response (PR) and 11 pts had stable disease (SD). The ORR was 30.8% (95%CI: 14.3-51.8) and DCR was 73.1% (95%CI: 52.2-88.4). **Conclusions:** IBI389 showed manageable safety profiles in pts with advanced solid tumors and preliminary efficacy in CLDN18.2-positive pts with G/GEJ C. Clinical trial information: NCT05164458. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Phase I study of MCLA-145, a bispecific antibody targeting CD137 and PD-L1, in solid tumors, as monotherapy or in combination with pembrolizumab.

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Background: MCLA-145, a human common light chain bispecific antibody targeting CD137 and the PD-1/PD-L1 axis, is designed to enhance both antigen-mediated T cell activation via CD137 costimulation, and blockade of inhibitory PD-L1. Interim data from the ongoing phase 1 study (NCT03922204) are presented. **Methods:** Patients (pts) with PD-L1 ≥1% advanced/metastatic solid tumors received MCLA-145 IV as monotherapy Q2W/Q3W in 21/28-d cycles respectively, or in combination with pembrolizumab 200 mg Q3W in 21-d cycles. Pts enrolled in combination had cancers that either relapsed after PD-(L)1 therapies or were immunotherapy naïve. Primary objectives are safety, tolerability and dose-limiting toxicity (DLT) of MCLA-145 alone or combined with pembrolizumab, and determination of the recommended dose for expansion (RDE). Secondary endpoints include efficacy, pharmacokinetics, pharmacodynamics (PD) and immunogenicity. **Results:** As of a December 4, 2023 data cutoff, 72 pts with 26 cancer types were treated; 25% of pts had non-small cell lung cancer (NSCLC). 3 pts were continuing combination therapy. Monotherapy: 53 pts (median age 60 y, 49% male) were treated across 8 dose levels (47 pts 0.4-75 mg Q2W, 6 pts 40 mg Q3W). Median number of cycles was 2 (range 1-39). 6 pts had DLTs in the 25-75 mg dose range (febrile neutropenia [2 pts], hemolytic anemia, myositis, ALT/AST increase, neutrophil/platelet decrease [1 pt each]). Most common adverse events (AEs; all grades/G3-4) were fatigue (51%/4%), decreased appetite (34%/2%), dyspnea (32%/0%), anemia (30%/9%), ALT/AST increase (25%/11%), and pyrexia (25%/0%). The incidence of any G3-4 AE was lower with 40 mg Q3W than across all Q2W dose levels (33% vs 66%). Combination: 19 pts (median age 61 y, 47% male) were treated with MCLA-145 10, 25 or 40 mg plus Q3W. Median number of cycles was 5 (range 1-16). No DLTs occurred. Most common AEs (all grades/G3-4) were fatigue (58%/11%), cough (42%/0%), constipation (32%/0%) and ALT/AST increase (21%/11%). The RDE was established at 40 mg Q3W for both monotherapy and combination. Preliminary antitumor activity was observed with monotherapy (52 evaluable pts): 5 partial responses (PRs) in glioblastoma (lasting >3 y), sarcoma, cervical, anal, and gastric cancer (treated for 2-11 mo); and combination (19 evaluable pts): 1 PR in Merkel cell carcinoma (treated 12+ mo), 1 complete response in PD-L1+ NSCLC (treated 6+ mo), both after prior immunotherapy. Disease control rate was 37% with monotherapy and 68% with combination. Exposure was dose-dependent with a terminal half-life of 69 h at 75 mg. Measure of peripheral blood Ki67+ CD8 T cells supports maximal PD activity at 40 mg. **Conclusions:** MCLA-145 given alone or in combination with pembrolizumab had a well-tolerated and manageable safety profile with encouraging clinical activity, including in pts who relapsed after PD-(L)1 therapies. Clinical trial information: NCT03922204. Research Sponsor: None.

2521 Rapid Oral Abstract Session

Safety and preliminary efficacy of EIK1001 in combination with pembrolizumab in participants with advanced solid tumors.

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Background: Immune checkpoint inhibitors (ICIs) relieve immunosuppression of tumor-reactive T cells and enhance antitumor immune response; however, not all patients benefit and some become refractory. EIK1001 is a Toll-like receptor (TLR)7/8 agonist that stimulates myeloid and plasmacytoid dendritic cells, activating immune and inflammatory responses. This dual activity provides another pathway, distinct from effects on checkpoint proteins, to enhance antitumor T-cell activity alone or in combination with ICIs. **Methods:** Study BDB001-101 was a Phase 1, open-label, dose-escalation/expansion study of EIK1001 as either monotherapy (mono Rx; previously reported) or combined with pembrolizumab (comb Rx). Enrollment criteria included participants (pts) ≥ age 18 with confirmed, RECIST-measurable advanced solid tumors. Primary study objectives included safety and tolerability, and secondary objectives included evaluation of dose-limiting toxicities, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy by RECIST 1.1. During comb Rx dose escalation, pts received a range of doses of EIK1001 (QW IV) in combination with pembrolizumab (200 mg Q3W). **Results:** Fifty-one pts (median age 67 [range 33 to 86]) with multiple, distinct histological tumor types and with a median of 3 prior Rx regimens were enrolled. Overall, a total of 42/51 (82.4%) comb Rx pts experienced a treatment-related adverse event (TRAE). A total of 9/51 (17.7%) experienced a ≥ Grade 3 TRAE, including fatigue, cytokine release syndrome (CRS), hemiparesis, hypertension, joint range of motion reduced, muscular weakness, pancreatitis, rash (maculopapular), skin plaque, and stomatitis. Overall, 5/51 (9.8%) experienced manageable CRS, with only 1 discontinuation due to CRS. There were no deaths due to TRAEs. Of the efficacy-evaluable pts (n = 50), complete response (CR) or partial response (PR) was observed for 7/50 (14.0%), including 3 CR and 4 PR. Disease control (including CR, PR, or stable disease) was observed in 24/50 (48.0%). The median duration of response was 10 months (range = 4 to 32 months). Responses were observed in pts with prior anti-PD-1 exposure as well as in those with low or negative PD-L1 tumor expression. EIK1001 PK was linear and dose-proportional, and combination with pembrolizumab did not affect EIK1001 PK. **Conclusions:** Overall, EIK1001 was well-tolerated with a manageable safety profile and showed encouraging preliminary efficacy across several tumor types in combination with pembrolizumab. Responses were observed even in heavily pretreated patients not anticipated to respond to pembrolizumab monotherapy. Further development of EIK1001 is underway. Clinical trial information: NCT03486301. Research Sponsor: Eikon Therapeutics, Inc.

Preliminary results from the phase 2 study of AFM24 in combination with atezolizumab in patients with EGFR wild-type (EGFR-WT) non-small cell lung cancer (NSCLC).

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Background: Immunotherapy combinations could be a promising strategy to overcome resistance to existing therapies. AFM24, a first in class, bispecific, tetravalent innate cell engager, binds CD16A on innate effector cells (NK cells and macrophages) and EGFR on solid tumors, redirecting and enhancing the innate and possibly the adaptive immune response towards tumors. Atezolizumab, a PD-L1 inhibitor, abrogates activation of the PD-1 immune checkpoint, potentiating the adaptive immune response. This Phase 1/2a study (NCT05109442) is evaluating if combining AFM24 with atezolizumab synergistically enhances both innate and adaptive immunity to effectively target $EGFR^+$ solid tumors. Here we report initial results of the EGFR-WT NSCLC expansion cohort. **Methods:** The recommended Phase 2 dose of 480 mg AFM24 is given intravenously (IV) weekly in combination with 840 mg atezolizumab IV fortnightly, in patients with advanced or metastatic EGFR-WT NSCLC who progressed on ≥1 prior line of therapy including at least a platinum doublet and a checkpoint inhibitor (CPI). The primary endpoint is overall response rate by RECIST v1.1 by Investigator assessment. Secondary endpoints include safety, pharmacokinetics, and immunogenicity. Treatment is given in four-week cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal of consent. Tumor assessments are performed at screening, cycles 2, 4, 6, 8, 10, 12; and every three cycles thereafter. **Results:** As of January 2024, 17 patients in the EGFR-WT NSCLC cohort received AFM24 and atezolizumab for a mean (range) duration of 14.4 (1–33) weeks. Median (range) age is 66 (45–75) years; 82.4% male; European Cooperative Oncology Status Performance Score 0–1; median (range) number of prior lines is 2 (1–5). The combination was well tolerated with no new or unexpected toxicities observed compared to each single agent. The most common AFM24-related adverse events were infusion-related reactions (10 Grade 1–2, two Grade 3). Of the 15 response-evaluable patients, one complete response and three PRs were confirmed; two showed shrinkage of ≥50% in target lesions from baseline. All responders were resistant to prior CPI. Seven patients achieved stable disease as BOR. After a median follow-up time of 5.5 (95% CI 3.45; 5.55) months, 8 patients are still on treatment including all responders. **Conclusions:** AFM24 with atezolizumab shows remarkable signs of clinical efficacy, even in patients with resistance to prior CPI, and a well-tolerated and manageable safety profile in patients with EGFR-WT NSCLC. The study is ongoing and up to 40 patients will be enrolled into this cohort. Clinical trial information: NCT05109442. Research Sponsor: Affimed GmbH.

First-in-human study of ZGGS18, a dual specific antibody targeting VEGF and TGF-β, as monotherapy in patients with advanced solid tumors.

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Background: ZGGS18 is a bifunctional antibody fusion protein, which consists of a monoclonal antibody (optimized Bevacizumab) against vascular endothelial growth factor A (VEGF-A) and an engineered human transforming growth factor-β receptor II extracellular domain (TGF-β RII ECD). It can specifically bind VEGF-A and "capture" TGF- β isomers. It plays a synergistic role in inhibiting tumor growth, such as inhibiting tumor angiogenesis and reducing tumor metastasis. In addition, ZGGS18 can also improve and regulate the tumor microenvironment, so it can enhance the tumor-killing effect in combination with anti-PD-(L) 1 antibody and other tumor immunotherapeutic drugs. We conducted a Phase 1 clinical study to assess the tolerability and safety of this drug. **Methods:** It was a dose-escalation study. Subjects were patients with advanced solid tumors who failed to the available standard treatments. The dose groups were set from 0.3 to 20 (0.3, 1, 3, 6, 10, 15, 20) mg/kg, intravenous infusion, once every 2 weeks. An accelerated titration design (ATD) was utilized in the first three dose groups and a standard "3+3" design was used in the rest doses. The first 28-day period was defined as the dose-limiting toxicity (DLT) observation period. Subjects could continue to receive ZGGS18 until treatment discontinuation criteria were met. Tumor response was assessed by RECIST1.1. **Results:** At the data cut-off (4 Jan 2024), 21 patients (14 males and 7 females) were enrolled, with a median age of 60 years. 13 (61.9%) of them received at least 2 lines of antineoplastic therapies. 76.2% (16/21) of patients experienced treatment-related adverse events (TRAEs) and 19.0% (4/21) of patients had grade 3 TRAEs (1 Lower gastrointestinal hemorrhage in the 10 mg/kg, 1 pneumonia in the 15 mg/kg, 1 anemia in the 20 mg/kg, and 1 blood fibrinogen decreased in the 20 mg/kg dose group). Wherein, the grade 3 blood fibrinogen decreased was a DLT event. The most frequent TEAEs (with incidence >10%) were anemia, lymphocyte count decreased, gingival bleeding, epistaxis, hypoalbuminemia, proteinuria, hypocalcemia, hypokalemia, fever, aspartate aminotransferase increased, bile acids increased, and disease progression. There is one subject with endometrial carcinoma who has received 19 infusions of ZGGS18 and is remaining in this study, and another subject with rectal carcinoma had 29.65% tumor shrinkage at week 12. The C_{max} and AUC increased from 0.3-20 mg/kg approximately in dose proportion. **Conclusions:** ZGGS18 demonstrated its safety and tolerability in this dose-escalation study, along with a good PK profile, providing a good basis for monotherapy and/or combination therapy for future use. Clinical trial information: NCT05584800. Research Sponsor: None.

Results from phase 1a/1b analyses of TTX-080, a first in class HLA-G antagonist, in combination with cetuximab in patients (pts) with metastatic colorectal cancer and head and neck squamous cell carcinoma.

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Background: TTX-080 is an IgG1 monoclonal antibody targeting HLA-G. This Ph1a/1b study evaluated the safety and preliminary efficacy of TTX-080 alone or in combination with cetuximab (Cetx) or pembrolizumab (Pem) in multiple solid tumor cohorts (NCT04485013). Herein, we report the safety from the Ph1a and preliminary efficacy data from Ph1b cohorts evaluating TTX-080 + Cetx in pts with head and neck squamous cell carcinoma (HNSCC) and WT RAS/BRAF, HER2-Neg metastatic colorectal cancer (mCRC) tumors. **Methods:** In Ph1a, pts with advanced solid tumors received single agent TTX-080 at escalating doses in a 3+3 design from 0.2-20 mg/kg IV Q3W. In the mCRC and HNSCC arms of Ph1b, pts were treated with RP2D of TTX-080 + Cetx. Patients were followed for safety and anti-tumor activity. Biopsies and blood samples were collected for biomarker analyses. **Results:** As of 08-Dec-23, 202 pts have received TTX-080 alone or in combination (40 pts in Ph1a and 162 pts in Ph1b). In Ph1a TTX-080 monotherapy dose-escalation, MTD was not reached and no DLT was reported. TTX-080 treatment-related AE (TRAE) of arthralgia, fatigue, and decreased appetite were seen in at least 5% of pts. R2PD for TTX-080 was determined to be 20 mg/kg IV Q3W. In Ph1b of TTX-080 alone or in combination (Cetx or Pem), the most common TRAEs in at least 5% of subjects were fatigue, nausea, anemia, diarrhea, AST increase, headache, vomiting and pruritis. Preliminary efficacy data from the select Ph1b TTX-080 + Cetx subset of pts are shown in Table. Significant HLA-G related immune cell changes in the peripheral blood and in tumors will be presented. **Conclusions:** TTX-080 is well tolerated alone and in combination with Cetx. TTX-080 + Cetx demonstrates promising activity in pts with HPV-Neg HNSCC and WT RAS/BRAF/Her2-Neg mCRC as manifested by the responses and PFS. These early findings warrant further investigation of TTX-080 + Cetx in a randomized controlled study against standard of care in mCRC and HNSCC. Clinical trial information: NCT04485013. Research Sponsor: Tizona Therapeutics.

TTX-080 + Cetx treatment.

	mCRC *No Prior Treatment with Anti-EGFRs >90% pts Received at Least 2 prior lines of Tx*		**HNSCC** *All Received at Least 1 Prior Line of Tx. All HPV-Neg pts Received Prior IO*	
	WT KRAS	**WT RAS/BRAF/Her2-Neg**	**HPV-Negative**	**HPV-Positive**
Response Evaluable	22	14	7	10
ORR*	**23% (5 PR)**	**29% (4 PR)**	**57% (1 CR, 3 PR)**	**0%**
SD	45%	43%	14%	40%
DCR	**68%**	**71%**	**71%**	**40%**
PD	27%	21%	29%	60%
DOR, weeks (min, max)	**2.6, 37**	**4.1, 37**	**12.2, 30**	**NA**
mPFS, weeks (95% CI)	**18.3 (10.7, NA)**	**24.4 (2.5, NA)**	**23.9 (9, NA)**	**9.1 (8.3, NA)**

*ORR is the best response reported from start of treatment until end of treatment. Tumor assessment based on RECIST 1.1 per Central Assessment.

The anti-tumor immune response of radiotherapy combined with anti-CD200R1 in hepatocellular carcinoma.

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Background: Various clinical trials demonstrate the efficacy of regional radiotherapy or chemotherapy in augmenting the therapeutic response to PD1/L1 antibody in hepatocellular carcinoma (HCC). However, a significant proportion of HCC patients still exhibit suboptimal responses to these combination therapies. The immune-suppressive tumor microenvironment (TME) poses a formidable barrier to effective immunotherapy. Recent evidences underscore the pivotal role played by myeloid cells in modulating the immunosuppressive TME following regional treatments. Therefore, targeting the myeloid immunosuppressive checkpoint represents a promising strategy for enhancing the efficacy of current local-immune combination therapy. **Methods:** Initially, single cell RNA sequencing (scRNA-seq) was conducted on tumor infilitrating immune cells (TIICs) of mouse HCC tissues three days post-radiotherapy. Subsequently, the phenotype of tumor-infiltrating $CD200^+$ macrophages was characterized in mouse HCC tissues using flow cytometry. Next, the specific mechanism underlying CD200 up-regulation in tumor-infiltrating macrophages was investigated using wild-type mice and STING KO mice. Furthermore, the chemotactic and interactive mechanisms between $CD200^+$ macrophages and $CD200R^+$ myeloid-derived suppressor cells (MDSCs) were investigated through in vitro and in vivo experiments. Finally, the systemic antitumor effect of combined radiotherapy and anti-CD200R treatment was observed in multiple non-immunogenic HCC mouse models. **Results:** The infiltration level of $CD200^+$ macrophages in HCC tissues significantly increase following local radiotherapy. The accumulation of $CD200^+$ macrophage subset relies on potent STING activation subsequent to radiotherapy. In vitro and in vivo experiments demonstrate the robust capacity of $CD200^+$ macrophages in enhancing myeloid immunosuppression. Mechanistically, $CD200^+$ macrophages recruit $CXCR2^+$ $CD200R^+$ MDSC through secretion of CXCL1/3, thereby amplifying the proliferation and immunosuppressive capacity of this specific MDSC subset via interaction between CD200 and CD200R. Targeted blockade of CD200R improve the inhibitory immune microenvironment by suppressing the immunosuppressive capacity of myeloid suppressor cells. Lastly, combined anti-CD200R1 with radiotherapy sensitized the therapeutic effect of PD-1/L1 antibody in multiple non-immunogenic HCC mouse models. **Conclusions:** Our studies identify $CD200^+$ macrophages as a crucial immune suppressor that is essential for tumor immune resistance following radiotherapy. These findings unveil a novel mechanism of immune evasion mediated by STING activation, thereby offering a potential target for further optimization of local-immune combination therapy in HCC. Research Sponsor: National Natural Science Foundation of China; 82103448 82270688; Guangdong Natural Science Foundation; 2023A1515010322; the Science and Technology Program of Guangdong Province; 2019B020236003; the Guangdong Key Laboratory of Liver Disease Research; 2020B1212060019.

Phase I dose escalation trial of the first-in-class TNFR2 agonist monoclonal antibody, HFB200301, in monotherapy and in combination with tislelizumab, an anti-PD-1 monoclonal antibody, in adult patients with advanced solid tumors.

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Background: Tumor necrosis factor receptor-2 (TNFR2) is expressed on effector CD8+, CD4+, and regulatory T (Treg) cells, natural killer (NK) cells, and myeloid cells. Activation of TNFR2 is anticipated to yield effective anti-tumor immunity by stimulating T-cell and NK-cell activation and proliferation in the tumor microenvironment. HFB200301 is a first-in-class anti-TNFR2 agonistic monoclonal antibody that triggers both innate and adaptive immune stimulation by binding to a specific epitope on TNFR2. We report initial results of an ongoing Phase I dose escalation, multicenter study (NCT05238883) of HFB200301 in monotherapy and in combination with tislelizumab (TIS) in patients (pts) with advanced refractory solid tumors. **Methods:** A Phase I trial designed to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and initial efficacy of HFB200301 in monotherapy and in combination with TIS. Eligible pts, ≥18 years with an ECOG PS 0-1 and advanced solid tumors, will be enrolled in dose escalation at 5 different dose cohorts in monotherapy (Q4W), 3 different dose cohorts in combination with TIS (Q4W), or in dose expansion following determination of safety. Radiographic response is assessed every 8 weeks. **Results:** A total of 39 pts have been enrolled, 27 pts in monotherapy and 12 pts in combination. All pts received prior systemic therapy (median 2, range 1-4); 23 pts (59%) had prior checkpoint inhibitor treatment. No dose limiting toxicities were observed in either the monotherapy or combination arms. Treatment-related adverse events (TRAEs) occurred in 44% of monotherapy and in 50% of combination pts, with pruritis (11%), tremor (7%), fatigue (7%), asthenia (7%) and nausea (7%) being the most common TRAEs. No ≥ Grade 3 TRAEs were reported, and there were no drug discontinuations due to TRAEs. Preliminary HFB200301 PK analysis demonstrated non-linear clearance of HFB200301, with dose-proportional maximum concentration [C_{max}], achieving sufficient exposures for peripheral target engagement in all tested doses. Emerging PD data demonstrates evidence of immune activation and expansion of CD8+ T cells, but not Tregs, in the tumor microenvironment and peripheral blood. Single cell RNAseq analysis of peripheral blood mononuclear cells demonstrated PD modulation in TNFR2 positive immune cell types post-HFB200301 treatment. Early response evaluation reveals ongoing durable clinical responses (> 6 months) in a PD-L1+ pleural mesothelioma pt and an EBV+ gastric cancer pt from combination cohorts. **Conclusions:** HFB200301 demonstrates a favorable safety profile, dose-dependent PK, with PD and preliminary clinical activity in monotherapy and in combination with TIS in pts with heavily pretreated refractory solid tumors. Clinical trial information: NCT05238883. Research Sponsor: HiFiBiO Therapeutics Inc.

Updated results of a phase 1/2 study of AU-007, a monoclonal antibody (mAb) that binds to IL-2 and inhibits CD25 binding, in patients with advanced solid tumors.

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Background: AU-007 is a computationally designed human mAb that binds interleukin-2 (IL-2) on its CD25 binding epitope. AU-007 bound IL-2 cannot bind trimeric (CD25, CD122, CD132) IL-2 receptors (IL-2R) on regulatory T cells (Tregs), vascular endothelium, or eosinophils, but IL-2's binding to dimeric IL-2R (CD122, CD132) on effector T (T eff) and NK cells is unhindered. AU-007 thus redirects IL-2 towards T eff and NK cell activation, while diminishing Treg activation and vascular leak. AU-007 uniquely redirects IL-2 generated from T eff cell expansion, converting a Treg-mediated autoinhibitory loop into an immune stimulating loop. **Methods:** The study consists of three dose escalation arms followed by cohort expansion. Arm 1A evaluates escalating doses (0.5 – 12 mg/kg) of AU-007 (IV every 2 weeks [Q2W]). Arm 1B evaluates AU-007 Q2W + escalating doses (15K – 270K IU/kg) of one aldesleukin subcutaneous (SC) dose. Arm 1C evaluates AU-007 + escalating doses of SC aldesleukin, both Q2W. Nineteen solid tumor types are allowed in escalation. Cohort expansion Arm 2B evaluates 9 mg/kg AU-007 + one 135K IU/kg aldesleukin dose. **Results:** Fifty-three patients were enrolled as of 23 January 2024: 15 in Arm 1A, 12 in Arm 1B, 25 in Arm 1C, and 1 in cohort expansion. AU-007 (+/- aldesleukin) was well-tolerated, with no dose limiting toxicities through all Arm 1A and 1B cohorts and the 3rd cohort (of 4) in 1C. Enrollment is ongoing in the final Arm 1C cohort and Arm 2B expansion. All drug related adverse events (AE) were Grade 1 or 2 except for 4 patients with transient lymphopenia (Grade 3 and 4) and 1 patient with Grade 3 anemia. The most common drug-related AEs were pyrexia (18%), fatigue (16%), nausea (14%), lymphopenia (8%), and chills (6%). Two patients had transient Grade 2 drug-related serious AEs: pyrexia Arm 1B and cytokine release syndrome Arm 1C; both patients continued therapy. A confirmed partial response (32% decrease) occurred in a nasopharyngeal carcinoma patient in Arm 1C who progressed on anti-PD-1 therapy. Tumor shrinkage occurred in patients with non-small cell lung, bladder, head and neck, colorectal (CRC), and renal cancer. A melanoma patient (Arm 1B) who progressed on anti-CTLA-4 + anti-PD-1 therapy had a 48% decrease in target tumors; a small brain metastasis was found and irradiated at week 16 and the patient remains on treatment. A patient with microsatellite stable CRC had a 26% tumor shrinkage after the first cycle (Arm 1C). Serum Tregs and eosinophils decreased in patients while NK and CD8 cell counts trended upwards. The CD8:Treg ratio trends upward in all cohorts. **Conclusions:** The mild toxicity profile and promising early efficacy observed in dose escalation across multiple tumor types in heavily pretreated patients, along with initial pharmacodynamic data, warrant continued evaluation of AU-007 + low dose SC aldesleukin in the Phase 2 expansion cohorts of the study. Clinical trial information: NCT05267626. Research Sponsor: None.

A phase I/II open label, multicenter study to assess the safety, tolerability, pharmacokinetics, and efficacy of HB0028 in patients with advanced solid tumors.

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Background: HB0028 is a bifunctional fusion protein consisting of an anti-PD-L1 IgG1 single domain antibody and TGF-β RII receptor extracellular domain (TGFβRII-ECD). This is the first dose escalation and expansion phase I/II study to evaluate the safety and preliminary anti-tumor activity of HB0028 in advanced solid tumors. **Methods:** In the phase I portion of the study, the patients (pts) with advanced solid tumor were enrolled, and an accelerated titration followed by a standard 3+3 design was applied to dose escalation. The objectives were toxicity evaluation, maximum tolerable dose (MTD), and recommended phase 2 dose (RP2D). Eligible pts with advanced solid cancers of any histologic subtype, and ECOG performance status ≤ 1 were treated with HB0028 (0.3mg, 1mg, 3mg, 10mg, 20mg, Q3W), until unacceptable toxicity or disease progression. Radiologic tumor assessments (by RECIST v1.1) were performed every 6 weeks while on treatment. **Results:** 16 pts [12 females and 4 males; ECOG 0/1, 9/7; median age 52 years (range 36 – 60)] were enrolled in phase I (0.3 mg/kg [n = 1], 1 mg/kg [n = 3], 3 mg/kg [n = 3], 10 mg/kg [n = 3], 20 mg/kg [n = 6]). Median number of prior lines of systemic therapy was 2 (range 1-4). 8(50%) pts received and progressed upon prior anti-PD-1/L1 therapy. All pts had measurable metastatic disease. No DLT and Death occurred. MTD was not reached. As of DEC 25,2023, among 16 patients' safety data are evaluable for toxicity. Any grade treatment-related adverse events (TRAEs) occurred in 15 subjects (93.8%), with 2 subjects (12.5%) reported with ≥ Grade 3 (G3 Anemia and G3 γ-glutamyltransferase). The most common TRAEs (all grades) were AST increased (n = 4, 25%), anemia (n = 7, 43.8%) and infusion-related response (n = 5, 31.3%). Two SAEs (G2 AST increased and G3 Neoplastic fevers) were reported, only AST increased was considered as possibly related to study drug, but recovered shortly. The efficacy data cutoff date of DEC 25,2023, 16 patients are evaluable for radiologic response. 1 subject with cervical cancer in HB0028 20 mg/kg group had a partial response (PR), 3 subjects (liver cancer, lung cancer, left submandibular gland cancer) had stable disease (SD) and 12 subjects had progressive disease (PD). The ORR per RECIST 1.1 by investigator was 6.25% (1/16; 95% CI, 0%-30.2%), and the DCR was 25% (4/16; 95% CI, 7.3%-52.4%). Durable clinical benefit (SD for > 32 weeks) was seen in 1 subject with malignant tumor in the left submandibular gland. To date, 2 responders are still on treatment. **Conclusions:** HB0028 was generally well tolerated, and therapy provided modest antitumor activity in patients with heavily pretreated advanced solid tumors. Based on these data, a phase II prospective clinical trial is being planned in specific cancer. Clinical trial information: NCT06223308. Research Sponsor: None.

Phase 1 trial safety and efficacy of ragistomig, a bispecific antibody targeting PD-L1 and 4-1BB, in advanced solid tumors.

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Background: Activation of T cells in the tumor microenvironment by 4-1BB agonist antibodies is a promising approach to augment PD-(L)1 inhibitor efficacy. Ragistomig(ABL503/TJ-L14B) is a bispecific antibody combining PD-L1 antagonist with 4-1BB agonistic activity, designed to induce 4-1BB signaling only when bound to the PD-L1 tumor antigen on cancer cells, which may overcome resistance to PD-(L)1 inhibition and avoid hepatoxicity seen with traditional 4-1BB mAbs. **Methods:** ABL503 was investigated at doses ranging from 0.7 mg (flat dose) to 10 mg/kg (weight-based dose) IV every 2 weeks (Q2W) in patients with advanced or relapsed/refractory solid tumors, to assess safety, preliminary anti-tumor effect and pharmacokinetic (PK)/pharmacodynamic (Pd) activity. The BOIN design was utilized during dose escalation (regardless of CPS/TPS score). Additional patients were enrolled in dose expansion cohorts at 3 and 5 mg/kg (CPS/TPS>=1 required). **Results:** As of Jan 2024, the study enrolled 49 patients (30 dose escalation, 19 dose expansion). At least 1 treatment related adverse event (TRAE) occurred in 37 patients (75.5%); most common TRAE (≥ 10%, any grade/grade 3-4) were elevated AST (30.6%/18.4%), elevated ALT (26.5%/18.4%), rash (14.3%/4.1%), nausea (12.2%/0%), pyrexia (12.2%/2.0%) and fatigue (10.2%/0%). Dose limiting toxicities occurred in 5 patients and were observed at dose levels of 1, 5, and 10 mg/kg. All DLTs were recovered/recovering. MTD was not reached. Based on the safety, efficacy, PK and Pd analysis, the optimal dose was determined to be 5 mg/kg Q2W. Objective responses were observed in 6 out of 39 efficacy-evaluable patients, and all responses were observed at 3 and 5 mg/kg, including 1 complete response (CR) in a patient with ovarian cancer who received 6 prior lines of treatment and 5 partial responses (PRs) in patients with ovarian (n=1), melanoma (n=1), gastric (n=1), head and neck squamous cell (n=1), and esophageal cancer (n=1). Overall response rate (ORR) for all dose levels was 15.3%, and ORR at 5 mg/kg was 30% (3/10). Clinical benefit rate (CBR) for all dose levels was 61.5%, and CBR at 5 mg/kg was 80% (8/10). 66.7% of responders received prior PD-(L)1 inhibitors. One patient achieved sustained tumor regression over 6 months, even after treatment discontinuation. PK was dose proportional, and half-life was ~5 days. Dose-dependent increase of Pd marker s4-1BB was observed, demonstrating target engagement. **Conclusions:** ABL503 had a manageable safety profile and demonstrated promising anti-tumor activity, with objective responses in 6 out of 39 efficacy-evaluable patients across multiple tumor types in heavily pre-treated patients, including patients previously treated with checkpoint inhibitors. The data support continued development of ABL503 alone and in combination with other compounds, as a potential therapeutic option for patients with solid tumor cancers. Clinical trial information: NCT04762641. Research Sponsor: None.

Tregs, gMDSCs, and levels of soluble MICA as prognostic biomarkers for combined NEO-201 and pembrolizumab.

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Background: The humanized IgG1 monoclonal antibody NEO-201 binds to Core 1 and/or extended Core 1 O-glycans expressed by several human solid and blood tumors, as well as neutrophils, and mediates killing of cancer cells, neutrophils, regulatory T cells (Tregs) and granulocytic myeloid-derived suppressor cells (gMDSCs) via ADCC and CDC. Resistance to PD-1/PD-L1 blockade may be due to the accumulation of Tregs and gMDSCs in the tumor microenvironment (TME). NEO-201 was proven to bind and reduce the amount of circulating Tregs in cancer patients. This supports the rationale of the ongoing phase II clinical trial (NCT03476681) evaluating the activity of NEO-201 with pembrolizumab in adults with solid tumors resistant to prior checkpoint inhibitors. Furthermore, elevated serum levels of soluble MICA (sMICA) have been correlated with decreased NK cell activity. **Methods:** Cancer patients were treated each cycle with 3 doses of NEO-201 1.5mg/kg every 2 weeks and pembrolizumab 400mg IV every 6 weeks and imaged for response every 2 cycles. PBMCs and serum from cancer patients pre- and at multiple time points post-treatment were used to evaluate the percentage of circulating gMDSCs and Tregs (flow cytometry) and sMICA levels (ELISA). **Results:** NEO-201 recognizes naïve Tregs (nTregs: $CD3^+/CD4^+/CD45RA^+/Foxp3^{low}$ cells) but not effector Tregs (eTregs: $CD3^+/CD4^+/CD45RA^-/Foxp3^{high}$ cells). NEO-201 also binds to gMDSCs, defined as $HLA^-DR^{neg}/CD33^+/CD15^+/CD14^{neg}/CD66b^+$ cells. In patients with durable SD, a patient with HNSCC (SD >11 months) showed >50% reduction of nTregs and >90% of gMDSCs at C3D1 (beginning of cycle 3) compared to baseline. One patient with cervical cancer (SD >8 months) showed 40% reduction of nTregs at C3D1 compared to baseline, while gMDSCs trended down to baseline levels at C3D1 after initial increase. Conversely, we observed a general uptrend of nTregs and gMDSCs in patients with PD after treatment. Median serum levels of sMICA pre-treatment were 33-fold higher in patients with PD compared to patients with SD. Levels of sMICA remained elevated in patients with PD and low in patients with SD at all time points post-treatment. **Conclusions:** Depletion of circulating Tregs and gMDSCs may prevent their accumulation in the TME and enhance the efficacy of pembrolizumab in subjects with tumors resistant to checkpoint inhibitors. The decrease in circulating nTregs and gMDSCs after treatment with NEO-201 and pembrolizumab was associated with durable SD. High levels of sMICA can impair ADCC mediated by NEO-201, resulting in poor clinical response. Low levels of sMICA in patients with SD, together with the reduction of both circulating nTregs and gMDSCs, could be favorable prognostic markers for clinical benefit following treatment with NEO-201 and pembrolizumab. Ongoing enrollment in this clinical trial will validate these findings in larger cohorts. Clinical trial information: NCT03476681. Research Sponsor: U.S. National Institutes of Health; Precision Biologics, Inc.

A phase I monotherapy dose escalation study of HFB301001, a novel next generation OX40 agonist monoclonal antibody, in adult patients with advanced solid tumors.

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Background: The immune co-stimulatory receptor OX40 is expressed on CD4+ T cells, including regulatory T cells (Tregs). First generation OX40 agonists faced limitations from interference with endogenous OX40-OX40L binding, leading to decreased surface OX40 levels on T cells. Distinguished by its unique epitope on OX40, the novel next generation IgG1 monoclonal antibody (mAb) HFB301001 facilitates agonistic activity without impeding endogenous OX40 ligand binding. This allows for effective co-stimulation of T cells without diminishing OX40 levels. Additionally, HFB301001 exhibited superior *in vivo*anti-tumor activity and ability to enhance effector CD8+ T cell function compared to a benchmark first generation OX40 agonist in preclinical studies. Here, we report initial data of an ongoing dose-escalation study (NCT05229601) of HFB301001 in patients (pts) with advanced solid tumors. **Methods:** A Phase I trial designed to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HFB301001. Eligible pts ≥18 years old (ECOG PS 0-1) with advanced solid tumors are enrolled in 4 different dose cohorts in monotherapy (Q4W) dose escalation. Solid tumor types were selected using Drug Intelligent Science (DIS®), employing integrative bulk and single cell RNAseq (scRNAseq) analyses to confirm and prioritize prospective targets in specific immune cell types. Sequential analysis of peripheral blood and tumor tissue biomarkers is performed. Radiographic response is assessed every 8 weeks. **Results:** As of January 06, 2024, 26 pts were enrolled, all having received prior systemic therapy (median 2, range 1-4); 81% received prior checkpoint inhibitor treatment. The majority of pts (77%) were male, median age was 62.5 years (range 41-78). Treatment-related adverse events (TRAEs) occurred in 34.6% of pts, none ≥ grade 3. Common TRAEs included rash (19%), pruritis (12%) and arthralgia (8%). No dose-limiting toxicities were observed. Preliminary results demonstrate dose-proportional increases in maximum concentration, typical mAb volume of distribution, and nonlinear clearance. On treatment biopsies revealed expansion of both natural killer and cytotoxic CD8+ T cells, with no notable expansion of Tregs. Analysis of peripheral blood by scRNAseq and immunophenotyping revealed expansion of cytotoxic CD8+T cells relative to CD4+ T cells post treatment. Preliminary efficacy analysis indicates a disease-control rate (DCR) of > 60% with greatest effect seen in hepato-cellular and renal cell carcinoma. Median time on treatment was 1.9 months (range 0.9-17 months). **Conclusions:** HFB301001 demonstrates a favorable safety profile, dose-dependent PK and PD immunomodulation, and DCR in heavily pretreated solid tumors. HFB301001 warrants further evaluation and expansion in specific tumor types is planned. Clinical trial information: NCT05229601. Research Sponsor: HiFiBiO Therapeutics Inc.

A phase 3 study to evaluate efficacy and safety of VYD222, an IgG1 monoclonal antibody for prevention of COVID-19 (CANOPY): Subset analysis of participants with significant immune compromise in the setting of solid tumor or hematologic malignancies.

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Background: CANOPY (NCT06039449) is a Phase 3 study to evaluate the efficacy and safety of VYD222 for prevention of COVID-19. VYD222 is a fully human IgG1 mAb demonstrating in vitro neutralizing activity across several SARS-CoV-2 variants of concern, including JN.1, the dominant variant in the U.S. as of Jan 2024, as well as HV.1, BA.2.86, XBB.1.5.10/EG.5, and HK.3. **Methods:** Here we describe a subset of participants in the single-arm, open label Cohort A of CANOPY, who were considered to have significant immune compromise due to active treatment for solid tumor or hematologic malignancies or a diagnosis of acute leukemia, chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, or multiple myeloma (regardless of treatment). Endpoints included safety and tolerability of VYD222 and evaluation of protection against COVID-19 based on calculated serum virus neutralizing antibody (sVNA) titers against SARS-CoV-2 after receiving VYD222. All Cohort A participants received 4500 mg IV of VYD222 on Day 1 and received the same dose at the Month 3 visit. Safety and tolerability were assessed as incidence of treatment emergent adverse events, including serious adverse events. Calculated sVNA levels were assessed for those participants who had serum concentration results at Day 28. **Results:** A total of 306 participants were enrolled in Cohort A. Of those, 55 (18%) were included in the solid tumor or hematologic malignancies subset. Median age was 65 years. 20 (36%) participants were being actively treated for solid tumor or hematologic malignancy, and 40 (73%) had one of the cancer diagnoses listed above; 29 (53%) participants had CLL. As of this data cut utilized for EUA submission, no participants in this open-label subset had RT-PCR confirmed symptomatic COVID-19, and two of 55 (3.6%) participants experienced adverse events (tachycardia, fatigue/night sweats) related to study drug. In both cases these adverse events occurred with administration of the first dose, were considered mild, resolved without treatment, did not cause discontinuation of study drug, and were not observed with the Month 3 dose administered. Safety data from the second dose in all patients in this subset was not yet available as of this analysis. In Cohort A overall and in participants in this subset with available data, VYD222 provided high calculated sVNA titers at Day 28 against a broad range of relevant SARS-CoV-2 variants of interest, including JN.1 and other recently circulating omicron subvariants. **Conclusions:** VYD222 4500 mg IV was well tolerated in a subset of adult participants with solid tumor or hematologic malignancies. VYD222 produced high calculated sVNA titer levels against SARS-CoV-2 variants of interest. Clinical trial information: NCT06039449. Research Sponsor: Invivyd, Inc.

Acasunlimab (DuoBody-PD-L1x4-1BB) alone or in combination with pembrolizumab (pembro) in patients (pts) with previously treated metastatic non-small cell lung cancer (mNSCLC): Initial results of a randomized, open-label, phase 2 trial.

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Background: Most pts with mNSCLC without actionable gene alterations have limited options after progression on first-line checkpoint inhibitor (CPI)–containing treatment (tx). Given failures of recent trials in this setting, single-agent chemotherapy remains the main tx option despite limited effectiveness (eg, docetaxel ORR 10–14%) and considerable toxicity. Acasunlimab is a bispecific antibody designed to elicit antitumor immune response via conditional 4-1BB activation strictly dependent on simultaneous PD-L1 binding. Preclinical and PK/PD findings support combining acasunlimab with additional PD-1 blockade to further potentiate anti-tumor activity and potentially extend durability. Initial results from the ongoing randomized, phase 2 trial (NCT05117242) evaluating acasunlimab as monotherapy (mono) and in combination with pembro (combo) in pts with mNSCLC are reported. **Methods:** Eligible pts had PD-L1+ mNSCLC, with progression after ≥1 prior anti–PD-(L)1 tx. Tumor PD-L1 status was assessed by central testing (TPS≥1%, PD-L1 IHC 22C3 PharmDx); this subset is presented in the efficacy analyses. Following safety run-in, pts were randomized to acasunlimab mono (arm A, 100 mg Q3W x 2 cycles then 500 mg Q6W) or combo (arm B, 100 mg + pembro 200 mg Q3W; arm C, 100 mg + pembro 400 mg Q6W). Primary efficacy endpoint was ORR per RECIST v1.1. Stratification factors were PD-L1 expression and histology. **Results:** As of Jan 9, 2024, 98 pts (63 with central PD-L1+ status) were enrolled: 23 (16) pts arm A; 39 (22) pts arm B; 36 (25) pts arm C. Among evaluable PD-L1+ pts, 86% received prior pembro tx; 64% had prior concurrent CPI + chemotherapy. Unconfirmed ORR and DCR were 31% and 50% for arm A, 25% and 65% for arm B, and 30% and 75% for arm C, respectively. Confirmed ORRs (and mDoR) were 13% (2 mo), 21% (6 mo), and 22% (NR), with 6-mo PFS rates of 0%, 18%, and 33% for arms A, B, and C, respectively. No responses were observed among centrally confirmed PD-L1-negative pts. The most common TRAEs (all grades; grade ≥3) were asthenia (17.4%; 8.7%), diarrhea (17.4%; 0%), nausea (17.4%, 0%), anemia (13%; 4.3%) and liver-related events (13%; 8.7%) for mono, and liver-related events (18.7%; 13.3%), fatigue (14.7%; 0%), asthenia (13.3%; 0%), and diarrhea (12%; 0%) for combo. Transaminase elevations were generally asymptomatic and manageable with steroids and/or tx delay. Early peripheral pharmacodynamics were consistent with acasunlimab-mediated immune activation in all arms, with a more pronounced increase in CD8 T-cell proliferation with combo. **Conclusions:** In PD-L1+ pts with mNSCLC following progression on prior CPI tx, acasunlimab + pembro combo showed a manageable safety profile and promising efficacy, with deeper responses and durable disease control in pts treated Q6W. Enrollment is ongoing. Clinical trial information: NCT05117242. Research Sponsor: Genmab A/S; BioNTech SE.

A phase 1, dose escalation/dose-expansion study of QLF31907, a bispecific antibody (BsAb) targeting PD-L1 and 4-1BB, in patients with advanced solid tumors and lymphoma.

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Background: Clinical development of agonistic 4-1BB mAbs is limited by their narrow therapeutic window or unsatisfactory efficacy. Development of novel molecules with improved efficacy and restricted 4-1BB activation to tumor microenvironment is crucial. QLF31907 is a BsAb targeting PD-L1 and 4-1BB and showed restricted activation of 4-1BB in preclinical studies. Here we present the results from an ongoing phase 1 study of QLF31907 in patients (pts) with advanced solid tumors and relapsed/refractory (r/r) lymphoma. **Methods:** This study consisted of dose-escalation and dose-expansion phases. Pts were enrolled if with histologically confirmed solid tumors or r/r lymphoma; failed in or intolerable to standard therapy; and with ≥ 1 measurable lesion. Pts received QLF31907 intravenously once every 2 weeks (Q2W) at 0.026 and 0.1 mg/kg (accelerated titration design), and 0.3, 1, 3, 10, 20, and 30 mg/kg (i3+3 design) in the dose-escalation phase. The DLT evaluation window was 28 days. Pts received QLF31907 10 mg/kg and 20 mg/kg Q2W in the dose-expansion phase. The primary endpoint was dose-limiting toxicity (DLT). **Results:** As of 30 Nov 2023, 38 pts were enrolled from 5 centers across China. Median age was 58 years and 52.6% patients had an ECOG PS of 1. Five (13.2%) pts had r/r lymphoma. 36 (94.7%) pts had stage IV disease. 31.6% pts previously received ≥3 therapies and 57.9% pts previously received PD-1/PD-L1 therapy. DLTs were observed in 1 pt (20 mg/kg): myalgia and platelet count decreased. All pts experienced TEAEs (treatment-related, 92.1%). The most common TEAE was anemia (73.7%), followed by hypertriglyceridemia (50.0%). Twenty-four (63.2%) pts experienced Gr≥3 TEAEs (treatment-related, 31.6%). The most common Gr≥3 TEAE was pneumonia (13.2%). TEAEs leading to treatment discontinuation occurred in 6 (15.8%) pts (treatment-related, 7.9%). Serious TEAEs occurred in 20 (52.6%) pts (treatment-related, 26.3%). Six (15.8%) pts had PRs and 3 PRs were confirmed. SD was observed in 20 (52.6%) pts. DCR was 60.5% (23/38). PR was observed in 3 patients who previously received PD-1/PD-L1 therapy. The median DoR was not reached and the 6 month DoR rate was 60.0% (95% CI, 12.6-88.2). Two patients had PRs lasting for more than 1 year: 1 with PD-1/PD-L1 naïve cervical cancer (PR>18 months) and 1 with PD-1/PD-L1 treated melanoma (PR>13 months). In the dose range of 0.026-30 mg/kg, the exposure increased proportionally with dose increase. At 10mg/kg Q2W and above, PD-L1 and 4-1BB receptor occupancy indicated by PBMCs stabilized >80% during the treatment period. **Conclusions:** QLF31907 showed an acceptable safety profile and preliminary clinical activity in heavily pretreated patients with advanced solid tumors and lymphoma. Encouraging clinical activity was observed in patients who have failed PD-1/PD-L1 therapy and further research on the mechanism is ongoing. Clinical trial information: NCT05150405. Research Sponsor: None.

2535 Poster Session

Phase 1 study of CTX-471, a novel CD137 agonist antibody, in patients with progressive disease following PD-1/PD-L1 inhibitors in metastatic or locally advanced malignancies.

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Background: CTX-471, a fully human immunoglobulin G4 (IgG4) anti-CD137 agonist antibody, binds to a distinct epitope on CD137, and binds to the target with intermediate affinity which results in optimal agonism of the receptor and improved activation of T-cells and natural killer cells. Extensive preclinical studies have demonstrated potent antitumor activity of CTX-471 used as monotherapy or in combination with anti-PD-1 therapy. CTX-471-001 (NCT03881488) is an ongoing phase 1 study that evaluates the safety and tolerability of CTX-471 alone and in combination with pembrolizumab. This report presents safety and efficacy data from the CTX-471 monotherapy arm, covering dose escalation and expansion cohorts. **Methods:** This Phase 1, open-label, first-in-human study evaluates CTX-471 as monotherapy or in combination with pembrolizumab in patients with metastatic or locally advanced malignancies that have progressed while receiving an approved PD-1 or PD-L1 inhibitor. The monotherapy portion of the study has two parts: Dose Escalation and Dose Expansion. Monotherapy Dose Escalation ranged from 0.1-1.2mg/kg IV biweekly, while Dose Expansion explores two dose levels: 0.3 and 0.6 mg/kg. The primary objective is to evaluate the safety and tolerability of CTX-471, with secondary objectives including PK, immunogenicity, and clinical activity. **Results:** As of January 19, 2024, 19 patients were treated in Dose Escalation and 60 patients were treated in Dose Expansion. 62% were male, and the median age was 66 years. Most common tumor types included non-small cell lung cancer (NSCLC) (25%), head and neck squamous-cell carcinoma (HNSCC) (21%), and melanoma (15%). There were patients with 17 different malignancies enrolled in the Dose Expansion cohort. The dose limiting toxicity observed in the Dose Escalation portion at 1.2 mg/kg was grade 4 thrombocytopenia, observed in two of 6 patients at that dose level. Treatment Related Adverse Events (TRAE) were reported in 64% of patients (51/79 of patients), and 87% of them were Grade 1-2. Treatment discontinuation due to AE was reported in 5 patients. Notably, a Complete Response (CR) was confirmed by PET scan in 1 of 3 patients enrolled with small-cell lung cancer. This patient, treated in the third-line setting, had a durable Partial Response (PR) for approximately 3 years prior to converting to a CR. Four additional PRs were also observed: 3 of 11 (27.3%) patients with melanoma and 1 of 4 (25%) patients with mesothelioma. **Conclusions:** In this phase 1 study, CTX-471 was shown to be a safe and well-tolerated, novel anti-CD137 antibody. CTX-471 monotherapy demonstrates promising monotherapy anti-tumor activity in refractory patients whose tumors have progressed on approved PD-1 or PD-L1 inhibitors. The combination arm with pembrolizumab is ongoing and will be reported at a later date. Clinical trial information: NCT03881488. Research Sponsor: Compass Therapeutics, Inc.

Updated results on the bispecific PSMAxCD3 antibody CC-1 for treatment of prostate cancer.

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Background: While being efficient in hematological malignancies, bispecific antibodies (bsAbs), like CAR T cells, are not yet established in solid tumors. Moreover, all T cell-mobilizing strategies cause side effects that endanger patients and may limit applicable doses and thus efficacy. We report on the clinical development of CC-1, a PSMAxCD3 bsAb in an IgG-based format that induces fully target cell-restricted T cell activity against prostate cancer (1). Targeting PSMA, which is expressed on both the malignant cells and the neovasculature, improves accessibility of the tumor site for immune effector cells as critical prerequisite for therapeutic success in solid tumors. **Methods:** A FIH trial evaluating CC-1 included patients with metastatic castration resistant prostate carcinoma (mCRPC) (NCT04104607) and consisted of two parts: Dose escalation (n=10-66) using a novel intra-individual dose escalation design to rapidly reach the target dose of 826μg to determine safety, tolerability and maximum tolerated dose (MTD) (2), and Dose expansion, which exposed patients to CC-1 at MTD and explored efficacy to define RP2D (n=14). Currently, subcutaneous (SC) application as different application mode is being evaluated. Based on very favorable safety and preliminary efficacy data, another phase I trial was initiated where CC-1 is evaluated as first line treatment in patients with hormone sensitive biochemical recurrence (BCR) of PC (NCT05646550), where tumor burden is low and accordingly lower side effects and long-lasting efficacy are expected. **Results:** Recruitment in the FIH trial in mCRPC has been completed. 28 patients completed treatment with the most frequently observed (86%) toxicity being cytokine release syndrome (CRS, max. 2°). Other adverse events (all $\leq$2°) included hematologic events (93%) as well as elevated liver enzymes (61%), hypertension (18%) and xerostomia (7%). A rapid and profound decline of PSA levels with up to 62% reduction compared to baseline was documented in all but one of the heavily pretreated patients that received the target dose. Twelve patients received multiple treatment cycles. Recruitment of patients to receive SC application of CC-1 is currently ongoing. In the phase I trial in BCR of PC, the first four dose cohorts have so far been completed. CC-1 application was well tolerated in all patients. In all but one of so far treated patients, mild CRS (transiently elevated temperature) that ceased within 24h upon dosing with antipyretics was observed. No other CC-1 related toxicities were observed and recruitment is ongoing. **Conclusions:** CC-1 is a promising compound with a favourable toxicity profile and promising clinical activity. Details on study designs and updated data from the clinical trials will be presented at the meeting. 1. Zekri et al, EMBO Mol Med, 2020. 2. Labrenz et al, Pharm Stat, 2022. Clinical trial information: NCT04104607. Research Sponsor: None.

Development of NTX-472, a formulated mRNA therapy targeting CD20, CD19, and CD47, for treatment of B-cell lymphoma.

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Background: The approval of anti-CD20 monoclonal antibody Rituximab more than 20 years ago opened a new class of highly effective immunotherapies for the treatment of B cell lymphomas. However, use of treatments that target only a single tumor antigen, such as CD20 or CD19, can apply selective pressure to tumors that results in loss or down-regulation of antigen expression in patients. To address this issue, Nutcracker Therapeutics has developed NTX-472, a nanoparticle formulated mRNA-based therapeutic candidate encoding a novel multispecific molecule that targets CD20 and CD19 as well as CD47, an innate immune checkpoint receptor upregulated by many tumors to evade immune surveillance. **Methods:** To understand the advantages gained from multispecific molecules for B cell lymphoma, we designed a panel of molecules targeting CD20, CD19 and CD47 and compared them to monospecific anti-CD20, Rituximab, or anti-CD19, Tafasitamab. A lead molecule was nominated based on in vitro tumor killing and B cell depletion assays, as well as on RBC binding. Efficacy of the lead molecule was evaluated in vivo as a nanoparticle formulated mRNA-based therapy (NTX-472) using Nutcracker Therapeutics' Nutshell delivery platform. NTX-472 was evaluated in the Raji xenograft model for anti-tumor efficacy. Pharmacodynamics of intravenous administration of NTX-472 was assessed by measuring B cell depletion in cynomolgus macaques. **Results:** We identified a multispecific molecule that showed improved tumor killing and B cell depletion over mono and bispecific controls in vitro. In addition to the increased in vitro potency, our lead multispecific also demonstrated improved tumor specificity with preferential engagement of CD47 in presence of co-engagement of CD20 and CD19. Nutcracker Therapeutics' Nutshell delivery platform enables in vivo production of mRNA-encoded complex biologics. Intravenous administration of NTX-472 in mice results in robust serum titers of our lead multispecific and control of Raji tumors in a xenograft model. To assess pharmacodynamics of NTX-472 in a relevant model, cynomolgus macaques were dosed intravenously with NTX-472, and protein expression and B cell depletion were measured in circulation. A single intravenous administration of NTX-472 results in rapid and durable depletion of B cells in circulation with no detectable multispecific binding to red blood cells. In addition, the in vivo expressed multispecific protein showed high purity both in mice and nonhuman primates. **Conclusions:** Here, we demonstrate the potency of NTX-472, a novel nanoparticle formulated mRNA therapeutic candidate encoding a multispecific protein targeting CD19, CD20, and CD47 that has increased specificity for tumor cells and has potential to enable broad efficacy while limiting hematotoxicity within a setting of increased tumor heterogeneity post-Rituximab treatment. Research Sponsor: None.

A phase 1b study of NC410 in combination with pembrolizumab in immune checkpoint inhibitor (ICI) naïve, and refractory microsatellite stable (MSS)/ microsatellite instability-low (MSI-L) colorectal cancer (CRC) and ovarian cancer.

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Background: Treatment options for advanced, refractory MSS/MSI-L CRC and Ovarian cancer are limited, with no FDA-approved ICI therapies. Such tumors have higher collagen deposition resulting in inherent resistance to ICI therapy partly due to the tumor extracellular matrix (ECM) functioning as a physical barrier to immune cell infiltration. Furthermore, dysregulated collagen in ECM inhibits immune cell function through binding to the inhibitory receptor, Leukocyte Associated Immunoglobulin-Like Receptor-1 (LAIR-1) expressed on immune cells. This inhibition can be reversed by endogenous LAIR-2 decoy protein, that competes with LAIR-1 binding. NC410 is a dimeric LAIR-2 protein fused to a human IgG1 Fc domain. NC410 promotes ECM remodeling by targeting collagen, promoting immune cell infiltration, and reversing LAIR-1-mediated immunosuppression. In preclinical models, NC410 in combination with anti-PD-1/anti-PD-L1 further potentiates immune function and anti-tumor activity in recalcitrant tumors. **Methods:** An open-label, single-arm Phase 1b/2 study was initiated to determine the safety, tolerability, and RP2D of NC410 when combined with pembrolizumab in metastatic solid tumors (NCT05572684). Participants received a fixed dose of pembrolizumab (400mg Q6W) on Day 1 and NC410 Q2W on Days 1, 15, and 29 of each 42-day cycle following a modified Toxicity Probability Interval (mTPI) design. The data cut-off was 4-Jan-2024 and the study continues to enroll. **Results:** To date, 65 participants with ICI naïve and refractory MSS/MSI-L CRC and Ovarian cancer received escalating doses of NC410 at 30 (n=3), 60 (n=11), 100 (n=39), and 200mg (n=12) in combination with pembrolizumab. The therapy appears safe and tolerable with diarrhea and fatigue being the most common, and Gr≥3 treatment emergent (14.8%) and related (1%) adverse events; one participant discontinued study due to myocarditis (Gr 3). Of the 32 MSS/MSI-L CRC treated with 100mg NC410, 28 are ICI naïve, of which 17 are currently evaluable with at least one 9-week scan. Of the 17, two confirmed PRs remain ongoing (>9 mo and > 4 mo), 6 durable SD (DCR 47%, ≥ 4 months), and 9 reported PD. Of the 11 Ovarian treated, 9 are currently evaluable: 2 ongoing PRs (>6mo at 200mg and 2mo at 100mg), 2 durable SD ≥4 months at 60mg NC410, and 5 PD. Preliminary assessment of pre- and on-treatment biopsies (N=12) shows decrease in immature collagen, suggesting ECM remodeling. Pre- and on-treatment peripheral blood immunophenotyping shows relatively higher $CD8^+$ effector memory T cells and lower myelosuppressive neutrophils in CRC subjects without liver metastasis. **Conclusions:** Taken together, NC410 in combination with pembrolizumab shows promising clinical activity in hard-to-treat, advanced metastatic CRC and Ovarian cancer. Clinical trial information: NCT05572684. Research Sponsor: None.

A phase I study to evaluate the safety and tolerability of JCXH-211 (a self-replicating mRNA encoding IL-12) intratumoral injection in patients with malignant solid tumors: Results from the phase Ia dose escalation.

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Background: Although interleukin (IL)-12 demonstrated strong preclinical antitumor activity and potent immune-stimulating potentials clinically, systemic administration of IL-12 protein was associated with poor clinical safety profiles. IL-12 functions locally through paracrine and autocrine mechanisms, thus maximizing local concentration of IL-12 in the tumors is important. JCXH-211 is a self-replicating ribonucleic acid (srRNA) encoding human IL-12 encapsulated in lipid nanoparticles. Intratumoral (IT) administration of JCXH-211 is expected to produce the desired spatiotemporal distribution of IL-12 in the cancer lesions. srRNA features enhanced translatability in immunosuppressed tumor microenvironment (TME) than in normal tissues further limiting off-target toxicity. Additionally, the self-replicating nature of JCXH-211 engages multiple immune effector mechanisms and helps inflame TME. We present interim results of the dose escalation part of JCXH-211 IT injection as monotherapy in patients (pts) with malignant solid tumors. Enrollment for the 100 μg cohort is ongoing and updated data will be presented at the meeting. **Methods:** Pts with advanced solid tumors suitable for IT injection are enrolled. JCXH-211 at 5, 25, 50, and 100 μg are given every 4 weeks (Q4W). Dose Limiting Toxicities (DLT) are monitored for 28 days after 1st dose. Dose escalation follows "3+3" principle. Tumor assessment is performed Q6W using RECIST v1.1. **Results:** Ten pts with advanced cancers have been enrolled in 5 μg, 25 μg, and 50 μg cohorts: 3 melanoma (MEL), 3 breast cancer (BC), 2 head and neck cancer (HNSC), 1 nasopharyngeal cancer and 1 sarcoma. Nine pts completed DLT observation without DLT; 1 pt withdrew early. No drug-related SAE was reported. Most drug-related AEs were Grade 1/2 and recovered quickly. Only 1 pt in the 25 μg cohort reported 3 Grade 3 AEs possibly related to drug: lymphocytopenia (2 events) and anemia. Seven pts completed at least one post-dose tumor assessment. Three pts experienced shrinkages of the treated lesions by 13.0%, 33.3% and 43.0%, corresponding to BC, HNSC and MEL in the 5 μg, 25 μg, and 50 μg cohorts, respectively. Tumor shrinkage of 31% was also observed in a non-injected lesion of an HNSC pt receiving 25μg JCXH-211 suggesting abscopal effects. Histopathological analysis of the treated lesions demonstrated increased T and NK cell infiltration (as high as 138 folds) post study drug administration. **Conclusions:** JCXH-211 IT administration with doses of 5μg, 25μg, 50μg Q4W demonstrated good safety profile. Antitumor activities were observed in the heavily pretreated late-stage pts. Significant increases of T and NK cell infiltration were observed. These data support continued evaluation of JCXH-211 IT. Clinical trial information: NCT05727839. Research Sponsor: None.

Effects of pre-treatment on odds of immune-related adverse events.

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Background: For many tumor types, there is an option to start an immune checkpoint inhibitor (ICI) at the time of diagnosis or to sequence ICI after chemotherapies or targeted therapies. The risk of immune-related adverse events (irAE) may vary by the line of therapy. Prior systemic therapies might release cancer epitopes and increase the risk of an irAE through awakened subclinical autoimmunity. Conversely, prior systemic therapies may lead to residual immunosuppression and reduce the risk of irAEs. **Methods:** We created an IRB-approved retrospective registry of all patients who received at least one dose of an ICI for any indication between 2/1/2011 and 4/7/2022 at a comprehensive cancer center and its outreach clinics. Study personnel reviewed the electronic medical record and defined irAEs according to Common Terminology Criteria for Adverse Events. Research specialists at Vasta Global captured most clinical outcomes. Line of therapy was defined ordinal manner, with four or more combined into a single group due to data sparsity. A multivariable logistic regression model was built to assess effect of line of therapy on any irAE while controlling for confounders identified either a priori or in univariate analysis. Given potential for heterogeneity, interaction between tumor primary and line of therapy was tested. SAS v9.4 was used for all analyses. **Results:** Among the final cohort of 3,101 patients, 1,169 (38%) were noted to have an irAE of any grade. ICI were used as first-line therapy in 1,432 patients and second-, third-, or at least fourth-line in 1,119, 328, and 222 patients, respectively. The most common tumor type was non-small cell lung cancer (36%), followed by melanoma (14%). At baseline, any-grade irAE were more common among first-line ICI with 618 (43.2%) than for second-line (395, 35.3%), third-line (102, 31.1%), or at least fourth-line (54, 24.3%; $p<0.01$). After adjusting for age (over 65), sex, smoking history, and body mass index, the model revealed significant heterogeneity, indicated by a significant interaction between the ICI line and the primary tumor type ($p=0.01$). The impact of the ICI line on the odds ratio (OR) of irAE for each primary calculated: melanoma (OR) 0.54 (95% confidence interval [CI] 0.32-0.93), non-small cell lung cancer OR 1.14 (CI 0.96-1.35), head-neck cancer OR 0.82 (CI 0.58-1.14), and renal cell carcinoma OR 0.78 (CI 0.57-1.06). **Conclusions:** The effect of pre-treatment with prior systemic therapy was significantly associated with the odds of developing an irAE, though this effect was significantly heterogeneous between tumor primaries. Melanoma was significantly less likely to develop irAE when heavily pre-treated. In contrast, NSCLC suggested a trend of increased odds of irAE with more pre-treatment however it was not statistically significant. Further study is indicated to clarify the types of prior systemic therapy that may modulate the risk of irAE and better clarify the optimal sequencing of ICI. Research Sponsor: None.

Use of IL-3RB to mediate antitumor effect of CAR-T cells through the JAK-STAT signaling pathway.

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Background: The application of CAR-T in solid tumors has not yet demonstrated significant clinical benefits. The continuous proliferation and decreased terminal differentiation of CAR-T cells in vivo are considered potential strategies that could alter this predicament. Cytokines, as the 3rd signal for T-cell activation, play a crucial role in the lifecycle and fate of T cells. In this study, we innovatively incorporated the IL-3 receptor β chain (IL-3RB) into the CAR structure to enhance signal transduction, potentially activating the anti-tumor function of CAR-T and maintaining the persistent proliferative activity. **Methods:** Transcriptional profiling analysis performed on HER2 or VEGFR1 CAR-T cells, with a specific focus on the gp140 cytokine family (IL-3/IL-5/CSF-2) and the receptor expression, validated by ELISA and Western blot. By cloning CAR genes containing different structural domains of the IL-3RB into the lentiviral vector pWPXLd, CAR expression, activation, depletion, proliferation, cytotoxicity, pSTAT3 and pSTAT5, and cytokine release of CAR-T cells were assessed using flow cytometry (FCM), Western blot (WB), RTCA, CCK-8, and ELISA. Subcutaneous/abdominal injections of SKOV3 cells or SKOV3-Luc cells into NSG mice, followed treated by CAR-T cells. Tumor burden was regularly monitored, and FCM and Q-PCR were utilized to assess the quantity and phenotype of CAR-T cells in vivo. **Results:** RNA-sequence, ELISA and WB revealed that upon activation of CAR-T cells, the expression of genes such as IL-3/IL-5/CSF-2 rapidly increased. However, their receptors were hardly expressed. IL-3RB modification did not affect the phenotype of resting CAR-T cells. But, co-cultured with target cells, IL-3RB significantly enhanced the anti-tumor effects of CAR-T cells. This was manifested by more rapid activation, promotion of persistent proliferation, delayed exhaustion phenotype, secretion of higher levels of cytokines (IL-2, IFN-γ, TNF-α) and efficient cytotoxicity. IL-3RB-expressing CAR-T cells exhibited activation of the JAK kinase and STAT3, STAT5 transcription factor signaling pathways in vitro. We established solid tumor models of subcutaneous (SKOV3) and intraperitoneal metastasis, where HER2/VEGFR1 CAR-T cells partially inhibited tumor cell growth in vivo. In contrast, IL-3RB-enhanced CAR-T cells completely eradicated tumor cells, and even achieving a state of complete remission. FCM and Q-PCR also confirmed that IL-3RB significantly improved the proliferation and survival of CAR-T cells in vivo. **Conclusions:** IL-3RB is scarcely expressed in T cells and not regulated by T cell activation. IL-3RB-modified CAR-T cells exhibit superior persistence and significant anti-tumor advantages in a solid tumor through the JAK-STAT signaling pathway. Our innovative CAR structure design has the potential to demonstrate promising anti-tumor effects in clinical translational applications. Research Sponsor: The National Natural Science Foundation of China (82303745).

Initial data from a phase 1, first-in-human clinical trial for T-Plex, a multiplexed, enhanced T cell receptor-engineered T cell therapy (TCR-T) for solid tumors.

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Background: Solid tumors are notoriously heterogenous with highly variable antigen expression and an immunosuppressive microenvironment. HLA loss of heterozygosity (LOH) has also been identified in up to 40% of solid tumors, allowing tumor cells to evade T cell attack. To overcome these issues and a lack of potent endogenous antitumor T cells in cancer patients, TScan has developed T-Plex, a multiplexed cell therapy comprising two to three different TCR-Ts, chosen from a collection of TCR-Ts called the ImmunoBank. Product and study design details were presented at ASCO 2023 (Abstract #2554). **Methods:** A screening protocol (NCT05812027) pre-identifies patients with solid tumors any time during clinical care, enabling rapid enrollment into the treatment protocol (NCT05973487) upon disease progression. TCR-Ts currently in the master protocol target PRAME on HLA-A*02:01; HPV16 on HLA-A*02:01; MAGE-A1 on HLA-A*02:01, HLA-A*01:01, or HLA-C*07:02; or MAGE-C2 on HLA-B*07:02. All TCR-Ts in the ImmunoBank and master protocol are first tested as single therapies in dose levels 1 and 2 before becoming available for multiplexing in dose levels 3 and 4. **Results:** From September 2023 to the time of abstract submission, 140 participants with a variety of solid tumors were enrolled in the screening protocol and are in different stages of screening. To date, 65% have ≥1 HLA match, and 20% and 6% have 2 and 3 HLA matches, respectively, highlighting the advantage of including TCR-Ts targeting multiple different HLA types within the same master protocol. Of those who have completed target screening, 92% express at least one target and 65% qualify for at least one TCR-T. Intratumoral heterogeneity of target expression was observed even with the most prevalently expressed target, PRAME, supporting the rationale for multiplexed TCR-T treatment. Although HLA-LOH affects only half of HLA genes and the remaining intact HLA alleles in tumors can still be recognized by TCR-Ts, about 13% of participants had LOH of the targeted HLA allele, excluding them from TCR-T treatment. **Conclusions:** Initial data indicate that the combination of HLAs and targets in the ImmunoBank results in ≥1 TCR-T match for the majority of solid tumor patients evaluated to date, and many patients qualify for multiplexed TCR-T treatment. LOH testing can prevent selection and treatment with a TCR-T that would not confer benefit. The proportion of patients eligible for multiplexing is expected to increase as the ImmunoBank grows. Updated data on screened and treated patients will be presented at the meeting. Clinical trial information: NCT05973487; NCT05812027. Research Sponsor: None.

Updated results from first-in-human phase 1 dose-escalation trial of TAK-102, a GPC3-targeted armored CAR T cells, in patients with advanced solid tumors.

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Background: Glypican 3 (GPC3) is a member of the glypican family of heparan sulfate proteoglycans that are attached to the cell surface by a glycosylphosphatidylinositol anchor. High GPC3 expression rates are reported in numerous cancer types with a high unmet medical need, including hepatocellular carcinoma (HCC). TAK-102 is a GPC3-targeted autologous chimeric antigen receptor T cell (CAR-T) immunotherapy armored with IL-7 and CCL19. The addition of IL-7 and CCL19 to the construct was designed to support the expansion of memory subsets and persistence of CAR-T cells. We hypothesized TAK-102 would help overcome the challenges associated with an immunosuppressive tumor microenvironment that limit the activity of nonarmored CAR-T therapies in solid tumors. **Methods:** The first-in-human, Phase 1 dose escalation study evaluated TAK-102 in patients (pts) with GPC3-expressing solid tumors who were refractory or intolerant to standard treatments. TAK-102 was administered via a single infusion to 3 dose cohorts after lymphodepleting chemotherapy (LDC; consisting of fludarabine and cyclophosphamide): dose level (DL) 1 (starting cohort), $1x10^7$ CAR+ cells/body; DL2, $1x10^8$ CAR+ cells/body; DL3, $5x10^8$ CAR+ cells/body. Objectives included evaluation of safety, dose-limiting toxicity (DLT), recommended phase 2 dose, cellular kinetic (CK) parameters, tumor markers, cytokine/chemokine and antitumor activity based on RECIST 1.1. **Results:** Eleven pts were enrolled and infused TAK-102 (DL1: 3 pts, DL2: 3 pts, DL3: 5 pts): 1 gastric neuroendocrine carcinoma, 2 liposarcoma, 8 HCC. Five pts achieved stable disease (SD), HCC (GPC3 H-Score: 36) . In patients achieving SD, the greatest reduction in tumor size was 26.4%. No DLTs or neurotoxicity were observed. Six pts experienced cytokine release syndrome (Grade1: 5 pts, Grade2: 1 pt); all cases were manageable. AFP was measured as a tumor marker for HCC. Among 8 pts with HCC, 4 had SD after treatment with TAK-102 and 3 showed a decrease or stabilization of AFP levels corresponding to their clinical status. CK profiles for pts were assessed by flow cytometry and qPCR-based assays. Overall, there was improvement in TAK-102 exposure (Cmax, AUC) when escalating from DL1 to DL2. There was a slight decrease in Tmax from DL2 to DL3. Homeostatic cytokine (IL-7) spiked post-LDC and showed no further increase after TAK-102 infusion across all the DLs. There was dose-dependency observed in peak CCL19, IFN-γ and IL-6 levels. **Conclusions:** TAK-102, an armored CAR-T, is well tolerated and has a manageable safety profile with some early signs of anti-tumor activity. For CK, TAK-102 exposure (Cmax, AUC) showed improvement from DL1 to DL2, and slight decrease in Tmax from DL2 to DL3. Dose-dependency was observed in peak CCL19, IFN-γ and IL-6 levels, which may point towards increased signal of activity from DL1 to DL3. Clinical trial information: NCT04405778. Research Sponsor: Takeda Pharmaceutical.

The role of obesity on outcomes of adoptive cellular therapy in solid tumors.

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Background: Anti-tumor response and toxicity outcomes with adoptive cell therapy (ACT) have been heterogeneous in solid tumors, and it is still unclear how host factors such as obesity may contribute to efficacy and immune-related safety events. **Methods:** We conducted a retrospective study including 95 consecutive advanced solid tumor patients who received ACT on protocol in the Department of Investigational Cancer Therapeutics between August 2017 and June 2023. We analyzed baseline clinical characteristics, immune-related safety events, response to ACT, and survival outcomes between obese and non-obese patients. Overweight was defined as body mass index (BMI) 25-29.99 kg/m^2 and obesity was defined as BMI $\geq$ 30 kg/m^2 at the time of treatment. Fisher's exact test was used to compare the proportions of categorical variables between two groups. Pairwise comparison with Bonferroni correction was performed if necessary. T-test was used to compare the mean of continuous variables between two groups. The distributions of overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier method. Log-rank test was used to compare the distributions of OS and PFS by baseline characteristics. Hazard ratio was estimated in Cox proportional hazard regression model. A two-sided p-value < 0.05 was considered statistically significant. **Results:** The median age at treatment was 60.9 (range 20.5 – 84). Thirty-nine patients (41.1%) had a BMI (kg/m^2) defined as normal weight, 26 (27.4%) as overweight, 27 (28.4%) as obese, and 3 (3.2%) as underweight. Eighty-four (88.4%) were Caucasian; 54 (56.8%) were female. The most prevalent cancers were gastrointestinal (21.1%), gynecologic (15.8%), sarcoma (11.6%), mesothelioma (10.5%), breast (8.4%). The median follow-up was 39.9 months, with a median PFS of 2.8 months (95% CI: 2.3, 3.5) and a median OS of 8.4 months (95% CI: 6.4, 11.0). The risk of death among the obese patients was 0.56 (95% CI: 0.31, 0.99) times the risk of death among normal weight patients (p = 0.045). No weight difference was found between responder and non-responder. While BMI was not associated with the development of cytokine release syndrome (CRS), the patients with normal weight had a higher proportion of immune effector cell-associated neurotoxicity syndrome (ICANS) than the obese patients (23.1% vs 0%, p = 0.049). **Conclusions:** Obesity was associated with improved survival and decreased ICANS rates following ACT. Our findings may suggest a differential interaction between obesity, different immunotherapeutic modalities, and hematologic vs nonhematologic cancers. Research Sponsor: None.

Updated results on multiple antigens stimulating cellular therapy (MASCT-I) in metastatic urothelial carcinoma: A randomized, open-label, phase I trial.

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Background: The appropriate treatment for mUC remains unmet medical needs. MASCT-I, an adoptive transfer of dendritic cells (DCs) presenting 15 types of tumor-associated antigens (TAAs), showed valuable treatment in solid tumors. We previously reported the efficacy and safety of MASCT-I alone, or plus camrelizumab or chemotherapy in mUC (NCT03034304). The biomarker analysis and long-term follow-up to for this promising approach was unknown. **Methods:** All enrolled patients were divided into in five groups (G) as previous reported. Patients in G2 receiving maintenance therapy of MASCT-I after first-line platinum based-chemotherapy were allowed to enter enrolled in G3 and receiving MASCT-I plus camrelizumab when disease progressed. We updated the exploratory endpoint of the IFN-γ ELISPOT assay, which was used to measure activation of the cytotoxic T Lymphocyte (CTL) response in eligible patients. Long-term follow-up results for safety, progression-free survival (PFS) and overall survival (OS) were reported. **Results:** 39 patients were enrolled. By January 31st, 2024, median follow-up time was 31.1 months. No new safety signals were updated. As previously reported, the most common adverse events (AEs) associated with MASCT-I included grade 1 and 2 flushing, pruritus, rash, muscle cramp, fever, and arthralgia. No MASCT-I-related death occurred. Median PFS and OS for all patients were 2.3 months, and 16.9 months, respectively. Patients in G2 presented superior OS of 41.2 months and duration of response (DOR) of 6.4 months. Nine patients treated with MASCT-I and camrelizumab after progression on MASCT-I in G2 presented a 24-month PFS rate of 55.6% and a 48-month DOR rate of 71.8%. Five patients had prolonged PFS for more than 20 months while two of them had PFS of more than 43 months. To identify the potentially beneficial population, IFN-γ ELISPOT data analysis revealed that patients who had positive TAAs ELISPOT response had significant prolonged PFS and OS compared to the non-responders (median PFS: 10.1 months vs 4.8 months, HR=0.30, 95% CI: 0.14-0.61, $P<0.005$; median OS: not reached vs 13.6 months, HR=0.16, 95% CI: 0.05-0.57, $P<0.005$). The C_{max} value of INF-γ-positive T cells after cell infusion was also higher in patients with better PFS. In addition, we observed a significant increase in INF-γ-positive T cell activities in patients who progressed from G2 and were subsequently treated with a combination of MASCT-I and camrelizumab (C_{max} mean (SD): 72 spots per million bulk PBMCs at G2 to 186 spots per million bulk PBMCs after transfer to G3, $P=0.002$). **Conclusions:** MASCT-I alone or in combination with immunotherapy or chemo-therapy are safe and well tolerated, with inspiring survival benefit. The combination of PD-1 inhibitors may enhance the antitumor activity of MASCT-I. IFN-γ ELISPOT might be able to predict potentially beneficial populations. Clinical trial information: NCT03034304. Research Sponsor: HRYZ Biotech Co, Shenzhen, China.

Effect of novel autologous immune training platform on end-stage patients with cancer.

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Background: SUPLEXA therapeutic cells are the initial autologous and non-engineered candidate to emerge from the novel ENLIST cells training platform. Manufacturing is robust, reproducible and with an acceptable cost of goods. The method requires 35 days to produce multiple doses. Multiple mechanisms of SUPLEXA therapeutic cells have been delineated and all appear to complement that of immune checkpoint inhibitors (ICIs) with SUPLEXA cells serving to enhance the number of primed anti-tumor host T cells while ICIs serve to increase the durability of primed T cells by blocking their premature down-regulation. **Methods:** A 35 patient Phase 1 single-agent study survey study is currently ongoing in Australia to test the safety and clinical activity of SUPLEXA cells in end-stage patients with various tumor types. No chemo preconditioning or concomitant cytokine treatment was employed. CYTOF analysis of longitudinal peripheral blood is used to monitor changes to the host immune system. **Results:** To date, SUPLEXA therapeutic cells have demonstrated safety and significant clinical benefit with an observed CR, PR, and many durable SD in approximately half the patients. Several solid tumor patients remain on study beyond 1 year and doing well. Longitudinal analysis of PBMCs from SUPLEXA cell treated cancer patients demonstrated durable changes in the composition of myeloid immune cell subsets in SUPLEXA treated patients, impacting the anti-tumor bias of the host immune system. Specifically, we identified a dramatic decrease in the number of peripheral myeloid derived suppressor cells (MDSCs), within 3 weeks of SUPLEXA treatment. In patients with CR and PR, we also identified stable increases in activated classical CD14+ blood monocytes. **Conclusions:** SUPLEXA therapeutic cells are a highly differentiated approach to cellular therapy. The first-in-human experience demonstrated a pristine safety profile and strong clinical benefit as a single-agent. The pharmacodynamic decrease of in the number of MDSCs, known to suppress the anti-tumor immune response and limit immune checkpoint inhibitors (ICIs) efficacy, supports the further clinical testing to test the hypothesis that the multiple mechanisms of SUPLEXA cells will enhance the clinical activity of ICIs. Clinical trial information: NCT05237206. Research Sponsor: None.

Exploring the safety and efficacy of GT201 as a first-in-class autologous tumor-infiltrating lymphocyte monotherapy in advanced solid tumors.

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Background: GT201, featuring a membrane bound IL-15 stably expressed on tumor-infiltrating lymphocytes (TIL), aims to augment TIL persistence and function as well as ameliorate immune suppression within the tumor microenvironment, offering potential for durable responses in advanced solid tumor patients. We present data from 7 patients enrolled in an open-label, single-arm, multicenter clinical study (NCT05729399), investigating the safety profile and efficiency trend of GT201 therapy. **Methods:** The GT201 phase 1 trial is designed with the primary endpoint of DLT evaluation and the secondary endpoint of measuring preliminary efficacy parameters including overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR, and overall survival (OS) following the RECIST v1.1. **Results:** As of January 22, 2024, a cohort of 7 pts has been enrolled in the study, with a median age of 48 and a median of 3 prior lines of therapy. Among these patients, 1 pt has a history of bone metastases, 2 pts have a history of liver metastases, and 1 pt has a history of brain metastases. Following the standard FC lymphodepletion, pts underwent infusion with GT201 at doses $\geq 5x10^9$ total viable cells. Five pts subsequently received IL-2 as part of the treatment protocol. Treatment-related AEs were observed in $\geq$ 50% of pts with no grade$\geq$3 AEs. Grade $\geq$ 3 AEs related to FC lymphodepleting chemotherapy and IL-2 included decreased lymphocyte count, decreased neutrophil count, and decreased white blood cell count, pyrexia and increased heart rate. Notably, all grade $\geq$3 AEs were either recovered or downgraded to grade $\leq$ 2 within 14 days. Among the 7 response-evaluable patients across various indications, including Non-Small-Cell-Lung Cancer (NSCLC), melanoma malignant, cervical cancer, and ovarian cancer, 3 patients (42.9%) achieved a confirmed partial response (PR), and 2 patients (28.6%) demonstrated stable disease (SD) as their best response. Notably, among the NSCLC subgroup, disease control (SD $\geq$ 24 weeks or any PR) was observed in all 3 pts (3/3, 100 %). GT201 cells can be detected in all patients receiving treatment, indicated by both staining IL15RA protein on peripheral T cells and measuring the transgene copy number in peripheral white blood cells. GT201 cells expanded robustly in patients and persist in peripheral blood beyond at least 6 months post cell infusion. **Conclusions:** In patients with heavily pretreated advanced or metastatic solid tumor, GT201, when infused after FC lymphodepletion and followed by high dose IL-2, exhibits a manageable safety profile. Notably, GT201 has demonstrated a favorable clinical profile in NSCLC, with an encouraging objective response rate, response durability, and no GT201-treatment related grade$\geq$3 AEs. Clinical trial information: NCT05729399. Research Sponsor: None.

Phase 1 study of GT101 as an autologous tumor infiltrating lymphocyte (TIL) therapy in advanced solid tumors.

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Background: Adoptive cell therapy utilizing autologous TIL has demonstrated efficacy and durable long-term responses in patients with certain advanced solid tumors progressed after conventional therapies. We present data from 14 patients enrolled in the study of GT101, a Phase 1, open-label, single-arm, multicenter trial (NCT05430373) of autologous TIL therapy, aiming to investigate the safety profile, efficiency trend and the duration of response. **Methods:** The trial was designed with the primary endpoint on evaluating DLT and characterizing the safety profile of GT101 in solid tumor patients measured by the incidence of Grade $\geq$ 3 treatment-emergent adverse events (TEAEs). The secondary endpoints were to assess efficacy parameters including overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS) according to RECIST v1.1. **Results:** As of November 10, 2023, a cohort of 14 patients received treatment with a median age of 46.9 and a median of 2.6 lines of prior therapies. Following a standard FC-based lymphodepletion, patients underwent GT101 infusion at doses $\geq 5x10^9$ cells with median dose of $3.7x10^{10}$ cells, followed by high-dose IL-2 administration. Most of observed Grade $\geq$ 3 AEs were related to the FC conditioning regimen and IL-2, including decreased lymphocyte count, decreased white blood cell count, decreased neutrophil count, anemia, pyrexia and decreased platelet count. The majority of these AEs were recovered within 14 days, while a few were downgraded to $\leq$ Grade 2 within 4 weeks. Among 14 enrolled patients across various indications (small-cell-lung cancer, melanoma, cervical cancer), the ORR was 35.7%. Specifically, 4 pts (28.6%) had a confirmed partial response (PR), 1 pt (7.1 %) achieved complete response (CR), and 8 pts (57.1 %) had stable disease (SD) as their best response. One pt had unconfirmed disease progression (PD). Notably, among 11/14 patients with cervical cancer, the ORR was 45.5% (5/11) with 4 pts (36.4%) achieving PR and 1 pt (9.1 %) achieving CR. Disease control was observed in 10/11 pts (90.9%), and the median PFS was 4.2 months for this cohort. The CR patient underwent a long-term follow-up and the duration of CR and PFS (estimated by Kaplan-Meier) was 24 weeks and 36 weeks, respectively. Post GT101 infusion, T cell expanded robustly in the peripheral blood of all patients with median Tmax 6.83 days and average 15.9 days. **Conclusions:** In the GT101 Phase 1 study, no treatment-related SAEs and DLT were observed. In patients with heavily pretreated advanced or metastatic solid tumors, GT101 exhibited a manageable safety profile under the treatment protocol of lymphodepletion and high-dose IL-2 and a favorable clinical profile, particularly in cervical cancer, with an encouraging ORR and sustained response duration. Clinical trial information: NCT05430373. Research Sponsor: None.

A first-in-human study of CRISPR/Cas9-engineered tumor infiltrating lymphocytes (TILs) product GT316 as monotherapy in advanced solid tumors.

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Background: A next-generation TIL product GT316 was engineered with CRISPR/Cas9 to genetically disrupt two key immunoregulatory targets identified from a genome-wide CRISPR screening platform and demonstrated significantly enhanced anti-tumor efficacy and persistence in pre-clinical animal studies with ameliorated TIL exhaustion profile. A first-in-human trial was initiated to evaluate the preliminary safety and efficacy of GT316 in advanced solid tumors. **Methods:** The first-in-class study is to enroll patients (pts) with advanced treatment-refractory solid tumors, especially gynecological tumors. Once the optimal biological dose (OBD) is identified, a monotherapy expansion phase will be initiated for pts with various solid tumors. Enrolled pts were preconditioned with a nonmyeloablative (NMA) lymphodepletion regimen and treated by infusion of the GMP-grade G316 product followed by IL-2 administration. **Results:** As of January 22, 2024, the dose escalation study enrolled 4 pts, all of whom were female with a median age of 58 years with 1 to 9 prior lines of systemic treatment. The median number of infused TIL cells was 1.0E+10. All pts experienced TRAEs with the majority being grade 1 or 2. Grade 3/4 TRAEs included lymphocyte count decreased, white blood cell count decreased, monocyte count decreased and neutrophil count decreased, which were related to the NMA regimen. No dose-limiting toxicities (DLTs) or TIL-related grade≥3 TRAEs were observed. Median time on study was 33.4 wks (8–35 wks). One pt with treatment-refractory cervical cancer experienced a confirmed complete response (CR) after 4 wks and the duration of response is 32 wks by now (RECIST 1.1). One ovarian cancer pt with 9 lines of previous systemic therapies experienced a confirmed partial response (PR) after 4 wks and the duration of response is 22 wks by now (RECIST 1.1). Response data will be continuously collected. The other two ovarian cancer pts experienced stable disease (SD) and progressive disease (PD), respectively. Despite varying doses of TILs (3.2E+09 to 1.90E+10) and IL-2 (up to 3.0E+05 IU/kg), all pts receiving GT316 showed robust TIL expansion post-infusion, which is positively correlated with administrated IL-2 doses. Enhanced IFN-γ secretion could be detected in the serum of the CR and PR pts compared to the SD and PD pts, indicating potential tumor antigen-specific response. **Conclusions:** The first-in-human study of GT316, a CRISPR/Cas9-dual KO anti-exhaustion TIL product, demonstrates good tolerability with encouraging preliminary anti-tumor efficacy as a monotherapy in pts with advanced solid cancers. The infusion of GT316 was associated with robust TIL expansion and IFN-γ secretion. Updated data with additional follow-up will be continuously collected, and OBD will be determined based on the overall data of safety and preliminary efficiency. Clinical trial information: NCT06145802. Research Sponsor: None.

Effect of CD22-directed CAR-T cells secreting anti-CD19 T cell engagers on control of leukemia progression compared to tandem anti-CD19/CD22 CAR-T cells.

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Background: Antigen-specific cancer immunotherapies, based on engineered T cells bearing chimeric antigen receptors (CARs) or the systemic administration of bispecific T cell-engagers (TCEs), have a significant impact on relapsed/refractory (R/R) B cell malignancies. However, a significant percentage of patients relapse following CAR-T or TCE therapy, with antigen loss accounting for up to one third of relapses/progressions. To avoid antigen loss after administration of single-targeted CAR-T cells and to minimize tumor escape, strategies targeting two antigens simultaneously have been developed and validated in both preclinical models and clinical trials. Nevertheless, despite lowering the risk of antigen loss, these strategies still have some limitations, mainly related to design and manufacturing challenges. **Methods:** In this context, we have generated the first dual-target strategy for hematological malignancies based on T cells bearing an anti-CD22 CAR and secreting an anti-CD19 T-cell engager antibody (CAR-STAb-T cells) and conducted a comprehensive preclinical study comparing its therapeutic potential with a previously validated anti-CD19/CD22 tandem CAR therapy (TanCAR-T) for B-cell acute lymphoblastic leukemia (B-ALL). **Results:** We have demonstrated in both short- and long-term assays, using contact and non-contact co-culture systems, that CAR-STAb-T cells efficiently redirect bystander T cells, resulting in enhanced cytotoxic activity compared to that exhibited by TanCAR-T cells at very low E:T ratios. In addition, CAR-STAb-T cells induce more potent and faster cytotoxic responses than TanCAR-T cells in both short- and long-term co-culture assays when reproducing antigen-downmodulated conditions *in vitro*. *In vivo* assays conducted in NSG mice transplanted with a B-ALL patient-derived xenograft (PDX), followed by intravenous injection of CAR-STAb-T or TanCAR-T cells under a T cell-limiting experimental setting, also showed that CAR-STAb-T cells maintained a tighter control of tumor progression than TanCAR-T cells in peripheral blood and bone marrow. **Conclusions:** In conclusion, we have demonstrated that the combination of a cell surface CAR and a soluble TCE recognizing different antigens may be advantageous over the use of conventional multi-targeted strategies based on cell surface-anchored receptors. Furthermore, we have proven that a small number of transduced CAR-STAb-T cells is sufficient to redirect non-transduced bystander T cells specifically and efficiently in the presence of leukemia cells, providing a significant advantage over current dual-targeted CAR-T cell therapies. CAR-STAb-T cells could therefore become an alternative to CAR-T therapies for the treatment of R/R B cell malignancies, especially in lymphodepleted patients with low T cell counts. Research Sponsor: Ministerio de Ciencia, Innovación y Universidades; Carlos III Health Institute; European Regional Development Fund (FEDER); Asociación Española contra el Cáncer (AECC); CRIS Cancer Foundation; Fundación ‘‘La Caixa’’; Fundación para la Investigación Biomédica Hospital 12 de Octubre.

IOV-3001, a modified interleukin-2 fusion protein, for potential use in tumor-infiltrating lymphocyte cell therapy regimens.

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Background: Tumor-infiltrating lymphocyte (TIL) cell therapy has shown promising efficacy in patients with solid tumor malignancies. Interleukin-2 (IL-2) administration after TIL infusion supports persistence and survival of infused TIL. Aldesleukin is a synthetic IL-2 with a short half-life administered every 8–12 hours, to support the expansion and persistence of the TIL *in vivo*. IOV-3001 is a modified dimeric IL-2 fused to palivizumab that has a longer half-life and potentially better safety profile, compared with aldesleukin. Here, we describe the preclinical activity, pharmacokinetics (PK), pharmacodynamics (PD), and *in vivo* safety profile of IOV-3001. **Methods:** Binding of IOV-3001 and aldesleukin to the IL-2 receptor (IL-2R), IL-2R-mediated activation via STAT5 phosphorylation, and T cell proliferation were assessed. Pharmacological activities of IOV-3001 and aldesleukin were evaluated in B16-F10 mice infused with pmel-1 T cells. Safety after a single dose of IOV-3001 (0.01–9.0 mg/kg) was assessed in cynomolgus monkeys across 3 independent studies. PK and PD parameters, clinical pathology, hematology, and histopathology were assessed. **Results:** Both IOV-3001 and aldesleukin induced comparable STAT5 phosphorylation and proliferation of T-cell subsets. Mice infused with pmel-1 T cells and subsequently treated with IOV-3001 or aldesleukin showed similar reductions in tumor burden. The half-life of IOV-3001 in cynomolgus monkeys ranged from 5–8 hours. IOV-3001 was well tolerated in monkeys across the dose range studied except for 1 animal administered IOV-3001 at the highest tested dose level, with recovery by Day 29. Inflammatory cytokines (IL-12 p40, IL-6, MCP-1) increased from 4 hours to ≤3 days after dosing and returned to baseline by Day 29. Fibrinogen, bilirubin, and triglycerides increased on Day 3 and returned to baseline by Day 29. No signs of capillary leak were observed. Increased numbers of hematopoietic cells were found in the bone marrow, spleen, and lymph nodes 3 days post dosing. During the 4-week recovery, these changes diminished or resolved, while bone marrow showed differential dose-dependent effects. IL-2–induced proinflammatory PD effects were observed, including >10-fold peak CD8+ T cell expansion in peripheral blood mononuclear cells at Day 5 versus preacclimation in most cynomolgus monkeys treated with IOV-3001. **Conclusions:** IOV-3001 exhibited a similar mechanism of action (MoA) to that of aldesleukin *in vitro* and has a longer half-life *in vivo*. PD effects were consistent with the MoA of IL-2. IOV-3001 showed a favorable preclinical safety profile. These results suggest a potentially improved safety profile for IOV-3001 with less frequent dosing compared with aldesleukin. These features of IOV-3001 strongly advocate for its development in TIL cell therapy regimens.
Research Sponsor: Iovance Biotherapeutics (San Carlos, CA, USA).

Non-clinical evidence supporting the upcoming CLD-201 clinical trial: Cell-based oncolytic virotherapy for multiple solid tumors.

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Background: Oncolytic virotherapy is a promising approach that uses viruses to target and destroy cancer cells while activating an anti-tumor immune response. However, a major challenge is the rapid elimination of oncolytic viruses (OVs) by the patient's immune system. Calidi's innovative platform addresses this issue by combining allogeneic stem cells with an OV payload, preventing immune system elimination, and promoting viral amplification at tumor sites. This induces immunogenic cell death and stimulates potent anti-tumor immune responses, effectively targeting primary and metastatic tumors. Prior clinical studies have demonstrated the effectiveness of autologous stem cells loaded with Vaccinia virus CAL1 (ACAM2000) in multiple tumor types, especially when combined with checkpoint inhibitors. However, this approach is costly, lacks scalability and reproducibility. To overcome those limitations, we developed CLD-201 (or SuperNova-1), an innovative concept based on CAL1-loaded allogeneic mesenchymal stem cells, specifically designed for intratumoral administration. This study presents selected non-clinical studies performed to support the upcoming clinical trial to treat multiple solid tumors. **Methods:** We tested the tumor selectivity and efficacy of CLD-201 in Melanoma, Triple Negative Breast Cancer, and Squamous Cell Carcinoma. We also assessed its ability to kill cancer cells in the presence of complement and neutralizing antibodies. Immune cell infiltration in treated and untreated tumors was analyzed using flow cytometry. We conducted dose escalation, safety, toxicology, and biodistribution studies of CLD-201 in multiple immune-compromised and immunocompetent mouse models. **Results:** Vaccinia virus CAL1 showed preferential amplification in tumor cells and, when loaded into adipose stem cells (CLD-201), demonstrated greater resistance to inactivation by the humoral immune system compared to the unprotected CAL1 virus. CLD-201 significantly inhibited the growth of tumors even at a very low dose of $1.5x10^3$ cells containing $1.6x10^4$viral plaque-forming units (PFU). Massive CD4 and CD8 T-cell infiltrations were detected in both treated and untreated tumors. CLD-201's safety profile is studied in both GLP and non-GLP toxicology/ biodistribution nonclinical studies. **Conclusions:** CLD-201 offers several important advantages over the autologous approach, including enhanced potency through significant viral amplification within the stem cells, improved manufacturing reproducibility, off-the-shelf ability to treat multiple cancer types, and significantly lower cost. Non-clinical studies revealed that both intratumoral and systemic administration were well-tolerated. A phase I non-randomized clinical trial has been designed to evaluate the safety and initial anti-tumor effects of intratumoral administration of CLD-201. Research Sponsor: None.

Effect of placental circulating T cells expressing CD16 on multiple hematological and solid tumor cancers through combination with various monoclonal antibodies.

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Background: PT-CD16VS is an allogeneic cell therapy derived from human postpartum placental circulating T (PT) cells that are genetically modified to express CD16 and endogenous T cell receptor (TCR) knockout. PT-CD16VS cells can be combined with various monoclonal antibodies to engage in anti-tumor antibody-dependent cellular cytotoxicity (ADCC) against diverse cancers with a "universal receptor" approach. Here we report the characterization and preclinical evaluation of PT-CD16VS in combination with monoclonal antibodies against both hematological and solid tumor cancers. **Methods:** PT cells were activated, transduced with a lentiviral vector containing a construct expressing a high affinity CD16 variant, CD16VS, and transfected to knock out the TCR. *In vitro,*functional activity of PT-CD16VS cells in combination with monoclonal antibodies was assessed in cytotoxicity, cytokine release, and proliferation assays. *In*vivo, PT-CD16VS was combined with Rituximab in a Raji xenograft model in NSG mice, and with Trastuzumab in a subcutaneous NCI-N87 xenograft model in NSG mice in which tumor volume was measured and tumor samples were evaluated for PT-CD16VS infiltration. **Results:** *In vitro*, PT-CD16VS exhibited potent ADCC and cytokine release when combined with Rituximab against CD20+ Burkitt's lymphoma (Daudi and Raji), with Trastuzumab against HER2+ gastric carcinoma (NCI-N87), with Trastuzumab or Avelumab against HER2+/PDL-1+ non-small cell lung carcinoma (NCI-H1975) and Trastuzumab-resistant metastatic mammary adenocarcinoma (JIMT-1), and with Cetuximab against EGFR+ triple negative metastatic mammary adenocarcinoma (MDA-MB-231). Moreover, examples of PT-CD16VS antigen-specific proliferation were demonstrated against Raji and NCI-N87 when cells were combined with Rituximab and Trastuzumab, respectively. *In vivo*, in combination with Rituximab in the Raji mouse model, PT-CD16VS exhibited significant survival benefit compared to vehicle and Rituximab alone treated groups. In the subcutaneous NCI-N87 solid tumor model, PT-CD16VS with Trastuzumab demonstrated significant reduction in tumor volume compared to vehicle, Trastuzumab, and Enhertu groups. In addition, PT-CD16VS infiltration into the tumor was shown to be Trastuzumab dependent, with infiltrating cells expressing high levels of CD16 and Ki67. **Conclusions:** Our results show that PT-CD16VS have potent *in vitro* and *in vivo* ADCC activity, and a single drug product has the potential to be combined with various monoclonal antibodies to target multiple cancers across hematological and solid tumor indications. This "universal receptor" with antibody-dependent targeting approach, together with the benefits of an allogeneic cell platform, may democratize accessibility of such therapies for patients. Research Sponsor: Celularity Inc.

Constructing adverse event timelines for patients receiving CAR-T therapy using large language models.

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Background: Chimeric antigen receptor T (CAR-T) therapy is associated with a high risk of severe adverse events often only detailed in clinical notes. Monitoring them demands significant time and effort for manual chart review. Recent developments in large language modeling (LLMs) show promise for large-scale information extraction from clinical text. We performed a pilot study to evaluate the capability of the GPT-4 LLM to extract adverse events documented in the progress reports. **Methods:** We extracted progress notes within 30 days of any CAR-T administration from the UCSF deidentified clinical data warehouse. GPT-4, accessed through a HIPAA compliant Microsoft Azure Studio API, was used to extract CAR-T adverse events resulting in clinical intervention. A random sample of adverse events from 10% of patient notes were evaluated by a clinical reviewer (JG, PharmD). Topic modeling using BERTopic was used to cluster all adverse events to identify trends over time. **Results:** We identified 4183 clinical notes written within 30 days of CAR-T administration from 253 patients (39.1% women, 60.9% men). Mean age was 60.6 (SD:17.7). Manual validation of clinical notes from 10% of patients with CAR-T therapies (n=25) demonstrated that GPT4 was able to extract CAR-T related adverse events with 64% accuracy. We used BERTopic to cluster all extracted adverse events into 19 topics. Clusters with key terms "hyponatremia, leukocytosis, encephalopathy, toxicities, and neurologic" occurred most often (n=277), and primarily documented 12.9 days after CAR-T administration (Table). **Conclusions:** Although limited by use of de-identified data and absence of prompt engineering, this pilot supports the further investigation of LLMs for extraction of adverse events from unstructured clinical text. Research Sponsor: National Insitutes of Health; UL1 TR001872.

Topic	Count	Top Terms	Mean Days After CAR-T Administration
0	277	hyponatremia, leukocytosis, encephalopathy, toxicities, neurologic	12.9
1	142	January, 01, March, ice, score	10.7
2	116	CNS, DLBCL, max, stage, CKD	14.2
3	78	pancytopenia, tocilizumab, requiring, cytopenias, pancytopenic	12.3
4	66	tachycardia, hypoxia, include, 38, febrile	8.5
5	59	neutropenic, state, drug, borderline, CMS	12.9
6	48	pain, back, extremity, chronic, abdominal	15.6
7	40	cell, effector, immune, associated, aplasia	11.3
8	35	confusion, obtundation, mental, status, altered	10.9
9	26	symptoms, resolution, observed, CRS, evidence	11.0
10	24	induced, anemia, mild, hyperglycemia, vomiting	14.0
11	23	liver, enzymes, significantly, ferritin, increased	10.6
12	20	Hx, damage, organ, end, XRT	14.9
13	18	disease, progression, interval, hypermetabolic, nodes	17.1
14	17	host, immunocompromised, polyneuropathy, peripheral, drop	19.1
15	16	intermittent, chills, vital, acetaminophen, oxygen	7.6
16	15	care, planning, advance, towards, aggression	12.7
17	14	g2, g0, anemia, October, eating	15.9
18	14	rvr, afib, sinus, bradycardia, tele	12.1

Gender disparity in chimeric antigen receptor T-cell therapy utilization and outcomes in the United States.

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Background: Chimeric antigen receptor T-cell [CART] therapy has marked a new era in the treatment of relapsed/refractory hematological malignancies since its approval in 2017. Racial disparity was studies previously but not gender. Current study aimed to evaluate gender disparity in CART therapy utilization and outcomes. **Methods:** This cross sectional study was done using National Inpatient Sample [NIS], the largest database available in the US. Inpatient admissions of adults who received CART therapy for various indications during year 2020 were included. **Results:** A total of 6915 patients were admitted to hospital for CART therapy in 2020 with an overall inpatient mortality rate of 1%. Mean age of the patients was 57yr. Majority were White [64%], with a higher median household income, admitted to urban and large sized hospitals and predominantly covered by Medicare or private insurance [~80%]. Study population was divided into males and females and outcomes were compared. Females were significantly younger with lower Charlson comorbidity index and higher utilization of CART therapy [81% vs 19%] compared to males. Females had 86% lesser odds of mortality compared to males (Odds Ratio [OR] 0.14; 95% confidence interval [CI] 0.04-0.47; p value 0.001). Females had significantly lesser hospitalization charges [mean decrease $471,193; p value 0.000] and length of stay [mean decrease 8 days; p value 0.000] compared to males after adjusting for confounders. Racial differences in outcome were compared after multiple imputation was used to correct for 4% missing data in the race category in NIS 2020. There was no statistically significant difference in mortality, length of stay or hospitalization charges between Whites, Blacks and Hispanic races similar to previous studies. **Conclusions:** Eligibility criteria for CART therapy includes patients with good performance status and organ function with less comorbidities. Our study found that females were younger, healthier and therefore qualified better for CART therapy compared to males. Hence they had significantly higher utilization of CART therapy. In addition, among the population receiving CART therapy, females had better outcomes compared to males in terms of mortality, length of stay and hospitalization charges. In general, males have higher incidence and mortality with poorer outcomes in most hematological malignancies where CART therapy is a treatment option. Measures at modifying and improvising CART therapy to cater to more male subjects will not only reduce gender disparity but also improve overall survival and reduce disease burden. Research Sponsor: None.

CART therapy comparison between males and females.

	Males	Females	P Value
Number of patients[%]	1314 [19]	5601 [81]	
Mean age[years]	60.2	56.8	0.001
Mortality[%]	3.5	0.5	0.01
Mean length of Stay[days]	18.5	4.3	0.000
Mean Hospitalization charge[$]	958615	206882	0.000

Erythrocyte-αPD-1 conjugates overcome resistance to checkpoint blockade immunotherapy: A first-in-human study.

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Background: While the immune checkpoint blockade (ICB) therapy has revolutionized the field of tumor therapy. the resistance remains a major challenge. We have previously developed WTX-212, an erythrocyte-antibody conjugate covalently linking anti-PD-1 antibody to erythrocyte membranes. Unlike conventional antibodies, WTX-212 exhibits natural accumulation in the spleen and remodels the splenic immune landscape in tumor-bearing mice. WTX-212 treatment efficiently activates CD8+ T cells in the spleen, which subsequently infiltrate into tumors and exhibit anti-tumor cytotoxicity. Additionally, activated T cells reduce the splenic reservoir of Myeloid-derived suppressor cells (MDSC) and those within tumors, further enhancing overall anti-tumor responses. Pre-clinical studies have demonstrated that WTX-212 can significantly suppress tumor growth in xenograft tumor models resistant to anti-PD-1 immunotherapies. A first-in-human (FIH) clinical trial is now investigating its potential in human cancer patients. **Methods:** The FIH trial (NCT05707325) is aimed to investigate the safety, pharmacokinetics and preliminary efficacy of WTX-212 in cancer patients with advanced malignancies. All of patients had previously received anti-PDs therapies and developed resistance to these treatments. By Feb 5th, 2024, the tumor lesions were assessed using RECIST v1.1 criteria. Blood and tumor samples were collected for correlative analysis. **Results:** 7 metastasized patients with various solid tumors, having undergone a median of 3.1 prior lines of therapy (ranging from 1-6), received WTX-212 monotherapy. None of patients treated with WTX-212 experienced treatment-related adverse events greater than Grade 3, indicating a high safety profile. WTX-212 was detectable in peripheral blood at the end of cycle in a dose dependent manner. Disease control was achieved in 5/7 patients (DCR=71%). Specifically, a patient with esophageal cancer, achieved a confirmed complete remission after 6-cycle treatment. Additionally, two patients, one with esophageal cancer (3L) and another with HPV-negative cervical cancer (4L), maintained stable disease for over 40 and 30 weeks, respectively. Consistent with our pre-clinical findings, a substantial reduction in MDSCs were observed in 6/7 patients (ranging from 24%-82%). Furthermore, a median 1.5-fold increase in T cells was noted in all patients in the peripheral blood after the 1st cycle of the treatment. **Conclusions:** WTX-212 treatment is safe and tolerable and shows promising clinical signs in cancer patients resistant to anti-PD-1 immunotherapy, supporting further investigation and exploration of WTX-212 monotherapy and combination therapy. Clinical trial information: NCT05707325.
Research Sponsor: None.

Antagonizing vasoactive intestinal peptide (VIP) receptors with Muc16CD-directed armored CAR T cells for pancreatic cancer.

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Background: Chimeric antigen receptor (CAR) T therapies for pancreatic ductal adenocarcinoma (PDAC) still face significant immunosuppressive obstacles in the tumor microenvironment (TME). We hypothesize that an optimal CAR T cell for PDAC combines targeting an ideal tumor-associated antigen (TAA) and overcomes unique immunosuppression in the PDAC TME. The retained ectodomain of Muc16 (Muc16CD) is a known TAA in ovarian cancer but has yet to be explored in pancreatic cancer. Vasoactive intestinal peptide (VIP) is an emerging checkpoint pathway for T cell function, which expresses VIP receptors (VIPR) and is abundantly expressed by PDAC. In this work, we present a novel armored CAR T cell that targets Muc16CD and antagonizes VIPRs (CAR/VIPRa) to overcome the immunosuppressive PDAC TME. **Methods:** Patient expression data was assessed based on data generated by the TCGA Research Network. Primary human T cells from healthy donors or PDAC patients were retrovirally transduced to express Muc16CD-directed CARs with or without secretion of novel, potent VIPR antagonist peptides. *In vivo*, PDAC PDX tumors were engrafted into SCID/Beige mice and treated with CAR T cells. **Results:** PDAC tumors have significantly increased expression of Muc16 compared to normal pancreas tissue and patients with high Muc16 expression have a significantly decreased overall survival. PDAC patient-derived tumors show robust expression of both Muc16CD and VIP. CAR/VIPRa T cells reveal that VIPR antagonism metabolically reprograms CAR T cells and drives a memory-rich product. CAR/VIPRa T cells are less activated and less exhausted by the manufacturing process, which lends to better viability and a metabolically quiescent phenotype at baseline. These distinct features allow CAR/VIPRa T cells, when antigen-stimulated, to have enhanced activation and expansion with repeated stimulation. To investigate clinical relevance, CAR/VIPRa T cells manufactured from PDAC patient blood are also significantly enriched for memory phenotypes. *In vivo*, CAR/VIPRa T cells have enhanced expansion, phenotype, infiltration, and persistence, which ultimately reduces PDAC tumor burden. In a patient-derived PDAC preclinical mouse model where CAR T is typically ineffective, CAR/VIPRa T cells significantly reduce tumor burden. **Conclusions:** This work demonstrates Muc16CD as a clinically relevant TAA target for CAR T therapy in PDAC. Furthermore, antagonizing the previously undescribed VIP checkpoint pathway in CAR T cells produces enhanced phenotypic and functional profiles. Collectively, this data demonstrates that novel CAR/VIPRa T cells create an advantageous cellular therapy product capable of treating PDAC. The long-term goal of this work is translating CAR/VIPRa T cells for the treatment of PDAC and expanding these preclinical findings of cellular therapies for other VIP-abundant tumors. Research Sponsor: None.

Transforming tumor immune microenvironments with a novel systemic enveloped oncolytic virotherapy targeting all tumor sites.

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Background: Systemic oncolytic virotherapy offers a promising solution for treating both local and metastatic diseases. However, the rapid inactivation of virotherapeutics by the immune system has resulted in disappointing clinical efficacy. To address this challenge, we have built a new program (ImmunoNova) to develop a cellular-based technology that protects oncolytic virotherapy, allowing for successful targeting of the therapy to tumor sites and effectively overcoming clinical challenges. This approach involves utilizing a newly selected and engineered, tumor-selective strain of vaccinia virus (RT-01). This strain produces high levels of extracellular enveloped virions (EEVs) that contain a second human cell-derived membrane, providing augmented protection against elimination by the immune system when administered systemically. The process requires specific manufacturing methods to preserve this crucial second human cellular membrane. **Methods:** The resistance of the manufactured enveloped RT-01 (envRT-01) virus against human humoral immunity and its rapid spread were assessed ex-vivo using a plaque assay. EnvRT-01 was administered in various xenograft and syngeneic models to evaluate its specificity in targeting tumors and its therapeutic efficacy, either alone or in combination with cell therapies. The amplification of virus-encoded RFP was monitored using an imaging system. Additionally, flow cytometry and immunohistochemistry (IHC) were employed to analyze immune infiltration in both treated and untreated tumors. **Results:** EnvRT-01 particles exhibited an approximately 80% survival rate in the presence of active complement. In animal studies, a single systemic dose of envRT-01 selectively targeted three distinct human cancer indications (lung, melanoma, head & neck), leading to the suppression of tumor growth in all three cases. Similarly, in an immunocompetent syngeneic lung tumor model, envRT-01 effectively targeted and reduced multiple murine lung tumors with just a low single dose of treatment. EnvRT-01 was capable of targeting and expressing viral-encoded proteins in all tumor sites and drastically modifying the tumor immune microenvironment, favoring an anti-tumor immune phenotype and facilitating other cell therapies such as innate-based cell therapies. **Conclusions:** The development of this innovative enveloped oncolytic virotherapeutic, coupled with advancements in its manufacturing methods, opens up new possibilities in the realm of cancer therapy. It addresses the limitations posed by untargetable and untreatable metastatic diseases, presenting a transformative solution with broad implications for the field. Research Sponsor: None.

Non-clinical evaluation of NT-175, an autologous T cell product engineered to express an HLA-A*02:01-restricted TCR targeting TP53 R175H and resistant to TGF-b inhibition.

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Background: Adoptive transfer of T-cell receptor (TCR)-engineered T-cells to target shared cancer neoantigens is a promising new immunotherapy approach for patients harboring mutations in tumor suppressor genes such as TP53. TP53 is the most commonly mutated gene across all cancer types, with the R175H mutation being the most prevalent across different indications. NT-175 is an autologous engineered T-cell product expressing an HLA-A*02:01-restricted TCR that specifically targets the TP53 R175H mutation. NT-175 is additionally engineered to lack TGF-β receptor II (TGFBR2) expression, rendering T-cells insensitive to TGF-b-mediated inhibition in the tumor microenvironment. **Methods:** For manufacturing of NT-175, CD4 and CD8 T-cells are enriched from leukapheresis material, activated in vitro and gene-edited to knock-out both endogenous TGFBR2 and TCR β constant 1/2 (TRBC1/2) and knock-in an HLA-A*02:01-restricted TP53 R175H neoantigen-specific TCR at the TCR α constant (TRAC) locus using CRISPR-Cas9 technology. NT-175 product functionality was evaluated in vivo models and in vitro. T-cell reactivity was assessed by measuring cytotoxicity, proliferation, and cytokine production. The benefit of TGFBR2 knock-out (KO) in the presence of TGF-b was evaluated by measuring phosphorylation of SMAD2/3 proteins, the impact on cell viability and serial killing of target cells. For determination of NT-175 product safety, cross-reactivity and HLA-specificity assessments were carried out. A comprehensive analysis of potential off-target editing by CRISPR/Cas9 was performed to assess potential risk of genotoxicity in clinical grade NT-175. **Results:** High reactivity of the NT-175 TCR against TP53 R175H and HLA-A*02:01 expressing target cells was observed. T-cell activation and functionality was highly specific, as demonstrated by a lack of reactivity against TP53 WT, minimal cross-reactivity against antigens with up to 4 mismatches to the minimal TP53 R175H encoding epitope recognized by the NT-175 TCR, and lack of T-cell activation in the absence of HLA-A*02:01. In the presence of TGF-b, TGFBR2 KO TCR-edited T-cells displayed inhibition of SMAD2/3 phosphorylation, increased cell viability and increased cytotoxicity and proliferation in serial stimulation assays. In vivo, NT-175 T-cells were able to induce tumor clearance in two independent models. Low frequency chromosomal translocation events (<0.1%) between on-target and off-target Cas9 cleavage sites were detectable in NT-175 T-cells. However importantly, these did not result in autonomous cytokine-independent growth. **Conclusions:** Non-clinical studies revealed a favorable safety and efficacy profile for NT-175 and supported further clinical development of a TGF-β-resistant TCR-edited T-cell product for mutant TP53-targeted cancer immunotherapy. Research Sponsor: None.

Combinatorial cellular therapy in pediatric solid tumors with natural killer (NK) and genetically engineered myeloid cells (GEMys).

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Background: Early human studies with Natural Killer (NK) cells have shown promise, harnessing their ability to infiltrate into tumors and be tumoricidal. However, these effects can be limited by adenosine, reactive oxygen species, and TGF-β in the highly immune suppressive tumor microenvironment (TME). TGF-β and downstream SMAD3 signaling in Natural Killer (NK) cells have been shown to cause decreased cytokine production, downregulation of activating cell surface receptors, and attenuated cytotoxic function against solid tumors. Exposure to TGF-β during cell culture generates expanded NK cells with increased resistance to TGF-β signaling, dubbed TGF-β imprinted NK cells. *In vitro*studies have shown that these cells have increased cytokine production and cytotoxic function in the presence of TGF-β. However, their *in vivo* trafficking, modulation of the TME, and therapeutic efficacy remain understudied. Our lab has previously shown that when given to tumor-bearing mice, myeloid cells modified to produce IL-12 (IL-12-Genetically Engineered Myeloid cells, aka IL-12 GEMys) are effective at homing to tumor and metastatic sites and, via IL-12 secretion and TME modulation, increase NK cell presence and activation in these sites. They hold great promise as combination therapy, enhancing the effectiveness of other cellular therapies such as NK cell therapy. A current clinical trial exploring TGF-β Imprinted, Ex Vivo Expanded, Universal Donor NK Cell Infusions in relapsed sarcomas is underway (NCT05634369). **Methods:** *In vitro* experiments were conducted with the xCELLigence real-time cell analysis system. The human osteosarcoma cell line 143B and human rhabdomyosarcoma cell line RH-30 were evaluated for cell death after co-culture with healthy donor NK cells or TGF-β imprinted NK cells (E:T ratio of 5:1) in isolation and in combination with IL-12 GEMys (E:T ratio of 2:1). **Results:** TGF-β imprinted NK cells are significantly more effective at tumor cell killing of both 143B and RH30 cell lines in-vitro compared to regular expanded NK cells (WT NK cells), with >90% decrease in cell index compared to 50-60%, respectively, after 48 hours of co-culture. IL-12 GEMys also significantly enhance the cytotoxic effects of WT NK cells, increasing cell killing to 70-80% compared to co-culture with untransduced GEMy controls. **Conclusions:** These initial in-vitro experiments provide insight into the promising effectiveness of NK-myeloid cell combination therapies in the treatment of pediatric sarcomas. Ongoing *in vitro*experiments include cytokine quantification by ELISA and flow cytometric analysis of NK cell activation and proliferation markers. Our preliminary results provide rationale to continue studying the *in vivo* efficacy of TGF-β imprinted NK cell monotherapy and in combination with IL-12 GEMys in the treatment of tumor-bearing NSG mice. Research Sponsor: U.S. National Institutes of Health.

Chimeric antigen receptor T-cell therapy in B-cell malignancies and DNA-methylation–based biological aging.

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Background: Chimeric antigen receptor T-cell (CAR T-cell) therapy, a type of cancer immunotherapy which leverages genetically altered T cells to target cancer cells, has shown to be an effective option for patients with acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Despite its growing use, the effect of CAR T-cell therapy on the aging process remains limited and findings may have implications for disease relapse and age-related diseases among survivors. The purpose of this study was to investigate the association between CAR T-cell therapy and markers of biological aging. **Methods:** DNA methylation and clinical data from a publicly available dataset (GSE179414) were used in this analysis. Transduced and untransduced T cells from patients with ALL (n=77) and NHL (n=37) underwent DNA methylation profiling using the Illumina Infinium MethylationEPIC BeadChip. Six DNA methylation-based biological age metrics were calculated: intrinsic epigenetic age acceleration (IEAA), extrinsic epigenetic age acceleration (EEAA), PhenoAge acceleration (PhenoAA), GrimAge acceleration (GrimAA), telomere length attrition (TLA), and DunedinPACE (Pace of Aging Calculated from the Epigenome). Multiple linear regression analyses were performed to examine the association between CAR T-cell therapy and the aging metrics by B-cell malignancy. Interaction and stratified analyses by chronological age was additionally performed. **Results:** DunedinPACE (P=0.002) was positively associated with CAR T-cell therapy among patients with ALL with an approximately 1-month higher pace of aging in transduced T cells compared to untransduced T cells after adjusting for chronological age and sex. Moreover, chronological age significantly (P=0.016) modified the association between CAR T-cell therapy and TLA among ALL patients. Specifically, transduced T cells exhibited a 0.46 higher (P=0.053) and a 0.39 lower (P=0.142) rate of TLA among patients 16 years of age or older and those younger than 16 years of age, respectively. **Conclusions:** We observed CAR T-cell therapy was associated with greater biological aging as estimated from DNA methylation among ALL patients and these associations are modified by chronological age. These findings suggest CAR T-cell therapy may be associated with age-related changes to the epigenome in ALL patients and strategies to limit or reverse this effect may have implications for the aging process in cancer survivors. Research Sponsor: None.

	ALL		NHL	
	β	*P*	β	*P*
IEAA	3.12	0.323	3.40	0.105
EEAA	2.46	0.507	0.01	0.996
PhenoAA	1.62	0.721	-0.22	0.940
GrimAA	0.78	0.316	-0.70	0.356
DunedinPACE	0.09	0.002	0.04	0.216
TLA	0.00	0.995	0.10	0.562

Investigation of a potential protein biomarker signature that may predict clinical benefit of NT-I7 and pembrolizumab in patients with cold gastrointestinal tumors.

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Background: Microsatellite stable colorectal (MSS-CRC) and pancreatic cancer (PDAC) are immunologically cold tumors due to low immunogenicity and lack of genomic diversity. NT-I7, a long-acting IL-7, and pembrolizumab (pembro) show efficacy in these hard-to-treat indications. While a limited set of patients (pts) achieve objective response, frequency and duration of the disease control rate point to a larger subset obtaining clinical benefit. To identify novel predictive biomarkers, we analyzed baseline peripheral and biopsy samples from pts based on treatment duration. **Methods:** Open-label Phase 2a study in pts with relapsed/refractory checkpoint inhibitor-naïve MSS-CRC and PDAC; NT-I7 1200 μg/kg IM every 6 weeks (Q6W), pembro 200 mg IV Q3W. Subjects were grouped by treatment duration, measured in NT-I7 doses administered before treatment discontinuation for any cause: 1 dose was short (ST), 2-3 doses medium (MT) and ≥4 doses long (LT). Correlative studies included peripheral (proteomics, T cell receptor sequencing [TCRseq], single cell RNA sequencing [scRNAseq]), and biopsy (genomics, transcriptomics, TCRseq). **Results:** As of 02OCT2023, 53 evaluable pts completed or discontinued treatment; 5 are still on follow up. ST group included 21 pts, MT 22 and LT 10 (including all 5 partial responders). Tumor biopsies were confirmed MSS with low tumor mutational burden (TMB). LT pts had similar age (59.0 [53.0-71.5] vs 66.0 [47.3-73.5]; ST vs LT) and lower baseline tumor burden (81.0 mm vs 58.0 mm; ST vs LT, p = 0.022). Biopsy analysis showed LT pts had, at baseline, upregulated pathways related to immune activity despite confirmed cold tumor status. Baseline scRNAseq in peripheral blood showed that stem-like CD8 T cells (precursors of exhausted [TPEX] and stem-cell memory [TSCM]) had a differential activation pattern in LT pts; those pathways were enriched in memory effector subsets in ST pts. Preserved antigen-specific stemness may be needed for NT-I7 + pembro efficacy. Baseline concentrations of 3 proteins that can be produced by growing tumors were significantly increased in ST pts. Pts were classified based on elevated levels of these potential biomarkers: POSITIVE (≥2 biomarkers; 20 pts) and NEGATIVE (≤1 biomarker; 33 pts). Pts with NEGATIVE signature at baseline had significantly higher overall survival, regardless of ST, MT or LT status (13.2 vs 8.9 months, p = 0.030). **Conclusions:** Preserved tumor-specific TPEX activity may be required for NT-I7 + pembro activity based on its presence in LT pts, who remained on treatment the longest. According to this analysis, there are 3 potentially predictive protein biomarkers that may help identify a pt subset more likely to experience clinical benefits from the combination treatment of NT-I7 + pembro. Further verification of the predictive nature of this signature in independent cohorts is ongoing. Clinical trial information: NCT04332653. Research Sponsor: NeoImmuneTech, Inc.

Circulating metabolic profiling as a biomarker for immune checkpoint blockade efficacy.

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Background: Immune checkpoint blockade (ICB) has changed the treatment landscape of non-small cell lung cancer (NSCLC). Despite being the mainstay of treatment for advanced NSCLC, the development of resistance to ICB is common. Hence, identifying biomarkers that can be used to select patients (pts) who will benefit from ICB is crucial. Here, we interrogate the circulating metabolome to identify the metabolic parameters associated with ICB effectiveness. **Methods:** This single-center retrospective analysis used a mass-spectrometry (MS) targeted metabolomics approach to assess the relative abundance of 115 metabolites in baseline (pre-ICB) plasma of 55 pts with advanced NSCLC. Pts treated with ICB at the Princess Margaret Cancer Centre from 2018-2020 were included. Electronic medical records were reviewed to collect clinicopathological and treatment data. All pts had tumour next-generation sequencing (NGS) by a targeted gene panel. Descriptive statistics were used to summarize the patient characteristics, treatment modalities, and outcomes. Time-to-event outcomes were analyzed using the Kaplan-Meier method. Progression-free survival (rwPFS) and overall survival (rwOS) were defined as the time from the first treatment dose to radiographic or clinical progression or death from any cause and time from the first dose of treatment to death from any cause, respectively. The response rate was assessed using RECIST 1.1. Statistical significance was determined as a p-value <0.05. **Results:** Amongst the 55 pts profiled, 42 (76.3%) had adenocarcinoma. The most common molecular alterations included KRAS (n=15), BRAF non-V600 (n=5), and METex14 (n=3). The median PD-L1 score was 65% (IQR 22.5 – 59%). All pts were treated with a single-agent PD-1 inhibitor, and 67.2% of pts received ICB as the first line of treatment. Metabolomic analysis of the pre-ICB initiation plasma samples identified 8 metabolites whose relative abundance significantly differed between responding (CR/PR) and non-responding pts (SD/PD). Amongst these metabolites was the endogenous danger signal Glucosylceramide (d 18:1/24:0), whose abundance was increased in the plasma of the responding pts. When we stratified pts by circulating levels of glucosylceramide, we found a statistically significant higher rwPFS (8.5 vs. 1.6 months, p=0.0001) and rwOS (13.5 vs. 6.1 months, p=0.0001) in pts who had high baseline plasma levels of Glucosylceramide (d 18:1/24:0) (top 50%) versus those with lower levels (bottom 50%). **Conclusions:** Utilizing a targeted metabolomics approach, we identified the metabolite and endogenous danger signal glucosylceramide (d 18:1/24:0) as a potential metabolic biomarker of response to ICB therapy. Future work will aim to validate this finding in a larger cohort and to understand the biological mechanism underpinning this correlation. Research Sponsor: None.

Soluble mesothelin neutralizes mesothelin antibody-based therapies.

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Background: Mesothelin (MSLN) is overexpressed in mesothelioma and other solid tumors making it the focus of multiple targeted therapies, including antibody drug conjugates (ADCs), T cell receptor (TCR) fusion constructs, and chimeric antigen receptor T-cell (CAR-T) products. However, the clinical efficacy of these treatments remains limited. We hypothesize that soluble MSLN (sMSLN) in the plasma binds to MSLN-targeted therapies before reaching the tumor. Our study aimed to evaluate the effects of sMSLN on a MSLN-targeting antibody, anetumab, and explore methods to reduce sMSLN. **Methods:** Exploratory analysis in NCT03126630: sMSLN testing was performed on blood samples from participants enrolled in NCT03126630 at the Molecular Targets Core Lab, National Cancer Institute. The median was used to categorize high and low levels of sMSLN. Survival was estimated with the Kaplan-Meier method and compared between groups with the log rank test. Anetumab immunoprecipitation: Anetumab was covalently coupled to Dynabeads at 5 μg per mg of beads to immunoprecipitate MSLN from two plasma samples. Assays were performed in duplicate. Therapeutics plasma exchange (TPE): Whole blood samples were collected before and after one plasma volume of TPE with albumin as the replacement fluid in patients undergoing routine TPE for various medical conditions, such as autoimmune diseases and hyperviscosity syndromes. Plasma levels of sMSLN were measured with an ELISA assay in matched pre- and post-TPE plasma samples. **Results:** We obtained sMSLN levels from 40 patients enrolled in NCT03126630. For patients treated with both anetumab ravtansine and pembrolizumab, median progression free survival (PFS) was shorter in the high sMSLN group (5 months) vs the low sMSLN group (12 months). For patients treated with pembrolizumab alone, PFS was similar for patients with high and low sMSLN (4 vs 3.4 months). Anetumab significantly reduced the concentration of sMSLN in plasma samples as detected by MSLN ELISA ($p<0.05$), demonstrating that sMSLN can bind to and sequester anetumab. Next, we evaluated TPE as a mechanism to reduce sMSLN. We obtained pre- and post-TPE plasma samples from 15 patients undergoing routine TPE for various medical conditions. TPE consistently reduced sMSLN ($p<0.05$) with an average decrease of 43.6% or 15.4 ng/mL. **Conclusions:** We found that high sMSLN levels are associated with shorter PFS for anetumab ravtansine, but not pembrolizumab. Additionally, anetumab binds to sMSLN in the plasma, which suggests that sMSLN can sequester anti-MSLN antibodies and may limit the efficacy of MSLN-targeted therapies. High levels of sMSLN could potentially be used as a biomarker to select which patients should not receive MSLN-targeting therapies. Furthermore, our results indicate that sMSLN reduction is feasible with TPE. Decreasing sMSLN could restore the activity of MSLN-targeted therapies. Research Sponsor: None.

Effect of indoximod-based chemo-immunotherapy in patients with pediatric brain tumors on activation and clonal proliferation of a circulating population of early non-exhausted stem-like CD8+ T cells whose on-treatment expansion is predictive of long-term outcome.

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Background: Combination chemo-immunotherapy is a promising strategy, but it is difficult to determine whether clinical responses are associated with on-target immune activation or just due to chemotherapy. The field lacks well-accepted readouts of on-treatment T cell activation/expansion to answer this question. **Methods:** We analyzed longitudinal blood samples from 30 patients with pediatric brain tumors treated with the IDO-inhibitor drug indoximod combined with either chemotherapy (n=27, NCT02502708, NCT04049669) or chemotherapy plus ibrutinib (n=3, NCT05106296). Patients in this "Training Set" were selected to include multiple trials, various histologies/molecular risk factors, and a range of outcomes (overall survival (OS) range 6-55 months). Longitudinal blood samples (2-11 samples/patient) were obtained over 4-36 months, depending on duration of treatment, and analyzed by single-cell RNA and TCR sequencing (scRNAseq/TCRseq). TCR clonotypes of interest were defined as having at least 2-fold expansion (or appearance de novo) during treatment compared to baseline. To calculate a "Clonal Expansion Index" (CEI), the total number of T cells belonging to treatment-expanded clonotypes was summed for each sample and expressed as a percentage of total T cells. The peak CEI value for each patient was used to stratify subjects into "Immune Responders" vs "Non-responders", based on an optimized cutoff established by Receiver Operating Characteristic (ROC) analysis with Youden's J statistic. **Results:** In these patients, CEI ranged from <1% to >60% of all circulating T cells. The optimized cut-point was found to be a CEI of 8.6%, producing a sensitivity of 91% and specificity of 77% for this dataset. Kaplan-Meier analysis showed a highly significant 3-fold difference in median OS for the CEI-High patients (26.5 months) compared to CEI-Low (8.9 months, p=0.0003). The CEI metric was far superior as a predictor of long-term outcome than radiographic response by RANO, RAPNO or iRANO criteria, which were not predictive. UMAP clustering and Monocle trajectory analysis of the treatment-expanded T cells revealed that the majority arose from a population of early stem-like cells (TCF7+ LEF1+ FOXP1+), progressing through a more activated stem-like population (HOBIT/ZNF683+) to attain proliferation and effector maturation states. Throughout this sequence, the T cells showed minimal markers of exhaustion (PDCD1, HAVCR2, TOX) and acquired a lytic effector phenotype. **Conclusions:** We hypothesize that clonal expansion of this population of non-exhausted stem-like T cells, as quantitated by the CEI assay, provides a mechanistically based pharmacodynamic readout of T cell response to indoximod-based (and perhaps other) chemo-immunotherapy. Research Sponsor: NIH R01CA229646; Alex's Lemonade Stand Foundation; Press On Foundation; CureSearch for Children's Cancer; Hyundai Hope on Wheels Foundation; Beloco Foundation; Cannonball Kids' cancer Foundation; Miriam Lloyd Halsey Foundation; Trial Blazers for Kids Foundation; Lumos Pharma Inc (drug supply); Janssen Scientific Affairs LLC (drug supply).

Proteogenomic profiling of clonal hematopoiesis in the solid tumor microenvironment.

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Background: Clonal hematopoiesis (CH) is caused by somatic mutations that provide a fitness advantage in hematopoietic stem cells, contributing to inflammation and disease. CH is common in solid tumor patients, and has shown context-dependent associations with survival; however, its contribution to the tumor microenvironment (TME) remains unclear. Here, we employ proteogenomic methods to define CH-associated alterations in the TME. **Methods:** We tested 1,550 patients across 10 primary, treatment-naïve cancers in the Clinical Proteomic Tumor Analysis Consortium cohort. CH calls were derived from peripheral blood and tumour whole exome sequencing (WES) data, and CH was defined as the presence of a somatic driver mutation at variant allele frequency (VAF) ≥2% in blood. Overall survival (OS) analysis was conducted using Cox proportional hazard models, controlled for age, sex, tumor type, metastatic status, and smoking. Tumor bulk RNA-sequencing and mass spectrometry proteomics data were processed for differential expression and gene set enrichment analyses. Abundance of immune cell populations was estimated with CibersortX. **Results:** 349 CH mutations were identified in 283 patients (18.3%). CH was strongly associated with age and mutations were mostly found in the epigenetic regulators *DNMT3A*(37.8%, n=132) and *TET2*(20.6%, n=72). CH was most prevalent in ovarian cancer (30%, n=27/90) and colorectal cancer (CRC; 28.3%, n=30/106). 103 blood CH mutations were also detected in tumor WES (CH_{Tum}), with presence in the tumor associated with higher tumor immune infiltration and peripheral blood VAF ≥10%. CH_{Tum}, but not CH, was associated with worse OS (CH_{Tum} HR = 1.74 [1.13-2.69]; CH HR = 1.12 [0.83-1.50]). CH_{Tum} was also associated with a reduced likelihood of patients being classified as tumor free at follow up (OR = 0.39 [0.19-0.82]). We did not identify a pan-cancer proteogenomic signature of CH in the TME. At the tumor-specific level, we consistently observed associations between CH and its subtypes with dysregulated inflammation, with high transcriptomic-proteomic concordance. In CRC, *TET2*-mutant CH was associated with greater infiltration of CD4+ T cells, monocyte/macrophages, NK cells, and B cells, alongside an inflammatory response characterized by IL6/JAK/STAT3 signalling, TNF signalling via NFκB, and IL2/STAT5 signalling. **Conclusions:** CH is common, even prior to therapy, in solid tumor patients and the infiltration of CH-mutant immune clones into the TME is linked with poor outcomes. Beyond confounding molecular tumor diagnostics, CH in the TME also dysregulates the anti-tumor immune response, highlighting the value of a blood reference in precision oncology. The lack of a pan-cancer CH signature in the TME supports a tumor-specific influence of CH. Further study is needed for mechanistic discovery and biomarker development to realize the potential of CH in immuno-oncology and improve patient outcomes. Research Sponsor: Canadian Institute of Health Research.

A plasma-based proteomic platform for predicting clinical benefit from immune checkpoint inhibitors in multiple cancers.

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Background: Immune checkpoint inhibitor (ICI)-based therapies are preferred treatment options for multiple cancer types. However, there is an unmet need for predictive tests that can identify patients likely to benefit. PROphet-NSCLC is a commercially available pretreatment plasma proteomic test that predicts clinical benefit from first-line PD-(L)1 inhibitor-based therapy in patients with metastatic non-small cell lung cancer (NSCLC), guiding the choice between ICI monotherapy versus ICI-chemotherapy. Here, we evaluate the broader clinical utility of PROphet-NSCLC by testing its predictive capabilities across diverse cancer types. **Methods:** Pre-treatment plasma samples and clinical data were collected for an observational study from patients with metastatic melanoma (n=68) and HPV-related cancers (n=43; NCT03427411) treated with PD-(L)1 inhibitor-based therapies. HPV-related cancers included anogenital squamous cell carcinoma (n=16), cervical carcinoma (n=18), and head and neck squamous cell carcinoma (n=9). Patients were assigned a PROphet-positive or -negative result based on computational analysis of SomaScan-derived proteomic profiles in pre-treatment plasma samples. Overall survival (OS) and progression-free survival (PFS) in PROphet-positive- and -negative groups was analyzed with the Kaplan-Meier method. Hazard ratios (HR) were calculated from univariate and multivariate Cox proportional hazard models. **Results:** In the melanoma cohort, PROphet-positive patients (n=51) displayed a significant OS benefit in comparison to PROphet-negative patients (n=17; median OS 92.8 months vs. 9.5 months, HR=0.14, 95% CI: 0.06-0.34, $p<0.0001$), consistent with the clinically validated predictive performance of the test in patients with NSCLC. OS results remained significant after correcting for sex, age, histology, ECOG performance status, and treatment type (HR=0.05, 95% CI: 0.01-0.25, $p<0.001$). In PROphet-positive patients, PD-1+CTLA-4 inhibitor combination therapy (n=27) was superior to PD-1 inhibitor monotherapy (n=24; OS: median 118.4 vs. 48.3 months, HR=0.58, p=0.24; PFS: median not reached vs. 10.8 months, HR=0.48, p=0.04). PROphet-negative patients displayed similarly poor outcomes with either treatment, providing a rationale to consider alternative therapies for such patients. In the HPV-related cohort, the median OS in PROphet-positive (n=10) vs PROphet-negative (n=33) groups was 43.6 vs 4.4 months (HR=0.22, 95% CI: 0.08-0.59, p=0.001), with similar trends per sub-cohort. **Conclusions:** Our findings show that the PROphet-NSCLC test can be applied to PD-(L)1 inhibitor-treated melanoma and HPV-related cancers, suggesting applicability to cancers beyond NSCLC. Analysis of additional patient samples is needed to explore the potential utility of PROphet-NSCLC for informing treatment decisions for a broad range of cancer types. Research Sponsor: OncoHost LTD.

CD4 effector T cell expansion to identify objective responses to the CD40 agonist mitazalimab in combination with modified FOLFIRINOX (mFFX) as first-line therapy for metastatic pancreatic ductal adenocarcinoma (mPDAC) in the OPTIMIZE-1 study.

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Background: CD40 agonists have the potential to enhance the efficacy of standard of care chemotherapy and to trigger antitumor immunity. Preclinical models indicate that the success of this approach depends on appropriate sequencing of chemotherapy with a CD40 agonist. Preliminary efficacy results from the OPTIMIZE-1 Phase II study (NCT04888312) combining mitazalimab (anti-CD40) with mFFX chemotherapy in patients with mPDAC have been previously reported. Here, we investigated immunological determinants associated with favorable outcomes with this combination therapy. **Methods:** Newly diagnosed, chemotherapy-naive patients with mPDAC received mitazalimab (900 μg/kg) on day 1 prior to beginning an every 2-week mFFX regimen on day 8, followed by mitazalimab 48 hours later. Tumor response was determined using RECIST v1.1 criteria. Peripheral blood was analyzed for selected cytokines and chemokines and by flow cytometry to assess changes in leukocyte subsets including B cells, monocytes, T cells, and NK cells. Flow cytometric data from evaluable patients were subjected to unsupervised hierarchical clustering to identify immune subsets. A classifier was generated from an interim dataset (n=21) using a random forest model to predict cell populations and their association with tumor response, which were then applied to the full dataset (n=47). **Results:** Mitazalimab triggered an expected immune response characterized by transient cytokine (IFNg and MCP-1) release and B cell depletion. Chemotherapy caused a reduction in classical monocytes and proliferating $CD4^+$ T cells. Both mitazalimab and chemotherapy caused a transient reduction in circulating dendritic cells and NK cells. Tumor response was associated with an expansion in the frequency of effector CD4 T cells ($p < 0.0001$) at day 8 after receiving mitazalimab. In a blinded analysis based on the classifier, CD4 T cell expansion was linked to an early tumor response to treatment (accuracy 70%, sensitivity 68%, specificity 72%). **Conclusions:** Mitazalimab and mFFX differentially modulate immune responses in patients with mPDAC. Pharmacological analyses identify mitazalimab-induced expansion of CD4 effector T cells one week after first administration as a correlate of treatment outcomes. These data suggest the contribution of mitazalimab to tumor responses, and further substantiate a priming dose of mitazalimab, prior to administering chemotherapy. Research Sponsor: Alligator Bioscience.

Use of a tissue-free epigenomic circulating tumor DNA (ctDNA) assay for quantification of tumor fraction (TF) and association with outcomes from RADIOHEAD real-world advanced pan-cancer cohort.

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Background: The validity of ctDNA assays is well established for evaluating molecular response to therapy, and ctDNA levels may be monitored throughout a patient's (pts) journey to indicate when relapse or progression is present, often sooner than current methods (RECIST). Genomic assays using variant allele fraction (VAF) have limitations such as low ctDNA levels and interference from copy number variation and clonal hematopoeisis (CH), which may be overcome by methylation-based quantification. Here we describe the performance of a methylation-based assay to quantify ctDNA levels and correlate changes with outcomes in a real-world pan-cancer cohort. **Methods:** RADIOHEAD is an observational study of ~1200 solid tumor patients receiving standard of care ICI regimens with blood samples collected prospectively for retrospective analysis. 552 patients with stage III/IV lung, melanoma, bladder and other cancers were randomly chosen for evaluation. Available plasma samples from baseline and on-treatment timepoints (C3D1, 6mo and 12mo) were analyzed with an analytically validated NGS ctDNA assay measuring methylation and TF quantification. Cox proportional hazards (CPH) were used for comparison of real-world progression free survival (rwPFS). Gender, age, disease stage, and tobacco use were included as co-variates. Median rwPFS and rwOS were calculated using Kaplan Meier analysis. rwPFS ordinal groups (<3mo, 3-6mo, 6-12mo, ≥12mo) and association with early ctDNA changes were assessed with chi-squared test. **Results:** Methylation-based detection of ctDNA at baseline or C3D1 was associated with shorter rwPFS and rwOS (baseline: mPFS 10.7 mo vs NR; HR= 3.0 $p<0.001$ rwOS 19.9 mo vs NR; HR=2.9 $p<0.001$), (C3D1: mPFS 10.7mo vs NR; HR= 2.9 $p<0.0001$ rwOS 14.8 mo vs. NR; HR=3.1 $p<0.001$) independent of stage, gender, age or tobacco use. Longer rwPFS was associated with >95% reduction in TF from baseline to C3D1 or low ctDNA at both timepoints (rwPFS <3mo = 1.8%, 3-6mo = 7.8%, 6-12mo = 15.1%, ≥12mo = 75.3%; N=166 $p<0.001$). For pts with ctDNA not detected at C3D1, ctDNA detection at 6mo post first dose was strongly associated with shorter rwPFS vs ctDNA not detected at 6mo (mPFS 13.6mo vs. NR; HR= 7.43 $p<0.001$). For pts with ctDNA not detected at 6mo, ctDNA detection at 12 months post first dose was also associated with shorter rwPFS vs ctDNA not detected at 12mo (mPFS 22.8 mo vs. NR; HR= 5.2 p=0.02). **Conclusions:** These data demonstrate a significant association of methylation-based ctDNA detection and on-treatment changes in TF with rwPFS and rwOS. Furthermore, subsequent TF detection 6mo or 12mo on-treatment, without TF detected at previous timepoint was associated with worse outcomes. This suggests the value of serial monitoring throughout treatment for early detection of progression and the potential to inform treatment decisions. Research Sponsor: None.

Investigating peripheral blood biomarkers of immune checkpoint inhibitor associated fatigue.

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Background: Fatigue is the most common side effect of immune checkpoint inhibitor (ICI) therapy. Despite its prevalence, the mechanisms underlying ICI-associated fatigue are poorly understood. In this study, we characterized dynamic changes in peripheral immune cell populations and cytokines to identify biomarkers and mechanisms of ICI-associated fatigue. **Methods:** We prospectively collected clinical data and blood samples from patients with solid tumors at a single institution who received ICIs between July 2021 and November 2023. Blood samples were collected at baseline, early-on-treatment (month 1-2), and later-on-treatment (month 4-6). Patients were contacted on-treatment to query for worsening of fatigue compared to treatment baseline. We analyzed peripheral lymphocyte populations by Cytometry by Time-of-Flight (CyTOF) and peripheral levels of 39 cytokines with Luminex multiplex assay. Tumor response was characterized by RECIST v1.1. False discovery rate (FDR) was used for multi-testing adjustment. **Results:** 53 patients received ICI therapy and had fatigue assessment performed. Thirty-one patients (58.5%) reported worsening fatigue, and 22 (41.5%) did not. In patients with worsened fatigue, a cluster of cytotoxic effector CD8+CD28+TIGIT+ T-cells was significantly increased from baseline to early-on-treatment (Wilcoxon Signed-rank Test FDR adjusted $p<.05$). Early-on-treatment fold changes in Type 1 cytokines (IFN-gamma, IL-2, IL-12) were increased in patients with worsened fatigue compared to patients with no fatigue (Wilcoxon Rank-sum Test unadjusted $p<.05$; Table). There was no association between increase in fatigue and objective response to ICI therapy, although numerically high rates of fatigue were observed both in patients experiencing disease progression as well as complete responses. After excluding patients with tumor progression to account for tumor-related fatigue, early-on-treatment fold changes in IL-2 and IL-12 were still increased in worsened fatigued compared to non-fatigued patients (unadjusted $p<.05$). However, in patients with disease progression, changes in Type 1 cytokines were not associated with worsening fatigue. **Conclusions:** In a pan-tumor cohort treated with ICIs, increases in a cluster of cytotoxic effector CD8+ T cells in parallel with related Type 1 cytokines were associated with fatigue, implicating fatigue as a marker of immune activation in this population. Research Sponsor: NCI SPORE; P50 CA062924; U.S. National Institutes of Health; P30 CA006973; imCORE-Genentech; 137515.

Significant fold-change differences in cytokines among fatigued and non-fatigued patients.

Cytokines	Mean Fold Change for Fatigued Patients ± SD	Mean Fold Change for Non-Fatigued Patients ± SD	Unadjusted p-value
IFN-gamma	1.477 ± 1.160	0.872 ± 1.128	0.0078
IL-2	1.46 ± 1.567	0.659 ± 0.391	0.046
IL-12	1.523 ± 1.790	0.699 ± 0.360	0.017
IL-17a	1.14 ± 0.722	0.593 ± 0.408	0.032
IL-17e	1.371 ± 1.655	0.628 ± 0.369	0.012
IL-1a	1.513 ± 1.238	0.794 ± 0.269	0.015
IL-22	1.463 ± 1.256	0.754 ± 0.349	0.012

Impact of microbiota specific circulating memory T cells in response to immunotherapy.

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Background: The gut microbiota influences the cancer immune set point and response to immune checkpoint inhibitors (ICB), participating in the differentiation and function of T cells. We aimed to investigate the potential impact of microbiota-specific circulating memory T cells in cancer immunotherapy. **Methods:** NCT04567446 provided longitudinal blood samples (T0, before starting ICB until 1.5 months; T3, between 3 and 5.5 months) from patients with lung (NSCLC) and kidney (RCC) during ICB therapy (alone or combinations) in France. Different pools of harmful (ENTERO: *Enterocloster*spp, *Hungatella hathewayi*, VEILLEG: *Veillonella* spp, *Eggerthella lenta* and KLEBC: *Klebsiella pneumoniae*, *Escherichia coli*, *Fusobacterium nucleatum (Fn))* or single beneficial *(Akkermansia spp. (Akk)*, *Faecalibacterium prausnitzii* (*Fp*)) pasteurized bacteria (ppB) were used to stimulate whole blood sample (22h). The secretion of CXCL13, IL-17 (ELISA) and IFNg (VIDAS) was quantified at baseline and longitudinally to characterize memory T_{FH}, T_H17 and T_H1 responses, respectively and analyze the effects of antibiotics. Progression-free survival (PFS), overall survival (OS) were assessed according to bacteria-specific T cell responses. **Results:** From Mar. 2023 to Jan. 2024, a total of 75 patients were screened and 39 patients enrolled in this analysis (54 assessed samples). Median age was 66yr, 72% were male, 74% had NSCLC, 26% had RCC and 78% were treated in first line. Median progression-free survival was 5.3 months (0.9-12.4); median overall-survival was 5.9 months (1.5-12.4). Firstly, we analyzed the 33 samples at baseline. 15% of patients harbored *Akk*-specific T_{FH} memory responses and those patients with CXCL13 secretion superior to the median of the cohort tended to exhibit longer PFS (p=0.064) while 54% of patients harbored *KLEBC* T_{FH} memory responses that were clinically irrelevant. 15% of patients harboring circulating *Akk*-specific T_H1 memory responses had a shorter OS (p=0.055) while VEILLEG or KLEBC-specific T_H1 responses detected in 24% and 42% cases were clinically irrelevant. 26/32 patients who did not show *Akk*-specific T_H17 responses had a better OS. ATB tended to decrease bacteria-specific CXCL13 and IFNg responses but increased T_H17 memory T cells. While boosting the systemic T_H1 TCR tonus (IFNg secretion by fresh blood T cells stimulated with the positive control (mitogen)), ICB decreased the most prominent reactivities against KLEBC, VEILLEG or *Akk*, suggesting that bacteria-specific T cells may traffic to tumoral or intestinal locations. **Conclusions:** Although awaiting further validation and correlations with humoral IgG/A titers, circulating memory T cells against distinct commensals may be clinically relevant to predict benefit to immunotherapy, suggesting that such bacteria may invade tumor cells or share molecular homology with cancer antigens. Clinical trial information: NCT04567446. Research Sponsor: None.

Effect of MP0317, a FAP x CD40 DARPin, on safety profile and tumor-localized CD40 activation in a phase 1 study in patients with advanced solid tumors.

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Background: Major challenges of the clinical development of CD40 agonists are toxicity due to systemic CD40 activation and peripheral target-mediated drug disposition. MP0317, a CD40 agonist DARPin (designed ankyrin repeat protein), is exclusively activated by binding to fibroblast activation protein (FAP) on cancer-associated fibroblasts. This enables local CD40 activation in the tumor microenvironment (TME) and reduces systemic toxicity. **Methods:** This Phase 1, multicenter, open-label, dose-escalation study assessed safety/tolerability, pharmacokinetics/pharmacodynamics, and preliminary antitumor activity of MP0317 monotherapy (NCT05098405; data cut-off 15 Jan 2024). Eligible adults with selected advanced solid tumors (based on predicted FAP expression) were enrolled into 9 dose-escalation cohorts of MP0317 0.03–10 mg/kg administered IV 3-weekly (Q3W) or weekly (Q1W) until disease progression or unacceptable toxicity. Blood biomarkers were analyzed by immuno-assays and flow cytometry, and paired tumor biopsies by RNA sequencing and immunofluorescence. **Results:** Dose-escalation enrolment is complete and 46 patients received ≥1 MP0317 dose, including 24 women (52%) and 22 men (48%). Median age at enrolment was 63 years (range 35–79). Patients received a median of 4 prior treatment lines (range 1–13). Colorectal cancer was the most frequent tumor type (12 patients, 26%). MP0317 maximum tolerated dose was not reached; only one patient experienced a dose-limiting toxicity (asymptomatic Grade 3 alanine and aspartate aminotransferases elevation), at the highest planned dose of MP0317 (10 mg/kg Q3W). Grade ≤2 fatigue was the most frequent adverse reaction (15 patients, 30%), followed by Grade ≤2 infusion-related reaction, nausea and anorexia in 8, 7, and 5 patients, respectively. One patient achieved unconfirmed partial response, and stable disease was observed in 11 patients (24%). Serum PK data showed MP0317's half-life extended properties and sustained exposure at higher doses. Paired tumor biopsies confirmed the colocalization of MP0317 with FAP and CD40. MP0317 detection in tumor biopsies at doses ≥1.5 mg/kg was associated with an increase in antigen-presenting (dendritic and B cells), plasma and T follicular helper cell abundance, as well as enhanced dendritic cell maturation and IFNγ production in the TME. CXCL10 serum level increases post MP0317 treatment supported these findings. Only minor changes were seen in pro-inflammatory cytokines. **Conclusions:** MP0317 had a favorable safety profile in 46 patients across all 9 dose-escalation cohorts exploring Q3W and Q1W regimens. Doses ≥1.5 mg/kg showed evidence of pharmacodynamic TME modulation, indicating tumor-localized CD40 activation. The data support further clinical evaluation of MP0317 including combination with complementary anticancer therapies. Clinical trial information: NCT05098405. Research Sponsor: Molecular Partners AG.

Targeting a non-canonical STING signaling pathway in T cells to improve antitumor immunity.

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Background: While chimeric antigen receptor (CAR) T cell therapies have revolutionized the treatment of hematologic malignancies, they are less effective in treating solid tumors, which is in part due to the poor persistence and decreased survival of these cells in the tumor microenvironment (TME). The stimulator of interferon genes (STING) signaling axis has emerged as a promising target to remodel the TME to make it more immune favorable, and work from our group previously demonstrated that STING agonists could improve the persistence and antitumor activity of CAR T cells in an immunocompetent murine breast tumor model. Yet, the T cell intrinsic effect of STING activation is thought to decrease T cell proliferation and lead to T cell death. Thus, we sought to better understand the impact of activating STING in different T cell subsets to be able to more effectively target STING as an adjunct to cellular therapies. **Methods:** Primary T cell cultures generated from murine splenocytes and human peripheral blood mononuclear cells were polarized in vitro towards either a T_h/T_c1 or T_h/T_c17 lineage and treated with the mammalian STING agonist 2'3'-cGAMP. Cells were subsequently characterized by immunophenotyping, bioenergetic analysis, and RNA sequencing. Adoptive cell transfer experiments in a murine melanoma model and an immunocompetent murine breast cancer model utilizing an anti-Neu CAR T cell were employed to determine the differential impact of STING agonism on T cell subsets in vivo. **Results:** While treatment of T_h/T_c1 cells with cGAMP led to impaired proliferation and T cell death, T_h/T_c17 cells were immune to this effect. Instead, cGAMP triggered activation of a non-canonical STING pathway in T_h/T_c17 cells resulting in metabolic reprogramming in favor of fatty acid oxidation over glycolysis. T_h/T_c17 cells treated with cGAMP assumed more of a stem like memory T cell phenotype and displayed a more favorable bioenergetic profile with improved mitochondrial health and decreased reactive oxygen species production. Adoptive transfer of cGAMP conditioned T_h/T_c17 memory like cells enhanced tumor control in an aggressive murine melanoma model, which was secondary to improved persistence of T cells in the TME. Further, while intratumoral delivery of STING agonists augmented the antitumor activity of T_h/T_c17 cells, the function of T_h/T_c1 cells was impeded by activating STING. **Conclusions:** STING activation in T cells leads to differential responses within T cell subsets as T_h/T_c17 cells uniquely shift to a more fit T cell with improved antitumor properties. As cGAMP is found in the tumor microenvironment and can be secreted by tumor cells, CAR T cells with a greater T_h/T_c17 footprint may be able to better subsist in the TME. Our findings also provide insight into how to engineer cellular therapies to take advantage of this non-canonical pathway to optimize the integration of STING based therapeutics into patient treatments. Research Sponsor: Conquer Cancer, the ASCO Foundation; University Cancer Research Fund.

Efficacy, safety, and PK/PD of LVGN6051, 4-1BB agonistic antibody, with pembrolizumab in a phase Ib dose expansion in resistant NSCLC, melanoma, and GI malignancy.

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Background: LVGN6051 is a 4-1BB agonistic monoclonal antibody with Fcγ-receptor IIB binding designed for selective activation in the tumor microenvironment. A prior phase Ia trial of this combination showed RP2D to be 4 mg/kg LVGN6051 with 200mg pembrolizumab. We explored the activity of this combination in resistant NSCLC, Melanoma, and GI malignancies. **Methods:** A phase Ib expansion of LVGN6051 2 mg/kg in the first dose followed by 4 mg/kg in combination with pembrolizumab 200 mg IV Q3W was carried out in selected resistant malignancies (NCT04130542). Eligible pts received treatment until progressive disease, unacceptable toxicity, up to 35 cycles, or withdrawal of consent. **Results:** As of Dec 18, 2023, 48 pts were enrolled and received at least 1 dose of LVGN6051 combination regimen. 33 pts (68.6%) had prior ICI treatment. The median age was 62 years (range 20-89), 30 pts (62.5%) had ECOG PS 1, and the median number of prior therapies was 4. Treatment related adverse events were seen in 33 pts (68.8%) patients with Grade $\geq$ 3 AE in 18 pts (37.5%) and related SAE in 12 pts (30%). The most common Grade $\geq$3 AEs were thrombocytopenia (10.4%) and AST/ALT elevation (4.2%). Cmax and AUC were dose proportional and $T_{1/2}$ was 1.90-8.91 days. Sustained exposure (>1000 ng/mL) was achieved at 2 and 4 mg/kg Q3W. Anti-drug antibodies of LVGN6051 in low titers were detected in 20 of 48 subjects without apparent effect on PK. While the efficacy evaluation is still ongoing, 2 pts had a PR with one confirmed and another one unconfirmed, and 2 pts had an SD in the NSCLC cohort (n=14). Both patients with a PR had squamous histology and prior progression on pembrolizumab. In the Melanoma cohort (n=22), 1 pt had an unconfirmed CR but confirmed PR, 1 pt had a confirmed PR, and 4 pts had an SD. In the GI malignancy cohort (n=12), 3 pts had an SD. Cumulatively, for Phase Ia and Ib, this study has treated 33 melanoma pts, of whom 30 (90.9%) had prior exposure to ICI. 4 melanoma pts had a CR or PR, and 7 had an SD as the best objective response by RECIST. Melanoma pts with an objective response included 1 mucosal and 1 acral melanoma. The median duration of response for melanoma pts was 128 days (range 97 – >344) with several ongoing responses. Tumor single-cell RNAseq immune profiling was obtained and preliminary analysis shows increased Tem cells and immune pathway activity. **Conclusions:** Targeting 4-1BB and PD-1 with the combination of LVGN6051 and pembrolizumab appears to be well tolerated at this dose and schedule and shows predictable PK/PD parameters. In patients with ICI resistant Melanoma and NSCLC, durable objective responses were achieved with clinical benefits in patients resistant to prior ICI treatment. Further development of LVGN6051 is warranted. Clinical trial information: NCT04130542. Research Sponsor: None.

Identification of molecular subtypes for integrated multi-omics analysis for use in guiding precision medicine in hepatocellular carcinoma.

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Background: Tumor microenvironment (TME) heterogeneity leads to the discrepancy of survival prognosis and clinical treatment response for HCC patients. Although the documented molecular subtypes moderately describe the TME heterogeneity and characteristics, their clinical application is constrained by several issues. **Methods:** We integrated three single-cell datasets from 39 HCC patients to describe the TME landscape and identified prognosis-related cell subclusters. Unsupervised clustering of subcluster-specific markers (SSMs) was performed to generate transcriptomic subtypes. The predictive value of these molecular subtypes for prognosis and treatment response was explored in multiple external HCC cohorts and Xiangya real-world HCC cohort with patients who received immune checkpoint blockade (ICB) therapy. Cancer stemness was estimated using bioinformatic methods and in vivo and in vitro experiments. The features of TME were further validated using single-cell RNA-seq and immune repertoire sequencing, mass cytometry (CyTOF) and multiplex immunofluorescence (mIF). Ultimately, we constructed prognosis-related score (PRS)based on machine learning algorithm, and identified the potential therapeutic targets and agents for high-PRS patients. **Results:** The comprehensive single-cell analysis provided a high-resolution depiction of TME heterogeneity in HCC and confirmed 6 cell subclusters of prognostic relevance. Five transcriptomic subtypes were constructed using SSMs, which possessed different clinical prognosis, stemness characteristics, immune landscape and therapeutic responses. Class 1 indicated an inflamed phenotype with better clinical outcomes, while Class 2 and class 4 demonstrated immune-deserted phenotypes lacking T cells infiltration. Class 5 and class 3 indicated inhibitory tumor immune microenvironment enriched regulatory T cells and suppressive immune checkpoints. Multiple therapeutic cohorts suggested that Class 5 and class 3 were sensitive to ICB and targeted therapy, while Class 1 and Class 2 were more responsive to transcatheter arterial chemoembolization treatment (TACE). Class 4 displayed resistant to all conventional HCC therapies. The PRS performed well in prognostic prediction in multiple HCC cohorts. Four potential therapeutic agents and four targets were further identified for high-PRS HCC patients. **Conclusions:** Our study generated a clinically valid molecular classification, thereby providing guidance for precision medicine in HCC patients. Research Sponsor: None.

Characterization of T-cell receptor repertoire and correlation with tumor mutational landscape in lung cancer.

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Background: T-cell receptor (TCR) repertoire represents an overall immune condition which is closely related to pathogens- or tumor-associated T cell responses. Increasing evidence suggests that TCR repertoire is expected to undergo cancer-specific changes during tumorigenesis, supporting that TCR characteristics can serve as novel markers to indicate early cancer progression. Here, we performed a systematic T cell repertoire analysis in lung cancer. We identified cancer-enriched TCR signatures and constructed a comprehensive lung cancer database integrating TCR diversity, tumor mutational profiles, immune markers expression and HLA genotypes. **Methods:** A total of 988 tissue samples and 3,360 blood samples were obtained from patients with lung cancer, in addition to 2,699 blood samples from healthy individuals. Multiplex-PCR-based sequencing of the CDR3 regions of TCR-β chains was applied to the tissue and blood samples. TCR repertoires were analyzed using MiXCR and VDJtools. Whole exome sequencing was performed on partial tumor tissues to profile the mutational landscape and HLA genotypes. An in-house pipeline, considering the frequency and distribution of CDR3, was utilized to identify cancer-enriched CDR3 sequences. The PD-L1 expression was evaluated and quantified using CPS. Furthermore, an enrich score was developed to measure the content of cancer-related TCRs by aligning against the built cancer-enriched CDR3 dataset. Spearman's rank correlation was used to assess relationships between variables. **Results:** Lung cancer exhibited significantly lower Shannon index, Simpson index and evenness index in TCR repertoire ($p<0.001$), both in tissue and blood samples, when compared with healthy blood samples. Approximate 3% T-cell clonotypes within lung tissues were detected in blood TCR repertoires. A correlation was observed between the decreased TCR diversity and a higher tumor mutational burden (TMB)($r = -0.15$, $p < 0.01$), as well as a higher variant allele frequency (VAF) ($r = -0.19$, $p < 0.01$). In this study, 3,652 and 3,840 CDR3 sequences were identified to be enriched in lung cancer tissue and blood respectively. A significant difference in cancer-enriched score was observed between cancer and healthy TCR repertoires ($p < 0.001$). The cancer-enriched score showed a significant positive correlation with TMB, particularly in *TP53*- mutant tumors ($r = 0.27$, $p < 0.001$). A higher CPS (PD-L1) was associated with a higher cancer-enriched score ($r = 0.18$,$p < 0.01$). **Conclusions:** Cancer-related T-cell clonotypes in the tumor microenvironment and peripheral blood informs the changes in anti-tumor responses, supporting the potential application of TCR signatures in early cancer detection. This study identified the lung cancer-related TCR signatures and provided a comprehensive lung cancer TCR database, revealing the relationship between TCR characteristics and mutational profiles. Clinical trial information: ChiCTR2200055761. Research Sponsor: None.

SH2B3 mutation as a potential resistance mechanism to oncolytic virus therapy.

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Background: Oncolytic viruses (OV) are viruses that preferentially destroy cancer cells while sparing healthy cells. Currently, talimogene laherparepvec (TVEC) is the sole FDA-approved OV product; however, resistance to therapy often emerges. To further understand OV resistance mechanisms, we performed transcriptome and mutational analysis on patient samples using a discordant lesion approach. **Methods:** An 80-year-old woman was diagnosed with Merkel cell carcinoma of the right lower extremity and underwent wide local excision. Her disease recurred, and she developed multiple metastatic lesions over three years. During that time, she was further treated with radiation, immunotherapy, and intralesional TVEC. Despite the different treatments, her disease eventually progressed, leading to her death. We analyzed the primary lesion and four discordant lesions that either persisted or recurred following treatment. Treatment data were extracted from medical records, and lesions were classified based on their resistance to therapies. DNA and RNA were extracted from tissue, and whole exome sequencing and bulk RNA sequencing were performed. Whole exome data was compared between specimens to determine mutation enrichment over time. Gene Set Enrichment Analysis was used to interpret bulk RNA sequencing data and compare transcriptional states of lesions. **Results:** Lesions four and five recurred following TVEC treatment and were, therefore, classified as TVEC resistant. Whole exome sequencing of all five lesions identified a heterozygous point mutation (P521L) in the SH2B3 gene in lesions four and five only. Additionally, the variant allelic fraction of this point mutation increased from 33% in lesion four to 44% in lesion five, where it was the highest frequency variant. When comparing lesion five to lesion one, Gene Set Enrichment Analysis showed an increase in both the hallmark inflammatory response gene signature and the hallmark interferon alpha response gene signature. SH2B3 is a gene that encodes the LNK protein, which functions as a negative regulator of the JAK-STAT signaling pathway and is, therefore, a negative regulator of interferon signaling. A mutation leading to a loss of function in SH2B3 would conceptually lead to upregulation of interferon signaling, which has previously been shown to promote an antiviral state within the tumor microenvironment and limit the effectiveness of OV treatment. **Conclusions:** Sequencing of discordant MCC lesions revealed enrichment in the mutational fraction of SH2B3 associated with an increase in interferon alpha and inflammatory signaling among lesions that were resistant to TVEC treatment. This is the first study to report a possible genetic driver for OV resistance. We introduced using CRISPR-HDR P521L SH2B3 in MCC cell lines to investigate its impact on LNK expression and its role as a mechanism of OV treatment resistance, with results to be presented.
Research Sponsor: None.

Pharmacokinetics and biomarker analysis from a phase 1/2 open-label study of the anti-GPC3 T-cell engager SAR444200, in patients with advanced solid tumors.

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Background: SAR444200 is a novel NANOBODY T cell engager that simultaneously binds TCR$\alpha\beta$ and glypican-3 (GPC3) to co-engage T cells with GPC3-expressing tumor cells, resulting in T cell-dependent cellular cytotoxicity. Here we present updated safety, pharmacokinetics (PK) and biomarker data from 6 and 5 dose levels (DL), respectively in patients with advanced solid tumors in the dose escalation cohort (Part 1A) from the first-in-human Phase 1/2 trial (NCT05450562). **Methods:** This ongoing Phase 1/2 trial evaluated open label, intravenously administered SAR444200 (every week with lead-in doses) at DL1 (3 mg), DL1A (1 mg), DL2A (2.5 mg), DL3A (4.5 mg), DL4A (18 mg), and DL5A (36 mg) in adult patients with GPC3+ solid tumors. On study imaging was performed every 9 weeks after the date of first infusion of SAR444200. Whole blood samples were collected to assess the plasma concentrations of SAR444200 and for biomarker analysis. PK analysis was performed with electrochemiluminescence-based total PK assay using Meso Scale Discovery platform. Anti-drug antibody (ADA) monitoring was performed using a PandA assay. **Results:** As of 19 January 2024, a total of 24 patients with GPC3+ solid tumors received SAR444200, 4 patients per DL (DL1, DL1A, DL2A, DL3A, DL4A, DL5A). Most of the patients (17 patients, 71%) had hepatocellular carcinoma. No dose-limiting toxicities were observed. Twenty-two patients (92%) reported treatment-related adverse events (TRAEs) of any grade, including three patients with a serious TRAE (2 events with hospitalization prolongation for a Grade 1 and 2 cytokine release syndrome [CRS] that recovered completely without and with Tocilizumab, respectively, 1 event with pneumonitis Grade 3). All CRS (19 patients, 79%) and infusion-related reaction (7 patients, 29%) were Grade 1 or 2. C_{max} was observed at the end or shortly after completion of infusion. The maximum ADA titer, though high, stabilized despite the target dose increased from Cycle 2. Biomarker analysis showed an increase of interleukin-6 and interferon gamma during lead-in doses, supporting CRS. Cytokines declined after Cycle 1. Among 14 HCC patients with baseline alpha-fatal protein (AFP) higher than 20 ng/ml, 4 (29%) had at least a 20% AFP decrease on treatment. Two patients (both with HCC) have been on study drug for more than 6 months. **Conclusions:** These results suggest that SAR444200 is tolerable at the tested dose levels in patients with GPC3+ advanced solid tumors. Dose escalation continues at this time. Clinical trial information: NCT05450562. Research Sponsor: Sanofi.

Novel method (MAXIM) uses deep learning model to impute missing stains in multiplex images (mIF).

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Background: Multiplex staining and imaging, a state-of-the-art technology, has revolutionized the simultaneous visualization of multiple protein markers within a single tissue sample. Various techniques have emerged to capture multiplex images with up to one hundred markers, enabling a deeper understanding of complex biological processes. The increased marker count increased the likelihood of staining and imaging failure, leading to higher resource usage in multiplex staining and imaging. We address this challenge by proposing a deep learning method and leveraging latent biological relationships between markers to accurately impute unstained protein markers. **Methods:** A deep learning-based marker imputation model for multiplex images (MAXIM) was developed and trained. The model's imputation ability is evaluated at pixel and cell levels across various cancer types. Additionally, we present a comparison between imputed and actual marker images within the context of a downstream cell classification task. The MAXIM model's interpretability is enhanced by gaining insights into the contribution of individual markers in the imputation process. **Results:** MAXIM was successfully trained and evaluated on a whole slide multiplex immunofluorescence (mIF) imaging datasets (14,476 images), encompassing cases from four different cancer types: Urothelial, Anal, Cervical, Head and Neck Squamous Cell Carcinoma (HNSCC). A separate MAXIM model was trained for each marker in mIF images, using the remaining markers as input. MAXIM performance was evaluated using structural similarity index (SSIM) and mean absolute error (MAE) between the imputed marker images and corresponding real marker images. MAXIM achieved high median SSIM, and low median MAE scores as well as high precision scores (AUC 0.95-0.99). **Conclusions:** The MAXIM's method provides a platform with multiple potentials. First, laboratories can seamlessly train an in-house MAXIM model using images devoid of staining issues. The trained model can then be employed to accurately impute markers in multiplexed images that are marred by staining problems. Second, MAXIM can serve as a valuable tool for quality control in newly generated multiplex images, aiding in the detection of staining failures. The strong correlation between imputed and real markers in new images will be an indicator of staining integrity. In practice, MAXIM can reduce the cost and time of multiplex staining and image acquisition by accurately imputing protein markers with less staining. Third the interpretability of MAXIM provides the opportunity to uncover previously unknown latent biological relationships between different protein markers, leading to new insights in the field. Finally, the method can be scaled up for discovery of novel and clinically relevant biomarkers beneficial for offering targeted treatments in different cancer types. Research Sponsor: National Cancer Institute.

Phase 1/2 study of NGM707, an ILT2/ILT4 dual antagonist antibody, in advanced solid tumors: Interim results from dose-escalation.

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Background: The Phase 1/2, dose escalation/expansion study evaluates NGM707, a dual anti-ILT2/ILT4 humanized monoclonal antibody, as monotherapy or in combination with pembrolizumab in patients (pt) with advanced solid tumors. **Methods:** We enrolled pt with locally advanced or metastatic solid tumors into dose-escalating cohorts of 6-1800 mg NGM707 monotherapy and 200-1800 mg NGM707 combined with 200 mg pembrolizumab, administered Q3W IV. Primary aim was to assess safety/tolerability and dosing of expansion cohorts. Secondary/exploratory objectives included pharmacokinetics, biomarkers, and preliminary antitumor activity per RECIST v1.1. **Results:** As of November 6, 2023, we treated 82 pt with NGM707 monotherapy or combination at dose levels up to 1800 mg; five pt crossed over from monotherapy to combination. Primary tumor types included colorectal, NSCLC, gastric, pancreatic, and melanoma. Median age 59 yrs [28-85]; ECOG PS 0 (18.3%), 1 (81.7%). Pt received a median of 4 prior therapies (range 1-16) and 91.5% had metastatic disease. Fifty percent of the pt were pre-treated with anti-PD(L)1. Peripheral RO was dose-dependent, with NGM707 doses ≥200 mg maintaining full ILT2 and ILT4 RO. PK was typical for monoclonal antibodies, with a half-life of 12.8 days. Paired tumor biopsies showed evidence of myeloid and T cell activation. Treatment(tx)-related adverse events (TEAEs) any grade/grade ≥3 occurred in 46.3%/4.8% of pt in the monotherapy and 41.3%/4.4% of pt in the combination. Fatigue (12.2%), arthralgia (9.8%), nausea (9.8%) were reported in monotherapy; fatigue (17.4%), diarrhea (6.5%) were reported in combination. One dose-limiting toxicity (DLT; pneumonitis) occurred in monotherapy and no DLTs in combination. MTD was not reached for both tx; MAD was 1800 mg NGM707. Of 35 response-evaluable monotherapy pt, best overall responses (BOR) were one confirmed PR in pt with melanoma, SD (n=9) and non-CR/non-PD (n=1), leading to DCR ~31%. Eight pt had reduced target lesion (TL) size with maximum reduction of 71%. Of 37 response-evaluable pt in combination, the BOR to date are PR (confirmed; n=4), and SD (n=12), representing DCR ~43%. Nine pt had reduced TL size with a maximum reduction of 100%. Of the 4 pt who had PR, 3 pt were pre-treated with anti-PD(L)1. Two pt with MSS CRC achieved PR, one of them with liver/adrenal TL reduction allowing surgical resection of all residual disease with pCR; ctDNA was not detected. Durable response in this pt led to PFS of 11 months prior to the surgery and ongoing DFS post-surgery. **Conclusions:** NGM707 as monotherapy and in combination with pembrolizumab was safe and well tolerated at all dose levels. In heavily pretreated advanced and metastatic solid tumor malignancies, we observed early efficacy and biomarker signals, including in tumors considered unresponsive to anti-PD(L)1. These results support further evaluation of NGM707. Clinical trial information: NCT04913337. Research Sponsor: NGM Biopharmaceuticals, Inc.

Preliminary results of a phase 1 study of Decoy20, an intravenous, killed, multiple immune receptor agonist bacterial product in patients with advanced solid tumors.

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Background: Systemic activation of multiple immune receptors, such as Toll-like Receptor (TLR), Nucleotide oligomerization domain (NOD) like, and Stimulator of interferon genes (STING) may be required for efficient anti-tumor immune responses. Decoy20 is an attenuated, killed, non-pathogenic, bacterial product with ~90% reduction of lipopolysaccharide (LPS)-endotoxin activity to enhance intravenous (IV) safety, with retention of endogenous TLR1/2,2/6,8,9, NOD2 and STING agonist activity. Decoy20 produced pre-clinical single-agent and combination-mediated anti-tumor activity (colon, liver, pancreas, lymphoma), including innate/adaptive immune-mediated eradication of established tumors, involving combination with anti-PD-1, indomethacin, or cyclophosphamide. We hypothesized that, due to rapid clearance of systemic bacteria by the liver and spleen, Decoy20 may produce transient immune activation, suitable as monotherapy or in combination with approved agents (pulse-prime hypothesis). **Methods:** INDP-D101 (NCT05651022) is a single dose escalation and multi-dose expansion, Phase 1 trial of Decoy20 in patients with metastatic solid tumors refractory to standard therapy with a dose limiting toxicity (DLT) period of 28 days. Primary objectives: safety/tolerability. Secondary objectives: anti-drug immunogenicity, pharmacokinetics (PK) and preliminary efficacy. Exploratory objective: systemic immune activation via immune biomarkers. **Results:** As of January 2024, 11 patients (6F, 5M), mean age 56, with a relapsed solid tumor received a single dose of Decoy20 at $7x10^7$ (n=4) or $3x10^7$ (n=7) Killed Bacteria via 1-hour IV infusion and were evaluable for safety. Grade (G) 3 treatment related adverse events (AE's) included lymphopenia (n=3), AST increase (n=3), IRR (n=1), bradycardia (n=1) and malaise (n=1); the only related G4 AE was lymphopenia (n=8). Bradycardia (n=1 at $7x10^7$) and AST increase for greater than 72 hours (n=1 at $3x10^7$) were DLTs. Lymphopenia resolved in 2-3 days, an expected PD outcome suggesting trafficking of lymphocytes to tissues. Biomarker analysis (n=11) demonstrated immune activation, with transient ≥3-fold induction of plasma analytes, including CD40L, G-CSF, IFN-γ, soluble IL-2 receptor, IL-2, 6, 8, 9,10, 12p70, 15, 18, 21, 27, 31, IP-10, I-TAC, MCP-1, MIG, MIP-1α/β, TNF-α/β and TRAIL. Decoy20 clearance occurred within 30-120 minutes of infusion. One patient with MSS-colon cancer has had stable disease for more than 6 months. **Conclusions:** Decoy20 generated transient AEs expected for LPS exposure. Broad systemic immune activation and preliminary evidence of stable disease were observed with only one infusion of Decoy20. These observations and PK data support our pulse-prime hypothesis and continued Decoy20 trial enrollment as a multi-dosed monotherapy and planned combinations. Clinical trial information: NCT05651022. Research Sponsor: None.

Safety and activity of Diakine DK2^{10} (EGFR), a next generation tumor-targeted IL2 x IL10 dual immunocytokine, in patients with advanced cancer: Initial results of the phase 1 first-in-human trial.

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Background: DK2^{10} (EGFR) couples wild-type IL-2 to a high affinity variant of Epstein Barr Viral (EBV) IL-10 via a scaffold (scFv) that binds to epidermal growth factor receptors (EGFR). We report the dose escalation data from the DEKA-1 phase 1 (NCT05704985) study. **Methods:** Eligible patients (pts) had advanced/metastatic tumors known to express EGFR, progressive disease on ≥1 lines of systemic treatment, and ECOG ≤1. DK2^{10} (EGFR) (2-16 mg; 0.025-0.5 mg/kg for an 80 kg subject) was self-administered subcutaneously (SC) three times per week (TIW) as an outpatient in 21-day cycles following a BOIN design. Adverse events (AEs) including serious (SAEs) were evaluated using CTCAE version 5.0. Cytokines and anti-drug antibodies were monitored during the first cycle, and then every 3 cycles thereafter. RECIST 1.1 tumor responses were evaluated every 9 weeks. **Results:** 17 pts (8 CRC, 5 PDAC, 4 NSCLC) were enrolled at 4 dose levels (2-16 mg TIW). Median age was 70 yrs (range 46-75) and 5 pts (29%) received previous immunotherapy. Median time on treatment was 9 wks (range: 1-30 wks). No DLTs were observed. A maximum tolerated dose has not yet been identified. Treatment-related AEs (TRAEs; any grade) in ≥ 10% pts were injection site reactions (53%), fatigue (41%), fever (35%), nausea (29%), diarrhea (18%); the majority of TRAEs were G1-2. Only 2 G3 TRAEs were reported: syncope and fatigue. No patients exhibited vascular leak or cytokine release syndrome associated with high dose IL-2, nor IL-10-associated toxicity. Dose modifications due to G2 or G3 fatigue occurred in 2 pts. Eosinophilia was observed and correlated with drug concentration but did not require intervention. An EC90 trough of 1 ng/mL was maintained for ~100 hrs at 4 mg and ~150 hrs at 8 mg dosing. At 8 mg dose, ranges of Cmax 5.42 – 13.2 ng/mL and trough 0.453 – 7.56 ng/mL were achieved. Fifteen pts were evaluable for response. Best overall response of stable disease was reported in 4 patients (1 mPDAC, 2 mCRC, 1 mNSCLC). In pts with stable disease systemic immune activation was characterized by the expansion of ~40 – 350 unique T cell clones starting at Day 5, expected wtIL-2 driven eosinophilia, up to 200-fold dose related increased plasma IFNɣ [median 417 pg/ml (range 10-1,000)] but without other pro-inflammatory cytokines associated with CRS. Treatment also induced IL-18, IL-18BP, IL-5, IL-2Ra, soluble PD-L1, LAG3 and TIGIT. **Conclusions:** DK2^{10} (EGFR) was well tolerated and associated with therapeutically relevant on-target biomarker signals consisting of effector T cell expansion and elevated IFNɣ. These data suggest the EGFR targeted balanced combination of IL-2 with IL-10 improves safety and increases potency of anti-tumor function by dissociating CRS from T cell activation. Further exploration of DK2^{10} (EGFR) in RCC and NSCLC as monotherapy and in combination is planned. Clinical trial information: NCT05704985. Research Sponsor: Deka Biosciences.

A first-in-human phase 1a dose-escalation study of BGB-15025 (HPK1 inhibitor) as monotherapy and in combination with tislelizumab (TIS; anti-PD-1 antibody) in patients (pts) with advanced solid tumors.

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Background: Hematopoietic progenitor kinase 1 (HPK1), a critical negative feedback regulator of T-lymphocyte and dendritic cell activation, is a potential target for IO treatment (tx). BGB-15025, a potent, selective, small-molecule HPK1 inhibitor, showed preliminary antitumor effects in preclinical studies as monotherapy (mono tx) and enhanced antitumor effects in combination with TIS. We present dose-escalation results from an open-label, multicenter, phase 1 study (NCT04649385) of BGB-15025 mono tx and in combination with TIS in pts with advanced solid tumors. **Methods:** Eligible pts (≥18 yrs) with previously treated (pts with prior exposure to CPIs were eligible) locally advanced/metastatic solid tumors and ECOG PS ≤1 were enrolled. Oral BGB-15025 mono tx was escalated through 7 doses (20 mg QD–240 mg BID); 5 doses (60 mg QD–240 mg QD) were given in combination with TIS 200 mg IV Q3W (combo tx). Primary objectives were assessment of safety and tolerability, determination of the maximum tolerated/administered dose (MTD/MAD) and recommended dose(s) for expansion (RDFE) for mono tx or combo tx. Select secondary and exploratory objectives included preliminary antitumor activity, PK, and PD. **Results:** As of Nov 21, 2023, 60 and 49 pts received mono tx and combo tx, respectively (median age: 59.0 yrs and 62.0 yrs; median follow-up: 2.3 months and 2.8 months). Most pts were male (56.7% [mono tx]; 67.3% [combo tx]) and received a median of 2 lines of systemic therapy in the metastatic setting (range: 0–7 [mono tx]; 0–5 [combo tx]). The most common tumors were RCC, NSCLC, cervical cancer, CRC, GC/GEJC, and HNSCC. The most common TRAEs (Table) for mono tx were diarrhea (18.3%), vomiting (15.0%), and blood creatinine increased (15.0%); and for combo tx were nausea (30.6%), diarrhea (28.6%), and fatigue (20.4%). No DLTs were observed with mono tx. 5 DLTs were observed with combo tx (2 ALT/AST increased, 1 colitis, 1 immune-related hepatitis, 1 GGT increased). The MAD was 200 mg BID for mono tx and MTD was 150 mg QD for combo tx. For mono tx, there were no responders and disease control rate (DCR) was 35.0%; 3 pts remained on tx for >6 months (2 pts are still on tx for >60 and 84 weeks). For combo tx, the unconfirmed ORR was 18.4% for all doses combined and 31.3% for RDFE, DCR was 57.1% for all doses combined and 56.3% for RDFE. **Conclusions:** These preliminary results show BGB-15025 mono tx or combo tx with TIS was generally tolerable. The antitumor activity of BGB-15025 was improved when given in combination with TIS. Further investigation of BGB-15025 + TIS +/- chemotherapy is ongoing in the expansion phase. Clinical trial information: NCT04649385. Research Sponsor: BeiGene, Ltd.

Pts, n (%)	BGB-15025 (N=60)	BGB-15025 + TIS (N=49)
TRAEs		
Any	42 (70.0)	35 (71.4)
Grade ≥3	7 (11.7)	10 (20.4)
Serious	4 (6.7)	10 (20.4)
Leading to death	0 (0)	0 (0)
Leading to tx discontinuation	0 (0)	6 (12.2)
Immune-related AEs	7 (11.7)	13 (26.5)

Phase 1 dose escalation and cohort expansion study evaluating safety, PK, PD and clinical activity of STC-15, a METTL-3 inhibitor, in patients with advanced malignancies.

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Background: RNA modifications are involved in cancer initiation and progression. The most abundant modification of mRNA is m6A generated by METTL3. Inhibition of METTL3 causes double-stranded RNA formation and activation of cellular T1 IFN response. IFN signaling induces IFN-stimulated gene families i.e. IFIT and OAS, characteristic of an anti-viral response, and secretion of cytokines and chemokines. STC-15, a first in class small molecule inhibitor of METTL3 developed by Storm Therapeutics, demonstrated in pre-clinical models, activation of IFN signaling and remodeling of the TME towards pro-inflammatory state. We report the dose escalation results from a FIH trial in patients with advanced malignancies. **Methods:** This is a multi-center, open-label, dose escalation study. STC-15 oral capsules are administered daily or t.i.w. in 21-d treatment cycles. Dose escalation follows 3+3 modified Fibonacci regimen. Primary objectives are safety and PK. Secondary objectives are preliminary evidence of anticancer activity and RP2D. Exploratory objectives are PD (i.e. target engagement and immune activation biomarkers) and correlation of primary pharmacology with observed clinical efficacy. **Results:** As of 02/01/2024, 31 patients enrolled across 4 dose levels and 5 cohorts: 60mg QD (6 pats), 60mg t.i.w. (3 pats), 100mg t.i.w. (14 pats), 160 mg t.i.w. (5 pats) and 200mg t.i.w. (3 pats). PK profile supports t.i.w. dosing. A total of 169 AEs were observed with 45 AEs attributed to STC-15 treatment. AEs were manageable, mostly hematology (thrombocytopenia 31%; 4% Grade 3), skin (pruritis, rash 14% G1/2) and GI (N/V and diarrhea 14% G1/2). 12 SAEs occurred; 1 pt (60mg QD) had DLT with G3 pneumonitis. Of 14 patients with at least 1 on-treatment scan, DCR is 78% with 2 confirmed PR ongoing in angiosarcoma (60mg, 32 weeks) and IO-refractory NSCLC (100mg, 33 weeks) and 9 SD. An average of 63% reduction in m6A on mRNA in peripheral blood within the first 24h post dosing was observed in 60mg cohorts, confirming target engagement. Whole blood Nanostring and pathway analysis of gene expression confirms upregulation of innate immune pathways (i.e. T1,2 IFN activation and anti-viral responses) as early as 8h after first dose and throughout the treatment cycle. Updated PK/PD and clinical data will be presented. **Conclusions:** Treatment with STC-15 is well tolerated across pharmacologically active dose range with encouraging signs of clinical activity. Early biomarker data provide proof of mechanism in target engagement, strong activation of innate immune responses and correlation of pharmacological activity with clinical response. The study is ongoing and expansion cohorts are underway to further evaluate PK/PD, safety and clinical efficacy at optimized pharmacologically active doses. Clinical trial information: NCT05584111. Research Sponsor: None.

Recommended phase 2 dose (RP2D) of nemvaleukin alfa in patients (pts) with advanced solid tumors treated with less frequent intravenous (IV) dosing (ARTISTRY-3).

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Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokinedesigned to preferentially expand $CD8^+$ T and natural killer (NK) cells with minimal effect on regulatory T cells (T_{regs}). In ARTISTRY-1, IV nemvaleukin at 6 μg/kg once daily, days 1-5 (QD×5) in a 21-day (D) cycle showed antitumor activity across multiple tumors alone and in combination with pembrolizumab (1). ARTISTRY-3 (NCT04592653) is a phase 1/2, open-label study evaluating less frequent IV nemvaleukin dosing in advanced solid tumors. We report pharmacodynamic (PD) and pharmacokinetic (PK) results from ARTISTRY-3. **Methods:** Pts with select solid tumors having exhausted the standard of care therapies were eligible. Quantitative systems pharmacology modeling using different doses of nemvaleukin and schedules was employed to predict less frequent IV dosing that could achieve $CD8^+$ and NK cell expansion comparable to that of 6 μg/kg or 3 μg/kg QD×5 in a 21-D cycle. Based on this information, using Bayesian optimal interval design, escalating doses of nemvaleukin (10-40 μg/kg/d) were evaluated across 3 dosing schedules in a 21-D cycle: D1, D1+D8, and D1+D4. Primary endpoint was incidence of dose-limiting toxicities (DLTs) from the first dose through the end of DLT observation period. Secondary endpoints included objective response, PK, and safety. PD assessments included baseline and on-treatment absolute cell counts ($CD8^+$ T, $CD4^+$ T, NK, $CD19^+$ B, T_{reg}) and relative percentages of memory and activated T cells and NK cell subtypes. **Results:** As of Jan 1, 2024, 49 pts have been treated: 17, 13, and 19 in schedules 1, 2, and 3, respectively. No DLTs have been reported. NK and $CD8^+$ T cell expansion was seen at all doses in all schedules, thus confirming the PD effect of nemvaleukin. Dose-response relationship was observed for PD markers across all schedules. Fold change from baseline for absolute count of NK and $CD8^+$ T cells was significantly higher in schedules 2 and 3, along with better stabilization of disease (SD> 12-24 weeks). Minimal to no expansion of T_{regs} was observed across all schedules. Safety profile was consistent with nemvaleukin mechanism of action and as expected in pts with relapsed/refractory solid tumors. Most treatment-related adverse events (TRAEs) were grade (G) 1-2. There were 3 G3 TRAEs: anemia (schedule 2, 20 μg/kg) and neutropenia and decreased white blood cell count (both schedule 3). There were no G ≥4 TRAEs. Nemvaleukin exposure (C_{max} and AUC_{inf}) increased with escalating doses, with no evidence of nonlinearity. **Conclusions:** Nemvaleukin demonstrated PD proof of mechanism in all 3 schedules and was tolerable at all doses tested, with some stabilization of disease. Safety profile was similar across all schedules. Nemvaleukin RP2D for less frequent dosing schedule is expected to be completed in Q1 2024. 1. Vaishampayan U et al. *J Clin Oncol* 2022. Abs #2500. Clinical trial information: NCT04592653. Research Sponsor: Mural Oncology.

Cln-619 (anti-MICA/B antibody) alone and in combination with pembrolizumab (P) for advanced solid tumors: Updated results of a Ph1 study.

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Background: CLN-619 is a human IgG1 antibody that prevents proteolytic cleavage of NKG2D ligands MICA/B from tumor cells, increasing tumor cell lysis by innate and adaptive immune cells. CLN-619 monotherapy demonstrated favorable safety and objective responses in multiple tumor types in a Ph1 study (ASCO 2023). Results from dose escalation in combination with P and updated results of monotherapy are reported. **Methods:** This first-in-human study (NCT05117476) enrolled pts ≥18y, ECOG 0/1 with advanced solid tumors to receive IV CLN-619 either as monotherapy or in combination with P (200 mg IV Q3W). CLN-619 was dosed at 1-10 mg/kg IV Q3W in the combo arm. Corticosteroid pre-medication is mandated before the first dose of CLN-619. Response (RECIST 1.1) is assessed every 9 wks. **Results:** As of 24 Nov 2023 data-cutoff (DCO), enrollment in both arms of the dose escalation was complete. The combination cohort enrolled 22 (18 evaluable) pts (median 66y, range 38-82; 50% female); pts had received median 3 prior therapies (range 1-7), 41% prior checkpoint inhibitor (CPI). No protocol defined DLTs were observed. Treatment-emergent adverse events (TEAEs) in ≥20% of pts were fatigue (36%), constipation (27%), and nausea (23%). Four patients (18%) experienced Grade (Gr) 1/2 infusion-related reactions. Two patients with NSCLC (1 EGFRm, 1 ALKrearr) had achieved confirmed partial response (PR). After DCO, 1 pt with gastric cancer improved from stable disease (SD) to PR at cycle 7 (pending confirmation). The monotherapy cohort enrolled 42 pts (median 61y, range 26-83; 60% female; median 3 prior (range 1-7); 52% prior CPI). No DLTs were observed. TEAEs in ≥20% of pts were infusion related reactions (26%), fatigue (24%), and abdominal pain (22%). One immune-related AE of maculopapular rash was reported but resolved with steroid taper and did not result in treatment discontinuation. Three previously reported confirmed responses in mucoepidermoid parotid (CR), serous endometrial (PR), and endometroid endometrial (PR) were durable through 13, 7, and 8 (ongoing) months, respectively. Nine pts achieved stable disease (SD) extending through ≥18 wks: 1 HR+ breast, 1 platinum-resistant ovarian, 2 cervical, 1 STK11+ adenocarcinoma lung, 1 uterine carcinosarcoma, 1 pancreatic, 1 salivary adenoid cystic carcinoma, 1 mediastinal intimal sarcoma. Clinical benefit rate at doses ≥1mg/kg (CR+PR+SD≥18 weeks) was 41% (12/29 evaluable pts). **Conclusions:** CLN-619 + P was well tolerated at doses ranging from 1 to 10 mg/kg. Objective responses were observed, including in tumor types typically unresponsive to P. Longer term follow-up for CLN-619 monotherapy confirms favorable safety and durable clinical benefit with extended treatment, including objective responses in multiple tumor types and pts progressing after CPI. Based on these findings, expansion cohorts will be opened in endometrial cancer and NSCLC. Clinical trial information: NCT05117476. Research Sponsor: Cullinan Mica Corp.

EMITT-1: Proof-of-mechanism immunopeptidome (ImPD) effects at target PK exposure, in a phase 1 study of GRWD5769 (a first-in-class inhibitor of Endoplasmic Reticulum Aminopeptidase 1 [ERAP1]) in patients with solid malignancies.

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Background: GRWD5769 is a first-in-class, orally bioavailable ERAP1 inhibitor that significantly modulates the peptide repertoire displayed on MHC-1 on tumor cells, driving novel T cell response and causing tumor cell killing in preclinical studies. This unique approach has potential to overcome central mechanisms of immune resistance by driving de-novo recognition of previously hidden tumor neoantigens and addressing T cell exhaustion. Here we report initial safety, pharmacokinetic (PK) and pharmacodynamic (PD) endpoints from Part A (monotherapy dose escalation) in the ongoing multicentre, modular phase I dose escalation study (ACTRN12623000108617). **Methods:** Patients with advanced refractory solid tumors are enrolled using a BOIN escalation design. GRWD5769 is administered BID on days 1-14 during 21-day cycles. The first cycle is the dose-limiting toxicity (DLT) observation period. The PK / PD relationship of GRWD5769 is being evaluated using mass spectrometry analysis of the ImPD. Tumor responses are evaluated by RECIST v1.1 / iRECIST. **Results:** As of 03 January 2024, a total of 12 patients had been treated with GRWD5769 in 3 dose cohorts (25 mg, 50 mg, 100 mg BID). On average patients have remained on treatment for 4 cycles (range 1-10) No Serious Adverse Reactions, DLTs, immune related AEs or deaths were reported. Two Gr 3 serious adverse events have occurred in 2 treated subjects (aspiration pneumonia and Urinary Tract Infection, neither attributable to GRWD5769). Gr 1+2 AEs were infrequent and manageable. PK analyses for the first 3 cohorts show dose proportional plasma levels, with T_{max} at ~3 h and a ~8 h T_{half}. The minimum biologically active dose (MBAD) is defined as an average steady state plasma concentration above the IC50 for ERAP1, which was achieved at the 100 mg BID dose level. PD data shows dose-dependent target engagement, with marked shifts in the ImPD. This is consistent with the expected mechanistic effects of ERAP1 inhibition seen in preclinical models and is the first demonstration that the human ImPD can be manipulated pharmacologically in cancer patients, potentially allowing T cells to recognise new targets on tumors. Dose escalation with GRWD5769 monotherapy continues to determine the recommended phase 2 dose (RP2D). GWRD5769 in combination with Immune Checkpoint Inhibition will be investigated in Part B now that the MBAD has been reached. **Conclusions:** GRWD5769 has been well tolerated at doses up to 100 mg BID. PK / PD data support dose-dependent target engagement of ERAP1. Proof of mechanism has been achieved for this first-in-class therapy, and this is the first demonstration that the human ImPD can be manipulated pharmacologically in cancer patients. Further PD analyses will explore shifts in the T cell repertoire and modulation of immune cell phenotypes. Clinical trial information: ACTRN12623000108617. Research Sponsor: Grey Wolf Therapeutics Limited.

A phase I/II study to evaluate the safety, pharmacokinetics, and efficacy of PRJ1-3024 in patients with advanced solid tumors.

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Background: PRJ1-3024 is a small molecule hematopoietic progenitor kinase 1 (HPK1) inhibitor designed to potentiate T-cell function. It was demonstrated that HPK1 activity suppresses immune functions of a wide range of cells including cluster of differentiation $CD4^+$, $CD8^+$ T cells and dendritic cells (DCs), mediates T-cell dysfunction and is a potential therapeutic target for T-cell-based immunotherapies. These results strongly support inhibitor of HPK1 functioning as a potential cancer immunotherapy agent. **Methods:** This is a multicenter, open-label study. Primary objective of phase I study is to determine the maximum tolerated dose and recommended Phase 2 dose. Secondary objectives are to evaluate safety, PK, and efficacy of PRJ1-3024. It is dosed orally once daily. Dose-limiting toxicity (DLT) assessment to be completed after 24 days (from the first dose to the end of Cycle 1 continuous 21 medication days). Exploratory analysis of pharmacodynamic targets including multiple cytokines, SLP-76 phosphorylation, cfDNA and IgG typing. **Results:** As of Dec. 22, 2023, 30 patients were enrolled in 6 dose cohorts: 80, 160, 300, 320, 500, and 700mg. Median age was 59 years (range 36-69). Diagnoses were NSCLC (9), Melanoma (3), TNBC (3), Gastric Cancer (3), HNSCC (3), Esophagus Carcinoma (2), Colon Cancer (2), and other types (5). The most common TEAEs (in ≥2 pts) were diarrhea (12), vomiting (12), nausea (9), proteinuria (8), loss of appetite (6), etc. No DLT events, irAEs or treatment-related deaths occurred in all dose cohorts. 9 subjects reported SAEs, only 2 cases were evaluated to be probably related (6.7%), namely 'myocardial ischemic' and 'acute kidney injury'. 1 melanoma subject achieved sustained PR, had been on treatment for more than 7 months up to now. 4 subjects achieved SD (1 NSCLC, 1 HNSCC, 2 TNBCs). PK and PD assessments will be released in due course. **Conclusions:** PRJ1-3024 is shown to be well tolerated in Chinese advanced solid tumor patients. Further safety and efficacy results would be presented at the conference. Clinical trial information: NCT05315167. Research Sponsor: Zhuhai Yufan Biotechnologies Co., Ltd, Guangdong, China.

Anti-PD-1/TGF-βRII bispecific antibody fusion protein LBL-015 in patients with advanced malignant tumors: A phase I, first-in-human, open-label, multicenter, dose-escalation study.

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Background: LBL-015 is a bispecific fusion protein which consists of fully anti PD-1 monoclonal antibody and TGF-βRII ectodomain, designed to block PD-1/PD-L1 and TGFβ signal pathway, reversing immune suppression and promoting anti-tumor immunity. Here we report the preliminary safety and efficacy of LBL-015 in patients with advanced solid tumors. **Methods:** This is a phase I, open-label, multicenter, dose-escalation study to evaluate the safety, tolerability, and PK of LBL-015 in patients with advanced solid tumors that progressed after standard therapy. The dose escalation phase consists of 6 dose cohorts of LBL-015 at 0.3, 1.2, 4, 6, 10, and 20 mg/kg (iv Q2W), using an accelerated titration design (first dose) followed by a 3+3 design. The primary endpoints were tolerability and safety. The second objectives were pharmacokinetics, pharmacodynamics, and preliminary efficacy (per RECIST 1.1). **Results:** As of December 05, 2023, 25 patients [Demography: 11 (44%) male, median age 59 years (range:24, 72), 23 (92%) ECOG score of 1] received LBL-015 treatment. Tumor types included 7 (28%) colorectal cancer, 6 (24%) renal carcinoma (RCC), 2 (8%) gastric carcinoma, 2 (8%) naso-pharyngeal carcinoma and 8 (32%) other tumors. 15 (60%) previously received anti-PD(L)-1 treatment. During the study, 2 DLTs (respiratory failure at grade 5 and pulmonary infection at grade 3, respectively) were observed at the dose of 10 and 20 mg/kg, and the MTD was not reached. 25 patients (100%) experienced TEAEs of any grade and 11 patients (44%) at grade ≥3. The most common grade TEAEs (≥20%) were grade 1-2 and included anaemia, AST increased, γ−GT increased, gingival bleeding, pyrexia, LDH increased, proteinuria, ALT increased, weight decreased, asthenia, bilirubin conjugated increased, decreased appetite, hypoalbuminaemia, asthenia. Treatment interruption and permanent discontinuation of LBL-015 due to TEAEs occurred in 3 (12%) and 2 (8%) patients, respectively. Six patients (24%) experienced SAEs. Out of the 20 patients who underwent at least one efficacy evaluation per RECIST, 1 patient with RCC achieved PR at first image assessment which remained partial response for more than 28 weeks, and 4 patients achieved SD. The ORR and DCR were 5%, and 25%, respectively. **Conclusions:** LBL-015 has demonstrated good safety profiles in patients with advanced solid tumors. The encouraging preliminary efficacy signals indicated additional studies with a focus on TGFβ signaling pathway deregulated or activated tumors such as RCC, pancreatic cancer, etc. should be further explored. Clinical trial information: NCT05107011. Research Sponsor: None.

Phase 1/2a clinical trial of BI-1206, an anti-CD32b (FcγRIIB) antibody, in combination with pembrolizumab in subjects with advanced solid tumors previously treated with anti-PD-1/PD-L1.

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Background: PD-1 blockade has demonstrated positive anti-tumor activity across multiple tumor types. While the anti-tumoral response can be substantial and even curative, response rates remain low in many cancer types. Long-lasting responses are only observed in a minority of patients, and additional immunotherapeutic alternatives remain limited for patients who fail to respond or initially respond but subsequently experience progression. Combining anti-PD-1 with other immunotherapies may improve the durability and depth of anti-tumoral immune responses. Non-clinical data suggest anti-PD-1 interactions with macrophage Fc gamma receptors (FcγRs) compromise therapeutic activity by several mechanisms including the rapid removal of anti-PD-1 from its target on CD8+ T-cells and phagocytosis of anti-PD-1 coated CD8+ T cells. Accordingly, we and others have shown that blockade of Fc/FcγR interactions with immunocompetent antibodies to the inhibitory FcγRIIB, a receptor highly upregulated in the tumor microenvironment, overcomes these resistance mechanisms and enhances anti-PD-1 efficacy *in vitro* and *in vivo*. BI-1206 is a fully human IgG1 targeting CD32b (FcγRIIB). **Methods:** This is a Ph1/2a trial in patients with advanced solid tumors who received previous lines of treatment with anti-PD 1/PD-L1 agents to evaluate safety, tolerability and PK/PD of BI-1206 at ascending IV and SC doses after coadministration with pembrolizumab Q3W using a mTPI-2 design. **Results:** Dose escalation with BI-1206 IV has been completed with no formal MTD defined. The most frequent related adverse events were infusion-related reactions, thrombocytopenia and elevated liver enzymes. All were transient without any clinical consequences, and adequate pre-medication with corticosteroids or split dose administration reduced the risk and/or intensity of these events. Out of 15 evaluable patients, 5 patients showed SD, including one lasting >24 months in a metastatic melanoma patient. Furthermore, long-lasting PR (>24 months) was observed in a uveal melanoma patient, and CR was observed in a metastatic melanoma patient who previously received three prior anti-PD-1 containing treatments (one including anti-CTLA4). Enrollment to BI-1206 SC dose escalation began Nov2023. Dose level and administration route to be further explored in Phase 2a will be determined after an integrated review of PK, PD and safety. The Ph2a consists of 3 expansion cohorts at the RP2D, each comprising a specific subset of subjects with advanced solid tumors (e.g., NSCLC, MM, and other tumors responsive to PD-1/PD-L1 inhibition). More than one dose level may be evaluated if warranted. **Conclusions:** Coadministration of BI-1206 with pembrolizumab was well tolerated in a heavily pretreated population, with promising hints of responses to be further explored in Ph2. Clinical trial information: NCT04219254. Research Sponsor: BioInvent International AB.

Targeting GARP–TGF-β1 with livmoniplimab plus anti–PD-1 budigalimab to remodel the immunosuppressive tumor microenvironment.

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Background: Transforming growth factor (TGF)-β signaling has been shown to induce an immunosuppressive tumor microenvironment (TME) and promote tumor progression. Targeting key immune cells involved in this mechanism, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2 macrophages, by altering their function/depleting them is an important strategy in cancer therapeutics. Glycoprotein A repetitions predominant (GARP) is a membrane-bound receptor that complexes with latent TGF-β1 and plays a vital role in the immunosuppressive function of Tregs (1). In addition to Tregs, GARP–TGF-β1 is also expressed on other cells such as macrophages and tumor cells (2). Data from mouse models demonstrated that combined targeting of GARP–TGF-β1 and PD-1 improved antitumor effects compared with anti–PD-1 alone (3). Livmoniplimab (livmo), a first-in-class mAb, targets and stabilizes the GARP–TGF-β1 complex, sequestering TGF-β in its inactive form. Livmo is in clinical trials in combination with the anti–PD-1 mAb budigalimab (budi) (NCT03821935, NCT05822752). **Methods:** Recently, fresh human tumor-derived tissue culture platforms, which retain autologous TME and immune cell content, have emerged as powerful tools to address the gap between clinical data and preclinical models. To better understand the MOA of livmo + budi, we procured fresh tumors from patients (pts) undergoing surgical resection, minced and cultured them for 48h in the presence of livmo ± budi. The functional activity of livmo and budi was determined by assessing tumor cell viability, T-cell effector function, and modulation of immune-suppressive cells. **Results:** In tumor explant models from 10 pt samples from various indications (NSCLC: n=2; stomach cancer: n=3; HNSCC: n=2; pancreatic cancer: n=1; bladder cancer: n=1; RCC: n=1), treatment with livmo alone led to reduction of tumor cell viability, increase in T-cell effector function, and decrease in immune-suppressive myeloid cells. This effect was further enhanced in combination with budi. Specifically, within the immune cell components, livmo + budi treatment led to no change in the number of Tregs but a 40% reduction in MDSCs and macrophages, both of which depend on TGF-β1 for sustenance and survival. Furthermore, this decrease corresponded with a 50% increase in secretion of granzyme B/IFNγ antitumor T-cell effector functions. **Conclusions:** These data demonstrate that livmo induces decrease in tumor cell viability, increased antitumor immune cell activation, and remodeling of the immune-suppressive TME, which is further enhanced in combination with budi. These results support the hypothesis that pts would benefit from therapeutic intervention with livmo + budi. 1. Stockis et al. *Mol Biosyst* 2017;13:1925-35. 2. Zimmer et al. *Front Immunol* 2022;13:928450. 3. de Streel et al. *Nat Commun* 2020;11:4545. Research Sponsor: AbbVie Inc.

Phase 1/2 study of XTX202, a tumor-activated IL-2βγ, in advanced solid tumors.

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Background: Aldesleukin requires high systemic doses (up to 8.4 million IU/kg = 0.518 mg/kg per weekly cycle) to achieve therapeutic benefit; however, such doses typically result in severe toxicities. To overcome systemic toxicity of IL-2, we employed protein engineering to design XTX202, an investigational tumor-activated, half-life extended IL-2βγ activated by proteases enriched in the tumor microenvironment. βγ molecule design aims to stimulate CD8+T cells and NK cells without a concomitant regulatory T cell increase. **Methods:** NCT05052268 is evaluating safety and tolerability of XTX202 in advanced solid tumors (Phase 1); and safety and efficacy in metastatic renal cell carcinoma (RCC) and melanoma (Phase 2). XTX202 is administered outpatient IV once every 3 weeks. **Results:** As of 23-Jan-2024, 58 patients (pts) were treated in Phase (Ph) 1 across 7 XTX202 dose levels (0.27-4.0 mg/kg), median age 68 yrs (25-82), median 4 prior lines of therapy (LOT, 1-14). While MTD was not reached, based on the totality of clinical and pharmacokinetic (PK)/pharmacodynamic (PD) data, 2 doses were recommended for evaluation in Ph 2: 1.4 and 4 mg/kg [Hanna SITC 2023]. In Ph 2, 14 RCC and 18 melanoma pts had a median age of 63 yrs (33-80) and median 3 prior LOT (1-12). Treatment-related adverse events (TRAE, ≥10% incidence) of any grade (G) across Ph 1 and Ph 2 were: fatigue (22%), chills (22%), pyrexia (19%) and lymphocyte count decreased (11%). TRAEs ≥G3 with ≥2% incidence were: lymphocyte count decreased (7%), cytokine release syndrome (2%, all G3) and ALT increased (2%, all G3). Among 90 pts treated, 2 pts had dose reductions and 1 pt discontinued treatment due to TRAEs. In Ph 1, the overall disease control rate (DCR) was 31%. Long-term disease control was observed with stable disease ongoing for >18 months in a pt with MSS colorectal cancer with liver metastases. In Ph 2, among 13 disease-evaluable patients, DCR was 62% at the 1.4 mg/kg dose-level and 80% at the 4 mg/kg dose-level, with 19 pts ongoing and awaiting first response assessment. PK analysis demonstrated dose-proportional exposure. Calculated fraction of activated XTX202 in peripheral blood was negligible (0-3%). In contrast, bioanalytical (BA) data from an on-treatment biopsy demonstrated tumor-selective activation with ~15% activated molecule in the tumor. Dose-dependent PD in peripheral CD8+ T cells and NK cells was consistent with IL-2 biology while tumor-selective increases in CD8+ T cells in the absence of regulatory T cell expansion were observed consistent with intended design. **Conclusions:** Clinical and translational data demonstrated tumor-specific activation of XTX202, as supported by PK, tumor BA and PD data. Importantly, in a heavily pretreated population the safety profile observed at 4 mg/kg, as well as dose dependent, durable anti-tumor activity positions XTX202 for combination approaches not otherwise feasible with high dose IL-2. Updated data from Ph 2 will be presented. Clinical trial information: NCT05052268.
Research Sponsor: None.

Phase I dose-escalation and cohort expansion study of the anti-BTLA antibody, tifcemalimab, in combination with toripalimab (anti-PD-1) in heavily pretreated patients (pts) with advanced malignancies.

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Background: Tifcemalimab, a humanized IgG4 antibody against BTLA, showed a tolerable safety profile and preliminary single-agent anti-tumor activity in pretreated pts with advanced malignancies. Here we report the dose escalation and cohort expansion study of tifcemalimab in combination with toripalimab (anti-PD-1) in pts with pretreated advanced malignancies. **Methods:** Eligible pts with advanced malignancies refractory to standard therapies were enrolled in the dose escalation and the cohort expansion phases of this study (NCT04137900). During dose escalation, tifcemalimab was administered at escalating doses of 20, 70, 200 and 500 mg in combination with 240 mg toripalimab given intravenously once every three weeks (Q3W) until disease progression or intolerable toxicity. Dose-limiting toxicity (DLT) was evaluated. Study objectives included safety and efficacy. During cohort expansion, the combination of tifcemalimab (200mg Q3W) and toripalimab (240 mg Q3W) were further evaluated in five indication-specific cohorts (melanoma, non-small cell lung cancer [NSCLC], renal cell carcinoma [RCC], urothelial carcinoma [UC] and lymphoma) for safety and efficacy. **Results:** By December 16, 2023, a total of 16 pts received study treatment during dose escalation and 69 pts were treated during cohort expansion from 18 participating sites from the US. Pts were heavily pretreated with a median of 4 prior lines of therapy. The median age was 65 (range 32-85) years, 69% of pts were male. As of December 16, 2023, the median follow-up was 11.4 weeks. No DLT was observed during dose escalation. Treatment-emergent adverse event (TEAEs) occurred in 92% pts, 44% experienced grade 3 or higher TEAEs, including 2 (2%) treatment-related Grade 5 events. The most common TEAEs included: fatigue (27%), diarrhea (17%), nausea (17%), anemia (15%), arthralgia (15%), decreased appetite (15%), and dyspnea (15%). TEAE led to discontinuation of study drug in 6% of pts. Nineteen percent of pts experienced immune-related AEs. No new safety signal was identified outside the known risk profiles of tifcemalimab and toripalimab. Among 14 evaluable pts in the dose escalation phase, 8 had stable disease. Among 57 evaluable pts in the cohort expansion phase, 1 complete response (lymphoma), 6 partial responses (2 melanoma, 2 RCC, 1 NSCLC, 1 UC) and 17 stable disease were observed. The ORRs were 5%, 11%, 17%, 18% and 33% in the NSCLC, melanoma, UC, RCC and lymphoma cohorts respectively. All responders were refractory to prior immunotherapy and all responses were still ongoing by the cutoff date. **Conclusions:** Tifcemalimab in combination with toripalimab showed preliminary efficacy in immunotherapy-refractory pts with a manageable safety profile. Phase II combination studies in various advanced solid tumors are ongoing. Clinical trial information: NCT04137900. Research Sponsor: TopAlliance Biosciences.

Correlation of baseline ENPP1 and cGAS expression in advanced solid tumors with intratumoral immune activation and clinical outcomes after treatment with the first-in-class oral ENPP1 inhibitor RBS2418, alone or in combination with pembrolizumab.

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Background: ENPP1 is a nucleotide pyrophosphatase and phosphodiesterase. Its expression is associated with poor prognosis in cancer. ENPP1 inhibition protects cGAMP and ATP from hydrolysis and reduces adenosine levels in the TME, activates APCs and increases T-cell infiltration promoting anticancer immunity. RBS2418, a first-in-class, potent ENPP1 inhibitor, is evaluated as monotherapy and combination with pembrolizumab in advanced/metastatic solid tumors. **Methods:** Phase 1 dose escalation with 100, 200, 400 and 800 mg BID dose and selected expansion cohorts of RBS2418 alone or in combination with pembrolizumab (200 mg IV q3w) in patients who have failed all approved treatments including immunotherapy. Primary outcome measures are safety and PK. Tumor biopsy, and blood samples are collected to determine PK/PD and immune profiles using LC/MS, ENPP1 inhibition, immunofluorescence, IHC, flow cytometry, and TCR/RNAseq analysis. **Results:** All dose levels evaluated to date were safe and well tolerated with no DLTs. Median plasma concentrations of RBS2418 increased in a dose-dependent manner. Plasma and tumor concentrations of RBS2418 were above the ENPP1 inhibition EC90 level in all patients at all-time points tested. Preliminary analyses support the premise that ENPP1 and cGAS co-expression (EG+ phenotype) in tumors correlates with RBS2418 treatment associated immune activation and clinical benefit. Analysis of all currently available paired pre- and on-treatment biopsies showed on-treatment immune activation profiles in 100% (n=6) with EG+ phenotype and 0% (0/6) with EG- phenotype at baseline. Immune activation profiles include an increase in tumor-infiltrating T-cells and M2 to M1 macrophage switch, consistent with the mechanism of action. EG +/- phenotype and immune activation profile also correlated with observed clinical outcomes. **Conclusions:** Oral RBS2418 alone or with pembrolizumab has been safe, well tolerated with no DLTs at all dose levels evaluated to date in the ongoing Ph1 dose escalation and expansion study. The robust PK profile shows plasma levels enabling complete ENPP1 inhibition at all time points. Immune activation and observed clinical benefit of treatment in late line treatment of refractory metastatic solid tumors such as CRC and HCC was associated with baseline ENPP1 and cGAS protein expression in tumors. These results warrant further development of RBS2418 in advanced tumors and enrollment continues in expansion cohorts on this phase 1 study. Clinical trial information: NCT05270213. Research Sponsor: None.

A first-in-human, phase 1/2a study of GI-102 (CD80-IL2v3) in patients with advanced or metastatic solid tumors: Initial results from dose escalation.

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Background: GI-102 (CD80-IL2v3) is a novel immunocytokine designed to direct IL-2v3 to immune cells and tumor cells. IL-2v3 of GI-102 abolished affinity to IL-2Rα minimizing the impact of IL-2 on Treg cells. Preferential targeting of immune cells and further inhibition of CTLA-4 and PD-L1 via CD80 synergize with potent activity of IL-2v3, resulting in robust proliferation and activation of CD8+ T and NK cells. Here we report preliminary safety and efficacy data of GI-102 from a phase 1/2a trial in patients with metastatic solid tumors. **Methods:** NCT05824975 is an ongoing, dose escalation (3+3 design) and expansion study to evaluate safety, tolerability, PK, PD and anti-tumor activity of GI-102. Each dose level allows to enroll additional 7 patients to fully inform the safety, PK and PD at that dose level. GI-102 was administered intravenously every 3 weeks until disease progression or unacceptable toxicities. Disease was assessed every 6 weeks using RECIST v1.1. **Results:** As of 12 Jan 2024, 32 patients were treated in dose escalation: 8 at dose level 0.06 mg/kg, 10 at 0.12 mg/kg, 9 at 0.24 mg/kg and 5 at 0.45 mg/kg. Patients had received median of 3 [1-7] prior lines of therapy, including 25.0% (8/32) who had received ≥ 5 lines and 68.8% (22/32) had experienced immune checkpoint blockade (ICB). No dose-limiting toxicities (DLTs) were observed until the highest dose of 0.45 mg/kg Q3W. The most common treatment-related adverse events (TRAEs, ≥10%) were pyrexia [43.8%] and chills [34.4%]. 5 patients [15.6%] had ≥ Grade 3 TRAEs and no patient reported TRAEs leading to discontinuation of GI-102. In 23 patients (7 cutaneous melanoma, 4 non-small cell lung cancer, 3 ovarian cancer and others) who had at least 1 post-treatment tumor assessment, objective responses were observed in 17.4% (4/23). In patients with metastatic melanoma who previously experienced ICB, overall response rate (ORR) and disease control rate (DCR) was 42.9% (3/7) and 85.7% (6/7), respectively, including 3 confirmed partial responses (cPR). The median time to response (TTR) was 6 weeks and duration of response (DoR) was 6.0+, 2.4+ and 1.7+ month, respectively. In patients with metastatic ovarian cancer, ORR and DCR were 33.3% (1/3) and 66.7% (2/3), respectively, including 1 cPR [TTR of 6 weeks; DoR 1.9+ month]. Preliminary PK profile showed target-mediated drug disposition with a half-life of ~48 hours. 0.24 mg/kg of GI-102 resulted in a significant expansion of peripheral lymphocytes, CD8+ T cells (effector & memory) and NK cells, by 4.4 [2.1-9.6], 3.9 [2.0–5.7] and 20.4 [9.5–32.6]-fold change from baseline, respectively. There was no meaningful increase in Treg cells. **Conclusions:** GI-102 was well tolerated up to dose of 0.45 mg/kg Q3W with meaningful monotherapy activity, regardless of previous ICB experience, in patients who failed on standard of care. The dose-escalation is currently ongoing to identify RP2D. Clinical trial information: NCT05824975. Research Sponsor: None.

IK-175, an oral AHR inhibitor, as monotherapy and in combination with nivolumab in patients with urothelial carcinoma resistant/refractory to PD-1/L1 inhibitors.

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Background: IK-175 is an oral, selective, small molecule Aryl Hydrocarbon Receptor (AHR) inhibitor. AHR is a ligand-activated transcription factor that binds kynurenine causing gene expression that promotes an immunosuppressive tumor microenvironment, possibly driving resistance to PD-1/L1 inhibitors (CPIs). Urothelial carcinoma (UC) demonstrates increased AHR signaling and nuclear protein localization as shown by gene expression analysis and tissue-based immunohistochemistry. **Methods:** This is a first-in-human, open-label, multicenter, study of IK-175 monotherapy and with nivolumab initially in solid tumors and for expansion in UC. Dose expansion patients received 1200mg QD of IK-175. Nivolumab was given at 480mg q4w in the combination cohorts. Both monotherapy and combination expansion arms utilized Simon 2-stage designs, and enrolled heavily pretreated UC patients who progressed $\leq$ 12 weeks of last dose of PD-1/L1 inhibitors (CPIs) and were enriched for nuclear AHR+ tumors by IHC. Study objectives included evaluation of safety, pharmacokinetics, pharmacodynamics, MTD, RP2D and antitumor activity (RECIST 1.1) of IK-175 as a monotherapy and in combination with nivolumab. **Results:** Fifty-seven UC expansion patients were evaluated for safety. Median age was 69 years (range 26-81), 52/57 (91%) patients received $\geq$2 lines of prior therapy including CPIs. 5/14 monotherapy and 14/43 combo had nuclear AHR+ tumors. The most common treatment-related AEs were nausea, fatigue, and diarrhea. Infrequent immune-related AEs occurred in $<$9% of patients and included adrenal insufficiency, proteinuria, rash, pneumonitis, and immune-related arthritis. Significant reduction in tumor target lesions (-30% to -100%) was observed in 6/46 (13%) response-evaluable UC patients (both arms). DCR was 46% and 49% for monotherapy and combination. Confirmed partial responses were observed in 1/13 (7.7%) monotherapy (DoR 22.6 months) and 2/33 (6%) in combo (DoR 4.4 and 7.3 months). Two patients in combo were treated beyond progression (for 4 and 10 months) due to investigator-assessed clinical benefit, including tumor shrinkage of target lesions. **Conclusions:** IK-175 showed a predictable, consistent safety profile as a monotherapy and in combination with nivolumab. Meaningful clinical benefit and objective, durable, prolonged responses were demonstrated in both monotherapy and combination arms in heavily pretreated UC patients with tumors refractory to CPI and supports further development of this asset in solid tumors. Clinical trial information: NCT04200963. Research Sponsor: Ikena Oncology.

Initial results from a first-in-human phase 1 study of SNS-101 (pH-selective anti-VISTA antibody) alone or in combination with cemiplimab in patients with advanced solid tumors.

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Background: VISTA (V-domain Ig suppressor of T-cell activation), an inhibitory T-cell checkpoint expressed on myeloid-lineage cells, is a promising target in cancer immunotherapy. However, therapeutically targeting VISTA effectively has been challenging. We developed SNS-101, a novel pH-selective VISTA antibody, to address issues of rapid clearance and cytokine release syndrome (CRS) faced by previous VISTA antibodies. **Methods:** First in human, Ph 1/2, open-label, multicenter, dose escalation/expansion study of anti-VISTA (SNS-101) as monotherapy (mono) or in combination (combo) with cemiplimab (cemi) in pts with advanced solid tumors that have either progressed on prior anti-PD-1 therapy (acquired resistance) or are unfavorable candidates for immunotherapy (primary resistance). Primary objectives include safety and MTD/RP2D. Secondary objectives include PK and anti-tumor activity. SNS-101 +/- cemi was given once every 3 wks at dose levels of 0.3, 1, 3, 10 and 15 mg/kg for mono and 3, 10 and 15 mg/kg + cemi 350 mg for combo. Patients are not routinely prophylaxed for CRS. The study employs a BOIN design. **Results:** As of February 2, 2024, the dose escalation portion of the study completed accrual (n=31) to highest dose levels in both mono (n=16) and combo arms (n=15); 12 pts remain ongoing (2 mono/10 combo). Most common tumor types are colon (n= 7), kidney (n=4), pancreatic (n=3), and ovarian (n=2). Median age is 62 years. Median number of prior metastatic therapies is 2; 12 pts (39%) received ≥1 prior anti-PD-1/PD-L1 agent. No DLTs were observed. Most frequent AEs: cough (n=3), dermatitis acneiform and pyrexia (n=2 each) in the mono arm; fatigue (n=3), anemia, nausea and rash maculo-papular (n=2 each) in the combo arm. Immune-mediated AEs included CRS (G1, 15 mg/kg, n=1) in the mono arm; diabetic ketoacidosis (G3, 3 mg/kg, n=1), rash maculo-papular (G2, 3 mg/kg, n=1), and ALT increased (G3, 10 mg/kg, n=1) in the combo arm. One pt had a confirmed PR and 10 pts had SD as best response. In the mono arm, 1 pembrolizumab-resistant HPV+ H&N pt at 15 mg/kg had tumor regression of 17%. In the combo arm, 1 MSS endometrial pt at 3 mg/kg + cemi had a confirmed PR (45% decrease) and 1 MSS colon pt at 10 mg/kg + cemi had tumor regression of 27%. PK appears dose-proportional and consistent with lack of target-mediated drug disposition, with no notable difference between mono vs combo dosing. Dose-dependent changes in specific T-cell populations indicate potential SNS-101-related pharmacological effects. **Conclusions:** pH selective SNS-101, both alone and in combo with cemi, has been safely administered at doses that are ~50x higher than doses where severe CRS was observed with prior VISTA agents. Both mono and combo therapy have been generally well tolerated. Early signs of clinical activity were observed in both the acquired and primary PD-1 resistant tumor settings. Clinical trial information: NCT05864144. Research Sponsor: None.

TransCon IL-2 β/γ alone or in combination with pembrolizumab, standard of care chemotherapy or TransCon TLR7/8 agonist in advanced/metastatic solid tumors: Updated results of the phase 1/2 IL Believe study.

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Background: TransCon IL-2 β/γ (TC-IL2 β/γ) is a novel prodrug with sustained release of an IL-2Rβ/γ-selective IL-2 analog (IL-2 β/γ). IL-2 β/γ is transiently attached to an inert carrier by a TransCon linker, which under physiological conditions, releases active IL-2 β/γ in a predictable sustained manner. This results in lower Cmax and longer half-life, which is expected to widen the therapeutic index. **Methods:** Dose escalation of TC-IL2 β/γ IV as monotherapy (mono) or in combination with pembrolizumab (P) evaluated doses starting at 20 μg/kg IV every 3 weeks. Cohort 4 evaluated the recommended phase 2 dose (RP2D) 120 μg/kg of TC-IL2 β/γ IV in combination with intratumoral TransCon TLR7/8 Agonist in patients with melanoma who have progressed on anti-PD-1 therapy. Disease was assessed every 9 weeks per RECIST 1.1. Safety, efficacy, and biomarker analysis were evaluated. **Results:** As of 07Dec2023, 25 patients were treated with mono (TC-IL2 β/γ doses 20 to 160 μg/kg) and 21 in combination with P (TC-IL2 β/γ doses 20 to 120 μg/kg). The most common tumor types enrolled in dose escalation were head and neck squamous cell (n=7), colorectal (CRC) (n=4) and small cell lung cancer (SCLC) (n=4). Treatment Related Adverse Events ≥Grade 3 (G3) occurred in 11 (24%) patients in dose escalation cohorts. One Dose Limiting Toxicity of G3 Cytokine Release Syndrome was reported at 160 μg/kg. The RP2D was selected at 120 μg/kg in mono and in combination with P. Of patients who progressed on prior anti-PD-(L)1 therapy, one patient with SCLC had confirmed complete response (combination with P, 120 μg/kg) and 2 patients had confirmed partial response (cPR): CRC (mono, 120 μg/kg) and SCLC (combination with P, 80 μg/kg). Biomarker analysis demonstrated dose dependent increases in absolute lymphocyte counts (ALC), driven by selective expansion of cytotoxic lymphocytes (CLs) without meaningful expansion of Tregs. Expanded CLs displayed an activated phenotype along with an average 5-fold increase in soluble CD25. IFN-γ and CXCL10 were elevated for ≥5 days after first dose. Safety-related biomarkers like eosinophil levels remained in the normal range after treatment. Indication-specific dose expansion cohorts are currently enrolling with no new safety signals and early data from 4 patients enrolled in Cohort 4 as of 22Dec2023 indicate 1 cPR in a patient with anti-PD-1 refractory melanoma. **Conclusions:** TC-IL2 β/γ alone and in combination with P or TransCon TLR7/8 Agonist is generally well-tolerated with meaningful clinical responses in heavily pretreated patients with anti-PD-(L)1 relapsed or refractory disease. Initial evaluation of biomarkers shows a sustained significant expansion and activation of CLs, elevated levels of cytokines and chemokines in blood without the corresponding expansion of Tregs or eosinophils. Clinical trial information: NCT05081609. Research Sponsor: None.

Phase 1 study of BA3071, an anti–CTLA-4 conditionally active biologic, in combination with nivolumab in advanced solid tumors.

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Background: Immune checkpoint inhibition of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) in combination with programmed cell death protein 1 (PD-1) has demonstrated durable clinical benefit in patients with advanced solid tumors. However, dose density is limited due to toxicity. BA3071 is a conditionally active biologic (CAB) anti–CTLA-4 monoclonal antibody that blocks the interaction of CTLA-4 with its ligands CD80 and CD86 [1]. CABs are activated within the acidic tumor microenvironment. Conditional and reversible binding of BA3071 may reduce on- and off-tumor immune-related adverse events (AEs) and autoimmunity, avoid tissue-mediated drug deposition, and improve pharmacokinetics. We evaluated the safety and antitumor activity of BA3071 in patients with advanced solid tumors. **Methods:** Patients naïve to anti–CTLA-4 therapy with advanced solid tumors received escalating doses of single-agent BA3071 every 3 weeks (Q3W) at cycle 1, followed by combination BA3071 + nivolumab from cycle 2 onward. Treatment continued until disease progression or unacceptable toxicity. Response assessment was performed Q6W with RECIST v1.1. **Results:** Eighteen patients were treated with BA3071 (7–700 mg) and nivolumab (240 mg); 61% had received ≥3 lines of prior systemic therapy, and all patients had experienced failure of anti–PD-1 therapy. Four patients experienced grade 3 related treatment-emergent AEs (TEAEs; hypertension, increased lipase, atrial fibrillation, gastritis, and diabetic ketoacidosis); no grade 4 related TEAEs were observed. Two patients experienced grade 3 immune-related TEAEs (diarrhea [BA3071 350 mg] and diabetic ketoacidosis [BA3071 700 mg]). Among 16 efficacy-evaluable patients, 9 experienced stable disease, and 2 out of 5 patients receiving BA3071 in the 350-mg cohort achieved confirmed RECIST v1.1 responses (complete response in cervical carcinoma and partial response in gastroesophageal carcinoma). One patient with metastatic small cell lung cancer who received 7 mg BA3071 remained without progression for >1 year (69 weeks). **Conclusions:** Treatment with the novel, conditionally active anti–CTLA-4 agent BA3071, in combination with anti–PD-1 therapy (at doses higher than those currently approved for anti–CTLA-4/PD-1 therapy), yielded confirmed responses with a promising tolerability profile. Phase 1 dose escalation of BA3071 continues at 700 mg up to 1000 mg, and phase 2 monotherapy and combination therapy expansion cohorts are currently enrolling at a starting dose level of 350 mg. 1. Chang HW et al. *Proc Natl Acad Sci USA*.2021;118(9):e2020606118. Clinical trial information: NCT05180799. Research Sponsor: BioAtla Inc.

Correlative and spatial biomarker analysis of a phase 1/2b study to evaluate pepinemab in combination with pembrolizumab for first-line treatment of patients with recurrent or metastatic head and neck cancer.

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Background: Myeloid cells contribute to suppression of adaptive immunity within the TME and limit the efficacy of immune checkpoint inhibitors (ICIs) in head and neck squamous cell carcinoma (HNSCC). Semaphorin 4D (SEMA4D) signaling through its receptors (PlexinB1/B2, CD72) promotes recruitment and suppressive function of myeloid suppressor cells (MDSC). In preclinical and clinical studies, SEMA4D antibody blockade attenuated MDSC and increased penetration and organization of dendritic cells (DC) and T cells into tertiary lymphoid structures that enhanced activity of ICI. We hypothesize that SEMA4D blocking antibody pepinemab may regulate infiltration and crosstalk of immune cells in TME as a novel and complementary mechanism of immune enhancement when combined with immune checkpoint therapy. **Methods:** KEYNOTE-B84 (NCT04815720) is an ongoing single-arm open-label study evaluating the safety, efficacy, and PK/PD of pepinemab in combination with pembrolizumab as first-line treatment of recurrent or metastatic HNSCC. Exploratory biomarker analyses were performed to evaluate spatial interactions of tumoral immune cells. Pre- and on-treatment tumor biopsies were collected and assessed by multiplex immunohistochemistry for up to 36 biomarkers/biopsy. Unbiased algorithms identified co-localization of markers for advanced cell phenotyping, density, spatial and proximity analysis. Biomarker results were then stratified by demographic and clinical outcome measures. **Results:** An increase in activated APC (HLA-DR+CD11c+ and HLA-DR+CD68+) and reduced density of MDSC (Arg1+CD14+ and ARG1+CD15+) was observed in patients with durable disease control. Interestingly, spatial analysis of tumor biopsies revealed that combination therapy induced the formation of highly organized immune aggregates, including a high density of activated B cells, DCs, CD4+ and CD8+ T cells, including stem-like CD8+TCF1+PD1+ T cells. Presence of immune aggregates increased in on-treatment compared to pre-treatment biopsies, even in HPV-negative and PD-L1 low tumors. Favorable spatial interactions between DC-1, CD8, CD4, and B cells was associated with PFS and disease control. **Conclusions:** Results suggest that combination therapy induced formation of highly organized lymphoid aggregates in HNSCC tumors, with a high density of activated B cells, DC and T cells. Together with similar observations indicating that combination immunotherapy with pepinemab induces mature lymphoid structures in tumors of patients with metastatic melanoma, provides evidence of treatment-induced biologic activity corresponding with disease control and suggests a novel and independent mechanism of pepinemab to enhance immune interactions and ICI activity. Clinical trial information: NCT04815720. Research Sponsor: Vaccinex.

Examining response to immunotherapy in clear-cell renal cell carcinoma using baseline serum metabolic signatures.

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Background: Clear cell renal cell carcinoma (ccRCC) accounts for 80% of kidney cancer cases. While immune checkpoint blockade (ICB) is a front-line treatment, most patients do not have durable clinical benefit, and current biomarkers fail to predict response. Previous studies reported metabolic alterations in response to ICB based on profiling of 202 targeted metabolites. To identify metabolic signatures predicting response to ICB at baseline, we have developed mzLearn, a data-driven algorithm that overcomes obstacles in liquid chromatography/mass spectrometry (LC/MS) measurements of untargeted metabolomics at scale. **Methods:** We used baseline and post-treatment raw LC/MS data (n=1,650) from ccRCC patients in Phase I (n=91) and Phase III (n=741) trials (Workbench IDs ST001236 and ST001237), where anti-PD-1 treatment yielded a significant increase in overall survival compared to mTOR inhibitor. mzLearn detected 4,018 signals present in >60% of all samples. The identified signals have 90% accuracy in detecting targeted metabolites with 10% false positives while effectively overcoming signal drifts and batch effects. We then performed unsupervised K-means clustering of baseline metabolomic features and supervised linear and Cox proportional hazard models to find minimal subsets of those features associated with clinical benefit after adjusting for clinical variables, e.g., age and prognostic scores. We then developed logistic regression models to predict clinical benefit (CB), i.e., tumor shrinkage with ≥6 months progression-free survival (PFS). Finally, we used PIUMet (1), a network-based tool for untargeted metabolomic analysis, to identify linked mechanisms. **Results:** We identified three main metabolomic subtypes with distinct PFS in response to treatments. We identified a cluster of anti-PD-1 responders (n=279) with significantly higher PFS (p=2e-5, HR=0.56) and a non-responder cluster (n=261) who showed no significant effect from anti-PD-1 relative to mTOR inhibition (p=0.874, HR=1.02). Importantly, one subtype (n=201) tended to have higher PFS after mTOR inhibition (p=0.11, HR=1.27). Next, using supervised methods, we identified 97 baseline metabolite features associated with clinical benefit in the ICB arm. A smaller subset of top-scoring features predicts CB with a cross-validated AUC of 78% and the AUC=71% when tested in the independent Phase I cohort. PIUMet analysis of these features predicted their association with sphingolipid metabolism and arginine/proline metabolism. **Conclusions:** We showed baseline metabolic stratification of ccRCC patients can predict treatment response and discovered novel blood-based metabolic signatures of predicting response to ICB at baseline. These results establish a solid foundation for predictive biomarker discovery and potentially therapeutic recommendations after further validation. 1. Pirhaji et al. Nat. Met. 2016. Research Sponsor: None.

Tislelizumab first-line (1L) gastric/gastroesophageal junction cancer (G/GEJ) treatment efficacy on patient-reported outcome (PRO)-based symptom endpoints adjusting for informative missing data bias: Results from RATIONALE 305.

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Background: PRO-based symptom endpoints are rarely associated with treatment efficacy in oncology trials. PRO analyses emphasize early treatment cycles to avoid bias arising from study dropout (SDO; eg, due to death or other intercurrent events). SDO is thought to induce data missing not at random (MNAR), thereby biasing estimates and inference. However, separation between arms on other efficacy endpoints (eg, overall survival [OS]) typically occurs at cycles subsequent to the analysis period cutoff for PRO-based endpoints. This research examined treatment efficacy in PRO-based symptom endpoints in treatment cycles occurring later than typically analyzed. To protect against MNAR bias associated with later cycles, joint models (JMs) were employed. **Methods:** RATIONALE 305 was a randomized, double-blind, placebo-controlled, phase 3 trial comparing efficacy and safety of tislelizumab + chemotherapy (tislelizumab) with placebo + chemotherapy (chemo) as 1L treatment for patients with locally advanced, unresectable, or metastatic G/GEJ adenocarcinoma. EORTC-STO22 symptom domain scores were analyzed. Change from baseline (CFBL) in each domain was analyzed for up to 21 cycles between baseline and Cycle 38 (cycle with no less than 10% of baseline surviving). Treatment efficacy for STO22 endpoints was analyzed using JMs. The JM linked a linear mixed model (LMM) for STO22-domain CFBL to a Cox proportional hazards model for OS, adjusting LMM estimates for the potential MNAR bias arising from OS-based SDO. The LMM and Cox model were adjusted for study randomization factors of region (East Asia vs Rest of World), PD-L1 status (positive vs. negative), and peritoneal metastases (present vs. absent). All analyses were conducted using JMBayes2 package in R version 4.3.2. **Results:** STO22 pain results are reported; all domains will be presented. For tislelizumab (n=465) vs. chemo (n=467), subjects remaining at Cycle 38 were 46 (10%) and 28 (6%), respectively. Tislelizumab was associated with a constant lower level of pain compared with chemo (-2.08; P=0.0109). Tislelizumab was associated with a 21% reduction in risk of death (P=0.0269). **Conclusions:** In this analysis, compared with chemo, tislelizumab + chemo was associated with lower pain and longer survival. Joint models for PRO-based symptom endpoints may illuminate patient-centric therapeutic benefits. Research Sponsor: BeiGene.

Joint model for STO22 pain and OS.

JM Linear Mixed Model Estimates	Conditional Means	*P* Values
Intercept	9.54	<0.0001
Cycle	-0.02	0.5933
Tislelizumab vs. Chemo	-2.08	0.0109
Tislelizumab vs. Chemo x Cycle Interaction	-0.07	0.2131
Baseline score	-0.59	<0.0001
JM terminal event model: OS	**Hazard ratio**	***P* value**
Tislelizumab vs. Chemo	0.79	0.0269

The gut microbial characteristics and underlying mechanisms of patients with different clinical prognoses from immunotherapy by landmark analysis.

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Background: A subset of cancer patients could benefit long-termly from immune checkpoints inhibitors (ICIs), which was called smearing effect. Gut microbiota was widely found to be associated with the initial ICIs efficacy and immune-related adverse event (irAE). This study aimed to identify the baseline gut microbiota characteristics of long-benefit patients and explore the possible underlying mechanisms. **Methods:** Lung cancer patients initially treated with anti-PD-1/PD-L1 therapy were consecutively enrolled from May 2020 to September 2022. All patients were classified into Benefit group, Resistance group and Severe irAE group based on the long-term prognosis. The baseline gut microbiota characteristics were identified by metagenome sequencing. MelonnPan was used to predict the abundances of 79 metabolites. The sequences of autoantigen, lung cancer antigen and anticancer peptides (ACPs) from IEDB and CancerPPD databases were aligned against the scaftigs of fecal samples. **Results:** 54 patients were enrolled with 24 in Benefit group, 13 in Severe irAE group and 17 in Resistance group. The microorganism composition was significantly different between Benefit group and Resistance group (P=0.03), while no difference between Benefit group and Severe irAE group (P=0.93). The co-occurrence network showed the Benefit group patients had the most compact microbiota network. Metabolites prediction analyses showed the short chain fatty acids propionate (P=0.005) and butyrate/isobutyrate (P=0.03) were significantly enriched in Benefit group than Resistance group, wherein the acetyl-CoA pathway (P=0.04) accounted for the largest proportion of butyrate-production ability difference. The beneficial species had more positive correlations with butyrate-producing enzymes ($P<0.001$). The microbiota of irAE patients had abundant aligned sequences with antigen epitopes of multiple autoimmune diseases. The total counts of systemic lupus erythematosus-related epitopes were significantly more enriched in patients with immune-related colitis (P=0.04), especially FDNGRRGRPVTGP (P=0.02) and IDNGRRGRPITGP (P=0.02). Likewise, the microbiota of patients with good ICIs efficacy tended to have more abundant cancer-related antigen counts (P=0.07) and ACPs counts (P=0.06). Strain-level analysis revealed *Escherichia coli* and *Faecalibacterium prausnitzii*showed a centralized trend of genomic variations based on different clinical phenotypes. **Conclusions:** Long-term benefit patients had converging characteristics of gut microbiota, which coevoluted a compact microbial community with high butyrate-producing ability. The microbiota molecular mimicry of autoimmune and tumor antigen might contribute to irAE and ICIs efficacy. The strain-level genomic variations of specific species may also play a role in clinical phenotypes. Research Sponsor: CAMS Innovation Fund for Medical Sciences (CIFMS); 2022-I2M-C&T-B-010; Beijing Natural Science Foundation; 7232110; National High Level Hospital Clinical Research Funding; 2022-PUMCH-A-072; National High Level Hospital Clinical Research Funding; 2023-PUMCH-C-054.

Early opioid exposure (EOE) and impaired efficacy in patients with advanced NSCLC treated with PD-L1 inhibition: A pooled post hoc analysis of the POPLAR and OAK trials.

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Background: Mechanistic evidence suggests opioid signaling to modulate anti-tumor immunity. Whether opioids exposure may affect outcome of patients (pts) treated with immune checkpoint inhibitors is unproven, with clinical evidence being flawed by the negative associative bias between pain and higher burden of disease. **Methods:** We conducted a post-hoc analysis of the phase 3 OAK (NCT02008227) and phase 2 POPLAR (NCT01903993) trials, which randomized (1:1) pts with advanced NSCLC to receive either atezolizumab or docetaxel. We assessed the differential impact of early opioids exposure (EOE), defined as a minimum of 7 days exposure to any systemic opioids in the time window ranging between -30 to +30 from treatment initiation on efficacy from immunotherapy vs chemotherapy. Pts with ≤30 days survival follow-up were excluded to avoid immortal time bias. **Results:** After the exclusion of 60 pts, 718 and 686 pts treated with atezolizumab and docetaxel were included, with 341 (47.5%) and 308 (44.9%) pts with EOE respectively (p=0.32) and a median follow-up of 25.5 months (95% CI: 22.8-25.9). Baseline characteristics was balanced across cohorts. In the pooled population, EOE was significantly associated with poorer ECOG-PS (p<0.01) and burden of disease (p<0.01). Univariable analysis showed EOE to be significantly associated with decreased objective response rate (ORR, 11.7% vs 19.8%, p<0.01) and progression free survival (PFS, 1.9 vs 4.2 months, p<0.01) in the atezolizumab cohort, whereas no effect on ORR (17.7% vs 14.4%, p=0.25) and a less pronounced effect on PFS (3.5 vs 4.1 months, p=0.02) was reported for the docetaxel cohort. The pooled multivariable backward stepwise Cox regression used to select variables for validating the results individuated ECOG-PS, histology, tumor burden and race. In multivariable models EOE was associated with decreased ORR (OR 0.58, 95%CI: 0.37-0.92), increased risk of progression (HR 1.47, 95%CI: 1.26-1.72) and death (HR 1.70, 95%CI: 1.42-2.03) in the atezolizumab cohort while no negative impact on ORR/PFS was confirmed among the docetaxel cohort, with a less strong effect on OS (HR 1.44, 95%CI: 1.21-1.72). Multivariable interaction tests confirmed the differential impact of EOE on ORR (p<0.01) and PFS (p<0.01) between treatment modalities (immunotherapy vs chemotherapy). The results were additionally confirmed using IPTW models including all the baseline variables with an optimal distribution (SMD <0.05). **Conclusions:** EOE is associated with worse response/PFS from immunotherapy but not from chemotherapy exposure, suggesting a possible immune-modulating effect of opioids signaling on anti-tumor immunity. Considering that systemic opioids are the cornerstone of pain management in oncology further research for mitigation strategies, such as the potential use of PAMORAs, is needed. Clinical trial information: NCT02008227 and NCT01903993. Research Sponsor: None.

A phase 1 study of the small-molecule PD-L1 inhibitor INCB099280 in select advanced solid tumors: Updated safety, efficacy, and pharmacokinetics (PK) results.

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Background: INCB099280 has shown preliminary efficacy and acceptable safety in an ongoing phase 1, open-label, multicenter study in patients (pts) with advanced solid tumors (1). Here we present updated results and PK data. **Methods:** Eligible pts were ≥18 years of age with ECOG PS ≤1 and disease progression after available treatment (tx) or were ineligible for/without access to standard tx. Study started with dose escalation (100 mg qd to 800 mg bid), followed by dose expansion in 3 cohorts (IO-naive; IO-naive, MSI-H/dMMR tumors; anti–PD-1 previously treated). Primary endpoints are safety, tolerability, and determination of pharmacologically active dose/MTD. PK, objective response rate (ORR) per RECIST v1.1, and pharmacologic biomarkers were also analyzed. **Results:** As of January 14, 2023, 179 pts had received INCB099280 at doses from 100 mg qd to 800 mg bid (median age, 63 years [range, 21-86]; ≥2 prior lines of tx, 65.4%; prior IO, 16.2%). MTD was not reached. Overall, 96.6% of pts had ≥1 tx-emergent adverse events (TEAEs). Immune-related (ir) TEAEs occurred in 23.5% of pts. Best antitumor activity was noted with 400 mg bid (ORR, 17.8%) in pts with mixed tumor types. Updated clinical data will be presented. PK exposures increased proportionally as dose increased up to 800 mg bid (Table). Steady-state PK was achieved by cycle 1 day 8, with an accumulation ratio of 2-3. Inter-individual PK variability was high, but similar to that of healthy participants. Steady-state trough concentrations exceeded IC_{90} across 300-800 mg bid doses. In preliminary analyses correlating exposure with clinical outcomes, increased exposure was associated with a moderate trend of higher ORR and incidence of serious and/or ir-TEAEs. Preliminary electrocardiogram data suggested that large QTc effects (>20 ms) can be excluded at doses up to 800 mg bid. No association was detected between PK exposure and ctDNA change at cycle 4 day 1 or end-of-tx vs baseline, but decreased ctCNA was seen in all complete responders (n=2) and 6 partial responders (n=11). **Conclusions:** INCB099280 was generally well tolerated at all doses tested and showed promising antitumor activity. INCB099280 PK was dose proportional up to 800 mg bid, with high variability; steady-state trough exposure exceeded IC_{90} for ≥300 bid doses. These data support further development of INCB099280 as monotherapy and in combination regimens for solid tumors. Phase 2 studies are ongoing. 1. Prenen, ESMO-IO 2023; NCT04242199. Clinical trial information: NCT04242199. Research Sponsor: None.

Steady-state PK.

Regimen	Number of Patients	C_{max}, nM (%)	T_{max}, h (range)	AUC_{tau}, h*nM (%)
300 mg bid	34	1360 (76)	2 (0-4)	12,200 (80)
400 mg bid	41	1680 (66)	2 (0-8)	15,800 (70)
600 mg bid	20	2520 (68)	2 (0-8)	23,400 (65)
800 mg bid	23	3010 (73)	2 (0-8)	28,400 (80)
800 mg qd	23	1120 (153)	2 (2-8)	14,800 (136)

Values represent geometric mean (geometric coefficient of variation %) for C_{max} and AUC and median (min, max) for T_{max}.

Impact of concurrent antibiotics on survival with immunotherapy in metastatic colorectal and pancreatic cancer.

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Background: The interplay between antibiotics and the microbiome has been hypothesized to modify the immune response to cancer and may negatively affect immune checkpoint inhibitor (ICI) efficacy. **Methods:** We retrospectively reviewed concurrent antibiotics received in the randomized phase II Canadian Cancer Trials Group (CCTG) CO.26 and PA.7 clinical trials. CO.26 evaluated dual programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition (with durvalumab and tremelimumab) versus best supportive care only (BSC) in metastatic refractory colorectal cancer (CRC). PA.7 evaluated gemcitabine and nab-paclitaxel +/- durvalumab and tremelimumab in metastatic pancreatic ductal adenocarcinoma. In CO.26, T cell receptor sequencing (TCR-seq) was available at baseline and week 8. **Results:** In CO.26 (n=180), median (range) age was 65 (36-87) years, 33% (n=59) were female, and 29% (n=50) were ECOG 0. Concurrent exposure to antibiotics was associated with improved overall survival (OS) (7.4 vs 6.2 months, adjusted hazard ratio (aHR) 0.66 (95% confidence interval (CI) 0.46-0.93), p=0.018) in patients with metastatic CRC who received ICIs, but not in patients who received BSC (3.5 vs 4.5 months, HR 1.49 (95% CI 0.81-2.73), p= 0.20); (p-interaction=0.094). In antibiotic class analysis, concurrent exposure of ICIs to fluoroquinolones (9.4 vs 6.2 months, aHR 0.50 (95% CI 0.30-0.82), p=0.0067), but not penicillins or cephalosporins, was associated with improved OS. There was no difference in RAS/RAF status or tumor mutation burden in patients who received antibiotics/fluoroquinolones or not. The results were consistent when also controlling for TMB (antibiotics aHR 0.63 (0.44, 0.91), p=0.013; fluoroquinolones aHR 0.51 (0.31, 0.84), p=0.009). Patients treated with antibiotics did not have a different TCR diversity or clonality between baseline and 8 weeks (p=0.37 and p=0.47) compared to those who did not receive antibiotics (p=0.26 and p=0.60). In PA.7 (n=180), median (range) age was 65 (29-84) years, 48% (n=87) were female, and 24% (n=44) were ECOG 0. Antibiotics were not associated with OS in patients who did/did not receive ICIs (9.7 vs 10.8 months, HR 0.97 (95% CI 0.64, 1.46), p=0.87; 7.4 vs 10.3 months HR 1.22 (95% CI 0.72, 2.09), p=0.46, respectively). Fluoroquinolones were also not associated with OS regardless of whether or not the patient received ICI therapy (10.9 vs 9.8 months, HR 0.74 (95% CI 0.47, 1.15), p=0.18; 7.2 vs 10.2 months, HR 1.18 (95% CI 0.62, 2.27), p=0.62). **Conclusions:** Concurrent exposure to antibiotics, and specifically fluoroquinolones during ICI therapy was associated with a statistically significant improvement in OS in patients with metastatic CRC, but not metastatic pancreatic cancer. This is discrepant from prior reports in other tumor types and suggests that the gut microbiome may impact ICI efficacy uniquely in patient with CRC. Clinical trial information: NCT02870920, NCT02879318. Research Sponsor: None.

BGB-A317-212: A multicenter, open-label, phase II study to evaluate the efficacy and safety of tislelizumab in combination with lenvatinib in patients with selected solid tumors.

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Background: Tislelizumab, an anti-programmed cell death protein 1 (PD-1) monoclonal antibody, has demonstrated promising efficacy in several advanced solid tumors. However, some patients (pts) do not respond or develop resistance to tislelizumab monotherapy. Lenvatinib, a receptor tyrosine kinase inhibitor targeting VEGFR 1-3, FGFR 1-4, PDGFR alpha, KIT, and RET, has shown a potential synergistic effect with anti-PD-1 therapy. Here, we report the primary results of a phase II study evaluating the combination of tislelizumab plus lenvatinib in pts with solid tumors (NCT05014828). **Methods:** Pts with histologically/cytologically confirmed selected solid tumors, naïve to lenvatinib and anti-programmed death-ligand 1 (PD-L1)/PD-1 therapies were enrolled. Part 1 (safety run-in) determined the recommended phase II dose (RP2D) of lenvatinib in combination with tislelizumab 400 mg IV every 6 weeks. In Part 2 (expansion), pts received lenvatinib at the RP2D from Part 1 (20 mg orally/day) plus tislelizumab per the Part 1 regimen until disease progression, withdrawal, or death. The primary endpoints were safety and RP2D determination (Part 1) and overall response rate (ORR; Part 2). **Results:** At data cutoff (Oct 20, 2023; median follow-up 12.1 months [mo; renal cell carcinoma, RCC]; 10.8 mo [head and neck squamous cell carcinoma, HNSCC]; 14.8 mo [gastric cancer, GC], and 22.0 mo [non-small cell lung cancer, NSCLC]), 58 pts were treated in Part 2 (RCC, n=23; HNSCC, n=27; GC, n=3; NSCLC, n=5), 6 of whom were also included in Part 1. The ORR was 66.7% in pts with RCC, 33.3% (HNSCC), 33.3% (GC), and 20.0% (NSCLC). Median duration of response (mDoR) was 18.5 mo and 9.6 mo in pts with NSCLC and HNSCC, respectively; not estimable (NE) for RCC and GC (Table). No new safety signals were identified; grade ≥3 treatment-related adverse events were reported in 78.3%, 59.3%, 33.3% and 60.0%, of pts with RCC, HNSCC, GC, and NSCLC, respectively (Table). **Conclusions:** Tislelizumab plus lenvatinib had a manageable safety profile and showed preliminary antitumor activity in pts with selected tumor types. Longer follow-up is needed to further investigate the potential of this combination to benefit pts with advanced solid tumors. Clinical trial information: NCT05014828. Research Sponsor: BeiGene, Ltd.

	RCC	HNSCC	GC	NSCLC
Efficacy-evaluable	**n=21**	**n=24**	**n=3**	**n=5**
ORR, % (95% CI)[a]	66.7 (43.0, 85.4)	33.3 (15.6, 55.3)	33.3 (0.8, 90.6)	20.0 (0.5, 71.6)
mDoR, mo (95% CI)	NE (10.8, NE)	9.6 (2.8, NE)	NE (NE, NE)	18.5 (NE, NE)
Safety-evaluable	**n=23**	**n=27**	**n=3**	**n=5**
Any TRAE, n (%)	22 (95.7)	25 (92.6)	3 (100.0)	5 (100.0)
Grade ≥3	18 (78.3)	16 (59.3)	1 (33.3)	3 (60.0)
Serious	10 (43.5)	10 (37.0)	2 (66.7)	2 (40.0)
Leading to death	1 (4.3)[b]	3 (11.1)[c]	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	3 (13.0)	6 (22.2)	1 (33.3)	1 (20.0)

[a]Confirmed ORR by investigator;
[b]Due to organ failure;
[c]Due to pneumonia, left carotid hemorrhage and unknown cause.
CI, confidence interval.

2611 Poster Session

Preliminary results from a phase I expansion study of ZG005, a bispecific antibody targeting TIGIT and PD-1, as monotherapy in patients with advanced solid tumors.

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Background: ZG005, a PD-1 and TIGIT dual-specific antibody, is a promising immunotherapy for tumors as blocking these two pathways could synergistically activate T cells and enhance the anti-tumor activity of NK cells. Partial results from the dose-escalation stage of this first-in-human (FIH) study were revealed at ASCO 2023, and here we present the preliminary results from the dose-expansion stage. **Methods:** After a dose-escalation stage, patients (subjects) with solid advanced tumors were enrolled into this dose-expansion stage. Subjects in each cohort were randomized 1:1 to receive ZG005 treatment of either RP2D from the dose-escalation stage (10 mg/kg Q3W or 20 mg/kg Q3W) by intravenous infusion. Efficacy was assessed primarily according to RECIST v1.1. **Results:** The dose-escalation stage was completed with 32 subjects enrolled and the dose-expansion stage is currently ongoing. As of December 25, 2023, a total of 68 subjects were treated with ZG005 as monotherapy, including 33 males (median age 60) and 35 females (median age 58), wherein 33 had received PD-1/PD-L1 inhibitors before enrollment. Three subjects with either pancreatic neuroendocrine cancer, intrahepatic cholangiocarcinoma, or cervical cancer were treated for more than 20 cycles. The subject with cervical cancer maintained PR status for more than 35 weeks. A total of 1 CR, 6 PR, and 28 SD cases were reported from the 57 efficacy evaluable subjects, among them 1 CR, 5 PRs, and 8 SDs from the 17 subjects with cervical cancer. A total of 43 TRAEs (43/68, 63.2%) were reported, of which 6 were $\geq$ grade 3, including 2 liver function abnormalities, 1 elevated γ-glutamyl- transferase, 1 unknown death, 1 hypertriglyceridemia and lipase elevation, and 1 elevation in both aspartate aminotransferase and blood bilirubin. SAEs occurred in 19 subjects, 3 events were related to ZG005, including 2 liver function abnormalities (1 was a DLT event), and 1 unknown death. The death event occurred in one female, who received only one dose of ZG005, and the cause of her death was most likely due to poor underlying condition. The C_{max} and AUC increased approximately in dose proportion. **Conclusions:** ZG005 has demonstrated a tolerable safety profile and encouraging anti-tumor activity during the FIH study. Expansion cohorts in specific advanced solid tumors are underway to warrant further development. Clinical trial information: CTR20220021. Research Sponsor: None.

Pharmacodynamic (PD) and immunophenotyping analyses of ATR inhibitor (ATRi) tuvusertib + ATM inhibitor (ATMi) lartesertib in a phase Ib study in patients with advanced unresectable solid tumors.

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Background: Ataxia telangiectasia-mutated (ATM) and Rad3-related (ATR) protein kinases orchestrate the DNA damage response. A synthetic lethal relationship between ATR and ATM genes in cancer has been described[1] and ATMi synergistically potentiate the efficacy of ATRi *in vitro* and *in vivo*.[2] The combination of tuvusertib + lartesertib was investigated in Part A1 of the open-label, multicenter study DDRiver Solid Tumors 320 in patients with advanced unresectable solid tumors. Here, we report results of the PD and immunophenotyping analyses. **Methods:** PD analysis comprised γ-H2AX in serial blood samples, stimulated *ex vivo*with 4-NQO, bleomycin, or controls. Flow cytometry was used to measure target inhibition via γ-H2AX modulation in the CD45+ lymphocytes fraction and to explore the effect of tuvusertib + lartesertib on the immunophenotype (myeloid-derived suppressor cells, T and B lymphocytes, monocytes, and natural killer cells subsets) in serial blood samples. Pharmacokinetic samples were analyzed by a validated bioanalytical liquid chromatography/mass spectrometry method. Time-matched blood samples were collected at baseline, 1, 3, 6, and 24 hours after first tuvusertib and lartesertib administration on days 1 and 8 of cycle 1 for the γ-H2AX analysis, and on days 1 and 15 of cycles 1 and 2 before treatment for immunophenotyping. **Results:** Immunophenotyping data and γ-H2AX levels were obtained from 41 and 34 patients, respectively. For tuvusertib, complete or almost complete target inhibition was seen at 1–6 hours after treatment, followed by a rebound above baseline after 24 hours, on both days 1 and 8 at doses of 130 and 180 mg once daily (QD). For lartesertib, a variable target inhibition of approximately 50 % on average was seen across all time points at doses of 100, 150 and 200 mg QD. No target inhibition was seen for tuvusertib at 90 mg QD and lartesertib at 50 mg QD (cohort 1). Tuvusertib + lartesertib induced a transient decrease of monocytes and natural killer (NK) cells, with partial or complete recovery to baseline levels during treatment breaks in schedules of 2 weeks on treatment followed by a treatment break of 1 or 2 weeks, respectively. **Conclusions:** Tuvusertib and lartesertib combination PD outcomes were in line with respective monotherapy observations.[3,4] The combination did not cause any consistent change in the levels of immune cell subsets at all dose levels tested, except a mild, transient decrease in monocytes and NK cells, in line with the tuvusertib monotherapy observations. 1. Kantidze et al., Trends Cancer 2018;4(11):755–68. 2. Turchick et al., Mol Cancer Ther 2023;22(7):859–72. 3. Yap et al., Ann Oncol 2022;33(suppl_7):S197–S224. 4. Siu et al., Cancer Res 2023; 83(8_Suppl):CT171. Clinical trial information: NCT05396833. Research Sponsor: This study is being sponsored by EMD Serono (CrossRef Funder ID: 10.13039/100004755).

Phase 1 trial of TU2218, TGFβ-RI and VEGF-R2 dual inhibitor in monotherapy and combination with pembrolizumab in patients with advanced solid tumors.

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Background: Pembrolizumab interrupts PD-1/-L1 interaction and is efficacious in many cancers. However, resistance may emerge in some of the patients treated. VEGF and TGF-β pathways play an important role in the development and function of the tumor-microenvironment (TME), contributing to be the immunosuppressive. TU2218 is a highly potent, orally available dual inhibitor against TGFβ type I receptor (ALK5) and VEGFR2. This was a first-in-human study to investigate the safety and tolerability of TU2218 monotherapy and combination therapy with pembrolizumab. **Methods:** This non-randomized, open-label, multinational, multicenter study evaluated the safety, tolerability, PK, and preliminary efficacy of TU2218 alone and combination with pembrolizumab to determine the Recommended Phase 2 Dose of the Combination (RP2DC) in advanced solid tumors. Eligible patients were ≥ 18 years of age, ECOG performance status of 0 or 1 and had measurable lesion per RECIST 1.1. Part A of monotherapy was sequentially escalated to 6 dose levels of TU2218 ranging from 30 to 270 mg/day on a 2 weeks-on/1 week-off regimen using a BOIN design. In part B, patients received TU2218 doses of 105, 150 and 195 mg/day on a 2 weeks-on/1 week-off cycle in combination with pembrolizumab 200mg once every 3 weeks. Dose escalation followed a 3+3 design with a DLT evaluation period. **Results:** In the TU2218 monotherapy dosed BID (n=22), no Grade 3 or higher treatment related AE was reported, while all Grade 2 TRAEs were tolerable. Systemic exposure to TU2218 increased in a dose dependent manner. Following seven days of administration, TU2218 demonstrated reductions in PD markers and a correlation was observed between TU2218 exposure and the decrease of PD markers, particularly TGF-β1 (-16.5%) and CTGF (-45.4%) blood levels in groups of TU2218 Cmax ≥ 1.0 μM. Patients (n=12) received TU2218 at doses levels of 105 to 195mg/day in combination with pembrolizumab 200mg once every 3 weeks. The most frequently observed TRAE was pruritus (25%, n=3) and one patient experienced Grade 3 TRAE with maculo-papular rash (8.3%, n=1). No DLT was observed during the dose escalation and the MTD was not identified. The best ORR in the combination cohort demonstrated PR at 8.3% (n=1), SD 50% (n=6) and PD at 33% (n=4). The dose level at 195mg/day of TU2218 in combination with pembrolizumab was safe and tolerable. **Conclusions:** TU2218, a first-in-classoral dual inhibitor against TGFβRI and VEGFR2 was well-tolerated in the monotherapy and in the combination therapy with pembrolizumab. The RP2DC was established for subsequent trials in specific cancer types. Clinical trial information: Phase 1a: NCT05204862 / Phase 1b: NCT05784688. Research Sponsor: TiumBio Co., Ltd., Republic of Korea; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Pharmacokinetic (PK) and pharmacodynamic (PD) findings from a phase 1b study of ATR inhibitor tuvusertib + anti-PD-L1 avelumab in patients with advanced unresectable solid tumors.

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Background: Ataxia telangiectasia and Rad3-related protein (ATR) kinase is critical in the DNA damage response, and its inhibition modulates antitumor immunity. The combination of ATR inhibitor (ATRi) + immune checkpoint inhibitor (ICI) has shown activity in patients with ICI-resistant tumors and may have the potential to overcome ICI resistance and induce antitumor immune responses. **Methods:** Part B1 of the open-label, multicenter study DDRiver Solid Tumors 320 investigated safety, tolerability, PK, and PD, including effects on immune cells, of ATRi tuvusertib in combination with the ICI avelumab (anti-PD-L1) in patients with advanced unresectable solid tumors. Flow cytometry was used to analyze tuvusertib target inhibition via γ-H2AX modulation in the CD45+ fraction of *ex-vivo* stimulated peripheral blood mononuclear cells, and to explore the effect on the peripheral immunophenotype. Tuvusertib PK samples were analyzed by a validated bioanalytical liquid chromatography/mass spectrometry method. **Results:** 22 patients were enrolled and treated with tuvusertib 180 mg once daily on a schedule of 2 weeks (w) on treatment followed by a treatment break of 1 or 2 w, and avelumab 800 mg once every 2 weeks (Q2W). The 2 w on/1 w off schedule, corresponding to the recommended dose for expansion (RDE) for tuvusertib monotherapy, was chosen for further exploration. At this schedule, 2 of 9 patients evaluable for dose-limiting toxicity (DLT) experienced DLTs: Grade 3 ALT and Grade 3 AST increase (n=1), and Grade 3 anemia requiring transfusion (n=1). A patient with chordoma experienced a RECIST v1.1 partial response. Preliminary PK data for tuvusertib suggested rapid absorption with median T_{max} range of ~2–3 h and mean elimination half-life range of ~2.93 to 4.23 h, with ~2-fold accumulation of steady-state area-under-the-curve following multiple doses. Exposure of tuvusertib in combination with avelumab was consistent with tuvusertib monotherapy exposure (1). PD showed complete or almost complete target inhibition at 1–6 h after tuvusertib 180 mg followed by rebound above baseline after 24 h on days 1 and 8 of cycle 1. No clear trend of variation in absolute counts of myeloid-derived suppressor cells, T and B lymphocytes, monocytes, and natural killer cell subtypes was detected. **Conclusions:** Tuvusertib and avelumab were combined at established monotherapy doses with no new safety findings. Tuvusertib PD and exposure data were in line with monotherapy observations. The combination did not cause any consistent change of the immunophenotype. Given the accumulating evidence of ATRi as an immunosensitiser (2), further evaluation of this combination in patients with ICI-resistant advanced solid tumors is warranted. 1. Yap T et al., Ann Oncol 2022;33(suppl_7):S197–S224. 2. Besse B et al., JTO 2022; 17(suppl_9):S41–S42. Clinical trial information: NCT05396833. Research Sponsor: EMD Serono (CrossRef Funder ID: 10.13039/100004755).

A phase 2a safety run-in and preliminary efficacy study of liposomal gemcitabine (FF-10832) in combination with pembrolizumab in patients with advanced solid tumors.

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Background: FF-10832 (FF832) [liposomal gemcitabine (GEM)] has demonstrated superior activity preclinically compared to GEM via preferential tumor accumulation & induction of antitumor immune responses. Further enhanced activity has been shown in combination with immune checkpoint inhibitors. We evaluated the tolerability & preliminary efficacy of FF832 in combination with the PD-1 antibody pembrolizumab (PEM) in a Phase 2a safety run-in study in patients (pts) with advanced solid tumors. **Methods:** Pts received 200 mg PEM followed by 40 mg/m^2 FF832 on Day 1 of a 21-day cycle to validate the recommended Phase 2 dose (RP2D) for combination therapy; treatment was continued until disease progression or unacceptable toxicity. Response was assessed by RECIST 1.1 every 2 cycles. Tumor PD-L1 expression, mutational burden, and modulation of circulating immune cells were assessed, & population PK modeling performed. **Results:** Twelve pts [NSCLC (6), urothelial cancer, UC (4), renal cell carcinoma (2); 6M/6F; median age, 69 (42-82) & median # prior therapies, 5 (1-7); prior GEM (5), prior PEM (9)] received a median of 2 (1-8) cycles FF832+PEM. Median time on study was 6.1 (1.1–23.7) weeks. FF832+PEM was well-tolerated. Common AEs related to FF832 were Gr≤2 fatigue (50%) with 1 Gr 3, anemia (33%) with 2 Gr 3, & Gr ≤2 decreased appetite, diarrhea, ↑AST, ↑AlkPhos, muscular weakness, nausea, and pyrexia (25% each). Common AEs related to FF832+PEM were Gr≤2 fatigue (33%) & nausea (25%). Three pts had Gr≤2 infusion reactions with the first FF832 infusion; all resolved & were successfully rechallenged. FF832 dose was reduced to 30 mg/m^2 after Cycle 1 in 3 pts due to Gr 3 rash (1), Gr 2 fatigue (1), & one DLT of Gr 3 malaise, pain, and arthralgia. Of 9 pts evaluable for response, one achieved an unconfirmed PR after one cycle (UC, prior GEM/PEM, 42%↓ in target lesions). Five pts had a best response of SD with 2 maintained for 6-8 cycles. Median PFS was 6 weeks (95%CI: 3.1–NR); median OS was 23.3 weeks (95%CI: 4–NR). An extended plasma $t_{1/2}$ (~30 hours) & exposures consistent with FF832 monotherapy at the RP2D were observed. As with FF832 monotherapy, multi-log decreases were observed in circulating Ki67+ Tregs relative to total CD4+ cells while CD8+ cells increased, suggesting FF832+PEM could enhance shifts to a more immunocompetent tumor microenvironment. **Conclusions:** The safety and preliminary efficacy of FF832+PEM was demonstrated in heavily pre-treated pts with solid tumors whose disease progressed on prior GEM and/or PEM. Continuous GEM exposure from FF832 along with immune checkpoint blockade may improve antitumor activity. Evaluation of FF832 at the RP2D/schedule of 40 m/gm^2 Q 21 days alone and in combination with PEM is ongoing in a randomized expansion study in pts with metastatic NSCLC and UC with prior disease progression on PD-1/L1 therapy. Clinical trial information: NCT05318573. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

Modulation of lipid metabolism associated with response to metronomic capecitabine plus camrelizumab in patients with refractory gastrointestinal cancer: A prospective, single-center, exploratory trial.

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Background: Metronomic chemotherapy which can modulate tumor microenvironment is a potential partner of PD-1 antibodies. The association between lipid metabolism and efficacy of immunotherapy is recognized but has not been reported in metronomic chemotherapy. We aimed to evaluate the feasibility of metronomic capecitabine plus camrelizumab as a salvage treatment for refractory gastrointestinal cancer patients and to explore the involvement of lipid metabolism in response to this combination therapy. **Methods:** In this single-center, exploratory trial, advanced GI cancer patients who had disease progression after standard chemotherapy were treated with metronomic capecitabine (500mg twice daily) plus camrelizumab (200mg on day 1 intravenously every 2 weeks). The primary endpoint was safety. For lipid metabolism, body composition analysis based on CT scans at L3 level and peripheral blood lipidomic analysis were performed. Associations between treatment efficacy and body composition parameters as well as differential plasma lipids were assessed. Plasma samples of GI cancer patients treated with PD-1 antibody-based therapy were detected by lipidomic analysis as a test cohort. Differential expressed genes of C2C12 cells treated with metronomic dose 5-fluorouracil *in vitro* were detected and pathway enrichment analysis was performed. **Results:** Twenty-six patients with esophageal (9), gastric (8), bile duct (5), or pancreatic cancer (3) were enrolled. Sixteen patients (61.5%) had ≥2 previous lines of chemotherapy and 11 patients were ECOG 2. Treatment emergent adverse events (TEAEs) grade ≥3 occurred in five patients (19.2%), including biliary tract infection (11.5%), fatigue (7.7%), and increased AST/ALT (3.8%). Three patients suffered severe AEs that were not related to treatment. Objective response rate was 19.2% (5/26) including two patients with complete response. High skeletal muscle radiation attenuation (SMRA) was associated with disease control and better survival of patients. Differential plasma lipids were identified in disease-controlled patients compared with those achieved disease progression. High level of a plasma 6-lipid signature composed of SM40:1;3, TG54:4-FA20:2, LPC (16:0), TG52:0-FA20:0, TG56:3-FA20:2, and PE(P-18:1/18:2) indicated better survival of patients and was confirmed in the test cohort. Differential plasma lipids were increased after treatment. Differential expressed genes in C2C12 cells after treatment were involved in lipid metabolism pathways. **Conclusions:** Metronomic capecitabine plus camrelizumab showed low rate of grade ≥3 AEs and promising efficacy in refractory GI cancer patients. Lipid metabolism modulation was associated with treatment response to this combination therapy. Clinical trial information: NCT04508686, NCT04510818, NCT04932187. Research Sponsor: National Natural Science Foundation of China; National Natural Science Foundation of China; 81972707; Shanghai Municipal Health Bureau Project; 2020CXJQ03.

Phase 2 trial of brentuximab vedotin (BV) with pembrolizumab (pembro) in patients with previously treated metastatic non-small cell lung cancer (NSCLC) or cutaneous melanoma (SGN35-033): Overall survival.

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Background: BV, a CD30 directed antibody-drug conjugate, may selectively deplete a subset of regulatory T-cells (Tregs) that express CD30 and re-sensitize tumors to anti-PD-1 therapy. This ongoing, multi-cohort, multicenter, open-label trial evaluating the efficacy and safety of BV+pembro in patients (pts) with anti-PD-1 refractory solid tumors previously reported an ORR (8-22%), DCR (67-80%), and CD8+T cell infiltration in on-treatment biopsies of responders (Lee, SITC 2023). Here we report OS and biomarker analyses. **Methods:** Pts with primary refractory (progression without response or SD for $<$ 6 months) or secondary refractory (progression after response for $\geq$3 months or SD for $\geq$6 months) NSCLC or melanoma who progressed on anti-PD-1 therapy were included. Pts received BV (1.8 mg/kg) and pembro (200 mg) every 21 days. The primary endpoint was confirmed ORR. Exploratory endpoints included OS and biomarker analyses of blood and tumor samples. **Results:** 55 pts with NSCLC and 58 pts with melanoma were dosed (86% white, 63% male; 57% $\geq$ age 65 yrs). Pts received 3 median prior lines of therapy (as previously reported). Investigator-assessed response was measured according to RECIST v1.1. At a median follow up of 17.2 months, median OS (mOS) was 13.9 months (NSCLC) and 12.9 months (melanoma) (Table 1). The estimated probability of survival (Kaplan-Meier) at 12 months was 54.0% (95% CI 43.69, 63.22) for the study population. Immune mediated AEs were reported in 25% of pts, Grade $\geq$3 TEAEs in 56%, TESAEs in 42%, and TE peripheral neuropathy (SMQ) in 48% of pts. 17% of pts discontinued treatment due to TEAEs. No new safety signals were identified and no deaths due to treatment-related AEs were reported. Paired tumor biopsies from 19 pts showed increased CD8+T cell infiltration in 11 pts. **Conclusions:** These data support the immunomodulatory capacity of BV with pembro. This combination shows encouraging OS data in pts with solid tumors who have progressed on anti-PD-1 therapy. The safety profile is comparable to previously reported data. The study remains ongoing. Clinical trial information: NCT04609566. Research Sponsor: Seagen Inc. Seagen was acquired by Pfizer in Dec. 2023.; Merck & Co., Inc.

Best Overall Response, n (%)	Metastatic NSCLC, N = 55	Metastatic Cutaneous Melanoma, N = 58
Confirmed CR	1 (2)	1 (2)
Confirmed PR	6 (11)	11 (19)
ORR (95% CI)	7 (13) (5.3, 24.5)	12 (21) (11.2, 33.4)
SD	32 (58)	30 (52)
PD	11 (20)	13 (22)
NA	5 (9)	3 (5)
mPFS, mo (95% CI)	4.1 (2.76, 5.59)	4.1 (2.76, 5.32)
mOS, mo (95% CI)	13.9 (10.38, 17.25)	12.9 (8.61, 24.41)
Median duration of follow up, mo (95% CI)	15.4 (13.04, 19.15)	21.6 (13.60, 24.61)

Safety and preliminary efficacy of EIK1001 in combination with atezolizumab in participants with advanced solid tumors.

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Background: Immune checkpoint inhibitors (ICIs) relieve immunosuppression of tumor-reactive T cells and enhance antitumor immune response; however, not all patients benefit and some become refractory. EIK1001 is a Toll-like receptor (TLR)7/8 agonist that stimulates myeloid and plasmacytoid dendritic cells, activating immune and inflammatory responses. This dual activity provides another pathway, distinct from effects on checkpoint proteins, to enhance antitumor T-cell activity alone or in combination with ICIs. **Methods:** Study BDB001-102 was a Phase 1, open-label, dose-escalation/expansion study of EIK1001 combined with atezolizumab (comb Rx). Enrollment criteria included participants (pts) $\geq$ age 18 with confirmed, RECIST-measurable advanced solid tumors. Primary study objectives included safety and tolerability, and secondary objectives included evaluation of dose-limiting toxicities, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy by RECIST 1.1. During dose escalation, pts received a range of doses of EIK1001 (QW IV) in combination with atezolizumab (1200 mg Q3W). **Results:** Forty-one pts (median age 65 years [range = 32 to 79]) with multiple, distinct histological tumor types and a median of 3 prior Rx regimens were enrolled. Overall, a total of 28/41 (68.3%) receiving EIK1001 + atezolizumab experienced a treatment-related adverse event (TRAE). Of these, 4/41 (9.8%) experienced a $\geq$ Grade 3 TRAE, including fatigue, nausea, hyponatremia, and lymphedema. Only 1/41 (2.4%) experienced manageable cytokine release syndrome. There were no deaths due to TRAEs. Of the efficacy-evaluable pts (n = 37), complete response (CR) or partial response (PR) was observed for 3/37 (8.1%). Disease control (including CR, PR, or stable disease) was observed in 19/37 (51.4%). The median duration of response (DOR) was 13 months (range = 10 to 27). One responder was PD-L1 negative yet had a $>$ 12-month DOR; another had a history of prior anti-PD-1 Rx yet experienced a 10-month DOR on comb Rx. EIK1001 PK was linear and dose-proportional, and was not affected by combination with atezolizumab. **Conclusions:** Overall, EIK1001 was well-tolerated with a manageable safety profile and showed encouraging preliminary efficacy across several tumor types in combination with atezolizumab. Responses were observed even in pts not anticipated to respond to atezolizumab monotherapy. Further development of EIK1001 is underway. Clinical trial information: NCT04196530. Research Sponsor: Eikon Therapeutics, Inc.

Lung-MAP S1800D: A phase II/III study of N-803 (ALT-803) plus pembrolizumab versus standard of care in participants with stage IV or recurrent non-small cell lung cancer (NSCLC) previously treated with anti-PD-1 or anti-PD-L1 therapy.

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Background: IL-15 is a member of the IL-2 common gamma chain family of cytokines. N-803 is IL-15 administered in complex with IL-15 receptor alpha. Lung cancer, despite advances in targeted therapies and immunotherapy, remains the leading cause of cancer related death in the United States. Strategies to improve the performance of immunotherapy in advanced NSCLC is a clinical unmet need. **Methods:** Lung-MAP S1800D was a randomized study comparing N-803 plus pembrolizumab (NP) to investigators' choice standard-of-care chemotherapy (SoC) for previously treated advanced NSCLC. Patients were enrolled into an Acquired Resistance Cohort (ARC) if disease progression on prior anti-PD-(L)1 occurred $>$ 84 days from start of treatment and otherwise into a Primary Resistance Cohort (PRC). The ARC was a phase II/III study with a sample size goal of 334 patients. The PRC was a phase II with sample size of 134 patients. The first interim analysis (IA1) in the ARC evaluated futility among the first 25 patients treated with NP which required $\geq$1 response and $\geq$50% with disease control at 12 weeks to continue accrual. The primary endpoint in both cohorts was overall survival (OS). Secondary endpoints were progression-free survival (PFS), response, and toxicity. **Results:** Accrual in the ARC and PRC were closed at the IA1 in the ARC with 74 pts in the ARC and 8 in the PRC. Of the 74 ARC patients, 71 met eligibility (36 SoC, 35 NP), and 32 pts on each arm received treatment. With 44 events, OS was not significantly different between the two arms (HR (95%CI: 0.73(0.40-1.36), p=0.32) with a 12-month OS rate of 25% with SoC and 44% with NP. With 61 events, PFS was not significantly different but numerically worse (HR (95% CI): 1.29 (0.78-2.13, 95% CI), p=0.33). There were 3 unconfirmed partial responses and 1 confirmed complete response with NP and 3 unconfirmed partial responses and 2 confirmed partial responses with SoC. On the NP arm, there were 10 Grade 3 (1 hematologic) and 1 Grade 5 treatment-related adverse events reported as Disease Progression (34% Grade 3+ TRAE). The Grade 3+ TRAE rate on the SoC arm was 53% with 10 Grade 3+ hematologic toxicities. **Conclusions:** While the study failed to continue accrual past IA1, there is an indication of a subgroup that might benefit from NP with a potential OS difference at 12 months. NP was safe when compared to SoC, and responses were seen in both treatment arms, including partial and complete responses in the NP group. Evaluation of tumor and patient characteristics will be critical to define if there are those who may benefit from N-803 plus pembrolizumab. Clinical trial information: NCT05096663. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180888; National Cancer Institute/U.S. National Institutes of Health; U10CA180819; National Cancer Institute/U.S. National Institutes of Health; U10CA180821; National Cancer Institute/U.S. National Institutes of Health; U10CA180820; National Cancer Institute/U.S. National Institutes of Health; U10CA180868; National Cancer Institute/U.S. National Institutes of Health; 1R01CA222817-01A1; Foundation for the National Institutes of Health; Immunity Bio, Inc.

The efficacy of immune checkpoint inhibitors in patients with cancer with pseudoprogression.

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Background: Pseudoprogression (PsP) is quite a common phenomenon in cancer patients undergoing therapy with immune checkpoint inhibitors (ICI). It could be defined as temporary increase of tumor volume or the number of tumor lesions after beginning of ICI treatment (immune unconfirmed progressive disease - iUPD) followed by clinical response. However, many specialists in real clinical practice are hesitant to continue ICI therapy in patients with iUPD because of medical or financial constraints. We aimed to evaluate the efficacy of ICI in patients with clinical evidence of PsP. **Methods:** We retrospectively analyzed 1001 cases of ICI treatment (male 58,4%, age 28-90 years) in patients with various solid malignancies: melanoma – 316, lung – 280, kidney – 247, GI cancer – 96, cervix of the uteri – 62. The patients were treated in 2 regional referral centers in Moscow and Moscow Region between June 2018 and Dec. 2022. Unconfirmed progressive disease (iUPD) according to iRECIST criteria was diagnosed in 316 patients at the first imaging control after the beginning of ICI treatment (31,6%). **Results:** Among 316 patients with iUPD the presence of progression (immune confirmed progressive disease – iCPD) was verified in 105 (33,2%): melanoma – 109 (34,5%), lung – 86 (30,7%), kidney – 75 (30,4%), GI cancer – 42 (43,8%), cervix of the uteri – 4 (6,5%). Stable disease was found in 144 (45,6%), partial response in 50 (15,8% - iPR), complete response in 17 patients (5,4% - iCR). Altogether, PsP was diagnosed in 211 of 1001 patients (21,1%). Overall objective response rate in 316 patients with iUPD reached 21,2%, control over disease was achieved in 66,8% of cases. Severe immune-mediated adverse events (3-4 st. according to CTC AE 5.0) were diagnosed in 9 patients (2,8%). Median overall survival in patients with iUPD and ORR was 60,65 mon (95%CI 57,54-63,76), in patients without iUPD and ORR – 147,56 mon (95%CI 137,2-157,93). **Conclusions:** PsP was diagnosed in 21,1% of patients getting ICI treatment in real clinical practice with median survival in PsP patients with objective response of about 60 months. Only 10,5% of patients had iCPD after their second follow-up. We feel that close adherence to iRECIST criteria to verify true progression is mandatory in patients under ICI treatment to exclude unnecessary cessation of treatment. Research Sponsor: None.

A phase 2a study of NT-I7 (efineptakin alfa), a long-acting IL-7, and pembrolizumab to evaluate efficacy, including overall survival, in hard-to-treat gastrointestinal tumors.

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Background: Microsatellite-stable colorectal (MSS-CRC) and pancreatic cancer (PDAC) are immunologically cold tumors with null response to checkpoint inhibitors (CPI). NT-I7, a long-acting IL-7, in combination with pembrolizumab (pembro) has shown to significantly increase intratumoral T cell infiltration and elicit some tumor control in these hard-to-treat gastrointestinal indications. The original MSS-CRC and PDAC cohorts, enrolling 25 patients (pts) each, were expanded to 50 pts per indication. Here, we provide an updated analysis including the original and expansion cohorts. **Methods:** Open-label Phase 2a study in subjects with relapsed/refractory CPI-naïve MSS-CRC and PDAC; NT-I7 1200 μg/kg IM every 6 weeks (Q6W), pembro 200 mg IV Q3W. Antitumor activity assessed by RECIST v1.1/iRECIST. **Results:** As of 02OCT2023, 98 subjects were efficacy-evaluable (50 MSS-CRC, 48 PDAC); median age 61.0 years, all with baseline ECOG status 0-1. 95.9% (94/98) received study treatment ≥3rd line, with a median follow -up of 6.1 months. Safety profile for NT-I7 was similar to previous reports. In MSS-CRC pts, 1 pt and 3 pts achieved confirmed partial responses per RECIST and iRECIST, respectively; median duration of response (DOR/iDOR) was 13.1/13.0 months (mo) and 2 responders were alive with no progression at data cutoff. Disease control rate (DCR/iDCR) was 36.0% (18/50) / 38.0% (19/50), with a duration of response and stable disease (DORSD/iDORSD) of 3.2/14.5mo. Interestingly, iDCR was 71.4% (5/7) in MSS-CRC pts with primary tumor in the rectum, versus 30.8% (12/39) in pts with primary tumor in the colon. With 11 pts on follow up, progression free survival (PFS/iPFS) was 1.5/3.8 mo. Among PDAC pts, 2 and 3 pts achieved confirmed PR and iPR, with DOR/iDOR of NE/9.7 mo; 1 responder was alive with no progression at data cutoff. DCR/iDCR was 25.0% (12/48) / 27.1% (13/48), and DORSD/iDORSD was 2.9/9.8mo. With 11 pts on follow up, PFS/iPFS was 1.4/2.1 mo. Clinical benefit in MSS-CRC and PDAC was most evident by a notable median overall survival (mOS); 13.2 mo in MSS-CRC [95% CI 8.9 – 18.6 mo] and 11.1 mo in PDAC [95% CI 4.1 – 13.3 mo], compared to historical mOS for standard of care, 10.8 mo (MSS-CRC) and 6.1 mo (PDAC). **Conclusions:** NT-I7 and pembro treatment was associated with longer mOS relative to historical studies. Identification of predictive biomarkers that may define pts with higher likelihood of clinical benefit would be a promising step to maximizing potential of the NT-I7 + pembro treatment combination for pts with these indications. Research in this area is ongoing. Clinical trial information: NCT04332653. Research Sponsor: NeoImmuneTech, Inc.

PERIO-02: Phase 1b pressure enabled regional immuno-oncology trial of nelitolimod (SD-101), a class C TLR9 agonist, delivered via hepatic artery infusion +/- checkpoint inhibition in intrahepatic cholangiocarcinoma and hepatocellular carcinoma.

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Background: Immunotherapy (ICI) has shown limited survival benefit in patients (pts) with advanced HCC and intrahepatic cholangiocarcinoma (ICC). Nelitolimod (SD-101), a Class C toll-like receptor-9 (TLR-9 agonist), depletes MDSCs while broadly stimulating the tumor microenvironment. Given safety challenges with IV infusion and distribution limitations of needle injection, we studied hepatic arterial infusion (HAI) of nelitolimod with Pressure-Enabled Drug Delivery (PEDD) to enhance ICI responsiveness. **Methods:** Pts with advanced HCC or ICC were enrolled. Nelitolimod was dose-escalated without ICI (Cohort A), with pembrolizumab (Cohort B), or with nivolumab + ipilimumab (Cohort C). Nelitolimod administered with HAI for 2 cycles, with 3 weekly doses per cycle using the TriNav device. Primary endpoints included safety and optimal dose determination. Immune cells were examined in blood and tumor tissue using multiplex IF, flow cytometry, and Nanostring. **Results:** At data cutoff, 29 pts [70% ICC, 30% HCC] were enrolled, 23 received at least one dose of nelitolimod: 3 in Cohort A (4 mg), 8 in Cohort B (2 and 4 mg) and 12 in Cohort C (2 and 4 mg). Median age was 64.5. Only 1 pt was treatment-naïve; 4, 2L (17%); 5, 3L (22%); 14, > 4L (61%). 26% pts had > 10 liver tumors. 3 pts (13%) experienced serious treatment-related adverse events (AE); 1 pt dose-limiting toxicity. Five pts experienced LFT elevations, most G1 with 2 reported as G3. In cohort A, 1 of 3 evaluable pts had SD as best on-treatment response. In cohort B, 1 of 4 evaluable pts had SD as best on-treatment response, others experienced PD by RECIST 1.1. In cohort C 2 mg, 2 of 5 had SD reported at Day 53. At 4 mg dose in cohort C, 3 of 3 pts had disease control, with one CR in the liver (5L ICC) and 2 SD. Decreases were noted in the target liver lesion (31.3 to 17.5 mm), non-target liver lesion, and extra-hepatic lymph nodes on days 53 and 84 with complete response of target liver lesions and stability of extra hepatic nodal lesions reported on Day 154. Median PFS in the Cohort C 4 mg dose level is >120 days. Median OS for this group has not reached (range 120-170 days). Immune effects in cohort C 4 mg pts included increases in liver tumor CD4+ and CD8+ T cells, along with a decrease in the MDSC:CD8+ T cell ratio. Gene expression changes in cohort C 4 mg pts revealed increased Th1 programming in tumor tissue, with increased interferon, cytokine, TLR, Th1, and lymphocyte activation signals in surrounding normal liver. Changes among blood immune cells included increased IFNg and IL2-R expression, with decreased IL17A and VEGFA. **Conclusions:** HAI of nelitolimod has been well tolerated and associated with encouraging immunologic activity in HCC and ICC. Clinical and biologic activity in cohort C at 4mg is supportive of further enrollment in this cohort. Clinical trial information: NCT05220722. Research Sponsor: None.

A phase 1/1b study of the IL-2 prodrug WTX-124 in patients with locally advanced or metastatic solid tumors after checkpoint inhibitor therapy: Initial results of the combination dose escalation with pembrolizumab.

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Background: High dose IL-2 can produce durable remissions in patients who have progressed on checkpoint inhibitors but is infrequently used due to its life-threatening toxicities such as vascular leak syndrome (VLS). WTX-124 is a half-life extended, masked cytokine (INDUKINE molecule) rationally engineered to release wild type IL-2 in tumors. We previously reported that WTX-124 is clinically active as a monotherapy at doses safely administered in the outpatient setting. Here we update the data and present initial results from the combination dose escalation with pembrolizumab (anti-PD-1; NCT05479812). **Methods:** In this first-in-human trial, WTX-124 is administered IV Q2W alone or with pembrolizumab 400 mg IV Q6W. Eligible patients are adults with relapsed/refractory solid tumors who have previously received standard of care checkpoint inhibitor regimens. Primary endpoints are safety and ORR; secondary endpoints are PK, PD, immunogenicity, and PFS/OS. The dose escalation is guided by a mTPI-2 study design. **Results:** As of January 29, 2024, 32 patients have been treated with WTX-124 in five monotherapy dose escalation cohorts (1-18 mg; N=24) and two combination cohorts (3-6 mg; N=8). The most common AEs related to WTX-124 monotherapy were arthralgias, myalgias, fatigue and pruritis. Of ten evaluable patients treated with 12 or 18 mg WTX-124 monotherapy, three had objective responses, including a confirmed CR in a patient with cutaneous squamous cell cancer and unconfirmed PRs in patients with melanoma and gastroesophageal junction cancer. On-treatment tumor biopsies showed evidence of increased lymphocyte activation and PD-L1 expression. Addition of pembrolizumab to 3-6mg WTX-124 did not change the character of AEs observed with WTX-124 monotherapy. Related AEs occurred more frequently for the combination than for 3-6mg WTX-124 monotherapy, but all were mild to moderate in severity (Gr1: 74.2%, Gr2: 25.8%) and there was no increase in the percentage of Gr2 events. No DLTs, related serious AEs, treatment discontinuations due to related toxicities, or occurrences of VLS have been observed in any patient treated to date with either WTX-124 or WTX-124/pembrolizumab. Pembrolizumab did not affect WTX-124 or IL-2 PK. WTX-124 has been escalated to 12 mg IV Q2W, the initial monotherapy dose that produced objective responses, in combination with pembrolizumab. **Conclusions:** WTX-124 administered as a monotherapy IV Q2W in the outpatient setting is well tolerated and clinically active in patients with relapsed/refractory solid tumors after checkpoint inhibitor therapy. Preliminary results from the ongoing combination dose escalation with pembrolizumab show no new safety signals. Updated data on safety, biomarkers, and preliminary clinical activity for the combination will be presented. Clinical trial information: NCT05479812. Research Sponsor: Werewolf Therapeutics Inc.

Impact of body mass index (BMI) on survival outcomes in patients with cancer treated with immune checkpoint inhibitors (ICPI): A systematic review and meta analysis.

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Background: With the increased adoption of ICPI in treating various cancers, there is active exploration of individual-level factors that could predict treatment responses. A high-body mass index (BMI) induces a chronic inflammatory state and could drive T-cell dysfunction through high leptin levels, which may confer better outcomes with ICPI usage. However, there are conflicting outcomes in different studies. We performed this systematic review and meta-analysis to evaluate survival outcomes with ICPI in patients with BMI ≥25 vs <25 Kg/m^2. **Methods:** A comprehensive search was conducted across PubMed, Embase, Scopus, and web of science databases. The original studies evaluating response [overall survival (OS) and progression free survival (PFS)], to ICPI-based therapies among adult cancer patients, stratified by BMI groups (high, BMI ≥25Kg/m^2 or low, BMI <25Kg/m^2), were included. RevMan version 5.4.1 was used for statistical analysis. A random effect model with inverse variance as the statistical method was used for hazard ratio (HR) and 95% confidence interval (CI). **Results:** Of 1215 identified studies, 22 observational studies, comprising 5859 patients (60.3% males) met the inclusion criteria. ECOG performance score was reported as 0-1 for 40.3% patients, and ≥2 for 7.1% patients. In 12-studies only PD-1 and/or PD-L1 inhibitors were administered, but no CTLA-4 inhibitor. Most frequently reported cancers were non-small cell cancer of lung (40.9%), melanoma (36.6%), and renal cell cancer (31.8%) in advanced/metastatic stages. Higher BMI, compared to low BMI, favored significant improvement in PFS [HR 0.86; 95% CI (0.76, 0.99), P= 0.03, I^2 47%], and OS [HR 0.73; 95% CI (0.62, 0.85), P< 0.0001, I^2 53%] with any ICPI-based regimens. Similar findings were noted for patients treated with PD-1/PDL1 inhibitors [Table]. **Conclusions:** This study contributes to the evidence that BMI of 25 kg/m^2 or higher exerts a beneficial impact on PFS and OS among cancer patients treated with ICPI. The favorable impact underscores the significance of considering BMI as a potential prognostic factor in ICPI therapy. However, the precise underlying mechanisms responsible for this observation warrant further investigation to deepen our understanding and potentially optimize therapeutic strategies in this patient population. Research Sponsor: None.

Pooled hazard ratio (95% CI) for progression free survival (PFS) and overall survival (OS) among patients with high and low BMI treated with immune check point inhibitors (ICPI).

	BMI ≥ 25vs <25 kg/m^2	
ICPI Group	**PFS**	**OS**
PD-1/PD-L1 inhibitors	0.78 [0.61, 1.00]	0.63 [0.51, 0.77]
Any ICPI	0.86 [0.76, 0.99]	0.73 [0.62, 0.85]

PD-L1 immunohistochemistry in gastric cancer: Comparison of combined positive score and tumor area positivity across 28-8, 22C3, and SP263 assays.

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Background: The clinical application of programmed death-ligand 1 (PD-L1) immunohistochemistry is complicated by multiple available assays and different testing platforms, scoring algorithms, and cut-offs applied. This study assessed the analytical comparability of three commercially available PD-L1 assays (28-8, 22C3, and SP263) and two scoring algorithms used in gastric cancer (GC). **Methods:** Serial sections of 100 commercially procured GC samples, selected by the 28-8 assay to represent the dynamic range of PD-L1 expression, were stained with the three *in vitro*diagnostic (IVD)-grade PD-L1 assays. Stained slides were blindly and independently evaluated by three trained pathologists for intra- and inter-reader assessment. Scoring was performed using the combined positive score (CPS) and tumor area positivity (TAP) methods, followed by statistical analysis. Digital image analysis (DIA) was used to objectively assess the technical performance of each assay by simulating CPS and TAP scoring methods using the HALO platform. **Results:** Comparable, specific, staining patterns were observed with the three PD-L1 assays. Pathologist assessment of PD-L1 positivity was reproducible in GC sample cohorts despite discernible variability in the observed staining intensity. When the same PD-L1 cut-offs were applied, inter- and intra-assay assessments of all three assays, using either CPS or TAP scoring methods, demonstrated moderate to almost-perfect (inter-assay Cohen's kappa [κ] ranged from 0.47 to 0.83) and substantial to almost-perfect (intra-assay κ ranged from 0.77 to 1.00) agreement, respectively. Moreover, inter-pathologist evaluation showed a significant level of reproducibility (intraclass correlation coefficient (ICC) $\geq$0.92). DIA confirmed no difference in technical performance when specific digital algorithms were applied. **Conclusions:** This GC study highlights analytical concordance in PD-L1 testing among three major PD-L1 assays when TAP and CPS scoring algorithms are prospectively applied. Independently, DIA further supports the comparability of the technical performance of the assays. These observations support flexibility in cross-application of the different PD-L1 assays and scoring algorithms currently used to characterize PD-L1–positive GC samples. Research Sponsor: Novartis Pharmaceuticals Corporation.

Pan-cancer B- and T-cell transcriptome analysis of CXCL13 as a predictive marker for immune checkpoint inhibitor response.

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Background: Maturation of lymphoid structures and tumor-antigen presentation via B cells in the tumor microenvironment (TME) have been recognized as factors in tumor immunity. The presence of B cells and tertiary lymphoid structures appears to result in better prognosis in patients with cancer but their role in response to immunotherapy remains subject to research. This study aimed to leverage the transcriptome expression of B and T cell markers and elucidate their impact on response to immune checkpoint inhibitors (ICIs). **Methods:** Among 514 patients with cancer included in the Profile-Related Evidence determining Individualized Cancer therapy study (NCT02478931), 208 with advanced cancer and available date treated with ICIs were analyzed. Patients were divided into responders (progression-free survival [PFS] after initiation of ICI therapy: 6 or more months) and non-responders (PFS: less than 6 months). Transcriptome expression of 34 immunoregulatory markers associated with B and T cells was compared between these groups using odds ratios (ORs) of "High" transcriptome expression ["High" (75-100 percentile), "Intermediate" (25-74), and "Low" (0-24), rank compared to 735 controls] of each immune marker for immunotherapy responders. A logistic regression model was used to perform a multivariable analysis of ORs. Clinical characteristics between responders and non-responders were summarized, and rate of "High" transcriptome expression of identified markers contributing to immunotherapy response was summarized by cancer type. **Results:** In total, 82 and 126 patients were classified into responder and non-responder groups. Median age was 65.0 and 61.0, and women were 58.5% (48/82) and 54.8% (69/126) in each group, respectively. Cancer type in both groups was well balanced. In univariate analysis, "High" transcriptome expression of CXCL13, CD3, BTLA, CTLA-4, and PD-1 was significantly more frequent in the responder than non-responder group. Cluster heatmaps in both groups revealed more B and T cell enriched population in the responder group. In multivariable analysis, patients with "High" CXCL13 expression were more likely to be immunotherapy responders (OR: 3.91, 95% confidence interval [CI]=1.02-15.04, p=0.044). High CXCL13 transcriptome expression was most common in head and neck (25%, 3/12), breast (22.4%, 11/49), neuroendocrine (20%, 3/15), and lung (20%, 4/20) tumors. **Conclusions:** This pan-cancer analysis found an association between high CXCL13 mRNA expression and better response to ICI therapy. CXCL13 role in promoting a lymphoid structure in the TME by facilitating B-cell recruitment could enable anti-tumor immunity, resulting in better response to immunotherapy. This indicates that dissection of not only T cell but also B cell regulatory factors is necessary to cancer immunotherapy response and resistance mechanisms. Clinical trial information: NCT02478931. Research Sponsor: U.S. National Institutes of Health; 5U01CA180888-08; 5UG1CA233198-05.

Evaluation of the tumor microenvironment in African American and non-Hispanic White patients with non-small cell lung cancer associated with PD-L1 expression or the presence of tertiary lymphoid structures.

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Background: African Americans have higher incidence and mortality from lung cancer than non-Hispanic Whites, but investigations into differences in the tumor microenvironment and treatment response have been minimal. Due to the increasing utility of immunotherapy in the treatment of non-small cell lung cancer (NSCLC), we compared the immune cell composition and transcriptomic signature in the tumor microenvironment among African American and non-Hispanic White patients based on PD-L1 or tertiary lymphocyte structure (TLS) status to determine if there were differences of translational relevance. **Methods:** Using a cohort of 280 NSCLC patients from the INHALE study (non-Hispanic White: n = 155; African American: n = 125) with whole transcriptome microarray data, we determined the PD-L1 tumor proportion score ($< 1\%$ vs. $\geq 1\%$) and TLS status (presence/absence) within tumor tissue sections by immunohistochemistry. TLS were defined as dense aggregates of CD20 stained cells with a minimum diameter of 150 μm. Immune cell distribution within the tumor microenvironment was evaluated relative to differential gene expression. **Results:** Tumors from African Americans had a higher proportion of plasma cell signatures within the tumor microenvironment than tumors from non-Hispanic Whites. In addition, gene expression patterns in African American PD-L1 positive samples suggest these tumors contained significantly greater numbers of $\gamma\delta$ T-cells and resting dendritic cells, along with fewer $CD8^+$ T-cells compared to PD-L1 negative samples after adjusting for stage and histology. We also identified 22 genes that were differentially expressed between PD-L1 positive and negative tumors, along with 37 genes that were differentially expressed between TLS positive and negative tumors. Investigation of differential expression of B-cell/plasma cell related genes between the two patient populations revealed that four immunoglobulin genes in African Americans (*IGHA1*, *IGHD*, *IGKV2-29*, and *IGLL5*) were associated with decreased mortality risk, while none of these genes were associated with overall survival in the non-Hispanic White population. **Conclusions:** In the first known race-stratified analysis of tumor microenvironment in lung cancer based on PD-L1 expression or TLS status, differences within the immune cell composition and transcriptomic signature were identified among non-Hispanic White and African American patients that may have therapeutic implications. Future investigation of these unique aspects within the tumor microenvironment will make advances in immunotherapy more equitable, thereby reducing the health disparities African Americans currently experience. Research Sponsor: U.S. National Institutes of Health; R01CA141769; U.S. National Institutes of Health; P20CA262735; U.S. National Institutes of Health; P30-CA022453; U.S. National Institutes of Health; T32-CA009531.

Endogenous retrotransposable elements as a novel predictive biomarker of response to immunotherapy.

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Background: Non-coding DNA repetitive sequences such as the endogenous retrotransposable elements (EREs) can influence the transcription of adjacent genes and shape antitumor immune responses through viral mimicry. Here, we examine the role of EREs as a biomarker of response to immune-checkpoint inhibition (ICI) in the phase II INSPIRE trial (NTC02644369). **Methods:** Baseline (B) and on-treatment (T) tumor samples from patients (pts) with advance solid tumors treated with pembrolizumab were retrospectively analyzed. Response was evaluated by RECIST 1.1; pts were classified as responders (R) (complete or partial response) or non-responders (NR) (progressive disease). ERE expression was analyzed by total RNA-seq in B and T samples. Differentially expressed EREs between R and NR were quantified by the TPM*score* (mean of normalized transcript per million values for upregulated ERE in a sample comparison) and its standardized Z*score*. For survival analysis, EREs were dichotomized into high or low expression based on median Z*score* values of R versus NR. CD8+ population was inferred by CIBERSORT of RNAseq data. Multivariable Cox regression models were used to assess PFS and OS. **Results:** 82/106 pts with median age 52y (21-80), 59% female, in 5 tumor cohorts (head and neck 16%, triple negative breast cancer 16%, ovarian 22%, melanoma 12%, and mixed tumor cohort 34%) were available for analysis after data QC. Of 82 pts, 14 (17.3%) were classified as R and 44 (54.3%) as NR. Differential ERE expression was observed between R and NR to pembrolizumab at baseline (B Z*score* 0.22 vs -0.21 p <0.001) and on-treatment (T Z*score* 1.12 vs -0.29 p <0.001). The upregulated EREs were LINE (32.2%), SINE (30.5%) and LTR (20.9%) at baseline; and LINE (15.9%) SINE (59.9%) and LTR (9.1%) on treatment. An elevated ERE expression was observed in T samples compared to B, in both R (Z*score* 0.48 vs -0.26 p=0.009) and NR (Z*score* 0.25 vs -0.31 p <0.001). A strong positive correlation between EREs TPM*score* of all ERE subgroups and CD8+ was seen when comparing B vs T samples of responders (R 0.79, p=0.006), while in NR a weak positive correlation was seen only in some ERE subgroups (Alu R=0.38, p=0.02; LINE R 0.35, p=0.03). Of 74 pts with survival data and median follow-up of 14 months (m) (2.3-76.8), median PFS and OS were 1.9m and 14m, respectively. Multivariable analysis including ERE expression, cohort, PD-L1 and TMB, showed higher ERE expression was associated with longer PFS (1.9m vs 10.1m, aHR 0.07, 95% CI 0.03-0.18, p <0.001) and OS (8.3m vs 22.6m, aHR 0.4, 95% IC 0.22-0.74; p=0.004). Long-term survivors (OS ≥60m) had higher ERE Z*score* vs pts with OS <60m (0.18 vs -0.15, p=0.03), and specifically SINE (p=0.02) and LTR (p=0.03) subgroups. **Conclusions:** Tumor ERE expression analysis between ICI responders and NR suggests an association between ERE upregulation and radiological response, PFS and OS during ICI treatment. Further validation studies are warranted. Research Sponsor: Princess Margaret Cancer Consortium - Marathon of Hope Cancer Centres Network; Merck (Drug supply).

A distinct dimension of immunotherapeutic biomarker: Beyond immune infiltration and tumor antigenicity.

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Background: Biomarkers for immune checkpoint blockade (ICB) are classified into two categories: those reflecting inflammation (e.g., PD-L1 expression and CD8+ T cell infiltration), and those indicating antigenicity (e.g., tumor mutation burden [TMB] and neoantigen burden [NAB]). Most newly discovered ICB biomarkers are found to be associated with these two types of information. Consequently, they might simply represent alternative assessments of previously uncovered biology. Considering that ICB resistance largely occurred in 'hot' and antigenic tumors, the exploration of the third dimension of biomarker is warranted. **Methods:** A total of 2646 patients with RNA-seq data were collected from in-house and public randomized controlled trials (RCTs) (n=3) and cohorts (n=21) across multiple cancer types, including lung (n=1381), urinary tract (n=557), skin (n=345), kidney (n=214), stomach (n=76), liver (n=41), and esophagus (n=32). All patients received ICB mono- or combined therapy, except in the RCTs, where patients received ICB or chemotherapy (Chemo). We first identified genes that are independent of the two categories of biomarkers (i.e., PD-L1 expression, T-cell inflamed profile, CD8+ T cells, tertiary lymphoid structure, TMB, NAB, and microsatellite instability). Independence was defined as a spearman level within -0.2 to 0.2. These genes were then subjected to gene co-expression analysis to identify potential modules associated with ICB outcomes. **Results:** We revealed a novel functional module that shows weak correlation with previously established biomarkers. The bulk and single-cell RNA-seq confirmed its enrichment in subsets of stromal cells, thus it was named the Third Dimensional Stromal (TDS) score. High TDS consistently predicted less ICB efficacy in each cohort and jointly in meta-analysis (OS: HR=1.56, P<0.0001; PFS: HR=1.65, P<0.0001). The advantages of ICB over Chemo were lost in high-TDS tumors (meta-analysis: OS: HR=1.03, P=0.23; PFS: HR=1.14, P=0.25), demonstrating its predictive rather than prognostic role. The negative predictiveness of TDS further increased in 'hot' tumors with high CD8+ T cell infiltration (meta-analysis: OS: HR=1.96, P<0.0001; PFS: HR=1.69, P<0.0001), but was far less predictive in 'cold' tumors. Importantly, even in 'hot' tumors, high-TDS defined a population where ICB could not improve survival compared to Chemo (meta-analysis: OS: HR=0.83, P=0.23; PFS: HR=0.96, P=0.77). **Conclusions:** The TDS framework represents a unique classification of pan-cancer patients, rather than a repetition of existing systems, thus can be integrated into the current multipart biomarker panel. Additionally, since we found a distinct biomarker nature between 'hot' and 'cold' tumors, this study emphasizes the importance of exploring biomarkers and resistance mechanisms specifically among patients who harbor inflamed tumors. Research Sponsor: National Natural Science Foundation of China; 82172713; Guangdong Basic and Applied Basic Research Foundation; Fundamental Research Funds for the Central Universities, Sun Yat-sen University.

Use of CRTAM expression as a predictive biomarker for immune checkpoint blockade in a pan-cancer cohort.

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Background: Immune checkpoint blockade (ICB) has revolutionized the treatment of advanced cancers. Microsatellite instability (MSI) and tumor mutational burden (TMB) are tissue-agnostic predictive biomarkers for ICB. Still, more biomarkers are needed to identify patients who benefit from ICB accurately. Cytotoxic and regulatory T cell molecule (CRTAM) is a transmembrane protein expressed by T cells and NK cells and plays a role in the activation and differentiation of immune cells. The influence of CRTAM expression on the treatment outcome of ICB was analyzed. **Methods:** A total of 514 patients with various types of cancer included in the Profile-Related Evidence Determining Individualized Cancer Therapy study (NCT02478931) were analyzed. Gene expression levels were normalized to internal housekeeping gene profiles and ranked by percentile. (0 to 100) CRTAM expression was compared with histology, program death ligand 1 (PDL1) immunohistochemistry (IHC), MSI, and TMB. Among them, 217 patients received ICB (ICB cohort), and they were analyzed for overall survival (OS) from diagnosis of advanced/metastatic disease and OS and progression-free survival (PFS) from the first date of ICB. A cohort of patients with advanced melanoma who received nivolumab (N=49) from the GEO database was analyzed for validation (Accession: GSE91061). **Results:** CRTAM expression was significantly associated with histology, with melanoma and small intestine cancer having the highest expression levels. (p=0.023) CRTAM expression was also associated with PDL1 IHC (≥1%) and MSI-H (p=0.024 and 0.005, respectively), but not with TMB. "High" CRTAM expression was defined by expression levels 75 or greater, and expression levels below 75 were regarded as intermediate/low. 31 patients (15%) showed high CRTAM expression. High CRTAM was significantly associated with longer PFS from ICB initiation in a univariate analysis (hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.38-0.92), but not in a multivariate analysis adjusting histology, line of ICB, PDL1 IHC, MSI and TMB. On the other hand, high CRTAM was associated with longer OS from ICB (HR: 0.39, 95% CI: 0.21-0.73), and the significance was preserved in multivariate analysis. OS from advanced/metastatic disease diagnosis was significantly longer in high CRTAM in multivariate analysis in ICB cohort (HR: 0.42, 95% CI: 0.20-0.89), while the association between OS and CRTAM was not observed in patients who did not receive ICB (N=272, HR: 0.76, 95% CI 0.45-1.28). In an external cohort of advanced melanoma, high CRTAM was associated with a higher proportion of objective response in patients treated with nivolumab (42% vs. 14%, p=0.035). **Conclusions:** CRTAM promotes immune cell activation and differentiation, and high transcriptomic expression correlates with better outcome after ICB, including significantly longer survival in a pan-cancer cohort. Research Sponsor: None.

Identification of a predictive phosphoproteomic signature of response to atezolizumab and bevacizumab (AB) in patients with advanced hepatocellular carcinoma (aHCC).

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Background: The number of systemic therapy options for aHCC has increased in recent years. Whilst AB has become the standard of care since its approval in 2020, most patients will have progressed by 12 months and 25% will have no response to AB. In addition, there are no predictive biomarkers to guide aHCC therapy selection. We have previously used phosphoproteomics to identify predictive biomarkers from frozen clinical samples in other cancer types. In this study, we aimed to build a preliminary model of response to AB by performing phosphoproteomic analysis on formalin-fixed and paraffin-embedded (FFPE) resected and Tru-Cut liver biopsies from aHCC patients subsequently treated with AB. **Methods:** Proteins were extracted from 10x10μm sections of FFPE biopsies obtained at diagnosis from aHCC patients (n=30, aetiology: viral, n=16; non-viral, n=14). Reversal of crosslinks was followed by tryptic digestion and multiple clean-up/enrichment steps. Peptides were quantified by mass spectrometry, and data quality was assessed using multivariate and enrichment analyses. Patients were stratified into 'good responder' (GRG, n=20, duration of response (DoR)>7.5 months) and 'poor responder' (PRG, n=10, DoR<7.5 month) groups. Features distinguishing the two groups were used to train a random forest response prediction model, which was assessed via cross-validation. **Results:** To build an AB response prediction model, 40 phosphopeptides were selected based on their ability to distinguish between PRG and GRG patients. These included previously described phosphorylation sites, such as pGSTA1-3^{S202} and pHSPB1^{S9}, as well as several novel ones. In cross-validation, the model correctly predicted the outcomes of all good (20/20) and of 7/10 poor responders, demonstrating 100% sensitivity, 87% precision and 70% specificity. Overall, our model stratified patients with log-rank $p<0.001$ and $HR<0.1$ (Table), with similar performances in both viral (mean DoR 17.1 vs 0 months) and non-viral aetiology (mean DoR 14.4 vs 3.1 months). Interestingly, kinase substrate enrichment analysis revealed significant ($p<0.01$) modulation of several kinases, such as MAP kinases and PRKCI, between responder groups. Also of note, a subgroup of PRG patients displayed increased activity of the RAF-MEK-ERK pathway, suggesting that these individuals may have shown sensitivity to drugs targeting RAF kinases, such as sorafenib. **Conclusions:** We have defined a preliminary predictive model of response to AB using phosphoproteomic data from routine FFPE biopsies in aHCC. Following an ongoing validation in independent patient cohorts, this model will address an unmet clinical need for biomarkers of clinical response in aHCC. Research Sponsor: UK Research Innovation; Kinomica Limited.

DoR in months as a function of model phosphosignature.

Signature	Cases	Events	Mean DoR	SE	Median DoR
GRG	23	19	16.1	1.9	14.7
PRG	7	7	1.8	1.1	0

Genomic instability in advanced non-small cell lung cancer (NSCLC) treated with maintenance durvalumab in the UNICANCER SAFIR02-Lung/ IFCT1301 trial.

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Background: Genomic instability is a hallmark of cancer that has been associated to immune evasion, cancer progression and multidrug resistance. In SAFIR02-Lung, advanced NSCLC pts were enrolled to receive a platinum-based chemotherapy. After 4 cycles, pts with no targetable alterations were oriented to the immunotherapy sub-study, and if stable or in response, were randomized between maintenance durvalumab or Standard of Care (SoC) (PMID 35802649). Durvalumab prolonged survival only in the PD-L1 $\geq$ 1% subgroup. In this study we investigated a genomic instability score based on somatic copy number alterations as determined by Comparative Genomic Hybridization (CGH) array as a biomarker for maintenance immunotherapy. **Methods:** SAFIR02-Lung (NCT02117167) is a multicentric, randomized phase 2 clinical trial. Tissue samples were obtained before induction chemotherapy. Extracted DNA from fresh frozen tumor was analyzed using high-resolution Affymetrix Cytoscan arrays, DNA from FFPE samples was analyzed using the Affymetrix Oncoscan CNV platform. The absolute copy-number (ACN) profile was generated by ASCAT v3.1 through EaCoN v0.3.6 (https://github.com/gustaveroussy/EaCoN, PMID 36669143) on R v4.1.1 and then the genomic instability score was estimated as the sum of the segment length multiplied by the absolute difference between segment copy number and the ASCAT estimated sample ploidy. This sum is reported to the reference genome length. Progression Free Survival (PFS) was the primary endpoint, defined as the time from randomization until the date of objective radiological disease progression, clinical progression or death. The secondary endpoint was Overall Survival (OS). **Results:** CGH array data were available for 79 patients out of 183, 56 randomized to durvalumab and 23 to SoC. 47 were men, 72 had non-squamous histology and 12 had brain and 10 had liver metastasis. We divided patients in tertiles according to instability (INS) score. No correlation was seen between INS score and PD-L1 positivity (p = 0.5), or liver and brain metastasis. Pts with high INS had lower median PFS of 2.5 months (m) (95% CI 1.4 – 5.2) *vs* 4.3m (95% CI 2.6 – 13.7) for those with intermediate INS and 6.1m for those with low INS (95% CI 1.9 – 21.2), p 0.012. Similarly, low INS patients had longer OS of 29.6 m (95% CI 15.4 – NR) vs 17.9m for intermediate INS (95% CI 10 – NA) and 12.1m for high INS (95% CI 10.2 – 19.5), p = 0.039. No difference was seen in the control group (p=0.25 for PFS and p=0.4 for OS). A multivariable model showed that high INS was independently associated worse PFS (HR 2.60, 95% CI 1.36 - 4.98, p 0.004) and OS (HR 2.90, 95% CI 1.33 - 6.35, p 0.008). **Conclusions:** Genomic instability score based on CGH array-based copy number alterations profile is associated with worse PFS and OS in patients under response to chemotherapy who received durvalumab maintenance. Clinical trial information: NCT02117167. Research Sponsor: None.

AI based PD-L1 CPS quantifier software to identify more patients for checkpoint therapy in gastric cancer at pathologist-level interobserver concordance.

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Background: To determine whether gastric cancer (GC) patients are eligible for immunotherapy, PD-L1 expression is analyzed by immunohistochemistry (IHC) using the "Combined Positive Score" (CPS). This requires quantification of PD-L1 stained tumor and tumor-associated immune cells as well as all viable tumor cells. However, manual CPS scoring on whole-slide images (WSIs) is time-consuming and prone to error as evidenced by low interobserver concordance. While the use of artificial intelligence (AI) holds the promise to ameliorate this key challenge in clinical practice, AI models have not yet met the required accuracy thresholds for PD-L1 CPS scoring on GC biopsies. **Methods:** We investigated the use of an AI-based PD-L1 CPS quantifier software to support pathologists in standardized PD-L1 IHC assessment on GC biopsies.An AI software for automated PD-L1 CPS scoring was deployed on WSIs from GC biopsies (n = 97) stained for PD-L1 with the 28-8 pharmDx assay and scanned on a 3DHistech P1000 scanner. Manual CPS scores from 12 pathologists on all 97 slides were available for comparison. Pairwise correlation was calculated for continuous values using Lin's concordance correlation coefficient (CCC). Pairwise concordance was measured for scores binarized at the clinically relevant positivity cutoff of CPS $\geq$ 5 using unweighted Cohen's kappa. **Results:** For continuous CPS scores, the CCC between AI scores and pathologists' scores was higher (0.59) than the mean correlation among pathologists (0.56). In the majority of cases, the AI scores were found to be within the range of all pathologists, but slightly above the pathologist median. At a cutoff of CPS$\geq$5, the concordance between AI scores and pathologists' manual scores (κ=0.45) was higher than the mean concordance among pathologists' manual scores (κ=0.39) ($p<0.05$). Substantial variability is seen among pathologists when categorizing patients as positive (CPS$\geq$5), with approximately 30.3 $\pm$5.0 patients classified as positive on average by manual scoring and 46 patients (>50% more) categorized as positive by the AI model. **Conclusions:** An AI model for the assessment of PD-L1 expression in GC using CPS was applied successfully without human intervention. The correlation in continuous CPS scores as well as the concordance in clinical categories with all pathologists was higher for the AI model than for individual pathologists on average, while at the same time, the AI model found more positive patients. This shows that by using AI more positive patients eligible for PD-L1 targeted treatment might be identified while simultaneously ensuring a level of concordance that is non-inferior to pathologists. Research Sponsor: Bristol Myers Squibb.

Immune responses in a phase 2 clinical trial of peptide-based therapeutic human papillomavirus vaccine, PepCan, versus *Candida* adjuvant alone in treating cervical intraepithelial neoplasia 2/3.

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Background: A non-surgical alternative for treating cervical intraepithelial neoplasia (CIN2/3) would be desirable due to a risk of cervical incompetency in subsequent pregnancies. PepCan consists of four HPV 16 E6 peptides and a *Candida* skin testing reagent (Candin, Nielsen Biosciences),because of*Candida*'s ability to regress common warts in humans, and to promote T cell proliferation and interleukin-12 secretion *in vitro*. We previously demonstrated safety and efficacy of *Candida* alone in comparison to a historical placebo for regressing CIN2/3 to no CIN (p=0.0004 for intention-to-treat and p=0.0002 for per-protocol analyses). **Methods:** In this single center, randomized, double-blind Phase II study (NCT02481414), four intradermal injections of PepCan or *Candida* were given 3 weeks apart which were followed with two visits 6 months apart. Immune responses were assessed using interferon-g enzyme-linked immunospot (ELISPOT) assay for human papillomavirus (HPV), fluorescent-activated cell sorter (FACS) analysis for peripheral immune cells, and plasma measurements of 51 cytokines and metabolomics in patients who completed the 6-month visit (n=76). Cervical microbiome was also examined. For subjects who were HPV 16, 18, 35, or 52-positive at entry, epitope spreading was examined (n=32). In patients with sustained ELISPOT responses, bulk T cell receptor (TCR) b deep sequencing was performed (n=15). If the sustained ELISPOT responses were significant, single-cell RNA-seq and TCR sequencing were performed (n=5) for vaccine-induced HPV-specific T cells. **Results:** Following vaccination, new CD3 T cell responses to at least one region of the HPV 16 E6 protein were detected in 18 of 33 patients (54.5%) in the PepCan group and in 17 of 38 (44.7%) patients in the *Candida* group. Therefore, exogenous HPV antigens were not necessary to induce anti-HPV T cell responses. The histological responders demonstrated new E6 response in 14 of 31 (45.2%) and non-responders had it in 21 of 40 (52.5%). Pre-existing E6 responses were present in 12 of 31 (38.7%) of responders and 8 of 40 (20%) of non-responders. Epitope spreading was demonstrated in 7 of 18 patients (38.9%) in the PepCan group, in 8 of 14 (57.1%) patients in the *Candida* group, 6 of 10 (60%) histological responders and 9 of 22 (40.9%) histological non-responders. Plasma RANTES/CCL5 level was significantly and consistently decreased after vaccination (p=0.004). Single-cell RNA-seq revealed increased expression of granzymes, CCR5, and EOMES in a histological responder, compared to non-responders. **Conclusions:** Administration of immune-enhancing adjuvant alone is sufficient for inducing anti-HPV immune responses. Consistent systemic decrease in RANTES/CCL5 was demonstrated suggesting possible mechanism in which *Candida* works through reducing RANTES/CCL5. Clinical trial information: NCT02481414. Research Sponsor: National Instites of Health.

Efficacy and safety of recombinant human adenovirus type 5 (H101) combined with immune checkpoint inhibitors (ICIs) in patients with liver metastatic gastric cancer: A prospective multicenter phase II study (the TROJAN 021 study).

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Background: Immune checkpoint inhibitors (ICIs) have shown significant efficacy in metastatic gastric cancer, but some patients may not respond to them because of immune resistance. Recombinant Human Adenovirus Type 5 (H101), the world's first oncolytic virus antitumor drug in China, can induce cell death, expose tumor antigens, provide adjuvants for anti-tumor immune priming, and potentially increase responsiveness to immunotherapies. Here, we presented the efficacy and safety of H101 combined with immune checkpoint inhibitors (ICIs) in patients with liver metastatic gastric cancer. **Methods:** In this multi-center, phase II trial (the TROJAN 021 study, ChiCTR1900027922), patients with liver metastatic gastric cancer received 2 cycles of H101 ultrasound guided injections into liver lesions, bi-weekly in combination with anti-PD-1 antibodies and chemotherapy bi-weekly until progression or intolerable toxicity. The primary objective was safety and objective response rate (ORR). Secondary objective included progression-free survival (PFS), overall survival (OS) and disease control rate (DCR). Efficacy assessments were performed every 4 weeks following RECIST v1.1 criteria. PFS and OS were estimated using the Kaplan-Meier method. **Results:** From September 2020 to September 2022, 21 patients were enrolled. Of them, 18 were males, median age was 66 years (range: 36-71) and ECOG performance status was either 0 (n=15) or 1 (n=6). 10 patients (47.6%) received as first-line therapy, 1 (4.8%) as second-line and 5 (23.8%) as third line and above therapy. The primary endpoint was met with a median PFS of 4.8 months. The median OS was 13.2 months. Objective tumor responses were CR (n=0), PR (n=7), SD (n=12) and PD (n=2). ORR was 33.3% (7/21), and DCR was 90.5% (19/21). Treatment related adverse events (TRAE) occurred in 12 patients (57.1%). The most frequently observed TRAEs were injection site pain (48.1%), fever (57.1%) and fatigue (23.8%). Three patients (14.3%) had grade 3 treatment-related adverse events. There were no grade 4 and 5 treatment-related adverse events. Grades 3 toxicities included neutropenia (2/21, 9.5%) and hypertension (1/21, 4.8%). **Conclusions:** These promising results show that combination of Recombinant Human Adenovirus Type 5 (H101) and ICIs demonstrated acceptable toxicity and promising antitumor efficacy in patients with liver metastatic gastric cancer. Further validation of the efficacy in a randomized prospective trial is warranted. Clinical trial information: ChiCTR1900027922. Research Sponsor: None.

AMPLIFY-7P, a first-in-human safety and efficacy trial of adjuvant mKRAS-specific lymph node targeted amphiphile ELI-002 7P vaccine in patients with minimal residual disease–positive pancreatic and colorectal cancer.

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Background: Diverse KRAS mutations occur in 25% of solid tumors with G12D, V and R most frequent. ELI-002 7P is an expanded spectrum vaccine comprised of lymph-node targeted Amphiphile (Amph)-modified G12D, V, R, C, S, A, and G13D mutant KRAS peptides with an Amph-modified CpG oligonucleotide adjuvant designed to expand polyfunctional mutant KRAS-specific T cells. Earlier ELI-002 2P showed high rates of T cell and tumor biomarker response (both 21/25, 84%), with median relapse-free survival not reached versus 4.01 months (HR 0.14; p=0.0167) comparing patients (pts) above versus below T cell median (12.75X). **Methods:** This multicenter phase IA trial assessed safety, immunogenicity and preliminary antitumor activity of ELI-002 7P in pancreatic (PDAC) and colorectal pts with minimal residual disease (MRD) following standard locoregional treatment. Pts with elevated circulating tumor DNA (ctDNA) and/or serum tumor biomarker (CA19-9/CEA), and KRAS mutation were enrolled and treated with subcutaneous fixed dose Amph-CpG-7909 and 1.4 mg or 4.9 mg of Amph-Peptides 7P (Table). Safety, T cell change, and preliminary antitumor activity including biomarker reduction/clearance are reported. **Results:** No dose-limiting toxicities, no treatment related SAEs or cytokine release syndrome were observed, no maximum tolerated dose was identified, and the recommended phase 2 dose (RP2D) was 10.0 mg Amph-CpG-7909 with 4.9 mg Amph-Peptides 7P. Safety: all grade 1, fatigue (29%), malaise (21%), and injection site reaction (7.1%). At data cutoff Dec 18, 2023, polyfunctional mKRAS-specific T cells were observed in 100% (n=11/11). Both CD8+ and CD4+ responses were induced in 63.6% of pts (7/11), with higher median fold-change from baseline at RP2D and durable responses post-booster immunization in 100% of pts (7/7). Biomarker reductions were observed in 2/5 (40%) at the 1.4 mg Amph-Peptides 7P dose level and in 5/7 (71%) at the RP2D 4.9 mg dose level in pts with all the common G12X (D, V, R) and G13 (D) KRAS mutations; MRD clearance was observed in 1 G12V PDAC pt at 4.9mg. **Conclusions:** ELI-002 7P was safe with median RP2D T cell responses exceeding the prior formulation (7P median 109.2; 2P 12.75), and early indications of antitumor activity. The randomized phase II is now open in patients with pancreas cancer. Clinical trial information: NCT05726864. Research Sponsor: Elicio Therapeutics.

ELI-002 Amph-Peptides 7P Dose	1.4 mg	4.9 mg (RP2D)
mKRAS	6/ DDDDV 13D	8/ DDDDRVVV
Safety (DLT)^	0/6	0/8
Median T cell fold change*	9.3	109.2
Biomarker Response#	2/5 (40%)	5/7 (71%)

^14 pts safety evaluable;
*11 pts immunogenicity – 5 at 1.4 mg, 6 at 4.9 mg;
#12 pts biomarker response.

Development of an mRNA therapeutic vaccine for virally driven Merkel cell carcinoma.

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Background: Merkel Cell Carcinoma (MCC) is a neuroendocrine skin cancer associated with integration of a truncated form of Merkel Cell Polyomavirus Large T Antigen (LTA) in most U.S. cases. LTA is a robust antigen and its expression is required for proliferation of MCC, rendering it an ideal target for an mRNA therapeutic vaccine approach. **Methods:** B16-F10 murine melanoma cells that express the truncated LTA oncoprotein were generated for use as an *in vivo*MCC model. *In vitro* transcription was used to create an optimized mRNA coding for the LTA and was encapsulated in lipid nanoparticles for intramuscular injection. LTA expressing tumor cells were injected subcutaneously in C57BL/6 mice and treated with LTA mRNA or placebo +/- anti-PD1 antibodies. Tumor growth and survival were tracked, and flow cytometry of ex-vivo tumor samples was used to characterize immune infiltration. Separate mice were treated with a three-dose series of LTA mRNA or placebo 60 days prior to tumor cell injection, and tumor growth and survival were measured. MCC patient PBMCs were collected and used as a model for human *in vitro* vaccination. Monocyte derived dendritic cells were transfected with LTA mRNA or placebo and used to stimulate the remainder of the PBMC pool every seven days. LTA specific T cell proportion, activation markers, cytokine release, and MCC specific tumor cell killing were measured. **Results:** Treatment with LTA mRNA suppressed tumor growth compared to placebo (day 21 mean volume 47.28 mm^3 vs. 575.12mm^3 P<.001) and prolonged median survival (46 vs. 24 days P<.001). Combination treatment with anti-PD1 resulted in 100% tumor regression compared to 50% with anti-PD1 only (median survival 117 days) and 0% with placebo (median survival 28.5 days). Flow cytometry of *ex vivo*tumors from LTA mRNA treated mice revealed increased immune infiltration (mean CD45+ 11.56% vs. 7.81% P=.037) with an increased proportion of CD3+ cells (mean 69.74% vs. 57.36% P=.0013) and CD8+ cells with increased cytotoxic markers (MFI GZMB 26785 vs. 13607 P=.0026). Prophylactic vaccination with LTA mRNA resulted in 80% tumor rejection vs. 0% with placebo (median survival undefined vs. 31.5 days P<.0001). Furthermore, in the prophylactic vaccination group there were no detectable tumors until day 60 following tumor challenge. *In vitro* vaccination of patient PBMCs resulted in expansion of LTA tetramer specific CD8+ T cells by day 10 (0.3% vs. 0.077%). Exposure of treated cells to antigen loaded DCs resulted in increased IFNg release by day 10 (21.78ng/mL vs. 5.35ng/mL P<.0001) and increased specific MCC tumor cell killing on day 14 (mean tumor death 9.14% vs. 4.18% P=.0001). **Conclusions:** Therapeutic vaccination with LTA targeting mRNA suppresses tumor growth and prolongs survival *in vivo* by increasing infiltration of cytotoxic immune populations. *In vitro*human vaccination increases the proportion LTA specific CD8+ T cells, IFNg release, and specific killing of MCC cells. Research Sponsor: None.

Detection of immune-related adverse events among hospitalized patients using large language models.

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Background: Immune checkpoint inhibitor (ICI)-induced colitis, hepatitis, and pneumonitis are common immune-related adverse events (irAEs); however, the true incidence for these irAEs remains incompletely understood. Chart review is the gold standard for their detection but is time-consuming and cannot be implemented in large cohorts. The use of ICD codes is limited in sensitivity and specificity. Large language models (LLMs) are a scalable method of answering queries from human-generated text, though there is no data on the use of LLM for the identification of irAEs. Therefore, we investigated the application of a LLM to identify ICI-colitis, hepatitis, and pneumonitis among hospitalized patients, comparing its performance to manual chart review and ICD codes. **Methods:** Hospital admissions of patients on ICI therapy from February 5th, 2011, to November 3rd, 2021, were manually reviewed by a multidisciplinary immunotoxicity team using established published definitions for the presence of ICI colitis, hepatitis, and pneumonitis. Standard ICD codes and a LLM pipeline with retrieval-augmented generation (RAG) were used to detect irAEs. Performance was measured via sensitivity, specificity, and model runtime. The LLM was validated with a second dataset of inpatients with ICI colitis, hepatitis, and pneumonitis admitted from November 4th, 2021, to September 5th, 2023. **Results:** Among 5,677 hospitalized patients on ICI therapy in the initial cohort, there were 132 cases adjudicated with ICI colitis, 57 with ICI hepatitis, and 47 with ICI pneumonitis. The LLM was more sensitive in detecting all three irAEs compared to ICD codes (94.2% vs. 71.8%), achieving significance for ICI hepatitis ($p<0.001$) and pneumonitis ($p=0.006$), while having similar specificities (92.5% vs 91.1%, Table 1). The LLM approach was also efficient, spending an average of 9.42s per chart, compared to an estimated 15 minutes per chart for individual chart review. The mean sensitivity and specificity of the LLM on the validation dataset for adjudicated ICI colitis (n=20), hepatitis (n=24), and pneumonitis (n=6) were 96.9% and 93.2%, respectively. **Conclusions:** LLMs serve as a useful tool for the detection of ICI colitis, hepatitis, and pneumonitis, significantly outperforming ICD-codes in accuracy and manual chart review in efficiency. Research Sponsor: None.

Comparison of ICD codes and large language model (LLM) in detecting irAEs among hospitalized patients from February 5th, 2011, to November 3rd, 2021.

	ICD Sensitivity	ICD Specificity	LLM Sensitivity	LLM Specificity
Colitis	90.2	89.2	91.7	90.0
Hepatitis	50.9	95.2	93.0	93.0
Pneumonitis	74.5	88.8	97.9	94.6
Average (SD)	**71.8 (19.8)**	**91.1 (3.6)**	**94.2 (3.3)**	**92.5 (2.3)**

Phase 1 study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in patients with advanced solid tumors.

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Background: LB1410 is a recombinant humanized anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Biopharma Co., Ltd, which blocks the immune checkpoint PD-1 and TIM-3-mediated immunosuppressive signal pathways, and showed better T/DC cell activity and in vivo anti-tumor efficacy compared to TIM-3 and PD-1 antibody combination in preclinical studies. Here we report the results of the first-in-human, multicenter, open-label, phase I trial of LB1410 monotherapy in pts with advanced solid tumors (Keyplus-001). **Methods:** Eligible pts were ≥ 18 yr old with ECOG PS 0-1 and previous treatment. Dose escalation cohorts ranged from 0.001 mg/kg to 20 mg/kg IV Q2W: 0.001mg/kg-1mg/kg in an accelerated titration design, and 3 mg/kg-20 mg/kg using traditional 3+3 design. The primary objective is safety, including dose-limiting toxicities (DLTs). Secondary/exploratory objectives include efficacy, pharmacokinetics (PK), and immunogenicity. Data cutoffs were January 5, 2024 for safety, and January 25, 2024 for efficacy. **Results:** In total, 52 pts received LB1410 from 0.001 mg/kg to 20 mg/kg as of Jan 5, 2024, median age 58 yr, 69% male. All of patients enrolled had multiple organ metastases or multiple metastases in a single organ, and were heavily treated with anti-tumor treatment, 36/52 (69.2%) were resistant to or refractory to PD-1/PD-L1 inhibitors, and 16/52 (30.8%) were MSS CRC. Treatment related AEs (TRAEs) occurred in 65.4% of pts. The most common TRAE was anemia (19.2%). 2 patients developed Gr3 hypokalemia. There were no DLTs. Tumor response evaluation were available in 40 pts: 14 had stable disease, 25 had progression, and 1 was not evaluable. Target lesion shrinkage was observed in 9 pts, including one patient's sum of target lesion reduced by 48.7% from baseline. Of 14 pts who had stable disease, there were 2 pts with stable disease lasting for more than 6 months. PK was generally dose proportional within 1 mg/kg~15 mg/kg, with $t_{1/2}$ ~4.12 days in 10 mg/kg, and $t_{1/2}$ ~4.77 days in 15 mg/kg. Of the 22 subjects tested for ADA, only one produced ADA for LB1410, the positive rate was 4.5%. Antidrug antibodies had limited impact on PK. As of Jan 5, 2024, 39 pts remained on the study; updated data will be presented. **Conclusions:** LB1410 has manageable safety and shows preliminary efficacy. Additional dose and efficacy expansion study is ongoing in immunotherapy-naive pts with MSS CRC and pts who are resistant to immunotherapy. Clinical trial information: NCT05357651. Research Sponsor: L&L Biopharma Co., LTD., Shanghai, China.

Primary analysis of a phase 1/2 study of LM-101: An anti-SIRPα antibody as a single agent in patients with advanced malignancies.

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Background: LM-101 is a humanized monoclonal antibody which binds to both V1 and V2 isoforms of SIRPα that expressed on macrophages and dendritic cells and enables phagocytosis of tumor cells. LM-101 has shown optimal pre-clinical safety profiles and promising anti-tumor activity in animal models. Here we report the primary analysis of the single agent dose escalation results of a phase 1/2 study (NCT05615974). **Methods:** This is an open-label, phase 1/2, first-in-human, multicenter dose escalation study with dose expansion evaluating safety and clinical activity of LM-101 as a single agent in patients with advanced malignancies. Eligible patients were aged ≥ 18 years with advanced solid tumors or relapsed/refractory lymphoma who had progressed on standard therapy, or intolerable to the available standard therapy, or had no available standard therapy for treatment. In the dose escalation part, enrolled patients were administered with LM-101 intravenously every three weeks at dose levels of 3 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, and 40 mg/kg as per traditional 3+3 design. The objectives for this dose escalation part included safety and clinical activity as per RECIST v1.1 criteria or Lugano 2014 criteria. **Results:** As of January 24, 2024, 17 patients were enrolled in the single agent dose escalation part. No DLT was observed at all dose levels and MTD for single agent was not reached. The most frequent adverse event (AE) related to the study drug was lymphocyte counts decreased. Two patients experienced grade ≥ 3 AEs which were related to LM-101. Out of 16 patients from single agent dose-escalation groups who had at least one time tumor assessment post treatment, one patient achieved complete response (CR), one patient achieved partial response (PR) and five patients achieved stable disease (SD). **Conclusions:** LM-101 monotherapy showed excellent safety profile and promising anti-tumor activity in patients with advanced malignancies. Further investigation of LM-101 as a single agent and in combination with other anti-tumor agents are ongoing. Clinical trial information: NCT05615974. Research Sponsor: LaNova Medicines Limited.

19-BI-1808-01, a phase 1/2a clinical trial of BI-1808, a tumor necrosis factor receptor 2 (TNFR2) blocker/depleter with or without pembrolizumab.

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Background: BI-1808 is an IgG1 mAb that target TNFR2 by blocking interaction of TNFR2 with ligand TNF-α, confers FcγR-dependent depletion of Treg and mediates expansion of intratumoral CD8+ T cells. Upon co-administration of murine surrogate antibodies targeting TNFR2 and anti-PD-1 to immunocompetent tumor-bearing mice with partial sensitivity to checkpoint blockade, complete cures were observed in all treated mice. Thus, targeting TNFR2 by this approach offers a promising and novel treatment of cancer paradigm for patients. **Methods:** Safety and tolerability profile of BI-1808 as a single agent and in combination with pembrolizumab is currently being investigated in the Phase 1/2a clinical trial 19-BI-1808-01, enrolling patients with advanced solid malignancies or T-cell lymphomas, including CTCL. The study consists of Phase 1 dose escalation of single agent and combination with pembrolizumab. Phase 2a consists of dose expansion as single agent and as combination therapy in separate cohorts for OC, NSCLC, TCL/CTCL and Melanoma. Response is assessed according to RECIST and iRECIST. **Results:** As of Jan 12, 2024, 31 subjects received doses of up to 1000 mg BI-1808 as single-agent Q3W and 13 subjects received BI-1808 at 225 mg or 675 mg in combination with pembrolizumab 200 mg Q3W. Across the completed monotherapy arm dose escalation covering 25 to 1000 mg dose, no Gr3/4 AEs related to BI-1808 monotherapy were observed. Number of potentially related AEs of Gr1/2 have been evenly distributed across the dose range, with no target organ class of notice identified. 5 Gr1/2 IRR were observed, and in the combination arm 1 DLT (colitis) was observed in the 225 mg cohort. Best clinical response recorded in monotherapy arm was 1 iPR out of 20 evaluable patients, and 6 patients showing SD. The iPR was observed in a metastatic GIST patient with 12 prior lines of treatment. After initial pseudo-progression, a robust and ongoing response has been observed in this patient with several target lesions non-detectable and 60% SLD reduction from baseline. In addition, one previously untreated NSCLC showed reduction in several target lesions at 3 months when treatment terminated for unrelated reasons. Interestingly, both patients showed clear signs of T-cell activation in blood and tumor, strongly suggesting that T-cell responses underlie the tumor regressions. In the combination cohort with pembrolizumab 1/4 patients showed SD at 225 mg. At doses of $\geq$ 675 mg Q3W, BI-1808 $t^1/_2$ was approximately one week leading to accumulation of drug, leading to complete receptor occupancy throughout the dosing interval, a substantial increase in sTNFR2 and a significant reduction of regulatory T-cells. **Conclusions:** Preliminary data from dose escalation phase is promising. BI-1808 has a favorable safety profile, with early signs of monotherapy activity, and is well tolerated when combined with pembrolizumab. Clinical trial information: NCT04752826. Research Sponsor: BioInvent International AB.

Updated safety, efficacy, pharmacokinetics, and biomarkers from the phase 1 study of IMC-002, a novel anti-CD47 monoclonal antibody, in patients with advanced solid tumors.

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Background: Preliminary safety and efficacy data from the phase 1a dose escalation study of IMC-002 has been reported, showing no dose limiting toxicity (DLT) across 4 dose levels. Here we present updated insight into safety, efficacy, optimal dose determination through pharmacokinetics (PK) modeling, and CD47 expression. **Methods:** Eligible pts had metastatic or locally advanced solid tumors that progressed following at least 1 prior systemic therapy and an ECOG PS ≤1. A traditional 3+3 design was employed to evaluate DLT over 21 days, administering 4 doses of IMC-002 (5, 10, 20 and 30 mg/kg) every 2 weeks (Q2W). Tumor assessments were performed Q6W using RECIST 1.1. Optimal dosing was determined through target-mediated drug disposition (TMDD) PK modeling, incorporating FcRn recycling. CD47 immunohistochemistry (IHC) images were analyzed with an AI analyzer (Lunit SCOPE) that can distinguish staining positivity and cell type at the single cell level. **Results:** A total of 12 refractory patients (hepatocellular carcinoma 9, breast cancer 2, gallbladder cancer 1) were received IMC-002 with a median follow-up of 11 months (max 19 months). All treatment related adverse events (TRAEs) were grade 1-2 (92%) and TRAEs observed with over 20% incidence included skin rash, transient floaters and anemia. After the initial exposure, there was a decrease in hemoglobin levels, but these levels subsequently recovered without the evidence of hemolytic anemia. Among the 12 efficacy evaluable patients, the disease control rate was 50.0% and the clinical benefit rate (CBR, stable disease ≥ 6 months of treatment) was 33.3% with a median treatment duration of 10 months. Based on PK modeling, 20 mg/kg Q3W was selected as optimal RP2D. In the AI analysis of CD47 IHC, the density of CD47 positive macrophages tended to be higher in case with CBR compared to non-CBR cases (mean CD47+ macrophage density: 71.0 vs 44.3/mm^2), while the percentage of tumor cells expressing CD47 was similar between the two groups (mean CD47+ tumor cells: 54.5 vs 59.8%). **Conclusions:** IMC-002 has an excellent safety profile when administered intravenously at a dose of up to 30 mg/kg every 2 weeks intravenously for max 12 months treatment. IMC-002 monotherapy demonstrates meaningful clinical benefits in refractory HCC. The density of CD47+macrophages analyzed by AI is higher in CBR patients. Clinical trial information: NCT05276310. Research Sponsor: ImmuneOncia Therapeutics, Inc.

Clinical phenotype in patients with CBR (stable disease ≥ 6 months of treatment).

Subject (Sex/ Age)	Cohort (mg/kg)	Diagnosis	% Change of Target Lesion	Duration[a] (Month)	CD47 IHC (%)	CD47+ Tumor Cell Density[b]	CD47- Tumor Cell Density[b]	CD47+ Macrophage Density[b]	CD47- Macrophage Density[b]
A (M/56)	5	HCC	-17.24	6	61	5876.3	3784.0	9.2	0.4
I (M/73)	20	HCC	9.52	11	3	94.9	3339.9	17.9	8.1
J (M/48)	30	HCC	-14.63	8	84	3344.3	624.0	196.5	9.1
K (M/64)	30	HCC	-20.00	12 +	70	3841.7	1627.7	60.4	1.2

[a]IMC-002 treatment duration.
[b]Cells/mm^2.

Triple M overlap syndrome (TMOS): Evaluating immune checkpoint inhibitor-related overlap syndrome of myocarditis, myositis and myasthenia gravis using an international pharmacovigilance database.

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Background: Myocarditis (MC) secondary to ICIs is a severe immune-related adverse event (irAE) and may co-occur with myositis (MYS) and myasthenia gravis (MG), presenting as the triple M overlap syndrome (TMOS). Limited data have been reported on TMOS as a fatal irAE complication. We sought to understand the clinical complexities of TMOS and applied machine learning approaches using data from Vigibase, the WHO global database of individual case safety reports (ICSR). **Methods:** VigiBasewas used to extract data (cut off Jan 11, 2023) from ICSR for ICI-treated patients (pts) with MYS or MG either alone or co-occurring with MC. Pts were categorized into three groups: MG + MC, MYS + MC, and TMOS. Pearson Chi-squared test, Wilcoxon rank-sum/ANOVA test, and log-rank test were used to compare categorical, continuous, and time-to-event data. A machine learning model using the Weighted Subspace Random Forest (WSRF) classification was constructed to predict the occurrence of TMOS using available clinical features. **Results:** 1726 cases with ICI-induced MYS or MG were retrieved, of which 358 (20.7%) pts had co-occurring MC. Median age was 71 years (IQR: 65-77), with 66.7% males. MYS + MC, MG + MC, and TMOS were reported in 196 (54.7%), 59 (16.5%), and 103 (28.8%) pts, respectively. TMOS had a higher proportion of anti-PD-1/CTLA-4 combinations compared to MG + MC or MYS + MC (29.1% vs. 11.9% vs. 26%, $p < 0.001$). Melanoma was the most common cancer type (n = 107; 29.9%) and had a higher frequency of TMOS (39%) compared to MG + MC (29%) or MYS + MC (26%). There was no significant difference in median time-to-MC occurrence after adjustment for treatment duration between all three groups (TMOS: 24.5, MG + MC: 26, MYS + MC: 23 days, p = 0.81). Concurrent ICI-induced hepatitis had a significantly higher frequency (p = 0.035) in TMOS compared to the other two groups (20.4% vs 10.2% vs 10.2%). Fatality rates were significantly higher for TMOS compared to MC with MYS or MG (TMOS: 43.8% vs MC + MYS/MG: 29.8%, p = 0.033). WSRF modeling demonstrated an accuracy score of 0.87 (95% CI: 0.82 – 0.91, sensitivity = 0.66, specificity = 0.96) in the training set and 0.68 (95% CI: 0.57 – 0.77, sensitivity = 0.23, specificity = 0.81) in the testing set with longer treatment duration and older age having the highest association with TMOS occurrence. **Conclusions:** This is the largest dataset to date demonstrating that TMOS is associated with significantly higher mortality than MC with MYS or MG with risk factors of older age and treatment with doublet ICI, especially in pts with melanoma. These findings underscore the urgency of further research to identify the underlying biology, scale, and risk factors, as well as explore early immunosuppressive strategies in addition to steroids for improved outcomes in ICI-related TMOS. Research Sponsor: None.

Single cell sequencing reveals T follicular helper cells as the link between combination ICI therapy and the development of increased IRAEs.

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Background: Targeting multiple checkpoints via the combination of individual immune checkpoint inhibitor (ICI) therapies has increased anti-tumor effects compared to single agent ICI regimens. Despite these benefits, Dual ICI therapies have a higher risk of immune toxicity and incidence of immune related adverse events (irAEs) compared to single agent immunotherapies. Of note, T follicular helper (TFH) cells have been shown to contribute to both spontaneous and, more recently, irAE autoimmunity. Given the association of TFH cells and Tertiary Lymphoid Structures (TLS) with ICI response, a potential reason for the increased effectiveness of Dual ICI in anti-cancer therapy, TFHs may also be involved in the pathogenesis and increased incidence of irAEs seen with Dual ICI therapy. **Methods:** To understand the underlying mechanism by which Dual ICI therapy may increase the incidence of irAEs, we obtained thyroid fine needle aspirates from 9 individuals with ICI-thyroiditis, one of the most common irAEs. We performed single-cell RNA sequencing (scRNA-Seq) and compared immune infiltrates of patients receiving anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PD-L1) to Dual ICI patients who received PD-1 or PD-L1 in combination with anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4). **Results:** ScRNA-Seq analyses revealed a 3-fold expansion of TFH and T peripheral helper (TPH) cells in Dual ICI therapy compared to PD-1/L1 patients. CD4T cell trajectory analysis revealed a dominant transition among Dual ICI patients from a naïve SELL+ CCR7+ phenotype to the CXCR5+ TFH and later IL21+ IFNG+ TPH phenotypes ($p < 0.0001$). The differentiation involved an upregulation of IL21, CD40LG, BCL6, and CXCR5 genes within CD4 T cells. Differential gene analysis showed enrichment of Tertiary Lymphoid Structure (TLS) gene sets in B and TFH cell clusters indicative of TLS formation within which CD8 T, CD4 T TFH, and GC B cells interact. CD8 T cell analysis indicated a dominant expansion and differentiation towards a CXCL13+ IFNG+ FASLG+ phenotype in Dual ICI therapy compared to PD1/PDL1 monotherapy ($p < 0.0001$). Cell interaction analysis showed up-regulated TFH-mediated IL21 signaling and CD8 T cell-mediated CXCL13 signaling to BANK1 B cells in Dual ICI therapy. **Conclusions:** Dual ICI therapy led to upregulation of activation markers and preferential differentiation of CD4 T cells towards TFH cells in addition to upregulation of TLS signature genes and signaling pathways in TFH, CD8 T, and B cells. Given the previously established association between TFHs and the pathogenesis of autoimmune diseases and irAEs, their increased numbers and activity in Dual ICI therapy may explain the greater toxicities seen. Research Sponsor: U.S. National Institutes of Health; K08DK129829; Aramont Charitable Foundation; Doris Duke Charitable Foundation.

Comprehensive whole genome and transcriptome analysis of patients with advanced solid tumor treated with immune checkpoint inhibitor therapy in the pan-cancer cohorts from the Marathon of Hope Cancer Centres Network Study (MOHCCN).

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Background: Immune checkpoint inhibitors (ICI) improve survival in multiple advanced solid tumors but many patients do not benefit. We conducted a comprehensive whole genome transcriptome sequencing (WGTS) analysis to identify predictors of immune sensitivity. **Methods:** Clinical and molecular data from archival or pre-treatment FFPE tumor tissue were available for analysis from The Marathon of Hope Cancer Centres Network Study (MOHCCN). It includes patients (Pts) with advanced solid tumors and ECOG PS 0 or 1 treated with ICIs targeting PD-1, PD-L1, or CTLA-4 in the INSPIRE (NCT02644369) and OCTANE (NCT02906943) cohorts. Response (R) to ICI was defined as radiological and clinical response without PFS event at 6 months; versus non-response (NR) as radiological or clinical progression within 6 months. Responders without evidence of progression for >12 months were categorized as durable responders (DR). Nucleic acids were sequenced using Illumina NovaSeq 6000 system targeting minimum coverage of 80X and 30X for tumour and normal WGS, respectively and 80M reads for tumour RNA-seq. WGTS data were integrated with clinical data to identify associations with response to ICIs. Also, an analysis of immune cell types was conducted using multiplexed IHC and RNA-Seq deconvolution (CIBERSORT). **Results:** 59 Pts were included in this analysis: 28 (R) and 31 (NR). The most common tumor types were head and neck (n = 19) and melanoma (n = 7). Median age was 62 years (range 24-81); male 58% and median follow-up was 58 months (range 11-280). The most frequent ICI was pembrolizumab 76%, with 90% of all pts receiving ICI monotherapy and 10% combination. 75% of pts received chemotherapy prior to ICI. Higher tumor mutation burden (TMB) was observed in R vs NR (median 13 vs 5 coding mut/Mb, p=0.001), with the highest TMB in patients with DR (median 14 mut/Mb). Differential RNA gene expression analysis showed NR had increased expression of several oncogenic pathway signatures, including MYC targets, G2M checkpoint, and E2F targets. Differential abundance analysis of immune cell types did not yield any differences of immune cell populations amongst R versus NR after correction for multiple comparisons. Responders had significant enrichment in mutations in WNT/β-catenin pathway genes in both coding (APC, AMER1, LZTR1, TCF7L2) and promoter regions (CTNNB1). Notably, the 6 Pts with CTNNB1 promoter mutations had significantly increased CTNNB1 gene expression (p = 0.005). **Conclusions:** ICI responders showed enrichment in coding mutations of several negative regulators of the Wnt/β-catenin pathway and non-coding promoter mutations in CTNNB1 compared with non-responders. Further investigation is ongoing to biologically validate how these mutations in the Wnt/β-catenin pathway may lead to improved response to ICI. Research Sponsor: Marathon of Hope Cancer Centres Network, Dr. Siu's BMO Chair in Precision Genomics, University of Toronto.

Fecal microbiota transplantation combined with anti-PD-(L)1 inhibitors as first-line maintenance therapy for advanced gastric and non small cell lung cancer.

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Background: Immunotherapy(IT) combined with chemotherapy has gradually emerged as the first-line(1L) standard treatment for most advanced tumors; however, numerous studies have demonstrated that chemo-immunotherapy can lead to a reduction in intestinal microbiota diversity, subsequently resulting in compromised immunity. So we assumed whether supplement gut microbiota through fecal microbiota transplantation (FMT) and subsequent anti-PD-(L)1 inhibitor therapy as maintenance therapy could potentially prolong progression-free survival (PFS) in patients(pts) with advanced gastric and non small cell lung cancers (ChiCTR2100054928). **Methods:** This is a prospective, single-arm exploratory study. The key inclusion criteria encompassed pts with unresectable advanced gastric/gastroesophageal union carcinoma (GC) and advanced non small cell lung cancer (NSCLC), who demonstrated partial response(PR) or stable disease (SD) after 1L therapy with ECOG scores ranged from 0 to 1.There were 2 FMT healthy donors, FMT was performed via nasoenteric tubes or oral capsules after 1L therapy, followed by maintenance therapy with anti-PD-(L)1 inhibitors until unacceptable toxicity or disease progression(PD). **Results:** From Jan. 2022 to Dec. 2023, a total of 17 pts were enrolled, including 9 GC and 8 NSCLC. 82% were male, and the median age was 68 years (range, 49-80). All pts achieved either a partial response (PR, n=7) or stable disease (SD, n=10) after 1L therapy and subsequently underwent FMT prior to commencing maintenance therapy. The intestinal microbiomes used for FMT with nasoenteric tubes were from the same donor (GC [n=3], NSCLC [n=5]), while those in the capsules were from a different donor (GC [n=6], NSCLC [n=3]). We defined the time from receiving 1L therapy to FMT as PFS0; and from the FMT to PD as PFS1. The sum of PFS0 and PFS1 represents the time from the start of 1L therapy to PD as PFS. Of the 17 recipients, 12 showed SD (GC [n=6], NSCLC [n=6]) and 5 showed PD (GC [n=3], NSCLC [n=2]). In the GC group, median follow-up was 8.8 months (interquartile range [IQR] 5.1-9.7), with unreached median PFS1 and a one-year PFS rate of 78%. For NSCLC, median follow-up was 8.0 months (IQR 4.2-12.2), with unreached median PFS1 and a one-year PFS rate of 67%. No statistically significant differences were observed in pts who underwent FMT using two distinct methods. 53% of pts reported improved quality of life (QoL). 5 pts (29%) experienced grade 1-2 FMT-related toxicities, primarily gastrointestinal reactions, including diarrhea, gas, and abdominal pain, but no grade 3 or higher adverse events were identified. **Conclusions:** Administering FMT prior to 1L immune maintenance therapy in pts with advanced GC and NSCLC has the potential to prolong PFS, and demonstrate a favorable safety. However, these findings necessitate validation through larger-scale clinical trials. Clinical trial information: ChiCTR2100054928. Research Sponsor: Clinical Research Project of Changzhou Medical Center of Nanjing Medical University (CZKYCMCC202307).

Tocilizumab for advanced non-small cell lung cancer with concomitant inflammatory cachexia: A single-centre study.

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Background: Cancer cachexia significantly contributes to morbidity and mortality in patients with non-small cell lung cancer (NSCLC). Inflammatory pathways mediated by interleukin-6 play a crucial role in the development of cancer cachexia. This study aimed to investigate the use of tocilizumab, an anti-interleukin-6 receptor inhibitor, in the management of NSCLC with coexisting inflammatory cachexia. **Methods:** Data were collected from patients with NSCLC and concurrent inflammatory cachexia who received either tocilizumab plus anti-tumour therapy or anti-tumour therapy alone. The primary endpoints were overall survival (OS) and improved modified Glasgow Prognostic Score (mGPS) at week 12, while secondary endpoints included changes from baseline over 12 weeks in body weight, albumin, C-reactive protein and mGPS. Qualitative improvements in patient self-rated appetite and fatigue were reported as exploratory analysis. **Results:** The study included 49 patients diagnosed with NSCLC and coexisting inflammatory cachexia, of which 26 received tocilizumab in combination with anti-tumour therapy, and 23 received anti-tumour therapy alone. The tocilizumab group demonstrated a significantly longer median OS compared to the control group (15.1 vs. 3.2 months; hazard ratio 0.18, 95% confidence interval 0.08-0.38; $p < 0.001$). The rate of patients surviving with mGPS improvement at week 12 was significantly higher in the tocilizumab group than in the control group (OR 168.7, 95% CI 16.3-1746.5; $p < 0.001$). Over the 12-week period, significant improvements were observed in body weight, albumin, C-reactive protein, and mGPS in the tocilizumab group compared to the control group. Additionally, the tocilizumab group displayed significantly higher rates of improvement in appetite and fatigue. The incidence of grade 3 or higher adverse events was 34.6% in the tocilizumab group compared to 78.3% in the control group. Tocilizumab-related adverse events were observed in three patients (11.5%), including two cases of neutropenia and one case of skin and subcutaneous tissue infection. **Conclusions:** Tocilizumab demonstrated significant benefits in survival and various clinical parameters, including body weight, albumin, C-reactive protein, mGPS, and symptom burden in patients with NSCLC and concurrent inflammatory cachexia. Given the existing unmet medical need for effective interventions for cancer cachexia, tocilizumab may be considered as a potential treatment option. Research Sponsor: None.

The impact of COVID-19 mRNA vaccines on immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors.

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Background: Cancer patients are a vulnerable population to COVID-19. COVID-19 mRNA vaccines have shown to decrease hospitalization and death risk from COVID-19 in cancer patients. Concurrent COVID-19 vaccination and immune checkpoint inhibitors (ICIs) use may impact immune-related adverse events (irAEs) synergistically. Limited data exist on how COVID-19 mRNA vaccines affect irAEs in ICI-treated cancer patients, especially those with breakthrough infections. **Methods:** We retrospectively analyzed adult patients with malignant solid tumors receiving ICIs at a single cancer institute (January 2020 to July 2021). Fully vaccinated status is defined as two consecutive doses of mRNA vaccines (BNT162b2 and mRNA-1273). Patients who were partially vaccinated, fully vaccinated post COVID-19 infection, vaccinated with non-mRNA COVID-19 vaccines, or last visit within 30 days post vaccination were excluded. All COVID-19 infections were confirmed by PCR. In the vaccinated group, only post-vaccination irAEs were considered as events. **Results:** 443 patients were included in our study, with 251 (56.7%) vaccinated and 192 (43.3%) unvaccinated. The baseline characteristics were similar between the two groups, except for age (vaccinated median 68 years, unvaccinated median 62 years, p=0.004). With a median follow-up of 12 months, incidences of all-grade irAEs (19.1% vs. 20.3%, p=0.72) and severe irAEs (5.6% vs. 4.2%, p=0.66) were comparable between vaccinated and unvaccinated groups. 34 breakthrough COVID-19 infections occurred. In the vaccinated group, a non-significant trend of higher all-grade irAEs incidence was noted in the COVID-19 infected subgroup compared to uninfected subgroup (29.4% vs. 17.5%, p = 0.11). Univariate analysis linked COVID-19 vaccination (OR 1.54, 95% CI 1.01-2.35, p=0.04) and ipilimumab + nivolumab use (OR 5.57, 95% CI 1.79-17.35, p=0.003) to a higher risk of all-grade irAEs in the entire cohort. After multivariate adjustment, ipilimumab + nivolumab use remained the only variable associated with all-grade irAEs (OR 4.95, 95% CI 1.57-15.64, p=0.006). **Conclusions:** Our study suggests that COVID-19 mRNA vaccines do not increase irAE risk in cancer patients on ICIs. Fully vaccinated patients with breakthrough COVID-19 infections may safely continue ICI treatment without an increased irAE risk. Research Sponsor: None.

IrAE Clinical features between vaccinated and unvaccinated groups.

Variable	Vaccinated Group n= 251	Unvaccinated Group n=192	P-value
All-grade irAE, n (%)	48 (19.1)	39 (20.3)	0.72
Severe (grade 3 and above) irAE, n (%)	14 (5.6)	8 (4.2)	0.66
Corticosteroid use, n (%)	26 (10.4)	22 (11.5)	0.76
Additional immunosuppressant use, n (%)	3 (1.2)	1 (0.5)	0.63
Treatment interruption due to irAE, n (%)	30 (11.9)	28 (11.2)	0.48
Time to irAE, median (range)			
Treatment cycle	6 (1-52)	7 (1-72)	0.60
Days	161 (8-1505)	117 (7-1662)	0.68
Death-related to irAE, n (%)	1 (0.4)	0 (0.0)	1.00

Development of a novel risk stratification model for immune-related adverse events for patients with advanced melanoma and non-small cell lung cancer treated with immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICI) transformed treatment paradigm across cancers. There remain few reliable, clinically accessible predictors of ICI-induced immune related adverse events (irAEs). We derive a novel risk stratification model for irAEs using baseline patient, tumor and treatment variables in a large cohort of patients with advanced melanoma (AM) or non-small cell lung cancer (NSCLC) treated with ICI. **Methods:** We conducted a multi-centre retrospective observational cohort study of consecutive patients with AM or NSCLC receiving ≥ 1 cycle of single-agent or combination ICI, in any line, 2015 - 2023, in Alberta, Canada. Clinically significant irAEs, defined as those requiring treatment delay or systemic steroids/steroid sparing agents, were identified as outcome of interest. The association between irAEs, overall survival (OS), and time to next treatment (TTNT) was assessed with Cox Proportional Hazards regression. Stepwise logistic regression was used to select and weight baseline variables associated with development of irAEs to derive a predictive risk score. Model validation was carried out on 500 iterations of bootstrapped samples. Harrel's C-index was calculated and internally validated to ascertain the model's discriminatory performance. **Results:** 1,292 total patients were included, 519 (218/489 [44.6%] AM and 301/803 [37.5%] NSCLC) developing a clinically significant irAE. Using a subset of 801 patients with available baseline characteristics, the following variables were identified and weighted for creation of risk model (risk score attributed): tumor type (NSCLC) (+1), age >60 (+1), ECOG ≥1 (-1), BMI ≥ 25 (+1), ICI after first line (-1), combination ICI (+4), >10 cycles of ICI (+2), albumin level < LLN (+2), adrenal metastasis (+1), multiple sites of metastasis (-1). Patients were stratified into 3 irAE risk groups based on combined score: low (n = 230, risk score ≤ 0), intermediate (n = 412, risk score 1-2), high (n = 159, risk score ≥3). The risk model performed well with an optimism-corrected c-index of 0.707 in internal validation, and strong association with odds of irAE occurrence (Table). The development of irAE was associated with an improvement in OS (HR 0.48, 95% CI 0.41-0.44, p<0.001), with a median OS of 34.3 (95% CI 28.8-39.6) months compared to 12.0 (95% CI 10.6-14.3) months for those who did not develop an irAE. Similar robust stratification was also seen with TTNT. **Conclusions:** We presented and internally validated, a simple risk stratification tool that utilizes readily available baseline patient, tumor, and treatment characteristics to robustly stratify risk of irAE development. Research Sponsor: None.

irAE Risk Group	Cumulative irAE Events (%)	OR (95% CI)
Low	43/230 (18.7%)	Ref
Intermediate	233/412 (56.6%)	1.28 (1.19-1.38), p<0.001
High	120/159 (75.5%)	1.76 (1.61-1.93), p<0.001

A phase 1 study of REGN6569, a GITR mAb, in combination with cemiplimab in patients (pts) with advanced solid tumor malignancies: Initial dose-escalation results.

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Background: REGN6569 is a fully human immunoglobulin G1 monoclonal antibody (mAb) that is highly specific for glucocorticoid-induced tumor necrosis factor receptor–related protein (GITR). GITR is expressed on several immune cell subtypes, notably regulatory T cells (Tregs), and activated natural killer (NK) cells. REGN6569 demonstrated greater in vitro antibody-dependent cell-mediated cytotoxicity against GITR-expressing Tregs, as compared to GITR-expressing CD8+ T cells. Mouse studies showed that REGN6569 + cemiplimab (anti-PD-1) combination treatment achieved longer-term tumor responses compared with either drug alone. **Methods:** This is a first-in-human study (NCT04465487) evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of REGN6569 administered intravenously (IV) every 3 weeks (Q3W) + cemiplimab 350 mg IV Q3W, in pts with advanced solid tumors for which immune checkpoint inhibitor therapies have not been approved or are not available. The study includes a dose-escalation part with 5 dose levels (DL1-DL5) for REGN6569 ("4+3" design), with an initial dose of REGN6569 monotherapy given as a safety lead-in followed by REGN6569 + cemiplimab in subsequent doses. **Results:** As of the data cutoff date Oct 20, 2023, the dose-escalation part has been completed. 29 pts (median age 58.0 years, 62.1% male) were treated with REGN6569 + cemiplimab, up to the 1200 mg dose level (DL5), across many solid tumor types. The most common tumor type was colorectal cancer (34.5%). One pt (40 mg DL2) experienced a dose-limiting toxicity (Grade 3 hepatic failure); maximum tolerated dose was not reached. Twelve pts (41.4%) had a Grade ≥3 treatment-emergent adverse event (TEAE) and 16 pts (55.2%) had a treatment-related TEAE (any grade). The most frequent TEAEs (any grade) were arthralgia (24.1%), infusion-related reactions, and abdominal pain (20.7% each). There were no treatment-related deaths; 19 (65.5%) pts had disease progression leading to death. Two pts achieved ongoing partial responses by investigator assessment with REGN6569 + cemiplimab treatment: 1 pt with mucoepidermoid tumor of the parotid gland treated with 120 mg (DL3) REGN6569 and 1 pt with B3 thymoma treated with 400 mg (DL4) REGN6569, with duration of responses, 5.6 and 10.4 months, respectively. Full receptor occupancy on circulating Tregs was observed in all dose cohorts following REGN6569 treatment. Increased frequency (~10–50%) of proliferating NK cells in peripheral blood was observed post REGN6569 treatment across all dose cohorts. **Conclusions:** In this dose-escalation study, REGN6569 was administered up to 1200 mg (DL5) in combination with cemiplimab with one dose-limiting toxicity. The study has progressed to dose-expansion cohorts in anti–PD-1-resistant head and neck cancer, with pts treated with REGN6569 (DL5) + cemiplimab. Clinical trial information: NCT04465487. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Can immune therapy prevent pre-clinical cancer from progression? The impact of immune therapy on secondary cancer incidence.

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Background: 40% of people will develop cancer (Ca) in their lifetime, and 18% of those will develop secondary (2ry) Ca. Currently, there are no known therapeutic interventions to prevent Ca. Immune therapy (IT) revolutionized Ca care and increased survival in many Ca types. Because IT increases immune surveillance, it might halt pre-clinical Ca from progression into clinical disease. We hypothesize that IT acts to prevent or delay the development of 2ry Ca in those treated with IT for primary (1ry) Ca. **Methods:** We conducted a retrospective cohort study on Ca patients (pts) $\geq$ 18 years & treated between 2010-2022 at Cleveland Clinic, Ohio. We included Ca diagnoses where IT was utilized in first line therapy, per 2022 NCCN guidelines. We excluded pts who were not treated or whose 1ry therapy was not determined. 2ry Ca was defined with strict criteria and excluded recurrent 1ry Ca. We collected the following data: 1ry Ca and stage, 2ry Ca type and incidence, type of first & subsequent line therapy, comorbidities, smoking & alcohol use. Molecular data and PD-1/PDL-1 are currently being collected. The comparison groups were pts who received IT +/- Chemotherapy (CTX) +/- radiation (RT) (IT-G) vs. pts who received CTX or targeted therapy +/- RT (Non-IT). IT included anti-(PD-1, PD-L1, LAG-3, CTLA4: 99.9% of cases) or others (IL-2, IL-12, IL-15, Inf α: 0.1%). Outcome was 2ry Ca-free survival. Multivariable regression was used to account for confounding. **Results:** The initial sample size was 19,253 pts, and 6,376 met the criteria. There was 10.2% bladder stage II-IV, 2.5% endometrial stage IV, 21.7% esophagus/gastric stage II-IV, 13% head/neck stage IV, 4.9% clear cell renal stage III/IV, 0.7% BRAF mutated melanoma stage IV, 28.2% lung adenoCa stage IIIb/IV, 9.1% squamous cell lung Ca stage IIIb/IV, and 10% small cell lung Ca stage IIIb/ IV. Baseline characteristics of comparison groups are presented in table below. 1,173 (18%) received first line and 1,023 (16%) received subsequent line IT. With a median follow up of 12.2 months for whole population, 319 2ry Ca were diagnosed. The two-year 2ry Ca free survival was 98% (CI: 97-99) in pts who received first line IT, compared to 93% (93-94) in pts who did not get first line IT. On multivariable regression, pts who received IT at any time compared to pts who received non-IT had a 77% decrease in 2ry Ca incidence (Hazard ratio: 0.33, 95CI 0.22-0.50, P$<$0.001). **Conclusions:** Our study concludes that incidence of 2ry Ca in pts treated with IT was lower than pts who received non-IT. In this proof-of-concept study, we showed that IT may increase immune surveillance to prevent Ca in its pre-clinical stage. Future interventional studies are needed to explore if IT can be utilized in 1ry & 2ry prevention in high risk, Ca-free populations. Research Sponsor: None.

	Non-IT N=5208	IT-G N=1171
Median Age, years	64	67
Sex, female	1790	490
Race, White	4528	1006
Smoking, current/former	3987	891
Alcohol, current/former	3095	782

A phase I open-label study of a novel IL-2Rβ/γ cytokine agonist, LTC004, in patients with advanced or metastatic solid tumors.

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Background: LTC004, a novel IL-2Rβ/γ cytokine agonist, designed to minimize toxicity with improved potency. It has selective affinity for the receptor IL-2Rβγ subunits, preferentially stimulates $CD8^+$ effector T cells and natural killer cells which are associated with tumor killing, while minimizing the activation of immunosuppressive regulatory T cells. LTC004 has shown significant in vitro and in vivo anti-tumor activity in multiple cell lines and murine models respectively. **Methods:** This is a first-in-human, multicenter, open-label, dose-escalation and dose-expansion phase I study of LTC004 in advanced solid tumors. Dose escalation part assessed safety and tolerability of intravenous LTC004 with doses ranging from 3.0 to 360 μg/kg. The dose escalation schedule utilized an accelerated titration and Bayesian Optimal Interval (BOIN) design. Eligible pts with advanced solid tumor were required to have received prior standard therapy. LTC004 is administrated intravenously once every 3 weeks. **Results:** The study completed dose-escalation part (3.0 to 360 μg/kg) as of cutoff date (Jan 10, 2024). 17 pts of multiple tumor types (including non-small cell lung, cervical, colorectal, sarcoma, melanoma, parotid adenocarcinoma, thymic adenocarcinoma, gastric and ovarian cancers) were enrolled and received ≥1 dose of LTC004. At baseline, 12 pts (70.6%) had received ≥2 prior lines therapy, 11 pts (64.7%) had received prior targeted therapy, 10 pts (58.8%) had received prior immune checkpoint inhibitor (ICI) therapy. LTC004 generally well tolerated and no dose-limiting toxicities (DLTs) up to and including 360 μg/kg was observed. The most common TEAEs overall in ≥30% of pts were fever, white blood cell decreased, anemia, AST/ALT increased, neutrophil count decreased, GGT increased, nausea and hypotension. Most of the reported AEs were G1 and G2, all drug related events reversible and responsive to supportive care therapy. Fever can be resolved with standard anti-pyretic treatment or steroids, transient hypotension can be preventable with prophylactic fluid infusion. Of 17 pts enrolled evaluable for efficacy per RECIST v1.1, the ORR were 5.9% (1/17), DCR were 58.8% (10/17). A confirmed PR was achieved in a pMMR/MSS CRC patient with prior therapies including fluoropyrimidines, irinotecan, oxaliplatin, targeted therapy and TKI. The starting dose was 45μg/kg, titration to 90μg/kg after 4 consecutive doses at 45μg/kg Q3W. As of cutoff date, the patient sustained PR for 4.8 months with follow-up ongoing. **Conclusions:** LTC004 demonstrated encouraging anti-tumor efficacy including cold tumor, and well tolerated in patients with advanced or metastatic solid tumors. The further dose expansion in selected tumor types is ongoing, and evaluations in combination with other agents are being planned. Clinical trial information: NCT05666635. Research Sponsor: Leto Laboratories.

Safety and efficacy of immune checkpoint inhibitors (ICI) in patients (pts) with pre-existing neurologic autoimmune diseases (NAID) and Parkinson's disease.

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Background: Patients with pre-existing NAID often flare with ICIs; neurological (neuro) immune related adverse events (irAEs) are often morbid or fatal, and little is known about safety of ICI in pts with NAID and other neuro conditions (e.g. Parkinson's). Thus, we aimed to determine their safety and efficacy in these contexts. **Methods:** We retrospectively analyzed 71 pts from 5 institutions receiving ICIs with NAIDs and Parkinson's disease. NAIDs included multiple sclerosis (MS), myasthenia gravis (MG), inflammatory neuropathy, transverse myelitis, Lambert-Eaton, myotonic dystrophy, and multifocal motor neuropathy. We collected demographics, cancer outcomes, NAID characteristics, and safety outcomes. We used descriptive statistics to analyze treatment outcomes, NAID flares, and irAEs. **Results:** We collected 71 pts, 40 with NAID and 31 with Parkinson's. 24 had melanoma, 12 non-small cell lung cancer (NSCLC), 3 small cell lung cancer (SCLC), 6 urothelial/bladder, 4 renal cell carcinoma, and 22 other; 60 had metastatic and 11 had localized disease. Median age at ICI start was 72 years (61% male, 39% female); 8 received combination ICI and 63 received monotherapy. Of 40 pts with NAID, 30% had either NAID flares or neurologic irAEs and 33% experienced other (non-neuro) irAEs (Table). Toxicities were particularly severe in MG; 70% (n=7) had MG flare/neuro irAE, 3 of which were fatal. In addition, 31 had Parkinson's; of these, 12.9% (n=4) had Parkinson's flares, 3% (n=1) had neuro-irAEs, and 42% (n=13) had other irAEs. One pt died of grade 5 myocarditis/myositis following combination ICI (Table). 5 MS patients responded to therapy (23%), but none were those with NAID flare/neuro irAE. Both MG patients who had non-neuro irAEs responded to treatment. **Conclusions:** In this cohort of ICI treated pts with prior neuro disorders, we demonstrated that MG pts have high rates of MG flare/neuro irAEs, hospitalizations, and fatalities, but low response rates. In contrast, other NAID (particularly MS) as well as Parkinson's appeared to have modest risks of flares/neuro irAEs. Notably, Parkinson's pts had high rates of non-neuro irAEs and response rates. Research Sponsor: None.

Disease	Number	NAID Flare/neuro irAE n (%)*	Hospitalized n (% of Those Experiencing Flare)	Required Steroids n (% of Those Experiencing Flare)	Tumor Response (%)	Non-neuro irAE (%)
MS	22	6 (27)	2 (33)	3 (50)	5 (23)	6 (23)
MG	10	7 (70)	5 (71)	5 (71)	2 (20)	3 (30)
Inflammatory Neuropathy	4	0	0	0	3 (75)	3 (75)
Other	4	0	0	0	3 (75)	3 (75)
Parkinson's	31	4 (13)	1 (25)	0	13 (42)	13 (42)

*Fatal events occurred in pts with MG (n=3) and Parkinson's (n=1).

Patient experience with immuno-oncology-induced cytokine release syndrome: Developing a conceptual model of symptoms and their impacts on patients' lives.

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Background: Immuno-oncology (IO) therapy can cause cytokine release syndrome (CRS) events, which are a constellation of co-occurring signs and symptoms that usually present within 24–48 hours after treatment. There is no clinical consensus on the specific sign and symptom profile for IO-induced CRS. The objectives of this study were to better understand the experiences of patients with IO-induced CRS and to use data analysis, clinician insights, and patient interviews to develop a conceptual model to capture CRS symptoms and impacts on patients' lives. **Methods:** A targeted literature review was conducted to identify CRS signs and symptoms across IO therapies. Clinician interviews (n=4) further defined clinical signs and symptoms and explored the impacts of CRS events on patients' lives. An advisory boardof five academic oncologists then commented on this list of clinical signs, symptoms, and impacts. Finally, qualitative concept-elicitation interviews were conducted with US patients (ongoing at abstract submission; expected N=20 by March 2024)to confirm and describe symptom severity and impacts. The final intended patient interview sample will specifically examine symptoms and impacts across subgroups with different CRS severity levels. **Results:** A total of 35 signs and symptoms were initially identified from the literature review. These were assessed, confirmed, and sorted via clinician interviews, resulting in a refined list of 16 clinical signs and 28 symptoms relevant to IO-induced CRS. Based on inputs from the subsequent clinical advisory board, clinical signs indicative of CRS (such as, hypotension, fever and hypoxia) were confirmed, and a list of symptoms (such as chills, fatigue, nausea and diarrhea) recommended for inclusion in a new instrument suited to capture patient-reported experiences was generated. CRS impacts were also broadly described, emphasizing activities and behaviors affected by reduced energy and motivation levels, symptom-related distress, and the emotional burden of the experience. Ongoing patient interviews will confirm the importance of these identified CRS symptoms and provide more specific descriptions of the impacts of IO-induced CRS events on peoples' lives. **Conclusions:** Key symptoms affecting patients' daily activities included, but were not limited to, chills, fatigue, nausea, and diarrhea. These were used to develop a CRS-specific, patient-centered conceptual model that will be refined upon completion of ongoing patient interviews (full results to be presented at ASCO 2024). This research will serve as a framework to build a patient-reported outcome instrument that accurately captures patients' experiences with CRS and is sensitive to various CRS severity levels. The proposed instrument may aid in evaluating outcomes in clinical trials and support benefit-risk and tolerability assessments. Research Sponsor: This study was funded by Sanofi.

Correlations between first cycle toxicity and overall survival in patients with rare cancers treated with immune checkpoint inhibitors (NCI/SWOG S1609).

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Background: Associations between immune-related adverse events (irAEs) from checkpoint inhibitor therapy and outcomes have been previously evaluated, with most prior research finding a positive association between toxicity incidence and overall survival. This prior research has generally reported on more common tumor types. We use a unique data resource of a federally funded basket trial (NCT02834013) for patients with rare cancers to evaluate associations between irAEs and overall survival (OS) and progression-free survival (PFS) in a cohort of patients treated with combination checkpoint inhibitor therapy. **Methods:** We evaluated irAEs observed in the first cycle (6 weeks) of therapy that were possibly, probably, or definitely related to treatment; irAE grade was based on CTCAEv5. Patients received ipilimumab [1mg/kg intravenously (IV) every 6 weeks] plus nivolumab (240mg IV every 2 weeks). Landmarks methods were used to avoid immortal-time bias; PFS and OS were analyzed from day 43 with patients who died or progressed before that date excluded from analyses. Cox regression analyses were used to evaluate covariate associations. **Results:** We found that grade 1-2 treatment-related irAEs in the first cycle of therapy were associated with longer OS (multivariable hazard ratio, 95% confidence interval, p-value: 0.61, 0.49-0.75, $p<0.001$) compared to no treatment-related irAE in the first cycle, while grade 3-4 irAEs were associated with shorter OS (HR=1.41, 95% CI=1.04-1.90, p=0.025). Similar, but weaker, associations were observed with PFS, grade 1-2 treatment-related irAEs: HR=0.83, 95% CI=0.67-1.01, p=0.067 and grade 3-4: HR=1.35, 95% CI=1.02-1.78, p=0.037 compared to no treatment-related irAE in the first cycle. Grade 1-2 dermatologic toxicity were associated with improved OS compared to other grade 1-2 toxicities (HR=0.67, 95% CI=0.52-0.85, p=0.002). There were no significant differences between OS among patients with Grade 1-2 gastrointestinal, metabolic, hepatic, endocrine, and thyroid toxicities and fatigue and other Grade 1-2 toxicities. **Conclusions:** In this large cohort of patients with rare tumors receiving ipilimumab and nivolumab grade of irAE in the first cycle of therapy was prognostic for survival. Research Sponsor: National Cancer Institute; CA180888 and CA180819; Bristol-Myers Squibb Company.

Comprehensive analysis of TMB, TNB, and HLA via NGS sequencing in a large cohort of Chinese pan-cancer patients.

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Background: Evidence suggests that patients with high tumor mutational burden (TMB) and tumor neoantigen burden (TNB) are more likely to benefit from Immune checkpoint inhibitors (ICIs). Furthermore, loss of heterozygosity (LOH) in human leukocyte antigen (HLA) alleles, particularly HLA class I, impairs neoantigen presentation and contributes to resistance against ICIs. This study provides real-world insights into the distribution of TMB, TNB, and HLA variations within a large cohort of Chinese patients with various cancers. **Methods:** From 2021 to 2023, we performed a retrospective analysis on 1603 cancer patients, examining genetic mutations and HLA traits using the Med1 CDx DNA-based NGS panel targeting 601 cancer-related genes and HLA class I. TMB was calculated as the average number of coding mutations per megabase of the genome. HLA class I alleles (HLA-A, B and C) were identified and predicted using the OptiType and pVACtools software suites. TNB was defined as the number of high-affinity (IC50 $\leq$ 50 nM) neoantigens per megabase of the genome. Statistical analyses were performed to explore the relationship between TMB, TNB, and LOH status in critical regions of HLA. **Results:** This study enrolled participants across 25 cancer types. With 32.56% having non-small cell lung cancer (NSCLC), 11.79% colorectal carcinoma (CRC), and 18.34% unidentified solid tumors. The remaining 37.31% comprised cases of cholangiocarcinoma, hepatocellular carcinoma, pancreatic cancer, etc. High-affinity neoantigen-generating genes such as TP53, EGFR, KRAS, LRP1B, DMD, and FAT1 were identified. Our findings indicate substantial variation in tumor neoantigen burden (TNB) across various cancer types and even among different samples within the same type. Neuroendocrine tumors exhibited the highest TNB at 4 neoantigens/Mb, followed by esophageal cancer (3.3), melanoma and urothelial carcinoma (2.67 each), indicating higher TNB levels in these cancers compared to others. A significant positive correlation was observed between TMB and TNB ($p< 0.0001$). Analysis revealed no significant TNB differences attributable to age (cutoff at 60 years) or gender. However, individuals aged over 70 years demonstrated a higher TNB of 4 compared to those under 70 with 3.33, highlighting potential age-related differences in TNB. **Conclusions:** Our analysis highlights significant variation in TNB across cancer types, with the highest TNB found in neuroendocrine tumors and the lowest in gastrointestinal stromal tumors, indicating TNB's value as a biomarker for optimizing ICI therapy. Furthermore, we found that people over 70 years old have higher TNB levels than younger individuals, suggesting a potential for improved ICI efficacy without chemotherapy. The evident strong correlation between Tumor Mutational Burden (TMB) and TNB underlines their crucial role in the success of cancer immunotherapy.
Research Sponsor: None.

The impact of proton-pump inhibitor use on the incidence and severity of gastrointestinal toxicity to checkpoint inhibition.

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Background: Checkpoint inhibitors (ICIs) for cancer come with the risk of immune-related adverse events (irAE). Upper and lower gastrointestinal (UGI and LGI, respectively) tract inflammation are common toxicities. Proton pump inhibitors (PPIs) are frequently used to treat immune-mediated UGI irAEs. Studies have suggested that these agents may worsen LGI irAEs. Our study aims to observe the effect of PPI use on the incidence and severity of GI irAEs. **Methods:** This was a single-center retrospective chart review including all patients who received ICIs. Patients were categorized based on PPI usage and screened for upper or lower GI toxicities. PPI use was counted if the medication was received at least three months before starting ICI and one year after the last ICI dose. **Results:** 16,849 patients were included. 2,114 (12.5%) patients received PPIs (PPI group – PG), while 14,735 (87.5%) did not (non-PPI group - NPG). 46 (2.2%) PG patients developed UGI irAE compared to 43 (0.3%) in the NPG ($p<0.001$), with no difference in severity or need for immunosuppression ($p>0.05$). PG patients were more likely to be hospitalized however ($p=0.021$). 115 (5.4%) PG patients developed an LGI irAE compared to 173 (1.2%) in the nPG ($p<0.001$). 80.7% of the PG presented with ≥grade 2 diarrhea and 52.0% with ≥grade 2 colitis, compared to 69.1% and 38.5% of the NPG, respectively ($p<0.05$). PG patients more frequently needed steroid treatment (60.0% vs. 42.2% in the NPG, $p=0.004$) and SIT (41.7% vs. 24.9%, $p=0.003$), and were less likely to have symptom resolution (78.5% in the PG vs. 89.6% in the NPG, $p=0.020$). A dose-dependent effect was observed. Every 10mg increase in PPI dose led to more frequent hospitalization for UGI irAEs (OR: 1.6, $p=0.049$) and more reliance on steroids (OR:1.3, $p=0.044$) and SIT (OR: 1.3, $p=0.037$) for LGI irAEs. This was also associated with less hospitalization and recurrence rates for LGI irAEs ($p<0.05$). **Conclusions:** Our study shows that PPI use during immunotherapy may increase the risk of developing a GI irAE. PPI use does not seem to impact the severity of upper GI irAEs aside from a higher hospitalization rate. However, PPI use may lead to a more severe disease course for lower GI toxicities. Prospective studies are needed to validate these results. Research Sponsor: None.

Characteristics of GI toxicity among patients with and without PPI exposure.

Characteristic	No. (%) Non-PPI Group N=14,735	PPI Group N=2,114	p-value
Presence of upper GI toxicity	43(0.3%)	46(2.2%)	<0.001
Peak CTCAE grade			0.178
1	18(56.3%)	16(38.1%)	
2	12(37.5%)	18(42.9%)	
3	2(6.3%)	8(19.0%)	
Presence of lower GI toxicity	173(1.2%)	115(5.4%)	<0.001
Peak diarrhea CTCAE grade 2 and above	103(69.1%)	88(80.7%)	0.044
Peak colitis CTCAE grade 2 and above	52(38.5%)	52(52.0%)	0.047
Treatment			
Corticosteroids	73(42.2%)	69(60.0%)	0.004
SIT	42(24.9%)	48(41.7%)	0.003
Outcomes			
Resolution of GI irAE	120(89.6%)	84(78.5%)	0.020
ICI resumed	59(51.3%)	34(34.3%)	0.013

Intravenous delivery of oncolytic adenovirus TILT-123 results in systemic tumor transduction and accumulation of lymphocytes.

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Background: Immune checkpoint inhibitors provide limited benefit in patients with immunologically cold tumors, characterized by a lack of T cells. This creates a niche for T cell-inducing agents such as TILT-123 (igrelimogene litadenorepvec, Ad5/3-E2F-D24-hTNFa-IRES-hIL2). While the 5/3 chimeric oncolytic adenovirus platform prompts potent immunogenic capacity *per se*, this virus has been armed with TNFa and IL-2 selected based on their ability to activate and attract T cells into tumors. TILT-123 capsid modification, and double selectivity devices for virus replication in cancer cells only, allow intravenous use of TILT-123. This is an important advantage over conventional oncolytic viruses whose widespread use has been hindered by the need for intratumoral injection. **Methods:** Here we report tumor transduction, pharmacokinetic and immune effects of a single intravenous administration of TILT-123 from three Phase 1 dose escalation clinical trials (TUNIMO-NCT04695327, TUNINTIL-NCT04217473, and PROTA-NCT05271318), with a total of 52 patients. Overall, the most common tumor types were melanoma (20), ovarian cancer (18) and sarcoma (7). In each of these trials, the first TILT-123 injection was performed intravenously, and a tumor biopsy collected 7 days later. Peripheral blood was collected before and after systemic TILT-123 treatment. No other therapy was administered concurrently. Presence of virus in blood was detected with qPCR, while presence of virus in tumor biopsies was measured with immunohistochemistry (IHC) for adenovirus proteins. Immune changes in tumors were evaluated by IHC. **Results:** TILT-123 was detected in the peripheral blood of all treated patients. Virus concentration was highest at 1 hour after administration, with lower levels seen 16 hours post-injection. Concurrently, IFN-γ levels increased in the patients´ serum. The lowest TILT-123 blood concentrations were observed with the lowest dose, with progressive increases in subsequent cohorts. At higher doses, TILT-123 was detected circulating in blood one week post-administration. Treatment was safe and no dose-limiting toxicity was encountered. Overall, signs of TILT-123 transduction in tumors were observed in 75% of patients evaluated in all three trials, 80% in TUNIMO patients, and 63.64% in TUNINTIL patients. Early results from PROTA suggest a positive effect of TILT-123 in tumors from all cohorts´ dosages studied. **Conclusions:** In summary, intravenous injection of TILT-123 results in persistence of the virus in peripheral blood for up to 7 days. Tumor transduction was observed in 75% of patients in three Phase I trials on day 8 post TILT-123 systemic administration. These data suggest that TILT-123 could be developed as an intravenous therapy. However, further increases in tumor transduction could be achieved by using multiple intravenous injections of TILT-123. Clinical trial information: NCT04695327; NCT04217473; NCT05271318. Research Sponsor: TILT Biotherapeutics Ltd.

A multi-centre, single arm, phase 2 trial of pembrolizumab in treatment-naïve patients with carcinoma of unknown primary site.

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Background: Cancer of unknown primary (CUP) represents a heterogeneous group of cancers that present with metastatic epithelial disease with no identifiable primary lesion at the time of diagnosis. Patients with poor prognostic features have limited effective systemic therapy options. Researchers hypothesize that these primary lesions are occult, in part, due to anti-cancer immune surveillance. We hypothesize, pembrolizumab will have activity in this setting. **Methods:** This single arm phase 2 study evaluated the use of pembrolizumab in treatment naïve patients with poor prognosis CUP. Patients ≥18 years of age with ECOG PS 0-1 and histologically proven, measurable metastatic carcinoma with no primary site identified were eligible. Pembrolizumab was administered at 200 mg intravenously every 3-weeks for up to 24 months. The primary endpoint was safety and objective response rate (ORR) per RECIST 1.1. Secondary objectives included progression free survival (PFS) and overall survival (OS). The study used a Simon's two stage design based on a one-sided test with a type 1 error rate of 0.1, null hypothesis for ORR ≤ 20% yielding a power of 0.8 with an alternate hypothesis of ≥40%. The null hypothesis will be rejected if 8 or more responses are observed in 25 patients. Mismatch repair (MMR) and microsatellite instability (MSI) testing was not mandatory for patients. **Results:** There were 27 evaluable and 6 unevaluable (no response assessment, included in adverse event analysis) patients. The median age was 64 (range 21-80) and the majority were male (57.6%) and ECOG 1 (84.8%). Four patients experienced grade 3 treatment related adverse events (pain, anorexia, fatigue, confusion, and anemia). There were no treatment related deaths or new signals of toxicity. Of the evaluable patients, the ORR was 18.5% (4 partial responses and 1 complete response), disease control rate was 51.9% (9 stable disease) and thus the null hypothesis could not be rejected. For evaluable patients, the median PFS and OS were 2.56 (95% CI 2.10 – 7.46) and 9.79 (95% CI 3.84 – 16.03) months respectively. The one patient who developed a CR had MMR deficiency and has completed 2 years of therapy. Of the 4 patients with a partial response, one had an MMR proficient tumour, while the remaining 3 had unknown MMR status. **Conclusions:** Although not meeting the primary endpoint, pembrolizumab has some activity in CUP patients. Patients with CUP should be screened for MMR or MSI. Future studies should evaluate combination therapies with the addition of pembrolizumab. Clinical trial information: NCT03391973. Research Sponsor: MERCK.

First-line treatment of fecal microbiota transplantation for immune-mediated colitis.

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Background: The management of moderate to severe IMC includes immunosuppression with steroids and/or biologic agents. Long-term immunosuppression increases the risk for infections and steroid induced toxicities. Fecal microbiota transplantation (FMT) is increasingly used for the treatment of refractory IMC. Front-line FMT treatment has not been studied for IMC but could potentially alleviate IMC symptoms while reducing unnecessary extended exposure to steroids. In this study, we present a case series of 12 patients who received front-line FMT for the treatment of IMC as part of a clinical trial. **Methods:** This study reports preliminary data from a prospective clinical trial (NCT0403861) exploring the efficacy and safety of FMT as a first-line treatment for IMC. To be included, patients had to 1) have symptoms of immune-mediated diarrhea or colitis grade $\geq$ 2 (per Common Terminology Criteria for Adverse Events v5) within 45 days of FMT and 2) not have received any immunosuppressive treatment for IMC or any other indication around the time of FMT. **Results:** Twelve patients have been enrolled in the trial thus far. Patients received front-line FMT in a median of 31 days (IQR: 16-67 days) from IMC onset. 10 (83.3%) patients had symptom improvement in a median of 5 days (IQR: 1-7 days) after FMT. The only FMT-related adverse events reported were fatigue, transient fever, self-resolving abdominal cramping, and gassiness in six patients (50.0%) within the first week of FMT. One of the six patients additionally had recurrence of a previously existing frequent UTI due to bladder cancer within a week of FMT. Most patients (10, 83.3%) stopped immunotherapy due to IMC. Seven patients (63.6%) were able to resume cancer treatment after FMT, with four (33.3%) resuming checkpoint inhibitors. None of the patients that resumed ICI had recurrence of their colitis requiring immunosuppression. Nine patients (75%) had colitis remission by the end of the study period, with one additional patient showing signs of symptom improvement but passing away before his outcome could be assessed. Only two patients (16.7%) required immunosuppression for persistent colitis after FMT failure. **Conclusions:** This study is the first to evaluate the safety and efficacy of front-line FMT for the treatment of IMC. Our preliminary results are promising and show that FMT can be an effective first-line treatment for IMC that can quickly provide symptom relief in a majority of patients while avoiding the use of steroids. Our results also suggest that front-line FMT can be delivered in a timely manner and can allow for the safe resumption of immunotherapy in this population that typically responds well to immunotherapy. While more patients are needed before any solid conclusions may be drawn, there is mounting evidence to suggest that first-line FMT may be a safe and effective alternative to the current standard of care treatment for IMC. Clinical trial information: NCT04038619. Research Sponsor: Adopt a scientist, MD Anderson IOTOX research award, MD Anderson faculty fund; n/a.

Randomized clinical trial of infliximab versus vedolizumab for immune checkpoint inhibitor related colitis.

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Background: Immune-mediated diarrhea and colitis (IMDC) is an inflammatory consequence of immunotherapy that frequently necessitates discontinuation of immunotherapy. Current management strategies are adopted from inflammatory bowel disease practice and rely on selective immunosuppressive therapy (SIT) with infliximab or vedolizumab as first-line in more severe cases. While this practice is widely accepted, evidence supporting SIT use is limited to retrospective studies. Here we present the preliminary findings of 22 patients from the first clinical trial comparing the efficacy and safety of infliximab and vedolizumab in treating IMDC. **Methods:** We conducted a randomized controlled trial of infliximab and vedolizumab in the treatment of IMDC. To be included, patients must have received immunotherapy and developed immune-mediated diarrhea or colitis at CTCAE grade $\geq$2. Infusions were given around weeks 0, 2, and 6, and disease activity and incidence of adverse events were recorded over 12 weeks of follow-up. Remission was defined as symptom improvement to CTCAE grade $\leq$1 by week 2. Fecal transplantation or ustekinumab would be considered for patients who are refractory to two SIT doses. **Results:** 22 patients have been enrolled thus far, three of whom were removed from the study and one who withdrew consent at 2 months. Ten patients were randomized to the infliximab arm and nine to the vedolizumab arm. At two weeks, clinical remission rates are similarly high across infliximab (90%) and vedolizumab (88.9%) groups, with the one patient in the vedolizumab group having symptom improvement but failing to meet criteria for clinical remission and one in the infliximab group with treatment failure. Symptom improvement was typically seen in a median of 3 days (IQR: 1.5-5.5) across both groups. Eight patients (80%) in the infliximab group and seven patients (77.8%) in the vedolizumab group had steroid-free remission at one month. Four patients (40%) from the infliximab group and three (33.3%) from the vedolizumab group had symptom recurrence in a median of 43 days across both groups (IQR: 39-93). Three patients from either group were able to resume immunotherapy. In terms of safety, both groups had a similar rate of mild adverse events (AEs), most of which were deemed unrelated to SIT use. **Conclusions:** This is the first randomized controlled trial to evaluate the safety and efficacy of infliximab and vedolizumab in the management of IMDC. Our results suggest that both agents are equally effective at controlling symptoms within two weeks of the first infusion, with a small number of patients receiving either having recurrent disease. The two drugs have a comparable safety profile with primarily mild AEs occurring. Our preliminary findings suggest that both drugs can be used effectively in first-line treatment of IMDC, but further data is necessary to ascertain long-term outcomes. Clinical trial information: NCT04407247. Research Sponsor: MD Anderson IOTOX research award.

First-in-human phase I/II safety and preliminary efficacy of PM1032, a bispecific antibody targeting CLDN18.2 and 4-1BB, in patients with advanced solid tumors.

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Background: PM1032 is an anti-CLDN18.2 x 4-1BB bispecific antibody that activates immune cells, such as T and NK cells, via CLDN18.2-mediated crosslinking of 4-1BB. Potent anti-tumor efficacy is facilitated with limited toxicity as immune activation is only stimulated in the context of CLDN18.2 expression on target cells. Here, we present the preliminary safety and efficacy results from an ongoing Phase I/II trial, which is a first-in-human (FIH), dose-escalation, and expansion study of PM1032 in patients (pts) with advanced solid tumors. **Methods:** This FIH study of PM1032 with adults with previously treated, advanced or metastatic solid tumors includes dose escalation (3+3 design; regardless of CLDN18.2 expression) and dose expansion stages (CLDN18.2+ gastrointestinal (GI) cancers). During the dose escalation stage, PM1032 was administered at doses of 0.3, 1, 3, 5, 8 and 12 mg/kg for the assessment of drug limiting toxicity (DLT) after 3 weeks, followed by administration Q2W until disease progression (PD) or observations of intolerable toxicity. Responses were evaluated according to RECIST 1.1. Adverse events (AEs) were graded using CTCAE v5.0. CLDN18.2 positivity was defined as ≥1% of tumor cells with ≥1+ signal intensity by immunohistochemistry. **Results:** As of January 12, 2024, a total of 30 pts received PM1032 (18 pts during dose escalation and 12 pts during dose expansion) with no DLTs observed (median age 54y; most pts had ≥2 metastatic sites). CLDN18.2 expression was evaluable in 80% of the pts and 66.7% were positive. The most common tumor types were GI cancers including 14 gastric and gastroesophageal junction cancers (GC/GEJ), 10 pancreatic adenocarcinoma (PDAC) and 5 other GI cancers. All pts had ≥1 line of prior therapy and 17 pts (56.7%) had prior immunotherapy. TRAEs occurred in 22 subjects (73.3%), and ≥ Grade 3 TRAEs occurred in 3 subjects (10%). The most common TRAEs were nausea (20%) and aspartate transaminase increase (16.7%). Among a total of 16 CLDN18.2+ pts enrolled at the 5, 8, and 12 mg/kg dose levels who completed at least one tumor evaluation, 2 pts achieved PR, 7 pts had SD and 3 pts were Non-CR/Non-PD. Additionally, the ORR was 20% in 10 measurable and evaluable CLDN18.2+ GC/GEJ pts. The longest treatment duration was 18 months and 5 pts had treatment durations ≥ 6 months. Pharmacokinetics (AUC0-336h & Cmax) were dose-proportional across the dose ranges of 0.3 mg/kg – 12 mg/kg with a terminal half-life of 6.0~10.1 days. **Conclusions:** PM1032 was well-tolerated up to 12 mg/kg Q2W and demonstrated preliminary anti-tumor activity in CLDN18.2+ tumors. Further development of PM1032 as a monotherapy and/or combination therapy for CLDN18.2-positive cancers is planned. Clinical trial information: NCT05839106. Research Sponsor: Biotheus Inc.

Preliminary results of a phase 1, first-in-human, dose escalation study of the anti-CCR8 cytolytic antibody, CHS-114 (formerly SRF114) in patients with advanced solid tumors.

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Background: Depletion of intratumoral regulatory T cells (itTregs) represents an attractive therapeutic strategy to enhance antitumor responses. The chemokine receptor CCR8 is preferentially expressed on itTregs compared to peripheral Tregs and other immune cell types, and CCR8 expressing itTregs are highly immune suppressive. Our preclinical studies have demonstrated that treatment of a PD-1 resistant mouse tumor model with an anti-CCR8 monoclonal antibody (mAb) depletes itTregs, reduces tumor growth, and enhances anti-PD-1 antitumor activity. CHS-114 an afucosylated mAb that binds CCR8, depletes itTregs, and enhances toripalimab- (tori; anti-PD-1 mAb) mediated T cell activation. Here, we present preliminary results of the first-in-human phase 1 study of CHS-114. **Methods:** This phase 1, multicenter, single agent and combination (combo) dose escalation study (NCT05635643) of CHS-114 is enrolling patients (pts) ≥18 years of age with advanced solid tumors who progressed during or after standard therapy. CHS-114 dose escalation guided by the Bayesian optimal interval (BOIN) design will evaluate doses ranging from 5 to 1500 mg q3w. Five additional pts with advanced head and neck squamous cell carcinoma (HNSCC) will be enrolled at each of 2 selected dose levels (DLs) with required biopsies. Combo dose escalation will evaluate 2 DLs of CHS-114 combined with tori 240 mg q3w in pts with HNSCC using a standard 3+3 design. Primary objectives are to determine the recommended dose(s) for expansion of CHS-114 and the safety and tolerability of CHS-114 + tori. Secondary objectives are to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of CHS-114 alone and in combination with tori. Tumor and immune biomarkers are being evaluated as exploratory endpoints. **Results:** As of 15Dec2023, 15 pts received CHS-114 at doses ranging from 5 to 700 mg q3w. No dose-limiting toxicities (DLTs) were reported. Treatment-related adverse events occurred in 33% of pts; all were CTCAE grade 1-2, with pyrexia (13%) being the most common. Preliminary PK analysis indicates that CHS-114 exposure increases with dose with an elimination half-life between 9-17 days across the dose range of 10-700 mg. Preliminary receptor occupancy analysis using an immune profiling assay in peripheral blood at 100, 300, and 700 mg DLs revealed minimal detection of CCR8+ Tregs and a modest concomitant decrease in overall Treg frequency at the end of cycle 1, consistent with strong receptor occupancy. **Conclusions:** CHS-114 has an acceptable safety profile to date in heavily pretreated pts at doses up to 700 mg. CHS-114 administration at 100 to 700 mg shows robust decreases in peripheral CCR8+ Tregs following the first dose (cycle 1). Dose escalation is ongoing. Clinical trial information: NCT05635643. Research Sponsor: Coherus BioSciences.

A blind retrospective analysis of a novel predictive marker to ICB response in NSCLC, calculated directly from histopathological slides.

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Background: Immune checkpoint blockers (ICB), and primarily PD-1/PD-L1 inhibitors, are in the forefront of contemporary clinical oncology and have become an integral part of treatment of many malignancies, including non-small cell lung cancer (NSCLC). Nevertheless, tumor response to ICB varies widely. Predictive markers commonly used to distinguish patients likely to respond to ICB, such as PD-L1 expression and tumor mutational burden (TMB) have limited predictive value, which calls for the development of practical and more accurate tests. We present results of a blind retrospective analysis of a novel predictive marker of ICB response in NSCLC, relying solely on histopathological slides. **Methods:** We obtained high resolution Hematoxylin and Eosin (H&E) slides from tumor-tissue samples of 50 cases of metastatic NSCLC patients treated with first-line PD-1 inhibitors. We retrospectively applied our ENLIGHT-DeepPT (ENLIGHT-DP for short) pipeline to generate, in a blinded manner, an individual response score to PD-1 inhibition for each slide. ENLIGHT-DP is composed of two main steps: (i) predict mRNA expression directly from an H&E slide using DeepPT, our digital-pathology based algorithm; and (ii) use these values as input to ENLIGHT, our transcriptome-based precision oncology platform, which generates a score that predicts response to targeted therapies and ICB (based on a 10-gene signature in this case). We then unblinded the clinical outcome (RECIST1.1), and evaluated ENLIGHT-DP's performance vs. standard markers. **Results:** ENLIGHT-DP's score is predictive of response in this cohort, which had an overall response rate of 68% (34 of 50), with ROC AUC = 0.69 (p = 0.01, one-sided permutation test). Using a predefined threshold for binary classification of response derived from independent data, all 15 patients that were predicted to respond by ENLIGHT-DP indeed responded (100% PPV, 44% sensitivity). In comparison, predicting response according to PD-L1 $>$ 1% achieves 68% PPV and 62% sensitivity, while PD-L1 $>$ 50% achieves 65% PPV and 38% sensitivity, i.e, both thresholds exhibit no predictive power (PPV $<=$ baseline response rate). Patients with high TMB ($>$10) had 82% PPV and 26% sensitivity, showing lower predictive benefit than ENLIGHT-DP. ENLIGHT-DP was particularly good at stratifying patients with PD-L1 $<$ 1% (18 patients, ROC AUC = 0.8, p = 0.03). **Conclusions:** ENLIGHT-DP demonstrates high predictive power for response to ICB in NSCLC relying solely on accessible H&E slides, outperforming the commonly used PD-L1 and TMB markers. ENLIGHT-DP is also able to identify responders within patients with PD-L1 $<$ 1%, for whom ICB is usually considered ineffective. Importantly, our approach does not require training on prior treatment outcomes, and can therefore be generalized to drugs for which such data is unavailable or scarce. Research Sponsor: None.

Transcriptome-based response predictor to identify potential responders among patients with negative standard markers for response to immune checkpoint blockers.

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Background: Immune checkpoint blockers (ICB) are revolutionizing cancer treatment, and are being approved for an increasingly wide range of cancer types. The most common biomarkers currently in use to select patients for ICB are PD-L1 expression on tumor cells, as measured by IHC, and tumor mutational burden (TMB) and microsatellite instability (MSI), both measured by NGS. However, some patients that are negative for these markers still respond to ICB. This calls for complementary biomarkers to better identify responders to ICB, especially in patients that are negative to current biomarkers. Here, we focus on predicting response to anti-PD1 in patients with negative PD-L1, TMB or MSI. **Methods:** We employ ENLIGHT, our transcriptome-based precision oncology platform, which identifies and utilizes clinically relevant genetic interactions to predict a patient's response to a wide range of targeted drugs, including ICB. ENLIGHT generates an individual ICB response score calculated from a 10-gene expression signature - the ENLIGHT Matching Score (EMS). Patients with EMS above a predetermined threshold are considered *matched* by ENLIGHT to anti-PD-1 treatments. We have previously shown, based on more than 1000 cases analyzed retrospectively, that this signature can identify responders to anti-PD-1 with high accuracy. Here, we use ENLIGHT to perform a retrospective analysis of 125 cases from three different datasets, who had low PD-L1 presentation (<1%), low TMB (< 10) or microsatellite stable tumors (MSS), and were treated with anti-PD-1, to specifically assess ENLIGHT's performance in this biomarker-negative sub-population. **Results:** Patients who responded to anti-PD-1 treatments had significantly higher EMS in all three datasets. Correspondingly, ENLIGHT is highly predictive of response to anti-PD-1 in patients with negative ICB markers in the three datasets (ROC AUCs of 0.80, 0.84, 0.77, respectively, for low PDL1, low TMB and MSS). It is important to note that ENLIGHT was not trained on any of these datasets, and is applied as-is using previously published parameters. Overall, we find that patients who are ENLIGHT-Matched to anti-PD1 in this biomarker-negative cohort are almost 3 times more likely to respond than patients who are not (31% vs. 11%, p=5e-13). **Conclusions:** ENLIGHT is a powerful tool for predicting response to anti-PD-1 treatment in patients with negative standard biomarkers for ICB, a currently unmet need with considerable clinical importance. Research Sponsor: None.

Genetic drivers of severe skin toxicity with immune checkpoint inhibitors (ICIs) in Asian patients.

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Background: ICIs may cause severe skin toxicity associated with significant patient (pt) impact. Published data suggests Asian pts might be at higher risk of skin immune-related adverse events (SirAEs). Variation in human leukocyte antigen (HLA) is known to predispose to autoimmune (AI) conditions, but there is limited data to understand genetic drivers of severe SirAEs. **Methods:** The incidence of severe SirAEs was correlated with 30 HLA alleles of interest in 2 cohorts totaling 18 Asian pts (Dermatitis bullous n=4, Erythema multiforme n=10, Stevens-Johnson syndrome n=3, Toxic skin eruption n=1) treated with atezolizumab (A) across tumor types as monotherapy or as part of combinations- 8 Japanese pts received A in a non-interventional study (trial ID: UMIN000048702) and 10 Asian pts were enrolled in Roche trials with A. Data from the 18 cases was compared to 3 different controls of Asian pts identified from Roche trials with A (i.e. pts without any irAEs n=148, pts without SirAEs n=225, pts without severe SirAEs n=390). For each HLA allele, positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, (unadjusted) odds ratio (OR) and corresponding 95%-confidence interval (CI) were evaluated. Case-control populations were obtained by risk-set sampling with exact matching on indication, treatment arm and sex, and used in age-adjusted conditional logistic regression models to assess associations between each HLA allele and severe SirAEs. **Results:** There was an association between some HLA alleles and severe SirAEs, but sensitivity was low (<30%) and 1-NPV was only slightly smaller than background prevalence. Results for five HLA alleles with OR>1.5 in either the unadjusted or adjusted analysis compared to controls without severe SirAEs are presented in table. Results were consistent across the three control populations. **Conclusions:** Five HLA alleles previously reported in AI disorders were associated with severe SirAEs in Asian pts receiving A. Although the effect size is insufficient to be considered clinically relevant, further research is warranted to better characterize the pt-level drivers of severe SirAEs in Asians pts. Clinical trial information: UMIN000048702. Research Sponsor: Chugai Pharmaceutical Co., Ltd., Tokyo, Japan; F. Hoffmann-La Roche Ltd., Basel, Switzerland.

HLA Allele	N	% Severe SirAE	% Carriers	OR	95% CI OR	Sens	95% CI Sens	Spec	95% CI Spec	PPV	NPV	OR*	95% CI OR*	P value*
A*31:01	408	4.41	9.8	3.88	[1.02; 12.48]	27.78	[9.69; 53.48]	91.03	[87.74; 93.67]	12.5	96.47	5.03	[1.67; 15.17]	0.004
B*44:03	408	4.41	11.76	2.24	[0.51; 7.56]	22.22	[6.41; 47.64]	88.72	[85.15; 91.68]	8.33	96.11	2.41	[1.00; 5.85]	0.051
DPB1*13:01	408	4.41	7.35	1.61	[0.17; 7.44]	11.11	[1.38; 34.71]	92.82	[89.79; 95.18]	6.67	95.77	2.04	[0.24; 17.65]	0.518
DRB1*15:01	408	4.41	12.99	1.36	[0.24; 5.05]	16.67	[3.58; 41.42]	87.18	[83.45; 90.33]	5.66	95.77	2.36	[0.66; 8.48]	0.189
B*38:01	408	4.41	0.25			5.56	[0.14; 27.29]	100	[99.06; 100.00]	100	95.82	29	[3.49; 241.07]	0.002

*Adjusted analysis.

Phase I trial of talimogene laherparepvec for the treatment of peritoneal surface malignancies (TEMPO).

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Background: Peritoneal surface malignancies (PSM) constitute a group of difficult-to-treat metastatic diseases that respond poorly to standard chemotherapy. Talimogene Laherparepvec (T-VEC), the first FDA-approved oncolytic virus (OV), demonstrates potential in treating various malignancies by effectively initiating crucial immune responses. Yet, the utility of intraperitoneal (ip) T-VEC for unresectable PSM is still unexplored. **Methods:** TEMPO (NCT03663712) was a nonrandomized, open-label, multicenter phase I trial involving 18 patients with unresectable PSM originating from the appendix (n=14), ovary (n=3), or small bowel (n=1). The trial aimed to determine the recommended Phase 2 dose (RP2D) and maximum tolerated dose (MTD) of ip T-VEC, as well as to evaluate its safety and tolerability. An exploratory endpoint was the Restricted Mean Survival Time (RMST), the estimated non-parametric mean survival time up until the longest patient follow-up time (i.e. maximum of the longest follow-up, and generally an underestimate of the actual mean survival time especially in small samples). Patients received an initial dose of $4x10^6$ plaque-forming units (pfu) of ip T-VEC, followed by their assigned dose every two weeks for up to four additional doses, using a standard '3+3' dose escalation scheme. The doses tested were $4x10^6$, $4x10^7$, and $4x10^8$ pfu of ip T-VEC. Safety assessments were conducted regularly. **Results:** The RP2D is $4x10^8$ pfu of T-VEC. The trial reported no dose-limiting toxicities, thus the MTD was not reached. Treatment-Related Adverse Events (TRAEs) were recorded and categorized by the maximum dose received (Table).One patient treated with $4x10^6$ pfu had grade 3 abdominal pain and another grade 3 fatigue. No severe TRAEs occurred with $4x10^7$pfu. One patient showed a grade 3 neutrophil count decrease at $4x10^8$ pfu. The RMST, calculated with a truncation time of 5.5 months, varied across the doses. Patients receiving $4x10^6$ pfu had an RMST of 3.1 (95% CI= 1.550-4.733) months, while those treated with $4x10^7$ and $4x10^8$ pfu had RMSTs of 4.2 (95% CI= 2.492-5.884) and 4.6 (95% CI= 3.551-5.722) months, respectively. **Conclusions:** We conclude that ip T-VEC is safe in patients with unresectable PSM. TEMPO successfully identified $4x10^8$ pfu as the RP2D for TVEC. Notably, the RMST increased with increasing doses of TL. These results are promising, considering the limited benefit of conventional chemotherapy in treating PSM. This study positions T-VEC as a promising candidate for combination immunotherapies for PSM that amplifies the bystander immune response induced by OVs. Clinical trial information: NCT03663712. Research Sponsor: None.

	$4x10^6$ (n=7)	$4x10^7$ (n=3)	$4x10^8$ (n=8)
Adverse Event			
Abdominal distension	1 (14%)	0 (0%)	0 (0%)
Abdominal pain	1 (14%)	0 (0%)	4 (50%)
Nausea	0 (0%)	1 (33%)	1 (12%)
Chills	1 (14%)	0 (0%)	0 (0%)
Fatigue	1 (14%)	0 (0%)	0 (0%)
Fever	1 (14%)	1 (33%)	2 (25%)
Anorexia	1(14%)	0 (0%)	0 (0%)
Hyperhidrosis	0 (0%)	1 (33%)	0 (0%)

TPS2669 Poster Session

A phase Ia/Ib, non-randomized, open-label, dose escalation and expansion trial of the B7-H6/CD3 T-cell engager BI 765049 with or without ezabenlimab in Asian patients with advanced solid tumors.

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Background: Bispecific T-cell engagers represent a promising therapeutic approach for patients with solid tumors; however, these agents require an appropriate target antigen. B7-H6 is an encouraging target as it is expressed on multiple solid tumors but shows only limited expression on normal tissue (1). BI 765049 is a novel immunoglobulin G (IgG)-like T-cell engager designed to simultaneously bind B7-H6-expressing tumor cells and CD3 on T-cells resulting in the formation of a cytolytic synapse that triggers apoptosis of the tumor cells. **Methods:** NCT06091930 is a Phase I, non-randomized, open-label, multi-center, dose escalation and expansion trial that aims to assess the safety and tolerability of BI 765049 alone or in combination with programmed cell death protein 1 inhibitor ezabenlimab, in patients with advanced or unresectable gastric cancer, colorectal cancer (CRC), pancreatic ductal adenocarcinoma, hepatocellular cancer, head and neck squamous cell carcinoma, or non-small cell lung cancer. Patients must have progressed on, or be ineligible for, standard therapies. Key inclusion criteria include confirmed B7-H6 expression (central pathology review) except in CRC; ≥1 evaluable target lesion outside of the central nervous system (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1); and Eastern Cooperative Oncology Group performance status 0/1. Patients with prior B7-H6-targeted treatment are ineligible. The study is divided into four parts: dose escalation and expansion of BI 765049 monotherapy (Parts I and II, respectively), and in combination with ezabenlimab (Parts III and IV, respectively). BI 765049 dose escalation will be guided by a Bayesian logistic regression model with overdose control. Treatment will continue until progressive disease or discontinuation for other reasons, or for up to 36 months. The primary endpoint for Parts I and III is the occurrence of dose-limiting toxicities; and for Parts II and IV it is objective response (OR; determined by the investigator; RECIST v1.1). The secondary endpoints for Parts I and III are pharmacokinetic (PK) parameters and OR (RECIST v1.1); and for Parts II and IV secondary endpoints are progression-free survival, duration of response, disease control, PK measurements, and OR (immunotherapy RECIST [iRECIST]). 1. Zhang W, et al. Clin Cancer Res 2022;28(23):5190–5201. Clinical trial information: NCT06091930. Research Sponsor: Boehringer Ingelheim.

TPS2670 Poster Session

Phase 1 study of ASP1002, a bispecific antibody targeting claudin 4 (CLDN4) and CD137, in patients with locally advanced (LA) or metastatic solid tumors that express CLDN4.

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Background: The lack of benefit for many cancers from newer-generation combination chemotherapies has stimulated research into targeted agents. CLDN4, a claudin protein family member that regulates tight junction formation, is highly expressed in multiple tumor types including non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), colorectal cancer (CRC), prostate adenocarcinoma (PA), ovarian cancer (OC), and triple-negative breast cancer (TNBC). Following primary T cell activation, CD137 provides a costimulatory signal that enhances T cell proliferation and cytokine production. Together CLDN4 and CD137 represent promising therapeutic targets for solid tumors. ASP1002 is a bispecific antibody designed to target CLDN4 and CD137, thereby enhancing the antitumor response of T cells against CLDN4-expressing tumor cells. **Methods:** This phase 1 first-in-human, open-label, multicenter study (NCT05719558) is evaluating the safety and tolerability, maximum tolerated dose (MTD), and/or recommended phase 2 dose (RP2D) of ASP1002 in adult patients with LA or metastatic solid tumors that express CLDN4. The primary endpoint is safety and tolerability, as assessed by dose-limiting toxicities (DLTs), adverse events (AEs), serious AEs, laboratory tests, vital signs, ECGs, PEs, and ECOG performance status. Secondary endpoints are pharmacokinetic characteristics; confirmed objective response rate (ORR), duration of response, and disease control rate per iRECIST and RECIST 1.1; and incidence rate and expression levels of CLDN4 by immunohistochemistry. Dose escalation will include patients with LA or metastatic NSCLC, UC, CRC, PA, OC, or TNBC. ASP1002 will be administered at escalating doses Q1W IV on days 1, 8, 15 in a 21-day cycle until discontinuation to determine MTD and/or candidate RP2D regimens. At doses ≥10 mg, multi-participant cohorts will be included. Safety follow-up visits will occur within 7 days posttreatment, and on 30 and 90 days posttreatment. Next, dose expansion will enroll patients with LA or metastatic NSCLC, UC, CRC, and other tumor types with confirmed complete response (CR) or partial response (PR) in dose escalation. Candidate RP2D regimens based on dose escalation data will be evaluated in ≤40 patients per dose level, per tumor type in dose expansion. ORR (confirmed CR or PR) per iRECIST will be evaluated in tumor-specific expansion cohorts. The minimum number of responders needed to establish activity is 4 (NSCLC), 3 (CRC), and 7 (UC). Study enrollment is currently ongoing in the United States. Clinical trial information: NCT05719558. Research Sponsor: Astellas Pharma Inc.

TPS2671 Poster Session

ATTAINMENT: A phase Ib trial of MDX-124, a first-in-class annexin-A1 targeting antibody, alone and in combination with anti-cancer treatments, in patients with advanced solid tumors.

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Background: Annexin-A1 is a Ca^{2+}-dependent phospholipid binding protein that is secreted from both cancer and immune cells in response to several physiological stimuli. Secreted annexin-A1 activates formyl peptide receptors driving cancer cell proliferation, angiogenesis, migration, and drug resistance, as well as modulating the tumor microenvironment. Annexin-A1 overexpression is observed in multiple cancers, including pancreatic, triple-negative breast, colorectal, lung and prostate, correlating with poor prognosis and decreased overall survival. MDX-124 is a novel, first-in-class humanised monoclonal antibody that targets annexin-A1. It significantly reduces cancer cell growth via cell cycle arrest, inhibits tumour growth *in-vivo*, reduces metastasis and induces antibody-dependent cellular cytotoxicity in annexin-A1 expressing cancer cells. Additionally, MDX-124 has synergistic activity when combined with chemotherapy and immunotherapy in pre-clinical models. These data indicate blocking the action of annexin-A1 has anti-cancer and therapeutic activity. **Methods:** ATTAINMENT is a modular, multi-arm, First-in-Human trial to evaluate the safety and tolerability of MDX-124 alone and in combination with anti-cancer treatments, in participants with locally advanced, unresectable, or metastatic solid malignancies. Module 1 is a single agent dose escalation using a Bayesian optimal interval (BOIN) design with an expansion cohort, followed by Module 2, which will evaluate MDX-124 in combination with standard of care in indication-specific arms by using a traditional 3+3 dose escalation scheme. Adult patients (≥18 years) with ECOG performance score 0-1 and histologically/cytologically confirmed solid tumors believed to overexpress annexin-A1 which are not amenable to or refractory to standard therapy, or for which no standard therapy exists are eligible. The primary objective is to determine the recommended phase 2 dose (RP2D) of MDX-124 both as a single agent and in combination with anti-cancer treatments. Secondary objectives will assess the safety and tolerability of MDX-124 when given as a single agent or in combination with anti-cancer treatments, characterize pharmacokinetic parameters and assess evidence of preliminary anti-tumor activity per RECIST v1.1 criteria. Exploratory objectives will assess host immune response to MDX-124 (immunogenicity and immunophenotyping), circulating levels of annexin-A1 at baseline and after dosing to correlate with response and outcome to MDX-124, and the impact of MDX-124 on blood/tissue biomarkers. The study began enrolling patients at sites in the UK in August 2023. Cohorts at 1, 2.5 and 5 mg/kg have been completed without DLT and enrollment to cohort 4 (10 mg/kg) began in January 2024. Clinical trial information: ISRCTN78740398. Research Sponsor: Medannex Ltd.

TPS2672 **Poster Session**

Phase I/II trial of LAVA-1207, a novel bispecific gamma-delta T-cell engager alone, or with low dose IL-2 or pembrolizumab, in metastatic castration resistant prostate cancer (mCRPC).

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Background: LAVA-1207 is a humanized bispecific antibody that binds with high affinity to the Vδ2 chain of Vγ9Vδ2-T cells and to prostate-specific membrane antigen (PSMA). It comprises a heterodimer of two fusion proteins, each consisting of a VHH linked to a human IgG1 Fc domain. Preclinical evidence demonstrates that, upon binding both targets, LAVA-1207 leads to potent Vγ9Vδ2-T cell degranulation and cytolytic activity against PSMA-expressing prostate cancer cells. IL-2 is an immune modulator which has been shown to support expansion of activated Vγ9Vδ2-T cells. PD-1 is an inhibitory immune checkpoint receptor that can dampen (Vγ9Vδ2-) T cell reactivity, suggesting that pembrolizumab could potentiate the effect of LAVA-1207. **Methods:** This trial is a phase 1/2a open label study with a 3+3 design in patients with refractory mCRPC to assess the safety of LAVA-1207 alone or with low dose IL-2 or with pembrolizumab, and to determine the recommended Phase 2a dose (RP2D). Secondary objectives include evaluation of pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary anti-tumor activity. Exploratory endpoints include evaluation of the effect of study treatment on circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). LAVA-1207 is administered IV every two weeks. Two parallel cohorts assessing LAVA-1207 with low dose subcutaneous IL-2 have been implemented: (1) single IL-2 administration and (2) three IL-2 administrations on consecutive days per cycle for up to four cycles. An additional dose escalation arm evaluates LAVA-1207 in combination with pembrolizumab, 400mg Q6W, IV. Patients with mCRPC that have failed at least one prior AR therapy and taxane-based chemotherapy (unless deemed medically unsuitable to receive a taxane) will be enrolled on the study. Patients should have progressive disease either by PSA or by RECIST 1.1 or appearance of 2 or more bone metastases. Patients must have ECOG performance status of 0-1. PSMA-PET is performed at baseline. Paired biopsies are requested to further assess LAVA-1207 activity. Dose escalation is ongoing. Expansion arm(s) will be included based on available data from part 1 of the study and may include one or more of LAVA-1207, LAVA-1207 with low dose IL-2, or LAVA-1207 in combination with pembrolizumab. Clinical trial information: NCT05369000. Research Sponsor: LAVA Therapeutics.

TPS2673 **Poster Session**

The FIPO23 trial: First-in-human phase I/II study of XON7 in advanced solids tumors.

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Background: XON7 is a first-in-class glyco-humanized polyclonal antibody (GH-pAb) targeting selectively multiple tumor-associated antigens. XON7 induces tumor cell apoptosis and promotes the elimination of tumor cells by immune effector cells through CDC (Complement Dependent Cytotoxicity) and ADCP (Antibody-Dependent Cell Phagocytosis). XON7 demonstrated anti-tumor efficacy in mice xenograft models with human solid tumors such as colon, prostate, lung and triple negative breast cancers. Safety pharmacology and toxicology studies in non-human primates demonstrated an acceptable safety profile for XON7. Taken together, these preclinical data support the initiation of human trials in patients with advanced solid tumors. **Methods:** First-in-patient, multicenter, open-label, two phases (dose-escalation (ESC) followed by dose expansion (EXP)) study of XON7 single agent, in patients with relapsed refractory, locally advanced or metastatic solid tumors without standard available treatments (*NCT06154291*). Key eligibility criteria include disease progression after $\leq$ 4 lines of therapy; age $>$ 18 years; ECOG performance status $\leq$2; adequate organ functions; no known CNS involvement. All advanced or metastatic tumor types except glioblastoma, can be included during ESC. Primary endpoints: safety, tolerability and determination of MTD/RP2D. Secondary endpoints: pharmacokinetics (PK), pharmacodynamics, immunogenicity and preliminary anti-tumor activity (RECIST 1.1). AEs graded according to CTCAE 5.0. In the ESC part, XON7 is administered as 60-min intravenous infusion every 2 weeks according to an escalating schedule of doses from 1.5 to 20 mg/kg for up to 12, 28-day cycles. Dose escalation/de-escalation is based on the Bayesian Optimal Interval (BOIN) design, up to 45 pts are planned. At the recommended dose, up to 7 EXP cohorts (30 pts each) defined according to the primary tumor site are planned. Bayesian sequential monitoring will be used. Patient recruitment is planned or ongoing at 25 sites worldwide. **Results:** As of Feb 3rd, 2024, 3 pts are enrolled in the first dose cohort and have received XON7 at dose 1,5 mg/kg Q2W for the first 28-days cycle. **Conclusions:** Accrual is ongoing in this first-in-human trial of XON7. Clinical trial information: NCT06154291. Research Sponsor: None.

TPS2674 **Poster Session**

A phase 2, multicenter study of TILs treatment in advanced tumors with alterations in the SWI/SNF complex: The TILTS study.

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Background: Tumors associated with SWI/SNF complex (SWI/SNFc) mutations, mainly SMARCA4 and SMARCB1 loss, are a heterogeneous group of malignancies with rhabdoid features that typically affect young patients (pts). These are aggressive malignancies with poor prognosis for which no standard treatment is available. Despite not having a high tumor mutation burden, tumor infiltrating lymphocytes (TILs) are usually present in high numbers. The biologic reasons for this feature are not clearly understood but might be associated to changes in gene expression due to aberrant chromatin remodeling. However, these TILs indicate that tumor antigens are recognized by lymphocytes unveiling a vulnerability that can be exploited by immunotherapy. The objective of the TILTS study is to develop a personalized adoptive cell therapy using TILs in pts affected by these tumors. **Methods:** Single arm, multi center, phase 2 study of TILs in pts with advanced tumors associated with SWI/SNFc mutations. Pts are treated at 3 centers in Spain: Catalan Institute of Oncology (ICO), Barcelona, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, and Centro Integral Oncológico Clara Campal (HM CIOCC), Madrid. Primary endpoint is overall response rate (ORR) by RECIST 1.1. Secondary endpoints include toxicity evaluation, duration of response (DOR), progression-free survival (PFS) or overall survival (OS). After informed consent is obtained, tumor resection is performed. Total volume of tumor resected should be at least 1.5 cc to assure TIL isolation. Eligible pts enter the treatment phase. TILs are produced under GMP conditions. During the TILs manufacturing process, pts are allowed to receive standard treatment if clinically indicated. Before TIL infusion, pts receive non-myeloablative preconditioning lymphodepletion with daily intravenous (IV) cyclophosphamide (60 mg/kg; IV x2 doses) and daily fludarabine (25 mg/m2; IV x5 doses). Infusion of autologous TILs is given on Day 0 followed by administration of IL-2 at 600,000 international units (IU)/kg every 8-12 hours for a maximum of 6 doses. After 4 weeks, a new tumor biopsy is optional. First image evaluation is performed after 8 weeks from TIL infusion. Pts without progression enter the follow-up phase. An ancillary translational study will explore mechanisms of immunogenicity, antigen recognition, TILs anti-tumor activity, and changes in the stool microbiome and specific TCR population during treatment. Also, tumor immune microenvironment will be analyzed. Clinical trial information: 2023-504632-17-00. Research Sponsor: Instituto de Salud Carlos III (ISCIII); ICI21/00110.

Eligible Tumor Types
Epithelioid sarcoma
Malignant rhabdoid tumor
Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT)
Renal medullary carcinoma
Epithelioid malignant peripheral nerve sheath tumor (EMPNST)
Myoepithelial carcinoma
Extra-skeletal myxoid chondrosarcoma
Poorly differentiated chordoma
Sinonasal basaloid carcinoma
Other tumors associated with SWI/SNFc mutations

TPS2675 Poster Session

ATHENA: A phase 1/2 study of AZD5851, a chimeric antigen receptor (CAR) T-cell therapy directed against GPC3 in adult patients with advanced/recurrent hepatocellular carcinoma (HCC).

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Background: Checkpoint inhibitor therapy is the standard first-line treatment for advanced/recurrent HCC, but there is a significant unmet therapeutic need for patients (pts) who progress after first-line treatment. Adoptive cellular immunotherapy may provide a novel treatment option. Glypican-3 (GPC3), a heparan sulfate proteoglycan, is overexpressed by tumor cells in HCC and virtually absent in healthy tissues, making it an ideal target for CAR-T therapy. AZD5851 is an autologous CAR-T product that expresses a CAR specific for GPC3 and a dominant negative (dn)TGFβRII as an armoring strategy. Expression of dnTGFβRII can block TGFβ signaling, protecting CAR T-cells from the immunosuppressive effects of this cytokine. Early clinical data with C-CAR031, a CAR-T product with the same GPC3-specific CAR and dnTGFβRII-armoring transgene as AZD5851, showed promising tolerability and antitumor activity in pts with HCC [1]. ATHENA (NCT06084884) is a first-in-human, single-arm, open-label, multicenter phase 1/2 study to evaluate the safety, tolerability, and antitumor activity of AZD5851 in pts with GPC3+ advanced/recurrent HCC, for whom ≥1 prior line of standard therapy failed or was not tolerable. **Methods:** Eligible pts are aged ≥18 years with histologically confirmed advanced/recurrent or metastatic and/or unresectable HCC, GPC3+ tumor sample as determined by immunohistochemistry, ≥1 prior line of standard systemic therapy, ≥1 measurable lesion per RECIST 1.1, Child-Pugh A, ECOG PS 0/1, and adequate organ and bone marrow function. Approximately 24 pts will be enrolled in Part A (Phase I, dose escalation) and 50 in Part B (Phase II dose expansion). Pts will undergo apheresis to collect peripheral blood mononuclear cells for AZD5851 production, after which they may receive approved bridging therapy for disease control. Upon successful generation of AZD5851 product, pts will undergo lymphodepletion before receiving a single dose of IV AZD5851. Subsequent follow-up is divided into 3 stages: Stage 1, active follow-up of all pts through 6 months post AZD5851 infusion; Stage 2, further evaluation of pts who have not progressed or started a new anticancer regimen during Stage 1; Stage 3, long-term follow-up for all pts who have received AZD5851. The primary endpoints are to assess the safety/tolerability of AZD5851 (both study parts), and to determine the recommended dose(s) of AZD5851 for expansion and phase 2 trials (Part A). Secondary endpoints include efficacy (objective response rate, best overall response, duration of response, disease control rate, durable response rate, time to response, progression-free survival, and overall survival) and pharmacokinetics. Exploratory endpoints include pharmacodynamic biomarkers and immunogenicity. Enrollment began Nov 2023. 1. Zhang et al. AACR 2023. Abstract CT097. Clinical trial information: NCT06084884. Research Sponsor: AstraZeneca.

TPS2676 **Poster Session**

A phase 1/2, open-label, multicenter, dose escalation and cohort expansion study of the safety and efficacy of anti-CD70 allogeneic CRISPR-Cas9–engineered T cells (CTX131) in adult patients with relapsed or refractory solid tumors.

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Background: CD70, a type II transmembrane protein and member of the tumor necrosis factor (TNF) receptor family, demonstrates high expression across multiple malignancies making it an attractive target for chimeric antigen receptor (CAR) T cell therapy. CD70 is expressed in 80% of clear cell renal cell carcinoma (ccRCC) and in 40-60% of cervical carcinoma (CC), esophageal carcinoma (EC), pancreatic adenocarcinoma (PAC), and pleural mesothelioma (PM) (1). CTX131 is a CD70-directed allogeneic CAR T cell investigational product manufactured *ex vivo* from healthy donor T cells using CRISPR/Cas9 technology. Genetic modifications in CTX131 include targeted insertion of a CD70-directed CAR construct, and targeted disruption of 5 loci: TRAC (to reduce risk of GvHD), B2M (to improve persistence in the allogeneic setting), CD70 (to reduce fratricide and improve anti-tumor function), TGFBR2 (to reduce immunosuppressive effect of TGFB in the tumor microenvironment), and Regnase-1 (to improve functional persistence) (2). Preclinical studies show the combination of TGFBR2 and Regnase-1 disruption in CTX131 works synergistically to enhance anti-tumor activity, inhibit tumor growth in xenograft mouse models, prolong survival, and increase central memory T cell populations (3). **Methods:** We are conducting a phase 1/2 study in patients (pts) with unresectable or metastatic ccRCC, CC, EC, PAC, and PM. Part 1 is a dose escalation with two separate cohorts, one for ccRCC pts and another for CC, EC, PAC, and PM pts. Part 1 ccRCC cohort began recruiting in 2023. Part 2 is a single-arm expansion of disease-specific cohorts. Key eligibility criteria include at least one prior line of standard treatment, ECOG status 0-1, evaluable disease per RECIST v1.1 (or modified RECIST1.1 for PM), adequate hematologic and organ function, and availability of tumor tissue for CD70 IHC. Key exclusion criteria include prior treatment with CD70-targeting agents and active CNS metastasis. Pts will receive standard lymphodepleting chemotherapy with fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 daily x 3 days followed by CTX131 IV infusion at doses ranging from 30-900 million cells in 4 dose level cohorts. Redosing with CTX131 is permitted. For Part 1, the primary endpoint is DLTs with secondary endpoints including ORR, DOR, PFS, and OS. For Phase 2 the primary endpoint is ORR by IRC assessment. The trial is currently open with enrollment ongoing. 1. Flieswasser et. al. 2019. 2. Mai et. al. 2023. 3. Terrett 2023. Clinical trial information: NCT05795595. Research Sponsor: CRISPR Therapeutics AG.

TPS2677 Poster Session

An open-label, phase 1, multicenter study to evaluate the safety and preliminary anti-tumor activity of NT-112 in human leukocyte antigen-C*08:02–positive adult patients with unresectable, advanced, and/or metastatic solid tumors that are positive for the KRAS G12D mutation.

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Background: The landscape of cancer treatment is evolving with the emergence of innovative immunotherapies. Among these, T cell receptor-engineered T cell (TCR-T) therapy has shown promise for patients with solid tumor malignancies. Targeting driver mutations, such as KRAS, may offer novel therapeutic options for patients with limited treatment options. Oncogenic driver mutations in KRAS typically involve single-base mutations at genomic hotspot locations. The KRAS isoform is mutated in 84% of RAS-driven cancers and in nearly 100% of pancreatic ductal adenocarcinoma (PDAC). The KRAS G12D mutation is the most frequent mutation in PDAC (28%), followed by colorectal cancers (12%). Despite its well-established target role in tumorigenesis, there is no FDA-approved therapy targeting the G12D variant. NT-112 is an autologous TCR-T cell therapy targeting the KRAS G12D mutation presented by HLA-C*08:02, armored by disruption of the gene encoding the transforming growth factor beta receptor type 2 (TGFBR2) in order to reduce the immunosuppressive effect of TGF-β in the tumor microenvironment. **Methods:** This first-in-human, open label, multicenter, Phase 1, dose escalation study aims to assess the safety, identify the MTD and evaluate potential anti-tumor activities of NT-112 in subjects with solid tumors. The study will enroll up to 24 adult subjects harboring the KRAS G12D mutation that are HLA-C*08:02 positive, who exhibit progressive or recurrent disease after at least one line of standard of care treatment. Enrolled patients will undergo leukapheresis, from which, CD4 and CD8 T cells will be enriched and activated ex vivo. The genes encoding the TGFBR2 and the endogenous TCR α and β chains are knocked out from the activated T cells utilizing clustered regularly interspaced short palindromic repeats (CRISPR-Cas9). The HLA-C*08:02-restricted TCR specific to the KRAS G12D mutation is knocked-in in the TCR α locus. Subjects will undergo standard lymphodepletion followed by a single infusion of NT-112 and concurrent, daily, subcutaneous, recombinant IL-2 for up to 8 days. Dose escalation will occur across 3 ascending dose levels following the BOIN design. Subjects will be monitored for dose-limiting toxicities for 28 days following NT-112 infusion. Disease response will be assessed according to the RECIST v1.1 criteria. Comprehensive translational analysis will be conducted to gain insights into the mechanism of action, biomarkers associated with treatment response, and potential mechanisms of resistance. All subjects will be followed for up to 15 years. Clinical trial information: NCT06218914. Research Sponsor: Neogene Therapeutics, Inc.

TPS2678 Poster Session

A phase 1 trial of TSC-100 and TSC-101, engineered T cell therapies that target minor histocompatibility antigens to eliminate residual disease after hematopoietic cell transplantation.

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Background: Engineered T cell therapies such as CAR-T cell therapies have transformed the treatment of B-cell but not non-B cell hematologic malignancies. Allogeneic hematopoietic cell transplantation (HCT) remains the best curative option for hematologic malignancies but ~40% of patients relapse post-HCT with up to 90% mortality due to residual disease post-HCT. A potential solution is targeting minor histocompatibility antigens (MiHAs) that are homogenously expressed on all hematopoietic cells and are genetically mismatched between donors and patients undergoing HCT. These mismatches enable engineered T cells to selectively eliminate residual patient hematopoietic cells, normal or malignant, leaving donor cells untouched. TScan has developed allogeneic donor derived T-cell products TSC-100 and TSC-101, targeting MiHAs HA-1 and HA-2 respectively, both presented on HLA-A*02:01. By choosing HCT patients who are HLA-A*02:01 positive (>98% of whom are either HA-1 or HA-2 positive) and donors who are either HLA-A*02:01 or MiHA negative, TSC-100 or TSC-101 can potentially eliminate all residual patient-derived hematopoietic cells after HCT, to prevent disease relapse. **Methods:** Study NCT05473910 is a multi-center, multi-arm, non-randomized controlled Phase 1 umbrella study evaluating the feasibility, safety and preliminary efficacy of TSC-100 and TSC-101. Inclusion criteria include adults with AML, MDS or ALL eligible for reduced intensity conditioning-based haploidentical donor transplantation from HLA or MiHA mismatched donors. HLA-A*02:01-positive patients undergo HA-1/ HA-2 testing and are assigned to either TSC-100 or TSC-101 treatment arms in addition to HCT. HLA-A*02:01-negative patients in the control arm receive HCT alone. Upon count recovery after HCT, patients in treatment arms receive either TSC-100 or TSC-101, administered as single or two doses. Primary endpoints include adverse event profiles and dose limiting toxicities. Secondary endpoints include relapse rates, disease-free survival and overall survival. Exploratory endpoints include surrogates of efficacy such as donor chimerism rates and kinetics and minimal residual disease (MRD) rates. Donor chimerism is measured by standard STR-based and novel high-sensitivity NGS-based assays to quantify residual patient-derived hematopoietic cells. MRD is measured before and after HCT using flow cytometry and NGS. Together, these assays measure elimination of residual patient hematopoietic cells, malignant or normal, and could provide early evidence of biological activity. Clinical trial information: NCT05473910. Research Sponsor: None.

TPS2679 Poster Session

Binary oncolytic adenovirus in combination with HER2-specific autologous CAR VST for treatment of advanced HER2-positive solid tumors (VISTA).

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Background: Urgent therapies are needed for patients with refractory Human Epidermal Growth Factor Receptor 2 (HER2) positive solid malignancies. Our group has previously shown potent antitumor effect of a binary oncolytic/helper-dependent adenovirus (CAdVEC) with dual expression of IL-12 and PD-L1 blocker. Initial preclinical and clinical studies with direct tumor injection of CAdVEC has shown it to be safe and result in increased infiltration of CD8 T cells into the tumor microenvironment, with antitumor effect on locoregional and distant metastatic sites.[1] Based on these results, we describe an ongoing study with addition of HER2-specific autologous chimeric antigen receptor (CAR)-T cell therapy to CAdVEC. **Methods:** This is a single arm, dose escalation phase I clinical trial guided by Bayesian Optimal Interval Design (BOIN) for patients with advanced HER2 positive solid tumors. Patients who are deemed unsuitable for curative treatments and progressed after at least one standard first line therapy are eligible. HER2 positivity is determined by IHC and defined as $\geq$2+. Patients are required to have at least one tumor site appropriate for intratumor injection and radiographically measurable disease per RECIST v1.1. Patients with autoimmune disease requiring systemic corticosteroids greater than 10mg/day and those with active/untreated CNS metastasis are excluded. Patients will receive increasing doses of CAdVEC intratumor injection alone (first two dose levels) or in combination with HER2 specific autologous CAR-T cells (dose levels 3-7). A total of 45 patients are planned. The primary endpoint of the study is to evaluate safety and maximum tolerated dose as assessed by incidence of dose limiting toxicities (DLT) of CAdVEC intratumor injection in combination with HER2-specific autologous CAR T cells. Secondary endpoints include anti-tumor activity of the combination measured by overall response rate (ORR), disease control rate (DCR), median progression free survival (PFS) and median overall survival (OS). Exploratory endpoints include assessing the immunogenicity of combination therapy by determining the impact of treatment on cellular and humoral immunity, as well as assessing long-term persistence and functional status of HER2 CAR T-cells. Correlative analysis of levels of adenovirus antibodies with clinical outcomes and immunological findings are also planned. This study is currently enrolling. 1. Wang D, Porter CE, Lim B, et al: Science Advances 9, 2023. Clinical trial information: NCT03740256. Research Sponsor: None.

TPS2681 Poster Session

DUET-01: A first-in-human, phase 1/2 study of BOXR1030 in patients with advanced glypican-3-positive solid tumors.

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Background: Glypican-3 (GPC3) is a membrane-bound heparin sulfate proteoglycan involved in cell proliferation that is overexpressed in several tumor types. BOXR1030 is an autologous T-cell therapy that co-expresses a chimeric antigen receptor (CAR) targeting GPC3 on tumor cells and glutamic-oxaloacetic transaminase 2 (GOT2), a mitochondrial enzyme that plays an important role in maintaining mitochondrial function and improving T-cell functionality in the solid tumor microenvironment. In non-clinical studies, BOXR1030 showed GPC3-specific cytotoxicity, proliferation and cytokine release only in the presence of GPC3+ cells. **Methods:** DUET-01 (NCT05120271) is an open-label, dose escalation and expansion clinical trial to determine a safe dose of BOXR1030 in patients with advanced GPC3-positive solid tumors. Dose escalation will be guided by the occurrence of dose-limiting toxicities (DLTs) within 28 days of dosing. The Bayesian logistic regression model will be used on the accumulated DLT data to estimate the maximum tolerated dose (MTD). The Dose Escalation Committee will select the recommended phase 2 dose (RP2D) to be used in the expansion phase cohort(s) (10-20 subjects each) based on data accumulated in the dose escalation cohorts. Eligible subjects will undergo leukapheresis to obtain T cells for BOXR1030 manufacturing and will receive 3 days of lymphodepleting chemotherapy with fludarabine and cyclophosphamide within 5 days prior to BOXR1030 administration. The starting dose is 0.3×10^6 BOXR1030 T cells/kg body weight. Antitumor activity will be assessed every 6 weeks after cell infusion per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 and RECIST for immune-based therapeutics (iRECIST). Six months after BOXR1030 administration, subjects will enter long-term follow-up for up to 15 years. Long-term follow-up assessments will focus on long-term safety and disease status. Main inclusion criteria are histologically confirmed advanced unresectable or metastatic hepatocellular carcinoma, squamous cell carcinoma of the lung, myxoid/round cell liposarcoma, or Merkel cell carcinoma; GPC3 overexpression by immunohistochemistry assay confirmed centrally on tumor specimen taken within 6 months prior to signing consent and after the initiation of the subject's most recent systemic anticancer therapy; body weight of $\geq$ 50 kg ($\geq$ 65 kg for dose level 1); and life expectancy $>$ 16 weeks. The primary endpoints are the incidence of DLTs; determination of the MTD and RP2D; the type, frequency and severity of treatment-emergent adverse events; clinically significant abnormal safety laboratory findings and vital signs. Key secondary endpoints include efficacy parameters such as objective response rate, BOXR1030 T-cell expansion and persistence, and levels of inflammatory markers and cytokines. The first patient was treated with BOXR1030 in December 2022. Clinical trial information: NCT05120271. Research Sponsor: Sotio Biotech.

TPS2682 Poster Session

A phase 1, first-in-human study of autologous monocytes engineered to express an anti-HER2 chimeric antigen receptor (CAR) in participants with HER2-overexpressing solid tumors.

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Background: Myeloid cells are actively recruited to the solid tumor microenvironment (TME) and have the potential to mediate tumor control via phagocytosis, TME remodeling, and T cell activation. We previously developed human chimeric antigen receptor macrophages (CAR-M) and have shown potent anti-tumor activity in pre-clinical solid tumor models. The anti-HER2 CAR-M cell therapy product, CT-0508, is currently being evaluated in a Phase I trial as a monotherapy and in combination with pembrolizumab. Early clinical data have shown feasibility, safety, and validated the mechanism of action. We have developed a next-generation CAR monocyte (CAR-Mono) platform to increase the dose, improve tumor trafficking and engraftment, and shorten the manufacturing and vein-to-vein time as compared to CAR-M therapy. CT-0525 is an autologous anti-HER2 CAR-Mono cell therapy based on CD14+ monocytes engineered with an Ad5f35 adenoviral vector to express an anti-HER2 CAR. Pre-clinical studies have demonstrated the feasibility, phenotype, pharmacokinetics, durable CAR expression, cellular fate, antigen specificity, and anti-tumor activity of CT-0525. Pre-clinical studies have shown that CT-0525 differentiated into pro-inflammatory CAR-M *in vivo* and controlled tumor growth. The CT-0525 manufacturing process takes one day and enables the production of up to 10 billion cells from a single apheresis. CT-0525 is being investigated in a first-in-human, open-label, multi-center, Phase I study in patients with HER2 overexpressing solid tumors.
Methods: This Phase 1, first-in-human study evaluates the feasibility, safety, tolerability, trafficking, TME activation, and preliminary evidence of efficacy of the investigational CAR-Mono product CT-0525 in 6 participants (pts) with locally advanced unresectable/metastatic solid tumors overexpressing HER2. Pts previously treated with anti-HER2 therapies are eligible. Filgrastim mobilized autologous CD14+ monocytes are collected by apheresis, followed by manufacturing and cryopreservation. The 1st cohort of pts (n=3) will receive 3 x 10^{9} CT-0525 CAR positive monocytes administered IV in one infusion. If tolerated as per the modified toxicity probability interval algorithm (mTPI), the 2nd cohort of pts (n=3) will receive up to 10 x 10^{9} CT-0525 CAR positive monocytes in one infusion. CT-0525 will be administered without conditioning chemotherapy. Primary endpoints include assessment of safety and tolerability, as well as manufacture feasibility. Correlative assessments include pre- and post-treatment biopsies and blood samples for safety, immunogenicity, pharmacokinetics, tumor trafficking, TME modulation, epitope spreading, and other translational biomarkers. Clinical trial information: NCT06254807. Research Sponsor: None.

TPS2683 **Poster Session**

First-in-human autologous CAR-T for metastatic breast cancers to target growth factor receptor MUC1*.

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Background: MUC1 has been one of the most important therapeutic targets for solid tumor cancers for the past 20+ years. However, no MUC1 targeted therapeutic has yet succeeded or has been granted FDA approval. Although MUC1 is overexpressed on cancer cells, it is also widely expressed on normal epithelial cells. We previously reported that a MUC1 transmembrane cleavage product, MUC1* (muk 1 star), is a Class I growth factor receptor activated by ligand-induced dimerization of its truncated extra cellular domain. We generated monoclonal antibodies that recognize the specific conformation that is created when MUC1 is cleaved by specific enzymes expressed in the tumor microenvironment. 93% of human breast cancer tissues are recognized by one of these antibodies, huMNC2, which importantly does not bind to normal MUC1. We have incorporated this antibody into two CARs, wherein one bears the "1XX" mutations in CD3z that greatly increase CAR-T cell persistence, inhibit exhaustion and enable the killing of low antigen expressing cancer cells. **Methods:** Phase I for huMNC2-CAR44, an autologous frozen product, opened January, 2020, but as a 1st-in-human trial was paused during COVID. All patients receive 300 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine for 3 days prior to CAR-T treatment. Dose escalation from 3.3x10^5 – 1x10^7 CAR+ cells/kg follows a standard 3 + 3 design. In addition to standard organ function inclusion criteria, the trial was first open to breast cancer patients whose cancer had progressed after at least 2 or 3 prior therapies while metastatic, yet there was no limit on the number of prior therapies. A recent patient biopsy had to be at least 30% positive for MUC1* in a CLIA validated IHC assay. Importantly, there were no limits on the vein-to-vein time. Dose levels 1 and 2 for huMNC2-CAR44 were completed without DLTs. Phase I for huMNC2-CAR22, which bore the 1XX mutations in CD3z to increase persistence and increase the killing of low antigen expressing cells opened September, 2023. Based on responses of initial huMNC2-CAR44 patients, inclusion criteria were amended to an Enrichment Trial Design. The number of prior therapies was limited to less than or equal to 10. Anticipated survival at the time of product infusion should be at least 3 months. Vein-to-vein time, which historically had been 15-16 days at one site and as high as 83 days at another site, would be targeted to 16- 22 days. The tumors of eligible patients need to have a MUC1* membrane positive H-score equal to or greater than 120 out of a possible 300, defined as high MUC1* positivity. Based on IHC analysis of human breast cancer TMAs, the H-score restriction would include roughly 40% of breast cancers. The increased ability of huMNC2-CAR22 to kill low antigen expressing cancer cells may support future studies of patients expressing low levels of MUC1*. Clinical trial information: NCT04020575. Research Sponsor: Minerva Biotechnologies Corporation.

TPS2684 **Poster Session**

A phase 1/2, first-in-human, open-label, dose-escalation study of TAK-280, an investigational B7-H3 x CD3ε conditional bispecific redirected activation (COBRA) T-cell engager, in adult patients with unresectable, locally advanced, or metastatic solid tumors.

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Background: TAK-280 is a novel COBRA T-cell engager that targets the B7 homolog 3 protein (B7-H3), an antigen highly expressed in a range of solid tumors including metastatic castration-resistant prostate cancer (mCRPC) and non–small cell lung cancer. In its prodrug form, TAK-280 binds to B7-H3, but not to CD3ε. Once in the protease-rich tumor microenvironment, TAK-280 undergoes protease-mediated activation through formation of CD3ε-binding active dimers, which stimulate CD3 T-cell activation and cytotoxic antitumor response against co-engaged B7-H3–expressing cells. In preclinical studies, TAK-280 demonstrated cleavage-dependent conditionality, engagement of tumor target antigen, and induction of T-cell mediated tumor killing. TAK-280 has the potential to target solid tumors that are not amenable to treatment with conventional first- or second-generation T-cell engagers, while limiting toxicity to normal tissues. **Methods:** This phase 1/2 study is enrolling adult patients with unresectable, locally advanced, or metastatic solid tumors described in the literature to have enhanced B7-H3 expression, who are ineligible or intolerant to standard therapies. Other eligibility criteria include Eastern Cooperative Oncology Group performance status ≤1 and measurable disease per RECIST v1.1. Key exclusion criteria include history of autoimmune disease, major surgery ≤8 weeks before first dose of TAK-280, and history of clinically significant cardiac or gastrointestinal disorders. During phase 1 dose escalation, TAK-280 is administered as an intravenous infusion, once weekly, in 28-day cycles at a pre-defined dose level range. Patients who do not experience dose-limiting or other unacceptable toxicities may receive up to 14 treatment cycles depending on response; patients are treated until disease progression, unacceptable toxicity, or withdrawal from study. The dose-escalation phase will determine two recommended doses for expansion to be assessed during the cohort-expansion phase. The primary endpoint is incidence of dose-limiting or other toxicities during dose escalation; secondary endpoints include pharmacokinetic parameters, response assessment per RECIST v1.1, overall response rate, duration of response, progression-free survival, overall survival, disease control rate, and prostate-specific antigen response in patients with mCRPC. Cytokine release syndrome is closely managed and reported per American Society for Transplantation and Cellular Therapy consensus grading. Approximately 182 patients are planned to be enrolled (42 in dose escalation and 100–142 in cohort-expansion); as of the data cutoff date of Jan 10, 2024, 18 patients have received the study drug. Clinical trial information: NCT05220098. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA.

TPS2685 **Poster Session**

Two phase 2A clinical trials to evaluate the safety and efficacy of IMSA101 in combination with radiotherapy and checkpoint inhibitors in oligometastatic and oligoprogressive solid tumor malignancies.

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Background: The innate immune system plays a pivotal role in detecting cancer-induced DNA damage and signaling the adaptive immune system to initiate tumor-targeted immune response. However, many cancer cells develop mechanisms to evade immunosurveillance. IMSA101 augments tumor detection and killing via the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS)-stimulator of interferon genes (STING) pathway. Pre-clinical data suggests that IMSA101, combined with DNA-damage inducing personalized ultra-fractionated stereotactic adaptive radiation (PULSAR) therapy and PD-1-targeted immunotherapy (IO), can synergistically optimize anti-cancer response. A recently concluded phase 1 clinical trial demonstrated the safety and efficacy of IMSA101 administered both as monotherapy and in combination with IO. **Methods:** IMSA101-102 and IMSA101-103 are phase 2 randomized clinical trials, partially funded by a State of Texas, Cancer Prevention and Research Institute of Texas (CPRIT) grant, comparing the safety and efficacy of a PULSAR-IO doublet administered with or without IMSA101 in patients (pts.) with oligometastatic non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC)(102 study) and oligoprogressive solid tumor malignancies (103 study, see Figure 2). Both ongoing studies are being run at U.S. cancer centers and commence with an ascending dose level, safety lead-in component in which pts. receive PULSAR-IO + IMSA101 administered at either 800mcg or 1200mcg. Upon completion of the safety lead-in period, approximately 34 and 39 pts. respectively will be randomized to receive either the experimental triplet or the PULSAR-IO control arm. In both studies, the experimental treatment regimen will consist of 3 doses of PULSAR spaced 1 month apart, either Nivolumab or Pembrolizumab IO therapy per FDA product label and 5 intra-tumoral injections of IMSA101 over a 60-day period. All pts. will be assessed for RECIST-based anti-tumor efficacy at screening, prior to the end of cycle 3 and at 8-week intervals thereafter. A FACT-G quality-of-life assessment will additionally be performed for all evaluable pts. OMD Study: 40 OMD NSCLC and RCC patients, randomized 1:1 to control arm vs. experimental arm (control: PULSAR + PD-1 Ab, experimental arm: PULSAR + PD-1 Ab + IMSA 101). Primary endpoint: Progression-free rate at 18 months. OPD Study: 45 OPD solid tumor patients, randomized 1:2 to control arm vs. experimental arm (control: PULSAR + PD1 Ab, experimental arm: PULSAr + PD-1 Ab + IMSA 101). Primary endpoint: Progression-free rate at 12 months. Clinical trial information: NCT05846646 and NCT05846659. Research Sponsor: ImmuneSensor Therapeutics, Inc.

TPS2686 **Poster Session**

A phase 1, multi-center, safety, feasibility, and preliminary efficacy study evaluating a single dose of UNO101 in relapsed or refractory, unresectable, primary, or metastatic cutaneous and subcutaneous malignancies.

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Background: Tumor ablation is a minimally invasive technique commonly used to treat solid tumors in the liver, kidney, bone, and lung and is usually based on thermal and nonthermal approaches. Local and *in-situ* tumor ablation methods demonstrate enhanced anti-tumor immune responses resulting in the destruction of residual malignant cells in primary tumors and distant metastases. Nitric oxide (NO) is a colorless gas and a short-lived free radical. It is a ubiquitous, endogenously generated gas implicated in the homeostatic regulation of physiological processes. Preclinical studies evaluating the effect of high concentration exogenously administered NO demonstrated its anti-cancer properties and suggested that it may serve as a potent tumoricidal agent. We have previously shown that treating mouse colon carcinoma (CT26) tumor-bearing mice with ultra-high concentrations of nitric oxide (UNO101) upregulates innate and adaptive immune cells both locally and systemically. Beyond Cancer is currently conducting a first-in-human, first-in-class, Phase 1 safety, feasibility, and preliminary efficacy clinical study of UNO101 at multiple institutions in Israel. **Methods:** The study is a 2-part Phase 1 trial with a Dose Escalation and a Dose Expansion portion (NCT05351502). A conventional 3+3 dose escalation will evaluate three cohorts of UNO101 single dose: 25,000, 50,000 and 100,000 parts per million (PPM) delivered intratumorally over 5 minutes in subjects with an ECOG PS of 0–3, at least 3 months of life expectancy, with relapsed or refractory unresectable primary or metastatic cutaneous and subcutaneous measurable solid tumors being eligible for enrollment. Upon determination of the maximum tolerated dose or biological effective dose, whichever occurs first, the proposed recommended Phase 2 dose will be further evaluated in the Dose Expansion portion of the study. RECIST version 1.1 and iRECIST will be utilized to assess the rate of malignant tumor response after UNO administration and toxicity will be graded per NCI CTCAE version 5.0. Evaluation of response per itRECIST will also be explored. Up to thirty-eight enrolled subjects are anticipated. Cohort 1, 25,000 PPM have been completed without a reported DLT. Enrollment to Cohort 2, 50,000 PPM, began in January 2024. This study was approved by Israel Ministry of Health (IMOH) as well as the participating institution's Ethics Board. Written informed consent was obtained for all enrolled subjects and a copy of the written consent is available for review. Clinical trial information: NCT05351502. Research Sponsor: Beyond Cancer.

Combination therapy with the oncolytic virus CF33-CD19 and blinatumomab for the treatment of advanced solid tumors.

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Background: CF33-CD19 is a novel chimeric vaccinia virus that selectively replicates in tumor cells and can provoke anti-tumor immunity. CF33-CD19 expresses a truncated and non-signaling CD19 protein on the surface of infected tumor cells before virus-mediated tumor lysis, labeling them for CD19-targeted therapies. Preclinical studies with CF33-CD19 have shown that combination therapy with CD19 targeting chimeric antigen receptor *T* cells is more effective than either monotherapy in murine xenograft and syngeneic models [1]. Likewise, combination therapy with bispecific T-cell engagers (BiTE)s that bind CD3-positive T cells and infected solid tumor cells that express de novo CD19, showed pronounced recruitment of T cells to the tumor microenvironment, resulting in tumor growth inhibition in mouse models. CD19xCD3 targeting BiTEs such as blinatumomab may offer an off-the-shelf alternative to adoptive cell therapies. This phase I study, called OASIS, dose escalates CF33-CD19 administered intravenously (IV) or intratumorally (IT) combined with blinatumomab in adults with advanced or metastatic solid tumors. **Methods:** The OASIS study (NCT06063317) is enrolling patients with advanced or metastatic solid tumors with ≥ 2 prior lines of therapy. Patients who have received prior treatment with a poxvirus based oncolytic virus or a bispecific CD19-directed CD3 T-cell engager are excluded. A safety run-in will evaluate the safety of CF33-CD19 monotherapy administered IT or IV before initiating the combination therapy regimen. Combination therapy will be administered in 28-day cycles with CF33-CD19 on days 1 and 15. Following viral transduction to promote de novo CD19 expression, blinatumomab is given on days 2-9 and 16-23 via a 7-day continuous infusion. Patients > 45 kg will receive 9 mcg of blinatumomab during the first week of cycle 1, then 28 mcg during the third week of cycle 1 and subsequent cycles. The study consists of two parts. Part 1 follows a 3+3 dose escalation scheme independently of each route of CF33-CD19 administration (IT and IV) with dose levels of CF33-CD19 ranging from $1.0x10^7$ to $3.0x10^9$ PFU. Part 2 is a cohort expansion in select indications at the optimal dose. The co-primary endpoints are safety and identification of the recommended phase 2 dose. Secondary endpoints include objective response rate according to RECIST v1.1 and iRECIST. Enrollment began in October 2023. 1. Park et al. Sci Transl Med. 2020 Sep 2;12(559): eaaz1863. doi: 10.1126/scitranslmed.aaz1863. PMID: 32878978. Clinical trial information: NCT06063317. Research Sponsor: Imugene Limited.

TPS2688 **Poster Session**

Phase I, open-label, dose-escalation trial investigating the safety and efficacy of oncolytic virus BI 1821736 in patients with advanced solid tumors.

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Background: Despite some advances, the need for novel anti-cancer therapies remains high in patients with advanced solid tumors. Although immunotherapy with checkpoint inhibitors is the preferred treatment for several cancer types, a proportion of patients will have non-responsive tumors or develop resistance. Oncolytic viruses have potential as novel immunotherapies, due to their tumor-selectivity and ability to stimulate a systemic anti-tumor immune response. BI 1821736 is a genetically engineered pseudotype variant of VSV-GP encoding an immune-stimulatory cargo. The VSV-GP backbone is a recombinant chimeric vesicular stomatitis virus modified to replace the innate neurotropic G glycoprotein with the non-neurotropic GP glycoprotein from the lymphocytic choriomeningitis virus. BI 1821736 selectively replicates and lyses cells with defective interferon signaling, which is seen particularly in cancer cells. The immune-stimulating cargo leads to T-cell priming and reactivation within the immunosuppressed tumor microenvironment. Preclinical efficacy, toxicology, and environmental safety results support BI 1821736 administration in humans. **Methods:** 1467-0001 (NCT05839600) is a Phase I, open-label, dose-escalation study evaluating the safety and early efficacy of BI 1821736 in patients with advanced solid tumors. The study is enrolling adult patients who have exhausted available treatment options, with an Eastern Cooperative Oncology Group Performance Status of 0 or 1, ≥1 lesion amenable to biopsy, and adequate organ function. Patients with brain metastases are excluded unless they have completed brain radiotherapy and are asymptomatic. Patients will receive escalating doses of intravenous BI 1821736 for up to 3 months. Dose escalation will be guided by a Bayesian 2-parameter logistic regression model with overdose control (BLRM-EWOC). The primary objective is to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose based on occurrence of dose-limiting toxicities (DLTs) during the MTD evaluation period of the first treatment cycle (Cycle 1; 21 days). Other safety endpoints include the occurrence of DLTs and adverse events during the treatment period. Further objectives include the assessment of BI 1821736 preliminary efficacy, pharmacokinetics, immunogenicity, shedding, and biomarkers. Patients are being recruited from approximately 10 sites across North America and Europe. Enrollment began in May 2023. A total of six patients have received BI 1821736 as of January 29, 2024. Patients are currently being enrolled to dose level 2. Clinical trial information: NCT05839600. Research Sponsor: Boehringer Ingelheim International GmbH.

TPS2689 **Poster Session**

A phase 1, open-label, dose escalation study on the safety and tolerability of ANK-101 in advanced solid tumors.

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Background: IL-12 is a cytokine that can stimulate both innate and adaptive tumor immunity. Clinical trials of intravenous IL-12 demonstrated anti-tumor activity limited by significant systemic toxicity, including patient deaths. ANK-101 is an anchored immunotherapy that links IL-12 to aluminum hydroxide through an alum-binding protein (ABP). The ANK-101 complex anchors IL-12 in the tumor microenvironment (TME), resulting in prolonged local retention and low levels of systemic absorption. Preclinical studies in murine tumor models showed that ANK-101 is retained at the injection site for up to 28 days, recruits and activates T and NK cells, promotes M1 myeloid cell differentiation, induces regression of both injected and un-injected tumors, and induces immunologic memory. **Methods:** This is a first-in-human, open-label dose escalation study of ANK-101 in advanced solid tumors with a planned sample size of 12-36 participants. The first three dose escalation cohorts include a single participant, and then study enrollment follows a standard 3+3 dose escalation design. If no dose limiting toxicity (DLT) is observed, the dose level will be escalated until ≥1/3 or ≥2/6 patients experience a DLT. An additional ten patients will be enrolled at the recommended dose for expansion (RDE). Participants will be treated with intratumoral ANK-101 every 3 weeks for 4 cycles. Imaging or clinical assessments will be performed at week 12. If there is no significant clinical deterioration or unacceptable toxicity at this visit, participants may receive four more cycles. Eligible patients must have an advanced solid malignancy refractory to standard treatment and be accessible for injection and biopsy, measurable disease by RECIST v1.1, and ECOG PS of 0-1. Key exclusion criteria include tumors close to vital structures, uncontrolled bleeding disorders, and active autoimmune disease. Primary objectives of the study are to determine the safety and tolerability of ANK-101 and identify the RDE. Secondary objectives include pharmacokinetics (PK) and immunogenicity (ADA) of ANK-101 and clinical activity as measured by ORR, DCR, DOR and PFS by RECIST v1.1. Exploratory objectives include assessment of QOL using FACT-G and profiling immune-based pharmacodynamic (PD) changes. PD assessments will include serum cytokines and circulating immune cells, and local levels of PD-L1, CD8+ T cells, and CD68+ macrophages, and changes in gene expression within the TME. This clinical trial is in progress. Clinical trial information: NCT06171750. Research Sponsor: Ankyra Therapeutics.

TPS2690 **Poster Session**

Phase I trial of CRD3874-SI, a systemically administered STING agonist, in patients with advanced solid tumors.

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Background: Identifying novel approaches that harness and augment anti-tumor immune responses represents an important area of ongoing research and drug development. Stimulator of interferon genes (STING) is an endoplasmic protein receptor that acts as an innate immune mediator by generating protective type 1 interferons when cytosolic DNA is detected in cells. STING also channels protons across golgi membranes promoting autophagy and pyroptosis. CRD3874-SI is a first in class small molecule allosteric STING agonist and potent activator of all five human STING variants that promotes the release of inflammatory cytokines from downstream interferon genes. It has demonstrated promising pre-clinical anti-cancer activity in several tumor mouse models. CRD3874-SI demonstrated high levels of systemic safety in cynomolgus monkeys, thought to be related to its ability to inhibit STING proton channel activity. **Methods:** This is a single institution, phase 1a/b study of CRD3874-SI in patients with advanced sarcoma and Merkel cell carcinoma who have received at least one line of prior therapy. The dose escalation phase will explore the safety and tolerability of CRD3874-SI across 6 dose levels following a standard 3+3 design. Dose expansion in subtype specific sarcoma and Merkel cell carcinoma is planned on completion of the dose escalation phase of the study. CRD3874-SI will be administered by intravenous infusion once per week for 2 cycles. From cycle 3 onwards, participants will receive three consecutive weekly infusions followed by one week break, over a 28-day treatment cycle. The primary objective is to assess the safety and tolerability of CRD3874-SI by determining the maximum tolerated dose, recommended phase 2 dose and schedule of administration. Secondary objectives include further defining the safety profile, examining the pharmacokinetics and pharmacodynamics (CXCL10 analysis) of CRD3874-SI and evaluating the efficacy of CRD3874-SI as determined by best objective response rate and clinical benefit rate per RECIST v 1.1. Treatment will continue for up 6 cycles or until disease progression or unacceptable toxicity. Cross sectional imaging will be used to measure clinical activity. Adverse events will be evaluated using NCI-CTCAE v5.0 criteria. This study is currently open to enrollment and dosing has commenced. Clinical trial information: NCT06021626. Research Sponsor: Curadev Pharma, Inc.

A first-in-human phase I study of ATG-031, anti-CD24 antibody, in patients with advanced solid tumors or B-cell non-Hodgkin lymphomas (PERFORM).

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Background: ATG-031 is a first-in-class humanized cluster of differentiation 24 (CD24) antibody. By disrupting the interaction between CD24, a 'do not eat me' signal on cancer cells, and the inhibitory receptor Siglec-10 on tumor-associated macrophages (TAMs), it enhances macrophage-mediated phagocytosis of cancer cells and promotes cytotoxic T cell function in the tumor microenvironment. ATG-031 also triggers antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) towards target tumor cells through its immunoglobulin gamma 1 (IgG1) Fc-dependent effects. Preclinical studies indicated that ATG-031-induced phagocytosis transforms macrophages from a tumor-tolerant M2 phenotype to an antitumor M1 phenotype, significantly inhibiting tumor growth both as monotherapy and synergistically with immune checkpoint inhibitors (ICI) and/or chemotherapies in mouse models. **Methods:** ATG-031 is undergoing evaluation for safety and preliminary antitumor efficacy in a Phase I, multi-center, open-label clinical study, PERFORM (NCT04986865), in patients with advanced solid tumors or B-cell non-Hodgkin's lymphoma. The study includes a dose escalation phase and a dose expansion phase. The dose escalation phase enrolls patients with advanced solid tumors (preferred tumor types: lung cancer, breast cancer, ovarian cancer, urothelial cancer, and liver cancer) using a Bayesian Optimal Interval (BOIN) design with 3 to 9 patients at each dose level. A priming dose, defined as an initial lower dose followed by escalation to the full treatment dose, will be applied if Grade $\geq$2 cytokine release syndrome (CRS) is observed during the dose-limiting toxicity (DLT) period. The dose expansion phase will enroll patients with specific tumor types and will randomize patients into two or more dose levels to determine the recommended Phase II dose (RP2D). The PERFORM study explores an intravenous dose of ATG-031 once every 21 days (1 cycle) to assess DLT during the first two treatment cycles in dose escalation. Key inclusion criteria include histological or cytological confirmation of a solid tumor that has relapsed or has been refractory to standard therapy, at least one measurable lesion per RECIST, and an ECOG performance status of 0 to 1. The study excludes patients with CNS malignancies and those who have experienced Grade $\geq$3 immune-related adverse events (irAEs) or irAEs leading to prior immunotherapy discontinuation. As of January 2024, 2 sites in the United States have initiated the study, and 4 patients have received ATG-031 treatment at 0.03mg/kg (dose level 1). Clinical trial information: NCT04986865. Research Sponsor: None.

TPS2692 Poster Session

Phase 1 study of AM003, a novel individualized immunotherapy, in a basket of advanced solid tumors.

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Background: Aummune is developing a unique individualized immunotherapy ('AM003'), designed to have three activities mediated by three different domains: (1) the 'Variable Domain, identified de novo for each individual patient, based on its ability to specifically induce cell death on patient's tumor cells; (2) the 'General Domain', designed to engage with immune T cells to cause tumor cell lysis; and (3) a 'CpG-rich Domain' that stimulates Antigen Presenting Cells. Aummune's process begins with sampling the patient's tumor (via biopsy) and healthy cells (PBMCs). The cancerous cells are grown in a 3D culture and once the cells propagate and reach a critical biomass, they are subjected to Aummune's proprietary platform for the identification of the Variable Domain. Once a tumoricidal sequence is identified, it is manufactured and the drug product (DP) is assembled at the production facility. Following release, the DP is shipped to the medical site for treatment of the patient. **Methods:** AM003 is being evaluated as an immune-oncology agent in advanced/metastatic relapsed/refractory solid tumors. A First-In-Human Phase 1, open-label multicenter, dose-escalation study of AM003 is ongoing with the following cohorts: (1) 34mg (2) 68mg and (3) 136 mg of AM003 monotherapy administered intratumorally / local subcutaneously once per week for 4 weeks, followed by 6 doses administered every 2 weeks. Key inclusion criteria include (i) histologically confirmed locally advanced/metastatic solid tumors who received and progressed after, or were intolerant to, at least 1 prior systemic therapy and are not candidates for any therapy known to confer clinical benefit. (ii) lesions that are safely amenable to IT injection. The primary objective is to evaluate the safety and tolerability of AM003. Additional objectives include assessment of preliminary evidence of clinical benefit, pharmacokinetic and pharmacodynamics measurements as well as identification of biomarkers. Endpoints: AEs are assessed according to CTCAE v5, treatment response is determined according to RECIST 1.1 and iRECIST, changes in putative markers are evaluated based on multiple analyses methodologies. 10 patients were included in the dose-escalation part: 1(n=4), 2 (n=3), and 3 (n=3). Cohorts 1, 2 and 3 have been completed without DLTs. The DSMB last reviewed the escalation data in January 2024 and concluded that the trial can continue as planned. Enrollment of 136mg dose expansion is ongoing and completion of the trial will be mid 2024. Clinical trial information: MOH_2022-03-29_010690. Research Sponsor: None.

TPS2693 Poster Session

A phase 1 dose-escalation and expansion study of an intratumorally administered dual STING agonist (ONM-501) alone and in combination with cemiplimab in patients with advanced solid tumors and lymphomas.

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Background: The Stimulator of Interferon Genes (STING) pathway has garnered significant interest as a target for anticancer interventions due to its role in driving the production of pro-inflammatory cytokines and activating tumor-specific cell killing. Cyclic dinucleotides (CDNs) such as cGAMP, the endogenous STING agonist, are not ideal clinical candidates for exogenous routes of delivery. Early trials showed limited efficacy with CDNs due to rapid clearance, degradation and/or off-target toxicity. ONM-501 is comprised of a STING-activating pH-sensitive PC7A polymer conjugated with cGAMP. At physiologic pH, ONM-501 forms a micelle, preventing degradation of cGAMP. In the acidic tumor microenvironment, ONM-501 effects STING agonism through a multi-faceted mode of action: 1) endocytosis of nanoparticles and pH-activated micelle dissociation and payload release in endolysosomes enhances intracellular delivery of cGAMP 2) the combination of cGAMP canonical binding, and PC7A polymer non-canonical binding on STING yields synergistic STING activation and 3) stabilization of STING by PC7A polymers delays its degradation and prolongs STING activation. In pre-clinical models, these factors combine to help generate a stronger and more prolonged innate immune response that more effectively translates to a robust adaptive immune response. ONM-501 is being investigated in this first-in-human Phase 1 trial as monotherapy and combination therapy with the anti-PD1 antibody, cemiplimab, for patients with solid tumors and lymphomas. **Methods:** ONM5001 (NCT06022029) is a first-in-human, open-label, multi-center clinical trial. Adult patients with solid tumors or lymphomas for which no standard therapy exists or for which patients decline palliative standard therapy who have at least one injectable lesion are eligible for this study. This Phase 1 study consists of three parts: monotherapy dose escalation; combination therapy dose finding; and combination therapy dose expansion in specific tumor indication(s) that will be selected based on data from mono- and combination therapy dose finding. Each dosing cycle of ONM-501 is 21 days: patients receive an intratumoral injection of ONM-501 weekly for three weeks, followed by three weeks without injection. Cemiplimab is administered intravenously during combination therapy arms according to standard administration protocol, once every three weeks. The primary endpoint is to evaluate safety of ONM-501 monotherapy as evidenced by the number of dose limiting toxicities and treatment-emergent adverse events, and to determine the recommended dose for expansion. Secondary endpoints include characterization of pharmacokinetics and pharmacodynamics, as well as initial efficacy based on RECIST evaluation criteria. Enrollment began in November 2023. Clinical trial information: NCT06022029. Research Sponsor: None.

TPS2695 **Poster Session**

A phase 1/2 study of BDC-3042, a novel dectin-2 agonistic antibody, in patients with advanced cancers.

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Background: Tumor-associated macrophages (TAMs) are a major component of the immune infiltrate in most cancers and play a key role in establishing the immunosuppressive tumor microenvironment (TME) that enables tumor progression. However, TAMs are phenotypically plastic and have the potential to be reprogrammed into immunostimulatory cells that enhance innate and adaptive anti-tumor immunity. BDC-3042 is a novel agonistic antibody targeting an immune-activating receptor expressed on TAMs known as Dectin-2 (*CLEC6A*) [1]. Dectin-2 is a C-type lectin receptor best known for its role in pathogen recognition and induction of protective immune responses against fungi and other microbes. We have previously demonstrated that Dectin-2 agonism stimulates pro-inflammatory cytokine secretion and antigen presentation by TAMs, resulting in robust CD8+ T cell-mediated anti-tumor immunity in syngeneic mouse models [2]. Elevated gene expression of Dectin-2 has been found in a wide range of solid tumor types compared to non-malignant tissues. Nonclinical studies with BDC-3042 have demonstrated its potential to reprogram TAMs and elicit anti-tumor activity as a novel immunotherapeutic approach for diverse human cancers [2]. A phase 1/2, first-in-human, dose-escalation and dose-expansion study of BDC-3042 as a single agent and in combination with a cemiplimab in subjects with advanced cancers has been initiated. **Methods:** This study is enrolling up to 185 patients with advanced cancers, including non-small cell lung cancer, melanoma, triple-negative breast cancer, renal cell carcinoma, colon cancer, head and neck cancer, and ovarian cancer. Primary objectives of the dose-escalation phase are to define safety and tolerability and to determine the recommended phase 2 dose (RP2D) of BDC-3042 as a monotherapy (Part 1) and in combination with cemiplimab (Part 2). The dose-expansion phase will evaluate preliminary anti-tumor activity of BDC-3042 monotherapy (Part 3) and with cemiplimab (Part 4). Secondary objectives will evaluate pharmacokinetic parameters and pharmacodynamic biomarkers in tumor tissue and in peripheral blood associated with drug exposure. Exploratory analyses will also be conducted to assess BDC-3042's ability to reprogram TAMs and identify biomarkers associated with BDC-3042 biological activity and with cemiplimab. This study is being conducted in the US and is currently recruiting patients. 1. Kenkel J, et al. *Cancer Res*. 2023. 2. Kenkel J, et al. *J Immunother Cancer*. 2021. Clinical trial information: NCT06052852. Research Sponsor: Bolt Biotherapeutics.

TPS2696 **Poster Session**

A phase I trial of intratumoral STX-001: A novel self-replicating mRNA expressing IL-12 alone or with pembrolizumab in advanced solid tumors.

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Background: STX-001 is a multi-mechanistic lipid nanoparticle encapsulated synthetic self-replicating mRNA, engineered to express the IL-12 cytokine for an extended duration when administered intratumorally. A murine surrogate of STX-001 induces deep durable responses in multiple preclinical solid tumor models. This Phase 1 open-label, multi-center first-in-human dose-escalation trial evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of STX-001 alone, or in combination with pembrolizumab in patients with treatment refractory advanced cancers. **Methods:** Approximately 30 adults ≥18 years of age with histologically confirmed advanced solid tumors that are refractory to standard treatments will be enrolled. The study will consist of two arms, an STX-001 monotherapy arm and an STX-001 + pembrolizumab combination arm, enrolling approximately 15 patients each. Key eligibility criteria include ECOG status 0 or 1, a tumor lesion amendable to injection, and confirmed prior disease progression. STX-001 will be administered every 3 weeks (q3w) for 3 doses and then every 6 weeks (q6w) for a further 3 doses. Tumor biopsies will be obtained at baseline and after the first STX-001 administration. Primary endpoints will include safety and maximum tolerated dose (MTD), with secondary endpoints encompassing pharmacokinetics and preliminary efficacy as measured by RECIST 1.1. To determine the MTD, this study will employ the Bayesian optimal interval (BOIN) design, with the 3 + 3 design run-in and a recommended phase 2 dose (RP2D) will be determined. Tumor response will be assessed using RECIST 1.1 criteria. Exploratory pharmacodynamic analyses will assess tumor-infiltrating lymphocytes and STX-001 mRNA in baseline and on-treatment biopsies, evaluate inflammatory cytokine profiles in plasma, determine immune activation in circulating immune cells, and measure circulating tumor DNA (ctDNA) for molecular response assessment. Clinical trial information: NCT06249048. Research Sponsor: None.

TPS2697 **Poster Session**

A phase 1 trial in progress for in situ immunomodulation with CDX-301, radiation therapy, poly-ICLC, and CDX-1140 in patients with unresectable and metastatic solid tumors.

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Background: The prognosis for patients with unresectable and metastatic solid tumors that progress on standard of care therapy remains poor due to limited treatment options. Compelling evidence suggests that the induction and activation of tumor-residing conventional type-1 dendritic cells (cDC1) is critical to elicit anti-tumor immunity. Recently, we have demonstrated that a combinatorial regimen comprised of in situ delivery of Fms-like tyrosine kinase 3 ligand (Flt3L), radiation therapy (9Gy), and dual TLR3/CD40 stimulation 1) mobilizes cDC1 to the tumor microenvironment; 2) induces maturation of cDC1; 3) facilitates trafficking of cDC1 carrying tumor antigens to tumor-draining lymph nodes; 4) elicits de novo adaptive T cell immunity; 5) triggers regression of primary tumors, as well as non-irradiated distant tumors; and 6) develops tumor-specific systemic immunological memory using multiple syngeneic orthotopic murine models (1-4). Based on results from preclinical studies, we have initiated a phase 1 study as below. **Methods:** This is a phase 1 study of in situ immunomodulation with CDX-301 (Flt3L), radiation therapy, CDX-1140 and Poly-ICLC (dual CD40/TLR3 stimulation) in patients with unresectable and metastatic solid tumors. Eligibility for this study includes patients $\geq$ 18 yrs who have clinically or pathologically confirmed diagnosis of unresectable and metastatic melanoma, cutaneous squamous cell carcinoma, Merkel cell carcinoma, high-grade bone and soft tissue sarcoma or HER2/neu (-) breast cancer with no curative treatment options, and progressed on at least one line of standard systemic therapy. The unresectable disease to be irradiated and injected with medications must be located in breast, dermal, subcutaneous, or soft tissue, or lymph nodes with the longest axis of the tumor 2-7 cm, and should be considered safe for injection by the investigator. The metastatic disease must be measurable per irRECIST criteria. Patients will be treated with daily intratumoral injection of CDX-301 for 5 days (Day 1-5), radiation therapy (9Gy, Day 8) followed by administration of CDX-1140 and Poly-ICLC (Day 9). Up to 4 cycles of this combination therapy can be given every 3 weeks. The primary endpoints are safety/tolerability and to evaluate the MTD of for injection (intratumoral in the cohort A and intratumoral and intravenous in the cohort B) of CDX-1140. A standard 3+3 design, allowing for dose de-escalation, will be used within each cohort. Secondary endpoints are to evaluate immune signatures in blood and the tumor. This phase 1 trial opened to enrollment at the University of Southern California Norris Comprehensive Cancer Center in January 2023 (recruitment is currently 4 on February 6, 2024). 1. *Nature Communications* 2020. 2. *J. Immunology* 2021. 3. *Cancer Research* 2021. 4. *Scientific Reports* 2022. Clinical trial information: NCT04616248. Research Sponsor: METAvivor; National Cancer Institute/U.S. National Institutes of Health; R01CA255240.

TPS2698 Poster Session

EVEREST-1: A seamless phase 1/2 study of A2B530, a carcinoembryonic antigen (CEA) logic-gated Tmod CAR T-cell therapy, in patients with solid tumors associated with CEA expression also exhibiting human leukocyte antigen (HLA)-A*02 loss of heterozygosity (LOH).

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Background: Chimeric antigen receptor (CAR) T-cell therapies for treating solid tumors are challenging due to a lack of tumor-specific targets that discriminate cancer from normal cells. Previous studies using CEA T-cell receptors and T-cell engagers have resulted in dose-limiting, on-target, off-tumor toxicities (1,2). A2B530 is an autologous logic-gated, CEA-targeted Tmod CAR T-cell therapy that addresses the challenges of on-target, off-tumor toxicity by combining a CAR-activating receptor with a blocking receptor to discriminate tumor from normal cells (3). The activator recognizes CEA on the surface of both tumor and normal cells while specificity for tumor cells is provided by a blocker that binds HLA-A*02. In patients with both germline HLA-A*02 and tumor-associated HLA-A*02 LOH, the blocker prevents on-target, off-tumor toxicity on normal cells owing to retained HLA-A*02 expression (4). HLA-A*02 LOH can be detected using next-generation sequencing (Tempus AI, Inc.). With this definitive discriminator target, A2B530 can potentially provide a therapeutic window to treat patients with CEA-expressing solid tumors exhibiting HLA LOH. **Methods:** EVEREST-1 (NCT05736731) is a seamless, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B530 in adult patients. Patients are enrolled through BASECAMP-1 (NCT04981119), a master prescreening study that identifies patients with HLA LOH at any time in the course of their disease. BASECAMP-1–eligible patients undergo leukapheresis and, when clinically appropriate, their banked T cells are manufactured for the EVEREST-1 study. The key inclusion criteria include histologically confirmed recurrent unresectable, locally advanced, or metastatic cancers associated with CEA expression: non-small cell lung, colorectal, or pancreatic cancers. Patients should have received ≥1 line of prior therapy such as checkpoint inhibitor, molecular targeted, or chemotherapy. The primary objective of phase 1 is to evaluate the safety and tolerability of A2B530 and determine the recommended phase 2 dose (RP2D). The dose-escalation portion is based on the Bayesian optimal interval design. The dose-expansion phase will confirm RP2D and collect biomarker data to further characterize A2B530. Phase 2 will assess overall response rate per RECIST v1.1. As of January 29, 2024, 8 patients have been enrolled on EVEREST-1. A2B530 was successfully manufactured for all patients, and all patients have received A2B530 infusion, with the first patient dosed in May 2023. Dose escalation is ongoing. 1. Parkhurst, et al. *Mol Ther*. 2022. 2. Tabernero, et al. *J Clin Oncol*. 2017. 3. Hamburger, et al. *Mol Immunol*. 2020. 4. Sandberg, et al. *Sci Transl Med*. 2022. Clinical trial information: NCT05736731. Research Sponsor: A2 Biotherapeutics, Inc.

TPS2699 Poster Session

EVEREST-2: A seamless phase 1/2 study of A2B694, a mesothelin (MSLN) logic-gated Tmod CAR T-cell therapy, in patients with solid tumors that show MSLN expression and human leukocyte antigen (HLA)-A*02 loss of heterozygosity (LOH).

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Background: Despite the success in hematologic cancers, chimeric antigen receptor (CAR) T-cell therapies are challenging to implement in solid tumors owing to a lack of tumor-specific targets that discriminate cancer from normal cells. MSLN expression normally is limited to the mesothelium of major body cavities but can be upregulated in diverse solid tumor types (TCGA 2022), making it a potential target for cancer therapy. MSLN-targeted cell approaches, including CAR T-cell and T-cell receptor fusion therapies, have shown promising clinical activity; however, on-target, off-tumor toxicity including fatal events have occurred (1-3). A2B694 is an autologous logic-gated, MSLN-targeted Tmod CAR T-cell therapy that addresses the challenges of on-target, off-tumor toxicity by combining 2 CARs: an activating and blocking receptor. The activator recognizes MSLN present on the surface of both tumor and normal cells; the blocker binds HLA-A*02 and prevents CAR T-cell activity. Thus, in patients with both germline HLA-A*02 and tumor-associated HLA-A*02 LOH, the blocker prevents on-target, off-tumor toxicity on normal cells owing to retained HLA-A*02 expression (4). Through this unique discriminatory mechanism, A2B694 may provide a therapeutic window to treat patients with MSLN-expressing solid tumors exhibiting HLA-A*02 LOH. **Methods:** EVEREST-2 (NCT06051695) is a first-in-human, phase 1/2, open-label, nonrandomized study to evaluate the safety and efficacy of A2B694 in adults with recurrent unresectable, locally advanced, or metastatic cancers with MSLN expression, including non-small cell lung cancer, colorectal cancer, pancreatic cancer, ovarian cancer, mesothelioma, or other solid tumors with MSLN expression. Eligible patients should have received ≥1 line of prior therapy such as checkpoint inhibitor, molecular targeted, or chemotherapy. Enrollment to EVEREST-2 occurs through the prescreening study BASECAMP-1 (NCT04981119), which identifies patients with tumor-associated HLA-A*02 LOH via next-generation sequencing (Tempus AI, Inc.). Eligible patients enroll in the BASECAMP-1 study and undergo leukapheresis. A2B694 is manufactured from cryopreserved T cells when clinically appropriate for patients. The primary objective of phase 1 is to evaluate the safety and tolerability of A2B694 and identify the recommended phase 2 dose (RP2D). The dose-expansion phase will confirm RP2D and collect biomarker data to further characterize A2B694. Phase 2 will assess overall response rate per RECIST v1.1. 1. Beatty, et al. *Gastroenterology*. 2018. 2. Haas, et al. *Mol Ther*. 2023. 3. Hong, et al. ESMO 2021. Abstract 9590. 4. Hamburger, et al. *Mol Immunol*. 2020. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

TPS2700 **Poster Session**

A phase I pilot study of personalized neoantigen peptide-based vaccine in combination with pembrolizumab in advanced solid tumors (PNeoVCA).

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Background: Though immunotherapy with anti-PD-1 immune checkpoint inhibitors (ICIs) has led to improvements in clinical outcomes in patients with cancer, when used as monotherapy in the advanced setting, only 18-25% of patients respond to ICI. Notably, ICI frequently lacks anti-tumor activity in immune-cold cancers where T cell priming is missing. Recent breakthroughs in identifying personal neoantigens via a comprehensive analysis of cancer sequencing data have brought increased attention to neoantigen cancer vaccines. Personalized cancer vaccines targeting neoantigens have shown early promise. While neoantigens have recently been investigated in some cancer types, the current neoantigen prediction algorithms have often focused on the MHC class-I subtype, single nucleotide mutations (SNM), small insertions and deletions (INDEL). We recently developed an informatics workflow, REAL-neo, for the identification, quality control (QC), and prioritization of both class-I and class-II human leukocyte antigen (HLA) bound neoantigens that arise from somatic SNM, INDEL, aberrant RNA splicing, and gene fusions, generating much more potent neoantigen candidates. Furthermore, we demonstrated robust T-cell response and prolonged survival by combining ICI and cancer vaccines in preclinical models. This single-arm phase I clinical trial is in progress to assess the safety, feasibility, and immunogenicity of personalized neoantigen vaccines in combination with pembrolizumab in patients with advanced solid cancers. **Methods:** The vaccine consists of up to 20 peptides (15-30 mer) comprising patient-specific neoantigens identified from tumor DNA and mRNA sequencing data using REAL-neo and delivered with GM-CSF as an adjuvant. The first cohort of three patients will be treated at dose level 1 consisting of 4 or 5 peptides at 300 mcg/peptide and GM-CSF 125 mcg per injection site in each of four limbs. After Cohort 1 is deemed safe, the study will expand to cohort 2, when patients will be enrolled at the same dose level for vaccine plus Pembrolizumab 200 mg i.v. Neoantigen vaccine will be given via subcutaneous injection on days 1, 4, 8, 15, and 21 (cohorts 1 and 2) and weeks 5 and 8 (booster dose for cohort 2 only). Cohort 1 has been completed without dose-limiting toxicity (DLT). Enrollment in Cohort 2 began in January 2024. AEs are assessed according to CTCAE v5. and safety findings are reviewed by data safety medical board (DSMB). Key eligibility criteria include 1) histologically confirmed locally advanced or metastatic solid malignancies and 2) cancer progression after at least one line of the standard-of-care (SOC) systemic treatment. For cohort 2, patients must be eligible to receive pembrolizumab per SOC or the treating physician's judgment. Clinical trial information: NCT05269381. Research Sponsor: Mayo Clinic.

TPS2701 **Poster Session**

A randomized phase 2 trial of the IO102-IO103 (IDO and PD-L1) cancer vaccine plus pembrolizumab as neoadjuvant/adjuvant treatment of patients with solid tumors.

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Background: Immune checkpoint inhibitors have transformed the treatment of multiple tumor types, including melanoma and squamous cell carcinoma of the head and neck (SCCHN). However, some patients (pts) with locally advanced disease still recur after surgery and adjuvant therapies. In melanoma, neoadjuvant pembrolizumab followed by adjuvant pembrolizumab was shown to improve event-free survival (EFS) compared to adjuvant pembrolizumab only (1). In SCCHN, two cycles of neoadjuvant pembrolizumab resulted in a two-fold increase in the frequency of pathological tumor response compared with one cycle (2). IO102-IO103 is an investigational therapeutic cancer vaccine that targets both tumor and immune-suppressive cells in the tumor microenvironment. IO102-IO103 treatment promotes inflammation and potentiates anti-tumor activity via activation and expansion of T cells against IDO1 and/or PD-L1 positive cells. Treatment with IO102-IO103 plus nivolumab in anti-PD-1 naïve metastatic melanoma showed 80% objective response rate including 50% complete response and was well tolerated in a phase 1/2 trial (3). We aim to investigate the activity of IO102-IO103 plus pembrolizumab in the perioperative setting in melanoma and SCCHN. **Methods:** IOB-032// PN-E40 (NCT05280314) is a Phase 2, open-label, multi-cohort trial aiming to evaluate safety, anti-tumor and immunological activity of IO102-IO103 in combination with pembrolizumab as neoadjuvant and adjuvant treatment. Pts with resectable tumors classified as melanoma (Cohorts A and C) or SCCHN (Cohort B) are eligible. Cohorts A and B are single-arm 15 patient cohorts. Following completion of Cohort A, additional 30 stage III melanoma pts will be randomized 1:1 to receive neo-adjuvant treatment with either IO102-IO103 plus pembrolizumab or pembrolizumab alone (Cohort C). During the neoadjuvant period, study treatment is every 3 weeks (Q3W) for 3 cycles (melanoma) or 2-3 cycles (SCCHN). Surgery will be performed between 1 and 3 weeks after the last neoadjuvant dose, followed by adjuvant treatment with IO102-IO103 and pembrolizumab or pembrolizumab alone Q3W for 15 cycles. Pts in Cohort C with poor pathological response to pembrolizumab alone in the neoadjuvant phase (>10% residual viable tumor) may cross over to receive the combination treatment post-surgery at the discretion of the investigator. The primary endpoint is major pathological response (≤10% residual viable tumor) at surgery (central assessment). Secondary endpoints include safety, EFS and disease-free survival. Furthermore, paired pre- and post-treatment tumor tissue and blood samples will be collected for translational research. The study will be conducted in the US, EU and Australia and began enrolment in December 2023. 1. Patel, NEJM 2023. 2. Oliveira, Sci Immunol. 2023. 3. Kjeldsen, Nat Med. 2021. Clinical trial information: EudraCTNo.2022-502787-20-00; ClinicalTrials.govNo.NCT05280314. Research Sponsor: IO Biotech ApS & Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS2702 Poster Session

FusionVAC22_01: A phase I clinical trial evaluating a DNAJB1-PRKACA fusion transcript-based peptide vaccine combined with immune checkpoint inhibition for fibrolamellar hepatocellular carcinoma and other tumor entities carrying the oncogenic driver fusion.

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Background: The DNAJB1-PRKACA fusion transcript is the driving force behind tumor development in fibrolamellar hepatocellular carcinoma (FL-HCC) and other tumor types, such as oncocytic neoplasms of the pancreas and bile ducts. Consequently, it serves as a versatile target for innovative cancer therapies. Recently, the DNAJB1-PRKACA fusion protein was recognized as a source of HLA-presented neoepitopes targetable by to T cell-based immunotherapy (1). The FusionVAC-22 neoepitope, derived from DNAJB1-PRKACA fusion, is computationally predicted to bind to 1,290 different HLA class II alleles. Furthermore, it includes embedded HLA class I ligands for 13 out of the 20 most common HLA class I alleles, covering 93.8% of the global population This broad coverage enables the widespread application of FusionVAC-22-based immunotherapies. The initial use of FusionVAC-22-based peptide vaccines, adjuvanted with the TLR1/2 agonist XS15 emulsified in Montanide ISA 51 VG, in two FL-HCC patients was well-tolerated and demonstrated the induction of robust and long-lasting T cell responses. Notably, T cell responses coincided with 32 months and 13 months of progression-free survival for the respective patients. **Methods:** Building on these promising outcomes, we have initiated a Phase I open-label, multicentric clinical trial to assess the immunogenicity, safety, toxicity, and initial signs of efficacy of the FusionVAC-22-based peptide vaccine combined with the immune checkpoint inhibitor (ICI) atezolizumab. The trial includes 20 patients with locally advanced or metastatic FL-HCC or other malignancies carrying the DNAJB1-PRKACA fusion transcript without available standard therapy. Key eligibility criteria involve the absence of autoimmune phenomena due to prior immunotherapy agents (≥ grade 3) and no history of tissue or organ allografts. The FusionVAC-22-based peptide vaccine is administered twice with a 4-week interval, with an option for a booster vaccination after 11 months. ICI administration begins on day 15 after the first vaccination and continues every 4 weeks for 1 year, followed by a 6-month follow-up. Primary trial objectives include assessing immunogenicity in terms of peptide-specific T cell responses up to 28 days after the second vaccination, as well as evaluating the safety and toxicity of the peptide vaccine in combination with ICI. Safety assessment is based on the frequency of adverse events according to CTCAE v5.0. Clinical efficacy is determined through iRECIST assessment on imaging. Additionally, disease control rate, quality of life, and overall and progression-free survival will be evaluated. So far, 3 out of 20 planned patients have been enrolled. 1. Bauer et al., Nat. Commun, 2022. Clinical trial information: NCT05937295. Research Sponsor: None.

TPS2703 **Poster Session**

Repurposing ibrutinib for chemo-immunotherapy in a phase 1b study of ibrutinib with indoximod plus metronomic cyclophosphamide and etoposide for patients with childhood brain cancer.

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Background: In children, brain cancer is the leading cause of cancer related death. The indoleamine 2,3-dioxygenase (IDO) pathway is a metabolic checkpoint, expressed by host myeloid and dendritic cells, that suppresses anti-tumor immune responses following chemotherapy. We recently published results of a first-in-children phase 1 trial (NCT02502708) that showed the oral IDO-pathway inhibitor indoximod was well tolerated and provided meaningful clinical benefit for many patients with progressive childhood brain tumors, when given in combination with oral chemotherapy regimens (1). Using preclinical models, we have also reported the importance of the Bruton's Tyrosine Kinase (BTK) pathway as a key upstream driver of IDO during chemotherapy (2). Thus, we hypothesize that adding the BTK-inhibitor ibrutinib to the previously studied regimen of investigational indoximod IDO-inhibitor plus oral metronomic cyclophosphamide and etoposide will synergistically enhance anti-tumor immune responses, leading to improvement in Objective Response Rate (ORR) with manageable overlapping toxicity. **Methods:** The current study (NCT05106296) is an Investigator-Sponsored, open label, single-arm phase 1b trial comprised of a Dose-escalation Cohort (n=18) using a 3+3 dose escalation design to establish safety and dosing of ibrutinib in the combined regimen; followed by an Expansion Cohort (n=19) at the MTD to evaluate efficacy. Patients are treated with the all-oral 4-drug chemo-immunotherapy regimen in 28-day cycles using: (i) ibrutinib [Study Dose once daily on days 1-21]; (ii) indoximod [38.4 mg/kg/day divided twice daily throughout the cycle]; (iii) cyclophosphamide [2.5 mg/kg/dose, maximum dose 100 mg, once daily on days 1-21]; and (iv) etoposide [50 mg/m2/dose once daily on days 1-21]. Eligible patients are age 12 to 25 years with relapsed or refractory brain cancer, MRI evidence of current active disease not recently treated with radiation/proton therapy, ECOG performance score 0-2, and meet standard organ function requirements. Patients with systemic infection, autoimmune disease, recent live-virus vaccination, comorbid conditions that may overlap with expected regimen toxicities, or chronic treatment with anticoagulants or strong CYP3A inhibitors are excluded. Primary Objectives are to: (i) determine the pediatric recommended phase 2 dose (RP2D) of ibrutinib for the combined regimen (Dose-escalation Cohort), and (ii) evaluate preliminary evidence of efficacy for the combined regimen in terms of ORR (Expansion Cohort). Exploratory analyses use single-cell RNA and TCR sequencing (scRNAseq/TCRseq) of cryopreserved serial peripheral blood samples to monitor for treatment-expanded TCR clonotypes and study their phenotype. 1. *Neuro-Oncology* 26:348-361, 2024. 2. *Immunity*54:2354-2371, 2021. Clinical trial information: NCT05106296. Research Sponsor: CureSearch for Children's Cancer; Press On Foundation; Miriam Lloyd Halsey Foundation; Beloco Foundation; Alex's Lemonade Stand Foundation; Cannonball Kids' cancer Foundation; Trial Blazers for Kids Foundation; Lumos Pharma Inc (drug supply); Janssen Scientific Affairs LLC (drug supply).

TPS2704 Poster Session

A phase 1/1b, first-in-human, multi-part study of DF6215, an engineered IL-2Rα-active agonist, to investigate the safety, tolerability, pharmacokinetics, and biological and clinical activity in patients with advanced solid tumors.

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Background: IL-2 is a pleiotropic cytokine that stimulates strong anti-tumor responses by promoting expansion and activation of cytotoxic tumor-infiltrating immune cells including CD8+ T cells and NK cells (1). Aldesleukin is an approved rhIL-2; however, it has clinical limitations due to short half-life, requirement for 5 days of hospitalization per cycle, and high toxicity [eg, cytokine-related toxicity, capillary leak syndrome (CLS)] that limits its use [aldesleukin USPI]. DF6215 is a modified monovalent human IL-2 that binds to the IL2R. Preclinically, DF6215 administration results in sustained and modulated IL-2 pharmacology, leading to protracted pharmacodynamic (PD) effects and enhanced anti-tumor activity without observation of CLS in murine and primate toxicology studies. In response to the limitations of previous IL-2 therapeutics, DF6215 was designed as an IL-2Rα-active agonist with increased IL-2Rβγ stimulation to improve the benefit-to-risk ratio of historic IL-2 drugs. An additional design element is a prolonged elimination half-life due to Fc fusion, allowing for less frequent dosing. **Methods:** This is a first-in-human, open-label, multipart, Phase 1/1b clinical trial to characterize the initial safety, tolerability, pharmacokinetics, and preliminary efficacy of DF6215 in patients with advanced solid tumors. The Phase 1 dose escalation (DE) starting dose is 10 ug/kg IV every 2 weeks (up to 42 subjects expected to be enrolled), and the Safety/PK/PD will be explored at doses already characterized as safe in dose escalation and potentially efficacious (max of 40 subjects). Phase 1b includes an efficacy expansion (EE) cohort in subjects with advanced melanoma who have received prior anti-PD-1 agents and, if the tumor harbors a BRAF-activating mutation, a BRAF inhibitor. Key inclusion criteria include ≥ 18 years of age; ECOG PS of 0 or 1; adequate organ function, and locally advanced or metastatic solid tumors for which standard therapy options have been exhausted; and availability of baseline tumor biopsy. Primary objectives include determination of the MTD of DF6215 in DE and demonstration of clinical activity of DF6215 in the EE. Secondary objectives include assessment of safety and tolerability, pharmacokinetics, and immunogenicity of DF6215. This study plans to enroll up to 102 subjects across ~30 global centers in the US, European, and the Asia/Pacific regions, and is currently open to enrollment. 1. Arenas-Ramirez N, et al. 2015. *Trends Immunol.* Clinical trial information: NCT06108479. Research Sponsor: Dragonfly Therapeutics.