Assessment of efficacy of LBL-024, a novel and uniquely designed bispecific antibody against PD-L1 and 4-1BB, combined with etoposide/platinum-based chemotherapy in treatment-naive advanced extrapulmonary neuroendocrine carcinoma (EP-NEC): A multicenter phase Ib/II trial.

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Background: The prognosis for patients with EP-NEC is very poor. A recognized 1L treatment for advanced disease is etoposide/platinum-based chemotherapy with no standard 2L/3L treatment. LBL-024 blocks the immunosuppressive pathway of tumor cells by targeting PD-L1 and effectively co-stimulates T cells by targeting 4-1BB, to improve the anti-tumor immune response. Here we report the safety and efficacy of LBL-024 combined with etoposide and cisplatin or carboplatin (EP/EC) as first line treatment in patients with advanced NEC. (NCT06157827). **Methods:** This is a phase Ib dose escalation and phase II dose optimization/expansion clinical trial. Phase Ib enrolled previously untreated advanced EP-NEC and SCLC patients, phase II enrolled previously untreated advanced EP-NEC patients. Three dose levels of LBL-024 (6, 10 and 15 mg/kg, i.v. Q3W) plus EP/EC in phase Ib were evaluated, 2 dose levels (6 and 15 mg/kg, i.v. Q3W) of LBL-024 plus EP/EC were evaluated in a randomized dose optimization. The primary endpoints were tolerability, safety, efficacy (RECIST 1.1) and RP2D, the secondary endpoints were PK, PD and ADA. **Results:** As of December 26, 2024, a total of 53 patients were enrolled, with 13 patients in Phase Ib and 40 patients in dose optimization stage of Phase II. Phase Ib included 2 patients with SCLC, 1 with MiNEN, and 10 with EP-NEC. All 40 patients in Phase II were EP-NEC. During the Dose escalation stage, no DLTs were observed. During the Dose optimization stage, 15 mg/kg of LBL-024 was selected as RP2D based on PK/PD, efficacy, safety and ER analysis. Out of 49 patients, the ORR across all dose levels is 77.6% and the DCR is 93.9% among which 9 patients were unconfirmed. The ORR in 21 EP-NEC patients at RP2D dose is 81.0% and DCR is 95.2% among which 3 patients were unconfirmed. Additionally, 2 patients with SCLC achieved 100% ORR. LBL-024 TRAEs of all-grade occurred in 53 patients (100%), with grade ≥3 TRAEs in 17/53 patients (32.1%). **Conclusions:** LBL-024 combined with chemotherapy was well-tolerated. The extremely improved response observed in EP-NECs is significantly higher than the historic reports (about 30%~55%). Data including ER analysis of this ongoing study will be updated by a follow-up submission to ASCO. Clinical trial information: NCT06157827. Research Sponsor: None.

Clinical benefits of first line treatment in evaluable patients bin phase Ib/II.

	Phase Ib (Dose escalation)			Phase II (Dose optimization)		15 mg/kg (N=21) EP-NECs	Total (N=49)
	6 mg/kg (N=3)	10 mg/kg (N=4)	15 mg/kg (N=6*)	6 mg/kg (N=18)	15 mg/kg (N=18)		
ORR, N (%)	2 (66.7%)	3 (75.0%)	4 (66.7%)	14 (77.8%)	15 (83.3%)	17 (81.0%)	38 (77.6%)
DCR, N (%)	3 (100.0%)	4 (100.0%)	4 (66.7%)	17 (94.4%)	18 (100.0%)	20 (95.2%)	46 (93.9%)

*2 patients with SCLC, 1 with MiNEN and 3 with EP-NEC.

First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors.

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Background: CLDN6 is an oncofetal cell surface protein silenced in normal adult tissues but aberrantly activated in testicular, ovarian, non-small cell lung (NSCLC) and other cancers. The investigational therapeutic BNT142 is a novel lipid nanoparticle (LNP)-encapsulated mRNA encoding the anti-CLDN6/CD3 bispecific antibody RiboMab02.1. After intravenous administration, BNT142 RNA-LNPs are taken up by liver cells and are translated into RiboMab02.1. The first results of the dose escalation part of the BNT142-01 trial testing 7 dose levels (DL) are presented here. **Methods:** BNT142-01 (NCT05262530) is a Phase I/II, open-label, multi-center trial to evaluate weekly BNT142 treatment with premedication (antipyretics, antihistamines, fluids) at the investigators' discretion in pts with CLDN6+ (≥10% of cells with at least weak membrane positivity) advanced solid tumors. Primary objectives include safety, tolerability and identifying the recommended Phase 2 dose (RP2D), secondary and exploratory objectives include pharmacokinetics, pharmacodynamics and preliminary efficacy (RECIST 1.1). **Results:** As of 02 Dec 2024, 65 pts (median age 57 years [range 18 – 79]; 75% female; 60% ECOG 1; 44 ovarian, 10 testicular, 5 NSCLC, 6 rare cancers) received ≥1 dose (median 7, range 1 – 38) of BNT142. Of 65 pts, 46 (71%) had ≥4 prior lines of systemic therapy. Mostly mild to moderate treatment-related adverse events (TRAEs) occurred in 41 (63%) pts, including 15 (23%) pts with ≥G3 TRAEs. Most common (≥10%) TRAEs were cytokine release syndrome (CRS) in 14 (22%) pts (1 pt [2%] ≥G3), aspartate or alanine aminotransferase (AST, ALT) increased in 12 (19%) pts (8 pts [12%] ≥G3), and pyrexia, chills or fatigue in 8 (12%) pts (0/0/2 pts [0%/0%/3%] ≥G3, respectively). TRAEs leading to dose reduction, treatment interruption or discontinuation occurred in 1 (2%), 12 (19%) or 2 pts (3%), respectively (mostly G3; most common related terms AST or ALT increased and infusion related reaction). Two (3%) pts had a dose limiting toxicity (G4 ALT increased [DL5], leading to dose reduction, and G5 CRS [DL6]). BNT142 led to transient, dose-dependent increases in inflammatory cytokines. Translated RiboMab02.1 was detected in serum in a dose-dependent manner, peaking 24 – 72 h post-dose. Across all DLs, the disease control rate (DCR) was 58% with a tendency of higher efficacy in the higher DLs. In ovarian cancer, there were 7 RECIST 1.1 partial responses (PRs) and the DCR was 75%. **Conclusions:** BNT142 demonstrated a manageable safety profile and promising anti-tumor activity at the higher DLs, with 7 RECIST 1.1 PRs in CLDN6+ ovarian cancer, a tumor usually refractory to immunotherapy. We provide the first clinical proof-of-concept for an mRNA encoded bispecific antibody. Dose optimization is ongoing. Clinical trial information: NCT05262530. Research Sponsor: BioNTech SE.

Efficacy and safety results of a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein IBI363 in patients (pts) with immunotherapy-treated, advanced acral and mucosal melanoma.

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Background: Despite great success of immunotherapy (IO) in advanced melanoma, there remains an unmet clinical need for resistant tumors. Pts with acral and mucosal melanomas show limited benefit from current therapies. IBI363, a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein that blocks PD-1 and activates α-bias IL-2 to rejuvenate exhausted tumor-specific T cells, has shown encouraging efficacy in pts with advanced melanoma. Here, we present results of IBI363 from a phase 1 study (NCT05460767) and a phase 2 study (NCT06081920) of pts with IO-treated, advanced acral and mucosal melanoma. **Methods:** Eligible pts with IO-treated advanced acral and mucosal melanoma were enrolled. IBI363 was administered intravenously at 0.1 mg/kg every week, 0.3/0.6/1 mg/kg every 2 weeks (Q2W), or 1/1.5/2/3 mg/kg every 3 weeks (Q3W). Primary endpoints for the phase 1 study were dose-limiting toxicity (DLT) and safety, and for the phase 2 study were safety and investigator-assessed objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS) according to RECIST v1.1. **Results:** As of December 6, 2024, 91 pts were enrolled across the phase 1 (n = 76) and phase 2 (n = 15) studies (male: 47%; median age: 57 years; Asian: 100%; ECOG PS 1: 66%; stage IV: 89%); 47 pts had acral melanoma and 44 had mucosal melanoma. Median follow-up time was 8.2 months. Median treatment duration was 13.4 weeks (range: 2.0-72.4). Treatment-emergent adverse events (TEAEs) occurred in 90/91 (98.9%) pts including 27 (29.7%) pts with grade $\geq$3 ($\geq$G3) TEAEs. TEAEs led to treatment discontinuation in 3 (3.3%) pts, and 1 (1.1%) pt had a TEAE leading to death which was considered to be treatment-related (sepsis). Most common TEAEs were arthralgia (59.3%, with 4.4% $\geq$G3), rash (42.9%, with 3.3% $\geq$G3), and anemia (42.9%, with 2.2% $\geq$G3). Among all pts with at least one post-baseline tumor assessment (n = 87), 1 pt had a complete response, 22 had partial responses, 33 had stable disease, 31 had progressive disease. ORR was 26.4% (95% CI: 17.6-37.0) with 16 responses confirmed and 2 pts still waiting for confirmation; DCR was 64.4% (95%CI: 53.4-74.4). Among pts treated at 1mg/kg and above (n = 74), the ORR was 28.4% (95%CI: 18.5-40.1) and DCR was 68.9% (95%CI: 57.1-79.2). Patients treated at 1 mg/kg Q2W (n = 30) had median DOR 14.0 months with a median follow-up of 9.1 months and 50.0% events; the median PFS was 5.7 (95% CI, 3.6-6.7) months with a median follow-up of 11.0 months and 73.3% events. **Conclusions:** IBI363 showed encouraging efficacy in pts with IO-treated advanced acral and mucosal melanoma. The safety profile was acceptable and manageable. Further global clinical development of IBI363 in melanoma is ongoing. Clinical trial information: NCT05460767 and NCT06081920. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

A therapeutic vaccine for fibrolamellar hepatocellular carcinoma.

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Background: Fibrolamellar hepatocellular carcinoma (FLC) is a rare form of liver cancer affecting children and young adults that is driven by a chimeric protein, DNAJ-PKAc. The development of molecular inhibitors of DNAJ-PKAc has been hampered by unacceptable on-target toxicity, but the chimera results in a tumor-specific antigen (neoantigen) that may be targeted immunologically. **Methods:** We conducted a phase 1 clinical trial of a therapeutic vaccine targeting DNAJ-PKAc (FLC-Vac), in combination with nivolumab and ipilimumab, in children and adults with advanced FLC. The primary objectives were safety and T cell responses, defined as 2.5-fold increase of interferon gamma (IFN-γ)-producing DNAJB1-PRKACA chimera-specific T cells in the peripheral blood after week 10 (priming phase). The study was planned with 12 evaluable patients. FLC-Vac, consisting of a peptide encoding the DNAJB1-PRACA fusion plus poly-ICLC adjuvant, was administered on weeks 0, 1, 2, 3, 6, 9 during the priming phase of the study. Nivolumab, 3 mg/kg, followed by ipilimumab, 1 mg/kg, was administered every 3 weeks for 4 doses during the priming phase. After completion of the priming phase, FLC-Vac and nivolumab were continued in maintenance. Key exclusion criteria include age $<$ 12 years and prior treatment with immune checkpoint inhibitors. The trial incorporated a safety lead-in portion in which the first 3 patients received vaccine monotherapy for 3 weeks prior to receiving combination therapy. **Results:** Among 16 patients enrolled, 12 completed the vaccine priming phase and were evaluable for both immunological and clinical endpoints. The median age was 24 years (range: 12-47). Grade 3 treatment-related adverse events were reported by six patients (37.5%). DNAJ-PKAc-specific T cell responses were detected in 9/12 patients after treatment. In the subset of patients who completed the initial priming phase the disease control rate (DCR) was 75% (9/12), with three partial responses (25%). All 3 responding patients are without evidence of active cancer after undergoing surgical debulking of residual disease. All patients with clinical responses also had DNAJ-PKAc-specific T cell responses, from whom we identified multiple class II-restricted T cell receptors (TCRs) with specificity for DNAJ-PKAc. Correlates of response included both functional neoantigen reactivity and changes in TCR repertoire features over time. In two patients who experienced eventual progression after initial clinical response, we found evidence that the loss of efficacy was likely due to T cell exhaustion, and in one case was restored with checkpoint rechallenge. **Conclusions:** Our findings demonstrate the potential for therapeutic vaccines targeting DNAJ-PKAc in FLC and suggest a rubric for evaluating effective anti-neoantigen immunity. Clinical trial information: NCT04248569. Research Sponsor: ASCO CDA (Dr Yarchoan); Fibrolamellar Cancer Foundation; BMS; R01-CA265009.

2504 Oral Abstract Session

Clinical responses to SYNC-T therapy: In situ personalized cancer vaccination with intratumoral immunotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: Metastatic castration-resistant prostate cancer (mCRPC) has a poor response to immunotherapy limited by both a low ORR and high frequency of severe immune-related adverse events. SYNC-T is a novel *in situ* therapy that synchronizes the presence of tumor antigens, an immune therapy drug, and immune cells in the tumor and locoregional lymph nodes. SYNC-T Therapy combines device-induced partial cryolysis of a targeted tumor to create a personalized multi-antigen vaccine, followed immediately by intratumoral infusion of the multitarget novel drug candidate SV-102, leading to T-cell activation and an effective systemic immune response. **Methods:** 15 subjects, 13 with bone metastases, and documented failure to prior hormonal therapy (n = 10) or refused therapy (n = 5) were recruited to a single-arm study (NCT05544227). Image-guided partial cryolysis of a tumor was followed by intra-tumoral infusion of SV-102, comprised of fixed low dose of anti-PD-1 mAb, anti-CTLA4 mAb, CD40 agonist mAb, and TLR9 agonist CpG-ODN. All subjects received the same dose of SV-102. Subjects received SYNC-T Therapy q4 weeks for up to 12 cycles (median = 6). One site of primary prostate or soft tissue metastasis was targeted at each cycle. Primary objective was to evaluate safety and tolerability with a secondary objective to assess tumor response by PCWG3 and RECIST 1.1. **Results:** 15 subjects were treated and evaluable. Median age was 61 (48-74). Prior treatments included one or more of 1^{st}, 2^{nd} generation hormonal blockade, chemotherapy, immunotherapy, or radiation therapy. Within 15 evaluable subjects there were 8 radiographic CRs (53%, the two-sided 95% CI is 29.4% to 78.7%, rejecting 20% CR null hypothesis; p = 0.0085) with complete resolution of primary, bone, and soft tissue metastases and 5 PRs with an ORR of 87%. Median time to response was 3 months with a median duration of 12 months to date (range 1.2 -14.6). Among the 15 subjects, 3 have died resulting in 80% survival with 14 months median follow-up. SYNC-T Therapy was well-tolerated with 41 TEAEs in 13 subjects. The majority (95%) of TEAEs were Grade 1 or 2, most commonly fever and hematuria. There were 2 Grade 2 irAEs of hepatitis and hypothyroidism and 2 Grade 3 TEAEs of urinary retention and spinal cord compression. PSA analysis during and post SYNC-T Therapy will be presented. PK analysis revealed minimal systemic exposure to SV-102 components. PD analysis showed induction of inflammatory cytokines and the emergence of multiple, novel T-cell clones. **Conclusions:** SYNC-T Therapy was well-tolerated achieving an 87% ORR in subjects with mCRPC or who refused ADT. These encouraging clinical results have led to further study of SYNC-T SV-102 in a US, multicenter, Phase 2a trial for subjects with mCRPC. Clinical trial information: NCT05544227. Research Sponsor: Syncromune, Inc.

Phase 1 study of B440, an oral *Bifidobacterium*-engineered WT1 cancer vaccine, in patients with metastatic urothelial cancer.

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Background: B440 is an innovative oral cancer vaccine comprised of recombinant *Bifidobacterium* engineered to express WT1 tumor-associated antigen. By delivering the WT1 protein to dendritic cells in gut-associated lymphoid tissue, B440 is designed to induce a tumor-specific cellular immunity. Preclinical data demonstrated effective WT1-specific T-cell induction and anti-tumor activity in murine models of urothelial, prostate, and renal cancers. **Methods:** This open-label, single-arm, phase 1 study evaluated the safety and preliminary efficacy of B440 in patients with metastatic urothelial cancer who had progressed after all standard therapies, including cytotoxic chemotherapy, PD-1/PD-L1 inhibitors, and antibody-drug conjugates. Twelve patients were enrolled in two dose cohorts (800 mg or 1,600 mg, n = 6 each), administered once daily for five consecutive days per week over four weeks (20 total doses). The primary endpoint was dose-limiting toxicity (DLT), assessed during the treatment. Secondary endpoints included safety (adverse events [AEs] graded by CTCAE v5.0), best overall response (BOR), and progression-free survival (PFS) by RECIST v1.1. WT1-specific immune responses were measured via ELISPOT assays detecting interferon-γ-producing T cells. **Results:** All 12 patients completed the treatment: (median age: 74.5 years [range: 39–81]; primary tumors in bladder [n = 5], renal pelvis [n = 4], ureter [n = 3]). No DLTs were observed in either dose cohort. Treatment-related AEs were generally mild (Grade 1), with the most common events being transient IL-6 elevations and cold-like symptoms (n = 3 each). The disease control rate (DCR) was 50%, as six patients achieved stable disease (SD) as their BOR. Six patients also demonstrated WT1-specific T-cell induction confirmed by ELISPOT. ELISPOT-positive patients had a significantly longer PFS compared to ELISPOT-negative patients (median PFS: 113 days vs. 57 days; P = 0.0033). Although not included in the study protocol, six patients subsequently underwent pembrolizumab rechallenge at the discretion of their physicians. Of these, three achieved clinical responses (one complete response [CR] and two partial responses [PR]). Spider plot analyses indicated early tumor shrinkage among ELISPOT-positive patients, with maximum reductions of −100%, −49%, and −32.7% from baseline. Notably, three of the four ELISPOT-positive patients achieved objective responses upon rechallenge. **Conclusions:** B440 exhibited a favorable safety profile and no DLTs up to 1,600 mg. The induction of WT1-specific immunity correlated with improved PFS during B440 therapy and enhanced responses upon pembrolizumab rechallenge. These data support further investigation of B440 in larger, randomized trials and potential combination with other immunotherapies in WT1-expressing malignancies. Clinical trial information: jRCT2051220143. Research Sponsor: Japan Agency for Medical Research and Development (AMED); 23ym0126081h0002; Immunorock Co., Ltd.

Effect of erythrocyte-antibody conjugates on cancers resistant to checkpoint blockade immunotherapy: A phase I trial.

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Background: Despite the clinical success of immune checkpoint blockade therapy, the majority of patients do not benefit due to inadequate efficacy as well as immune-related adverse toxicities. We have previously developed WTX-212, an erythrocyte-antibody conjugate that covalently links anti-PD-1 antibodies to erythrocyte membranes. Unlike conventional antibodies, WTX-212 accumulates in the spleen, where it effectively remodels splenic immune landscape by expanding effector T cells and reducing the reservoir of immunosuppressive myeloid cells. These changes further reprogram the tumor microenvironment and suppress tumor growth in syngeneic mouse models. Based on promising preclinical results, we have investigated WTX-212 in cancer patients resistant to checkpoint blockade therapy (NCT06026605). **Methods:** This is an investigator-initiated trial designed to assess the safety, tolerability, and preliminary efficacy of autologous WTX-212 monotherapy in patients with advanced malignancies. The primary outcome measures include safety and tolerability according to NCI-CTCAE v.5.0. Secondary outcome measures preliminary efficacy based on RECIST 1.1 criteria. As of January 15, 2025, 14 heavily treated patients with 11 types of solid tumors, who had received PD-1/PD-L1 antibody-containing regimens as their last line of treatment but developed resistance, were enrolled. These patients received WTX-212 monotherapy in two dose cohorts (2×10^{11} or 3×10^{11} cells, with 6-10 mg of conjugated antibody). **Results:** Repeated WTX-212 treatment showed no DLTs or TRAEs ≥3. No patient discontinued treatment due to AEs. WTX-212 monotherapy demonstrated promising anti-tumor activity, with a DCR of 78.6% (11/14) and an ORR of 42.9% (6/14), including 1 CR and 5 PR. In the higher-dose cohort (3×10^{11} cells), DCR and ORR increased to 85.7% (6/7) and 57.1% (4/7), respectively, suggesting dose-dependent efficacy. Additionally, responders (CR+PR) exhibited higher baseline levels of circulating polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) compared to non-responders (PD+SD), indicating that patients with elevated PMN-MDSCs may benefit more from treatment. Importantly, WTX-212 treatment rapidly reduced PMN-MDSCs in the peripheral blood of responders compared with non-responders, consistent with preclinical data. These preliminary results suggest that WTX-212 is safe, well-tolerated, and effective at low doses, supporting further investigation into WTX-212 monotherapy and combination therapies. **Conclusions:** Our study suggests that PD-1 blockade in the spleen using erythrocyte-antibody conjugates triggers systemic anti-tumor responses while maintaining a favorable safety profile. Erythrocyte-drug conjugates represent a novel approach for targeting immune cells in the spleen, with broad implications for cancer treatment and drug development. Clinical trial information: NCT06026605. Research Sponsor: None.

2507 Oral Abstract Session

RETRACTED: Phase 1 clinical trial of EpCAM CAR-T cell therapy in patients with gastrointestinal cancers.

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Phase 1 clinical update of IMA203, an autologous TCR-T targeting PRAME in patients with PD1 refractory metastatic melanoma.

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Background: Frequent recurrence and limited long-term survival in unresected or metastatic melanoma after relapse from 1L checkpoint inhibitor treatment highlight the critical need for new therapies that deliver deeper, more durable responses. ACTengine IMA203 is an autologous TCR-T targeting PRAME, an intracellular protein displayed as peptide antigen at high density on the surface of multiple solid tumors, including melanoma. **Methods:** Patients treated in this ongoing Ph1a/b trial (NCT03686124) are ≥18yo, HLA-A*02:01+, PRAME+, have recurrent and/or refractory solid tumors with no additional standard of care treatments available, measurable disease (RECIST1.1) and ECOG PS 0-1. Patients receive Cy/Flu (500 mg/m^2 & 30 mg/m^2 x4 d) lymphodepletion prior to infusion, followed by low-dose IL-2 for 10 days. **Results:** As of Aug 23, 2024: 70 heavily pretreated patients with solid tumors (median 3 prior systemic therapies) across all dose levels (median total infused dose 2.09x10^9 TCR-T cells (0.08-10.02x10^9)) were enrolled and assessed for safety. Baseline tumor burden (median sum of diameter): 11.78 cm; LDH > 1 x ULN: 64% of patients. IMA203 had an overall favorable tolerability profile. Most common TEAEs: chemotherapy-related cytopenias (100%), mild to moderate CRS (G1-2: 83%, G3: 11%), infrequent ICANS (G1: 6%, G2: 4%, G3: 4%), no G5 events. Objective responses were observed in melanoma, ovarian cancer, synovial sarcoma, and other tumor types. Successful trafficking of IMA203 cells to various organs was evidenced by their ability to shrink metastatic tumor lesions in the lung, liver, pleura, peritoneum, skin, lymph nodes, adrenal gland, bladder, kidney, spleen, and muscle. Across patients treated in dose escalation and dose expansion, higher doses of IMA203 TCR-T cells were associated with a higher rate of confirmed responses ($p = 0.018$), whereas tolerability profile remained favorable. Exposure data (C_{max}, AUC) demonstrated a clear dose-dependent improvement in clinical efficacy: Patients with confirmed PR had a higher concentration of IMA203 TCR-T cells in the periphery, compared to patients with unconfirmed PR, SD, and PD. In heavily pretreated patients (median 2 prior systemic therapies) with melanoma at RP2D (1-10x10^9) in Ph1b, cORR was 54% (14/26), with tumor shrinkage in 88% (23/26) of patients. Median DOR was 12.1 months with 7/14 confirmed responses ongoing (longest > 2 years). Median PFS was 6 months and median OS not reached at 8.6 months mFU. Updated data with longer follow-up will be presented. **Conclusions:** IMA203 TCR-T was well tolerated and showed durable objective responses in patients with advanced melanoma. Given its promising risk/benefit profile and high PRAME prevalence in melanoma, a registration-directed Phase 3 trial (SUPRAME; NCT06743126) is underway to further evaluate its efficacy in patients with previously treated (2L) advanced cutaneous melanoma. Clinical trial information: NCT03686124. Research Sponsor: None.

2509 Clinical Science Symposium

Phase III randomized study comparing ultra-low dose immunotherapy to standard cytotoxic chemotherapy for solid tumors in second line and beyond setting (DELII: Development of Low dose Immunotherapy in India).

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Background: Although immunotherapy (IO) is approved in the second line and beyond setting for most solid tumors, cost limits its accessibility. Lower doses of IO have been shown to achieve adequate target occupancy, persisting for 3 months post administration. We hypothesized that nivolumab would retain efficacy at one-twelfth the approved dose. **Methods:** Open-label, phase III randomized superiority study in 500 patients with solid tumors, whose disease had progressed on at least one line of systemic treatment, with performance status 0-1. Patients were randomized 1:1 to ultra-low-dose nivolumab (20 mg intravenously every 2 weeks) or standard chemotherapy. Standard chemotherapy options for lung and head-and-neck cancers were docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 once-a-week; esophageal and urothelial cancers: paclitaxel 175 mg/m^2 every 3 weeks or 80 mg/m^2 once-a-week. Therapy continued until progression or intolerable toxicity. Primary endpoint was overall survival (OS). **Results:** Between Jun 2020 and Feb 2024, we enrolled 500 patients: 250 to each arm. Median age was 49.5 years (IQR, 42-58), 408 (81.6%) patients were male. Primary cancers included head and neck (259, 51.8%), lung (182, 36.4%), esophagogastric (31, 6.2%), urothelial (14, 2.8%), and microsatellite instability-high colorectal cancers (14, 2.8%). Patients had received a median of one prior line of systemic therapy (range: 1-8); 144 (28.8%) patients had received at least two prior lines of systemic therapy. PD-L1 positivity (TPS or CPS $>$ 0) was noted in 66.2% patients. Radiologic response was 7.7% and 8.1% in IO and chemotherapy arms, respectively; P = 0.882. Disease stabilization rate was 37.7% and 39.3% in IO and chemotherapy arms, respectively; P = 0.761. Median PFS was similar between the two arms: 2.04 months (95% CI, 2.0-2.1) in IO arm, and 2.09 months (95% CI, 2.04-2.17) in chemotherapy arm (HR, 1.03; 95% CI, 0.86-1.23; P = 0.77). Median OS was 5.88 months (95% CI, 4.99-7.13) in IO arm, versus 4.70 months (95% CI, 3.91-5.65) in chemotherapy arm; P = 0.022; HR, 0.80 (95% CI, 0.66-0.97). One-yr OS in IO and chemotherapy arms was 27.28% (22.19-33.54) and 16.88% (12.75-22.34), respectively; 2-yr OS was 11.19% (7.59-16.50) and 6.55% (3.95-10.89), respectively. Grade 3 and higher treatment-related adverse events were significantly lower in IO arm (42%) than chemotherapy arm (60.3%); P $<$ 0.001. **Conclusions:** Ultra-low dose immunotherapy dosed at one-twelfth the standard approved dose is efficacious and significantly prolongs survival in patients with solid tumors in the second line and beyond setting, as compared to standard cytotoxic chemotherapy. Low dose IO should be tested in various settings and multiple malignancies. This will substantially increase global accessibility to IO. Clinical trial information: CTRI/2020/02/023441. Research Sponsor: R G Manudhane Foundation for Excellence; Trilokchand Papriwal Trust; Tata Memorial Hospital, Mumbai, India.

Overall survival according to time-of-day of combined immuno-chemotherapy for advanced non-small cell lung cancer: A bicentric bicontinental study.

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Background: Circadian rhythms moderate immune cells trafficking and function over the 24 hours. This could account for the near doubling of overall survival (OS) in patients (pts) receiving immune checkpoint inhibitors (ICIs) as single agents at early times-of-day of administration (ToDA) in retrospective studies. Yet, (i) the cut-off time that differentiates ICI efficacy according to ToDA ranges from 11:30 to 16:30, and (ii) the relevance of ICI timing for OS is unknown in pts receiving immunochemotherapy (ICI-chemo). **Methods:** These issues are addressed using OS as the primary endpoint in retrospectively-included pts receiving 1st-line ICI-chemo for stage IIIc-IV non-small cell cancer (NSCLC) in France (Cohort 1) or in China (Cohort 2). The median ToDA of the initial four ICI-chemo infusions was computed for each patient. Hazard ratio (HR) functions of an earlier death or an earlier progression were computed for each cohort and for the pooled one, using ToDA cut-off times ranging from 10:30 to 13:00, with 30-minutes increments. Median ToDA of ICI-chemo determined the allocation of patients to "Before" or "After" treatment groups. The temporal relations between HRs and ToDA as a continuous variable were further determined, using Cox models incorporating periodic restricted cubic splines. Patients were dichotomized according to the best cut off ToDA candidate, with OS and PFS being estimated using Kaplan-Meier and compared using log-rank. The association between ToDA and OS, PFS and response rates were evaluated using the Cox and logistic models controlling for main patient characteristics. **Results:** A total of 713 pts started treatment between 01/2018 and 10/2023 (Cohort 1, 165 pts; Cohort 2, 548 pts; median age, 62 y.o., male sex, 84%; pembrolizumab as ICI, 51%; pemetrexed-carboplatin/cisplatin, 49%; paclitaxel-carboplatin, 51%). HR functions in each cohort and in the pooled one, and the fitted curve using ToDA as a continuous variable identified 11:30 as a likely best cut off time. Median OS was 33.0 months (mo.) [95% CI, 27.5 - 41.0] in the 345 patients, who received 2-4 immunochemotherapy courses before 11:30) compared to 19.5 mo. [18.0 - 22.5] in those, who received 2-4 courses after 11:30 (N = 368) ($p<0.0001$). In the multivariable analysis, a median ToDA before 11:30 was associated with prolonged OS with an adjusted HR of 0.47 [0.37-0.60]. Statistically significant differences in ToDA effects were found for OS, PFS in each cohort, and for response rate in each cohort and in the pooled data. **Conclusions:** In this large bicontinental study, ToDA of immunochemotherapy administration before 11:30 was associated with improved OS, PFS and response rates, compared to later ToDA in pts receiving standard first line immunochemotherapy for NSCLC. Randomized trials are needed to confirm this important finding and inform recommendations for clinical practice. Research Sponsor: None.

Safety and efficacy of immune checkpoint inhibitors in solid organ transplant recipients: A systematic review and individual patient data meta-analysis.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but pose unique challenges in solid organ transplant (SOT) recipients. Transplant rejection remains the predominant safety concern. We systematically evaluated the safety (focusing on allograft rejection) and efficacy of ICIs across all organ transplant types and ICI classes, providing updated evidence-based insights for clinical decision-making. **Methods:** A systematic review of PubMed, EMBASE, and SCOPUS databases was conducted in accordance with PRISMA guidelines. Studies reporting rejection or efficacy outcomes in SOT recipients treated with any class of ICI were included. The primary endpoints were the incidence of transplant rejection and survival following ICI therapy. Secondary endpoints included objective response rate (ORR) and progression-free survival (PFS) for malignancies. Analysis was performed using SPSS (V26.0) and R (V4.3.0). **Results:** Of 2682 screened abstracts, 198 studies involving 331 SOT recipients met inclusion criteria. The transplanted organs were liver (n=175), kidney (n=136), and heart (n=15). Rejection rates were highest in Kidney at 46.3% (63/136), followed by heart (40.0%, 6/15) and liver (26.9%, 47/175). Across ICI classes, rejection rates were: Anti-CTLA4 (25%) Anti-PD1 (40.6%) and Anti-PDL1 (0%). Rejection rates were lower in patients receiving ICI pre-transplant (25.9%) compared to post-transplant (40.9%). ORR varied by ICI class: Anti-CTLA4 (25%), Anti-PD1 (41.8%), Anti-PD1 + CTLA4 (28%), and Anti-PDL1 (72.7%). Cutaneous squamous cell carcinoma (cSCC) showed the highest ORR (49.1%), followed by hepatocellular carcinoma (40.8%) and melanoma (25.3%). Post-transplant rejection risk was lower with Anti-CTLA4 (OR 0.22), 3rd-line ICI therapy (OR 0.24), and corticosteroids (OR 0.46). Pre-transplant rejection risk decreased with >60-day washout periods (OR 0.10). Multivariate analysis identified key factors influencing rejection risk (Table 1). **Conclusions:** ICI therapy in SOT recipients is high-risk yet promising. Key strategies include prolonged washout periods, Anti-CTLA4 therapy, and late-line ICI use. Prospective studies are needed to refine protocols and identify predictive markers to improve outcomes in this population. Research Sponsor: None.

Multivariate analysis results.

Factor	Total (OR)	P-Value	Pre-Transplant ICI administration (OR)	P-Value	Post-transplant ICI administration (OR)	P-Value
Age (<60 vs > 60)	0.79	0.42	0.85	0.82	0.62	0.18
Sex (M vs F)	1.12	0.75	1.36	0.7	1.23	0.63
CTLA-4	0.21	0.03	-	-	0.22	0.04
Third line and later (vs 1st line)	0.26	0.01	0.17	0.44	0.24	0.01
NSCLC (vs HCC)	6.87	0.03	-	-	3.59	0.23
RCC (vs HCC)	9.9	0.04	-	-	5.88	0.11
Multiple tumors	19.18	0.01	-	-	9.3	0.06
Washout period (<60 vs>=60)	-	-	0.1	<0.001	-	-

LBA2512 **Rapid Oral Abstract Session**

The phase II NIBIT-ML1 study of nivolumab plus ipilimumab and ASTX727 or nivolumab plus ipilimumab in PD-1 resistant metastatic melanoma: Tumor methylation landscape and correlation with clinical outcomes.

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2513 Rapid Oral Abstract Session

Durable responses in ICI-refractory or acquired resistance: Phase 2 study of NP-G2-044 combined with anti-PD-1 therapy.

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Background: Although immune checkpoint inhibitors (ICIs) have transformed cancer treatment, many patients still develop primary or acquired resistance. NP-G2-044 is a first-in-class, oral fascin inhibitor that disrupts cancer cell motility, invasion, and metastasis while promoting intratumoral dendritic cell (DC) activation and CD8+ T-cell proliferation. Preclinical studies indicate NP-G2-044 synergizes with anti-PD-1 therapy to convert nonresponsive tumors into responsive ones. Early-phase clinical data support the feasibility of NP-G2-044 at pharmacologically active doses and its potential to prevent metastasis when used as monotherapy. **Methods:** In this open-label Phase 2 trial (NCT05023486), patients with advanced or metastatic solid tumors and documented primary or acquired resistance to anti-PD-(L)1 therapy received NP-G2-044 plus standard-of-care anti-PD-1. Efficacy was assessed using RECIST, with the primary endpoint being objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), duration of response, disease control rate (DCR), and safety. **Results:** Forty-five patients were enrolled, with 33 evaluable for efficacy. No dose-limiting toxicities were observed. Objective responses occurred in 7/33 patients (21%) [95 % CI 9 - 38.9%], including 4 complete responses (CRs)—2 by RECIST in cervical and endometrial cancers, and 2 pathological CRs in pancreatic and gastroesophageal junction adenocarcinomas—and 3 partial responses (cutaneous squamous cell carcinoma, non-small cell lung cancer, and cholangiocarcinoma). Three patients have been cancer-free for over 7 months, and 5 have remained on therapy for more than 15 months. The DCR was 76%, and 55% of patients showed no new metastases during the study. One-year PFS is projected at 30%. The most common adverse events were diarrhea, fatigue, nausea, and transaminitis (~30%), which was transient, reversible, and preceded tumor response. Mechanistic analyses using multiplex immunofluorescence and immunophenotyping revealed enhanced intratumoral cytotoxic T-cell infiltration, proliferation, and granzyme B expression, along with an increase in activated DCs—consistent with a strong immunomodulatory effect. **Conclusions:** NP-G2-044, in combination with anti-PD-1 therapy, appears to have clinical activity across multiple cancer types, overcoming both primary and acquired ICI resistance while producing durable responses. Ongoing expansion cohorts and biomarker analyses aim to refine patient selection. These findings underscore NP-G2-044's potential to address metastatic disease and improve cancer immunotherapy outcomes, offering a promising therapeutic option for patients with limited alternatives. Clinical trial information: NCT05023486. Research Sponsor: Novita Pharmaceuticals.

Preliminary results from the dose-escalation stage of a phase I trial of an anti-CCR8 antibody in patients with relapsed/refractory cutaneous T-cell lymphoma (R/R CTCL).

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Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common cutaneous T-cell lymphomas (CTCL). CCR8 is expressed in the skin resident memory T cells. ICP-B05 (CM369) is a humanized monoclonal antibody against CCR8 with potent ADCC activity. Here we report safety, efficacy and PK/PD findings for ICP-B05 during the dose-escalation stage of a Phase I study. **Methods:** Patients with R/R CTCL received ICP-B05 at 150 mg, 300 mg, 450 mg and 600 mg I.V. Q2W. Patients with R/R CTCL who failed at least 1 prior standard systemic regimen. Primary objectives included safety and tolerability of ICP-B05, MTD and RP2D. Secondary Objectives included the PK/PD and objective response per investigator. **Results:** By the cutoff date of 6th Jan, 2025, a total of 13 patients with R/R CTCL were treated, with 4 patients in 150 mg, and 3 patients each in 300 mg, 450 mg and 600mg, respectively. Eleven patients had a diagnosis of MF, one had SS and one had pcALCL. The median age was 46 years, and the median prior lines of therapy were 3 (2-6). There were 10/13 (76.9%) patients had lymph nodes involvement and 1/13 (7.7%) patient with SS had above 90% Sézary cells in peripheral blood at baseline. TEAEs occurred in 12 (92.3%) patients, and ≥Grade 3 TEAEs occurred in 6(46.2%) patients. The most common≥Grade 3 TEAEs is hematological AEs, including lymphopenia (8.3%), neutropenia (8.3%) and thrombocytopenia (8.3%). Two patients (16.7%) reported serious TEAEs, including edema and cardiac failure reported by the SS patient which was assessed as not related to ICP-B05, and thrombocytopenia and anemia reported by a MF patient. There was no fatal TEAE reported. There were 12 patients received at least one skin lesion assessment followed the mSWAT. 4/12 patients (33.3%) achieved PR, and 7patients (7/12, 58.3%) were assessed as SD with reduction (medium: - 27%) in skin lesion. The 6-month PFS rate was 82.5% (95% CI: 46.1%-95.3%). At baseline, CCR8+ in skin lesions (medium: 8.38%, range: 3.22–49.6%) was assessed in 11 out of 13 patients. Among the five patients with CCR8+ levels exceeding 10%, four (80%) achieved PR. PK analysis showed that serum exposure (C_{max} and AUC_{0-14D}) increased with dose escalation. PD analysis demontrated significant depletion of CCR8-expressing cells in CTCL skin lesions. Significant reduction of CCR8+ malignant T cells (-80%) and CCR8+ regulatory T cells (Treg, -68%) were observed at C3D1 compared with baseline in the skin lesion. Similar PD effects were observed in the peripheral blood as well with an average decrease of 91% in CCR8+ malignant T cells and 16% in Treg at C3D1 when compared with baseline. **Conclusions:** The current study is the first and only report on the preliminary efficacy data of anti-CCR8 targeted therapy for CTCL patients. The effectiveness of ICP-B05 was supported by the PD effects in both skin lesions and peripheral blood in the depletion of CCR8+ cells. ICP-B05 is safe and well tolerated and its safety profile made it a good candidate for combo therapies for CTCL patients with lymph node and other organ involvement. Clinical trial information: NCT05690581. Research Sponsor: None.

2515 Rapid Oral Abstract Session

An open-label, phase I trial of the SIRPα monoclonal antibody, BI 770371, alone and in combination with the PD-1 inhibitor ezabenlimab in patients with advanced solid tumors.

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Background: The signal regulatory protein alpha (SIRPα)/CD47 axis is a critical regulator of myeloid cell activation and serves as a myeloid-specific immune checkpoint, making it a potential therapeutic target. The pan-specific SIRPα monoclonal antibody, BI 770371, blocks the SIRPα/CD47 interaction, leading to reactivation of innate antitumor immune responses. This Phase I trial (NCT05327946) aimed to determine the maximum tolerated dose (MTD) and recommended dose for expansion of BI 770371 ± ezabenlimab in patients (pts) with advanced solid tumors. **Methods:** Pts with ≥1 measurable lesion and ECOG PS of 0/1 were enrolled. Pts received escalating doses ofBI 770371 alone or in combination with ezabenlimab 240 mg once every 3 weeks. Treatment continued until progressive disease, unacceptable toxicity, or pt withdrawal. BI 770731 dose escalation was guided by a Bayesian Logistic Regression Model with overdose control. Primary endpoint was dose-limiting toxicities (DLTs) in the MTD evaluation period (Days 1–21). Secondary endpoints were adverse events (AEs) and DLTs in the on-treatment period. **Results:** At data cut-off (Nov 22, 2024), 21 pts had received BI 770371 monotherapy across 6 dose levels, and 15 pts had received BI 770371 in combination with ezabenlimab (combination group) across 5 dose levels. In the monotherapy group, median age was 63 years (range: 26–77) and 95% of pts had received ≥3 prior lines of therapy. In the combination group, median age was 61 years (range: 27–78), and 80% had received ≥3 prior therapies. No DLTs were reported during the MTD evaluation period with BI 770371 monotherapy or with the combination; 1 pt in the monotherapy group had a DLT (grade 2 encephalitis, which resolved within 1 week) during the on-treatment period (likely due to prior nivolumab and ipilimumab treatment). In total, 14 (67%) and 10 (67%) pts in the monotherapy and combination groups, respectively, had a treatment-related AE (TRAE). Most common TRAEs with BI 770371 monotherapy were pruritus (24%) and fatigue (19%). Most common TRAEs with the combination were fatigue and decreased appetite (each 20%). Most TRAEs were grade 1/2, one pt in the combination group had two grade 3 TRAEs (diarrhea and fatigue); there were no grade 4/5 TRAEs. Two suspected unexpected serious adverse reactions were seen: grade 2 encephalitis (monotherapy) and grade 3 diarrhea (combination). One pt had an AE leading to discontinuation (grade 2 encephalitis). One pt in the combination group had a partial response; 13 (62%) and 8 (53%) pts in the monotherapy and combination groups, respectively, had stable disease. **Conclusions:** These preliminary data indicate that BI 770371 is well tolerated alone and in combination with ezabenlimab, with promising antitumor activity seen in heavily pretreated pts with advanced solid tumors. The MTD of BI 770371 was not reached in either group. Clinical trial information: NCT05327946. Research Sponsor: Boehringer Ingelheim.

A novel application of deep learning (DL)-based MRI with liquid biomarkers for immune effector cell-associated neurotoxicity syndrome (ICANS) after chimeric antigen receptor (CAR) T-cell therapy.

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Background: ICANS is a complication of CAR T-cell therapy, yet risk factors and quantitative diagnostic criteria, particularly neuroimaging criteria, remain incompletely characterized. We implemented a novel application of a deep learning (DL)-based MRI approach alongside clinical and liquid biomarkers to better characterize neurotoxicity after CAR T-cell therapy. **Methods:** We analyzed all patients with non-Hodgkin lymphoma (NHL) or acute lymphoblastic leukemia (ALL) who underwent CAR T-cell therapy at UCSD with a commercial product from 2018-2024. ICANS was graded as per American Society for Transplantation and Cellular Therapy (gr1-4). Variables included stage, performance status, and prior receipt of high-dose methotrexate (HD MTX), intrathecal (IT) chemotherapy, central nervous system (CNS) involvement, CNS-directed radiotherapy (CNS RT), and extracranial RT. Labs obtained pre-infusion, 3 days post-infusion, and during ICANS (or 7 days post-infusion for those without ICANS) were evaluated. Available post-infusion brain MRIs were processed with a 3D U-Net convolutional neural network to quantify T2 FLAIR hyperintensity volumetrics. Linear mixed regression models accounting for zero inflation assessed longitudinal DL-derived FLAIR. Multivariable regression models assessed factors associated with ICANS. **Results:** Of 163 patients (89% NHL, 11% ALL), 52 had IT chemotherapy, 27 had HD MTX, 24 had prior CNS disease, and 22 had prior CNS RT. Most (106) received axicabtagene ciloleucel (34 tisagenlecleucel, 23 brexucabtagene autoleucel) and most had CRS (133, 82%). ICANS occurred in 73 (45%) at a median of 7 days post-infusion (39 gr1-2, 34 gr3-4). Post-infusion, 21 patients had ³1 brain MRI (93 MRIs total). Baseline factors associated with ICANS were lactate dehydrogenase (LDH; odds ratio [OR] 1.03 $p = 0.002$) and prior IT chemotherapy (OR 2.5 $p = 0.01$). There was a trend toward association of gr3-4 ICANS with HD MTX (OR 2.8 $p = 0.07$). Post-infusion, CRS grade was associated with ICANS (OR 2.8 $p < 0.001$). LDH (1.02 $p = 0.004$) and C-reactive protein (OR 1.2 $p < 0.001$) were elevated during ICANS. Patients with ICANS had significantly greater FLAIR (intercept 23.8 cm^3 $p < 0.001$) and there was increased FLAIR over time across all patients ($b = 3.3$ cm^3 $p = 0.05$). There was a trend toward association between higher ICANS grade and DL-derived FLAIR ($p = 0.09$). **Conclusions:** Here, we demonstrate a novel application of DL-based MRI quantification of ICANS post-CAR T-cell therapy. This metric, along with clinical features, emerged as potential quantitative biomarkers of ICANS. These findings warrant further investigation and have informed a prospective study, including standardized brain MRI pre- and post-infusion, to develop a comprehensive phenotype of neurotoxicity following CAR T-cell therapy.
Research Sponsor: None.

Role of autoimmune reactivity in neurotoxicities (N-Tox) in melanoma patients treated with immune-checkpoint inhibitors (ICI).

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Background: N-Tox is a grossly understudied immune-related adverse event (irAE), despite its association with mortality (e.g. encephalitis) and morbidities (e.g. peripheral neuropathy). We reported that pre-treatment sera autoantibodies (auto-Abs) are implicated in the pathogenesis of irAEs (Johannet *et al. CCR* 2022). We here examined the rate and patterns of N-Tox in melanoma patients who received ICI in the adjuvant setting and whether baseline specific serum auto-Abs are associated with N-Tox. **Methods:** We examined clinicopathological features and baseline auto-Abs of 965melanoma patients (551 male and 414 female) enrolled in two phase III clinical trials: Checkmate 238 and Checkmate 915 (797 resected stage III, 166 resected stage IV, and 2 unknown). Patients received ipilimumab (n = 423), nivolumab (n = 347), or both (n = 195). We compared pre-treatment serum auto-Ab profiles using the HuProt Human Proteome Microarray v4.0 (CDI Laboratories, Mayaguez, PR) that has 21,000+ individually purified full-length human proteins and protein isoforms in duplicate, in patients who developed at least a single incidence of N-Tox grade $\geq$2 to those who developed only other types of irAEs grade $\geq$2. We used a threshold of logFC $>$ 0.3 and false discovery rate (FDR) adjusted P value $<$ 0.05 to determine differentially expressed auto-Abs in patients with N-Tox. **Results:** 329/965 (34%) patients developed N-Tox. There were 426 total incidences of N-tox (grade 1 n = 258, grade 2 n = 132, grade 3 n = 34, grade 4 n = 2). 97/329 patients developed more than one grade of N-Tox. Patients who received ipilimumab were more likely to experience any grade N-Tox (P = 0.002) in a multivariate model. Any grade N-tox was also associated with a lower recurrence rate (P = 0.004). Gender and melanoma stage were not associated with N-Tox (P $>$ 0.05). A signature of 160 auto-Abs, including those targeting mitochondrial proteins (ATP5PO, COX6C, NDUFA3, NDUFB6), calcineurin (PPP3CC, PPP3R1), cellular architecture (RAC1), and inflammation/apoptosis (TRAF2) were significantly overexpressed in the N-Tox grade $\geq$2 cohort (n = 143) compared to non-N-Tox grade $\geq$2 (n = 569). Pathway analysis revealed these auto-Abs were enriched in several pathways involved in neuroinflammation and neurodegeneration, including TNF-a signaling, B cell receptor signaling, interleukin-2 production, natural killer cell mediated cytotoxicity, and cellular senescence. **Conclusions:** Our data demonstrate that the incidence of N-Tox is higher than previously reported, possibly due to stringent assessment and follow up in clinical trial settings. The multiplicity of pathways involved, some of them directly involved in neurodegeneration and neuroinflammation, suggests a complex N-tox pathogenesis that requires further clinical and pre-clinical investigations. Research Sponsor: National Cancer Institute; P50CA225450.

Natural killer cell transcriptomic expression and prediction of survival after immune checkpoint blockade across cancers.

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Background: Preclinical and clinical evidence has suggested the role of natural killer (NK) cells in tumor immunity and prognosis across various cancer types, but their significance during immune checkpoint blockade (ICB) treatment is poorly understood. This study investigated the impact of tumor-infiltrating NK cells, surrogated by the RNA expression of genes related to NK cells in the tumor microenvironment, on the outcomes of the patients who undergo ICB, using real-world, pan-cancer data. **Methods:** We analyzed RNA sequencing data of 395 immune-related genes from 514 patients with various cancers included in the Study of Personalized Cancer Therapy to Determine Response and Toxicity (NCT02478931). After excluding 25 patients ineligible for survival analysis, we defined two distinctive cohorts: patients who received ICB (ICB cohort, N = 217) and those who did not (non-ICB cohort, N = 272). Among the 395 immune-related genes, 43 were selected as NK-related genes according to the Human Protein Atlas. Patients in each cohort were clustered into two groups based on the NK-related gene expression. The associations between the clusters and the clinical outcomes, including overall survival (OS) and progression-free survival (PFS), were analyzed using univariate and multivariate analyses. In the multivariate analysis, cancer types, line of immunotherapy, positive programmed-death ligand 1 immunohistochemistry (PD-L1 IHC, $\geq$ 1%), high tumor mutational burden (TMB, $\geq$ 10/Mb), and microsatellite instability (MSI) were adjusted. **Results:** The ICB cohort (N = 217) was divided into two clusters (hot vs. cold), characterized by general abundance and paucity of NK-related gene transcripts (N = 101 and 116, respectively). The clusters were not significantly associated with histology, positive PD-L1 IHC, high TMB, or MSI. Those in the hot cluster demonstrated significantly longer overall survival (OS) after starting ICB compared to those in the cold clusters in univariate analysis (hazard ratio [HR] and 95% confidence interval [CI]: 0.65 [0.45-0.92], p = 0.015) and multivariate analysis (HR and 95% CI: 0.57 [0.34-0.87], p = 0.010). The cluster was not significantly associated with PFS. The non-ICB cohort (N = 272) was similarly divided into two clusters (hot vs. cold), with the characteristics of generally high and low NK-related gene RNA expressions. (N = 114 and 158, respectively). However, in the non-ICB cohort, patients in the hot clusters did not demonstrate significantly prolonged OS compared with those in the cold cluster either with univariate or multivariate analysis (HR and 95% CI: 0.93 [0.65-1.32], p = 0.67 and 0.97 [0.76-2.01], p = 0.90 respectively). **Conclusions:** Transcriptomic expression of NK-related genes in tumor tissue independently and significantly predicted longer survival after ICB treatment, which implies a role of tumor infiltrating NK cells in immunotherapy outcome. Research Sponsor: U.S. National Institutes of Health; CA023100.

2519 Rapid Oral Abstract Session

Tumor-wide RNA splicing aberrations and their potential as therapeutic neoantigen targets.

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Background: Tumor heterogeneity and low mutational burden limits the availability of effective immunotherapy targets. Aberrant RNA-splicing (neojunctions) represents an underexplored yet promising source of neoantigens. To address this, we developed a neoantigen discovery platform (SNIPP) that characterizes a novel class of clonally-expressed, splicing-derived neoantigens. Furthermore, we validated the immunogenicity of these neoantigens by identifying specific TCRs that drive CD8+ T-cell-mediated tumor killing. **Methods:** SNIPP identified public neojunctions by analyzing TCGA RNA-seq data, selecting neojunctions with a positive sample rate (PSR) $>$ 10% and filtering out those found in GTEx normal tissue RNA-seq data (PSR $<$ 1%) across 12 cancer types. To characterize intratumorally conserved neojunctions, we performed maximally-distanced multi-site biopsies (n = 535) within glioma patients (n = 56) and generated RNA-seq data for each intratumoral site. Two independent algorithms were utilized to predict peptide processing likelihood and HLA-binding affinity of splicing-derived neoantigen candidates. Neoantigen-specific TCR sequences were identified via *in vitro* sensitization of PBMCs and subsequent 10x V(D)J scRNA-seq. These TCRs were transduced into CD8+ T-cells, which were tested downstream for immunogenicity and cytotoxicity against glioma cell lines. **Results:** Our pipeline identified 789 public neojunctions, including 32 neojunctions concurrently detected in transcriptomic and proteomic glioma datasets and confidently predicted to be presented by HLA-A*02:01. IVS and subsequent 10x V(D)J scRNA-seq identified TCR clonotypes reactive against neojunctions in *RPL22* (n = 7) and *GNAS* (n = 1), with the latter exhibiting high intratumoral conservation (detected in $>$ 90% of spatially-mapped biopsies across 17/56 patients (26.78%)). TCR-transduced CD8+ T-cells recognized and were immunogenically activated and demonstrated cytotoxicity against endogenously processed and presented neoantigens in GBM and melanoma lines. Additionally, IDH1-mutant oligodendrogliomas exhibited significantly higher neojunction expression compared to IDH1-mutant astrocytomas and IDH1wt subtypes. Differential gene expression analysis (DESeq2) revealed reduced expression of splicing factors in oligodendrogliomas, attributed to their specific co-deletion of chromosomes 1p and 19q. CRISPRi-mediated knockdown of these splicing factors (e.g. SF3A3, SNRPD2) in IDH1wt glioma cells resulted in significantly increased expression of corresponding neojunctions. **Conclusions:** Our study highlights a novel class of neoantigens derived from tumor-wide aberrant RNA splicing. The SNIPP platform effectively identifies public intratumorally-conserved neojunctions with strong therapeutic potential. Furthermore, elevated neojunction expression in oligodendroglioma underscores the mechanistic link between dysregulated splicing factor expression and RNA splicing abnormalities. Research Sponsor: None.

Perturbational single-cell RNA sequencing of patient tumors in Merkel cell and small cell lung carcinomas.

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Background: Despite the transformational impact of immune checkpoint blockade, many cancer patients do not experience long-term survival. T cells with innate immune signatures can secrete inflammatory cytokines/chemokines and deliver potent cytotoxic signals potentially ideal for tumor immunity. The novel double-stranded RNA sensor RIG-I agonist SLR14 improved the control of murine melanoma. We tested the hypothesis that SLR14 transforms T cells to a cytotoxic state in immunologically "cold" human tumor specimens. **Methods:** We developed an approach, called PERCEPT, to directly test the response of patient tumor and immune samples to novel and established therapies *ex vivo* using perturbational single-cell RNA sequencing (Table). We obtained 9 surgical resections from primary or metastatic melanoma and Merkel Cell Carcinoma (MCC) tumors and lymph node metastases and made suspension replicates of tumor and infiltrating immune cell co-cultures. We stimulated for 42-48 hours (Table). We Flourescently Activated Cell Sorted live cells and then barcoded for multiplexed single-cell sequencing using 10x scRNAseq. We used CINEMA-OT to identify factors associated with response and resistance to the perturbations tested. We developed and validated CRISPR-KO MCC and small cell lung cancer (SCLC) cell lines, and co-cultured with CD14+ monocytes or monocyte-derived DCs. **Results:** Stimulation with RIG-I agonist SLR14 induced expression beyond canonical IFN-stimulated genes in tumor cells, NK cells, and T cells. SLR14 stimulates tumor-infiltrating T cells into antiviral states in tumor-immune co-cultures and primes *in vitro* T-cell production of IFNγ. However, MCC immune infiltrate responsiveness to IFN or SLR14 was notably decreased compared to the melanoma samples, and perturbational computational analyses with CINEMA-OT identified the cytokine midkine (MDK) associated with nonresponse in MCC. Knockout of MDK restored response to IFN and SLR14 by MCC and SCLC tumor cell lines, as well as co-cultured CD14+ monocytes or monocyte-derived DCs. **Conclusions:** Our approach revealed that midkine, a multifunctional cytokine, suppresses innate immune sensing of IFN and SLR14 in both tumor and immune cells, disrupting the tumor immunity cycle at multiple points. We show that this effect, while comparatively infrequent in melanoma, is pronounced in MCC and SCLC. Our study thus uses a direct assessment of patient tumor and immune samples to identify a novel resistance mechanism enriched in neuroendocrine tumors MCC and SCLC. Research Sponsor: Conquer Cancer/ASCO Young Investigator Award 2023; Astrazeneca; U.S. National Institutes of Health; 1R37CA279834-01A1.

Therapeutic class	Stimulation	Target	Clinical development
Immune checkpoint inhibitor	αPD-1	PD-1	Standard of care
Cytokine	IFNγ	IFNGR	Early-phase clinical trials
	IFNβ	IFNAR	or
Innate immune agonist	Poly(I:C)-NT	TLR3	Pre-clinical
	Poly(I:C)-T	MDA5/TIG-I/TLR3	
	ADU-S100	STING	
	SLR14	RIG-I	
Combination	αPD-1 + IFNβ	PD-1/IFNAR	

Phase 1/2, open-label, first-in-human study of the anti-GPC3 T-cell engager SAR444200 in patients with advanced solid tumors: Updated efficacy and biomarker analysis.

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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+ tumor cells, resulting in T cell-dependent cellular cytotoxicity. We present updated safety, efficacy, and biomarker data from the dose escalation cohort (Part 1A) of a multicenter, first-in-human, Phase 1/2 trial (NCT05450562). **Methods:** Patients (Pts) with GPC3+ refractory solid tumors received SAR444200 intravenously (IV) weekly with lead-in doses at dose levels (DLs) 1 (3 mg), 1A (1 mg), 2A (2.5 mg), 3A (4.5 mg), 4A (18 mg), 5A (36 mg), 6A and 7A (different lead-in doses, target dose 70 mg). Pts with ECOG PS $\leq$1, and $\geq$1 measurable lesion per RECIST 1.1, were eligible. Primary objective for Part 1A was safety. Key secondary objectives included efficacy and PK/PD. Levels of interleukin-6 (IL-6) and interferon gamma (IFNγ) were evaluated with a multiplex ECL-based assay. Study imaging was performed every 9 weeks following first infusion. Circulating tumor (ct) DNA was analyzed in blood samples using a mutational profiling NGS approach. **Results:** As of October 15, 2024, 33 pts (23 pts with hepatocellular carcinoma [HCC]) were treated with SAR444200 (premedicated with dexamethasone 15 mg IV or equivalent) for a median of 23 cycles (range, 1–32). Median lines of prior therapies were 3–4. Most pts (32 [97%]) experienced $\geq$1 AE of any Grade. Grade $\geq$3 TEAEs in 16 (48.5%) pts and serious TRAEs in 8 (24.2%) pts were reported. 2 Grade 3 cytokine release syndrome events were reported as DLTs at DL6A and 1 at DL7A during the lead-in dosing. Key efficacy data are summarized in Table 1. An increase in IL-6 and IFNγ (maximum of 1326 pg and 461 pg on average per DL, respectively) was observed during lead-in-doses in pts from DL1 to DL5A, supporting CRS diagnosis. Cytokine levels declined after Cycle 1. Of 18 HCC pts with baseline alpha fetoprotein (AFP) $\geq$20%, 5 (27%) pts showed $\geq$50% AFP reduction. Median time of observing any AFP decrease was 4 weeks post-treatment. Among these, 3 pts had sustained decrease over 13 cycles. Stable disease (SD) was reported in 10 (30.3%) pts including 2 who were on study drug for 12 and 22 months. Of the 18 pts with measurable ctDNA, 4 (including 3 pts at DL5 and above) had reductions in ctDNA (18%–48%) from baseline. **Conclusions:** SAR444200 was tolerated at the investigated DLs in pts with GPC3+ advanced solid tumors. Decrease in AFP post treatment along with SD in a subset of pts is suggestive of preliminary anti-tumor activity. Clinical trial information: NCT05450562. Research Sponsor: Sanofi.

Efficacy analysis.

n (%)	DL1 3 mg 2W n=4	DL1A 1 mg 2W n=4	DL2A 2.5 mg 2W n=4	DL3A 4.5 mg 2W n=4	DL4A 18 mg 3W n=4	DL5A 36 mg 3W n=6	DL6A 70 mg 3W n=3	DL7A 70 mg 3W n = 4	All (N = 33)
BOR	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	2 (50.0)	3 (50.0)	1 (33.3)	0	10
Stable Disease	3 (75.0)	3 (75.0)	3 (75.0)	2 (50.0)	2 (50.0)	2 (33.3)	1 (33.3)	2 (50.0)	(30.3)
Progressive disease									18 (54.5)

BOR, best overall response; DL, dose level; W, weeks.

Lacutamab in patients with relapsed and refractory Sézary syndrome: Long term follow-up from the TELLOMAK phase 2 trial.

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Background: Sézary syndrome (SS) is a rare and aggressive cutaneous T-cell lymphoma, which commonly expresses KIR3DL2, a killer immunoglobulin-like receptor, reported in ≥ 85% of patients. SS is characterized by erythroderma, significant blood involvement, lymphadenopathy and poor prognosis (10-20% 5-year survival). Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis. **Methods:** TELLOMAK is an international, Phase 2 trial with multiple cohorts (NCT03902184). We report here long term follow-up results from Cohort 1, evaluating lacutamab in patients with relapsed/refractory (R/R) SS after at least 2 prior systemic therapies including mogamulizumab. Lacutamab 750 mg is administered until progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) based on the evaluation of 4 compartments: skin, blood, lymph nodes and viscera according to the International Consensus criteria Olsen 2011. Secondary endpoints included but were not limited to duration of response (DOR), progression free survival (PFS), safety, and quality of life assessments. **Results:** As of October 17, 2024, recruitment was completed with 63 SS patients enrolled. Median age was 69 years (range: 42-86), the median prior lines of systemic therapies were 5.0 (range: 2-13), 65.1% and 34.9 % patients had stage IVA1 and stage IVA2 at baseline respectively, all patients had blood involvement (B2), 63.5% had confluence of erythema covering ≥ 80% body surface area (T4), 34.9% had lymph node lymphoma involvement (N3). Median follow-up was 25.1 months (95% CI 21.0-29.4). Global confirmed ORR was 42.9% (CI 31.4-55.1) including 6 (9.5%) CRs who are all still in CR; with a median time to response of 2.8 months (range 1-10) and a median duration of response of 25.6 months (CI 11.0, NE). According to each compartment, ORR in skin was 52.4% (CI 40.3-64.2) including 9 (14.3%) CRs, ORR in blood was 50.8% (CI 38.8-62.7) including 21 (33.3) CRs, and ORR in lymph nodes was 28.8% (CI 18.3-42.3) including 9 (17.3) CRs. Median PFS was 8.3 months (CI 5.1-18.7). Grade ≥ 3 related Treatment-Emergent Adverse Events (TEAEs) were observed in 20.6% patients. Serious related TEAEs were observed in 9.5% patients and related TEAEs leading to study drug discontinuation in 6.3% patients. Data from additional key endpoints will be presented. **Conclusions:** The long term follow-up data from TELLOMAK study in a R/R SS population previously treated with 2 or more prior systemic therapies including mogamulizumab, confirm that lacutamab shows promising clinical activity with ORR 42.9% (95% CI 31.4-55.1) and median duration of response of 25.6 months (11.0, NE) and an overall favourable safety profile. These data support the further development of lacutamab in an effort to bring improved treatments to patients with SS. Clinical trial information: NCT03902184 // EU CT number: 2023-507777-18-00. Research Sponsor: Innate Pharma.

Lacutamab in patients with relapsed and/or refractory mycosis fungoides: Long-term follow-up and translational data from the TELLOMAK phase 2 trial.

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Background: The most common type of cutaneous T-cell lymphoma is Mycosis Fungoides (MF) accounting for 50-60% of cases. Extracutaneous involvement occurs mainly in lymph nodes or blood; 25% of patients are diagnosed at advanced stage with a 5-year survival of 15-25%. Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis. KIR3DL2 is a killer immunoglobulin-like receptor expressed in MF patients. **Methods:** TELLOMAK is an international, multi-cohort phase 2 trial (NCT03902184). MF patients who had received at least 2 prior systemic therapies were treated with lacutamab 750 mg until disease progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) by global response score based on the evaluation of 4 compartments: skin, blood, lymph nodes and viscera according to the International Consensus criteria Olsen 2011. Key secondary endpoints included duration of response (DoR), progression free survival (PFS), safety, and quality of life. Here we report long term follow-up data of MF patients. **Results:** As of October 17, 2024, recruitment was completed, with 107 MF patients enrolled. The median age was 62 years. The median number of previous systemic lines was 4 (range: 1-14). Median follow-up was 22.1 months (m) (95% CI 19.4, 23.6). Global confirmed ORR was 19.6% (CI 13.2, 28.1; Olsen 2011), and response in skin was 29.0% (CI 21.2, 38.2). Median time to response was 2.8 m (min, max 1-37) and median DoR was 13.8 m (7.4, NE), median PFS was 10.2 m (CI 8.0, 15.4). Among the KIR3DL2 $\geq$1% pts (N = 48), ORR was 20.8% (CI 11.7, 34.3; Olsen 2011), and response in skin was 33.3% (CI 21.7, 47.5), median DoR was 13.8 m (CI 4.6, NE) and median PFS 11.8 m (CI 5.6, 16.8). Among the KIR3DL2 $<$ 1% pts (N = 59), ORR was 18.6% (CI 10.7;30.4; Olsen 2011), and response in skin was 25.4 (CI 16.1, 37.8), median DoR was 15.7 m (CI 5.1, NE) and median PFS 9.5 m (CI 6.5;16.6). Grade $\geq$ 3 related Treatment-Emergent Adverse events (TEAEs) were observed in 5/107 (4.7%) patients, serious related TEAEs in 4/107 (3.7%) patients and related TEAEs leading to study drug discontinuation in 3/107 (2.8%) patients. The most common ($>$ 10%) related TEAEs were fatigue (12.1%), nausea (13.1%), asthenia (11.2%) and arthralgia (11.2%). Data from additional key endpoints and translational data will also be presented. **Conclusions:** The long-term follow-up data from the heavily pre-treated MF population enrolled to the TELLOMAK study confirms promising clinical activity of lacutamab regardless of KIR3DL2 expression, with ORR 20.8%, a median duration of response of 13.8 m, a median PFS of 10.2 m and a favorable safety and tolerability profile. These data support the further development of lacutamab in an effort to bring improved treatments to patients with MF. Clinical trial information: NCT03902184 // EU CT number: 2023-507777-18-00. Research Sponsor: INNATE PHARMA.

Safety and efficacy of OR502, an antibody targeting leukocyte immunoglobulin-like receptor B2 (LILRB2), ± cemiplimab in patients with advanced solid tumors from a phase 1 study.

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Background: OR502 is a humanized IgG1 antibody that targets LILRB2, blocking its binding to HLA ligands A, B and G. OR502 prevents and reverses myeloid cell-mediated immune suppression and rescues T cell effector functions. Preclinical data demonstrate best-in-class properties. We report on the completed monotherapy and combination dose escalation cohorts from the ongoing, first-in-human, phase 1-2 study of this novel antibody. **Methods:** Patients had progressive, histologically confirmed, metastatic/unresectable solid tumors with ≥ 1 prior systemic standard of care treatments. Primary objectives were OR502 safety/tolerability and identifying a dose for future study supported by LILRB2 receptor occupancy (RO) and pharmacokinetics (PK). Secondary objectives included assessment of anti-tumor activity. We used a modified toxicity probability interval-2 design with a 25% dose-limiting toxicity (DLT) rate and a 20–30% equivalence interval. Patients received OR502 IV (100–1600 mg) over 30 minutes, every 3 weeks (Q3W) as monotherapy (n = 19) or with cemiplimab (350 mg) (n = 20). **Results:** In dose escalation (n = 39), there were no DLTs, treatment-related deaths, related SAEs, grade ≥ 3 treatment-related AEs or signals from vital signs, ECGs or laboratory results. One patient (monotherapy, 400 mg) discontinued due to grade 2 AEs. Infusion-related reactions (IRRs) occurred in 6 patients (3 monotherapy [1 at 800 mg and 2 at 1600 mg] and 3 combination [400, 800 and 1600 mg]). All IRRs were grade ≤ 2 and were mitigated by extending infusion duration to 60 minutes, with secondary prophylaxis if necessary (acetaminophen, diphenhydramine). All but 4 patients were evaluable for efficacy, see table. Monotherapy responses were seen at 200 and 800 mg in melanoma and non-small cell lung cancer (NSCLC), respectively. In combination, 1 patient with soft tissue sarcoma (1600 mg) had a cPR. There were 13 deaths due to progressive disease. Durable stable disease (SD) was seen in: sarcomas, cutaneous squamous cell carcinoma, thymoma, thyroid, melanoma, hepatocellular carcinoma and colorectal cancer. OR502 RO was near-complete at ≥ 200 mg and PK was roughly dose-proportional. Combination with cemiplimab did not affect RO or PK. **Conclusions:** OR502 has excellent safety and tolerability ± cemiplimab. Based on efficacy, predictable PK and near-complete RO, two mini-expansion cohorts are evaluating OR502 800 mg Q3W ± cemiplimab in patients with cutaneous melanoma or NSCLC who have failed or progressed after ≥ 12 weeks of anti-PD-(L)1. Clinical trial information: NCT06090266. Research Sponsor: OncoResponse, Inc.; The Cancer Prevention and Research Institute of Texas.

Best objective response (RECIST 1.1), PK and RO.

	OR502 (n=17)	OR502 + cemiplimab (n=18)
PR	2	1
cPR	1	1
SD	9	8
Durable SD (≥ Week 12)	7	4
Best overall response rate %	12	6
Disease control rate (CR+PR+SD)%	65	50
PK (100–1600 mg) $t^1/_2$ (day)	7.6–15.9	8.4–12.4
Peripheral RO% (100–1600 mg)	91–101	88–99
Classical monocytes		
Neutrophils	89–100	84–100

A phase 1 study of the OX40 agonist BGB-A445, with or without tislelizumab, an anti-PD-1 monoclonal antibody, in patients with advanced NSCLC, HNSCC, or NPC.

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Background: BGB-A445 is a monoclonal antibody OX40 agonist that does not compete with the natural OX40 ligand, reducing the likelihood of a hook effect and distinguishing it from other OX40-targeting therapies. Here, we present results from the dose expansion portion of a ph 1, open-label, dose escalation/expansion trial of BGB-A445 in pts with advanced solid tumors (NCT04215978). Ph 1a results were previously presented (Desai *et al. J Clin Oncol.* 2023). **Methods:** Previously treated pts with NSCLC (Part A1), HNSCC (Part A2), or NSCLC with PD-L1 ≥50% (Part C) received BGB-A445 monotherapy, while pts with treatment-naïve recurrent/metastatic NPC (Part B) received BGB-A445 combined with tislelizumab and chemotherapy. Primary endpoints included ORR per investigator (RECIST v1.1); secondary endpoints were to assess PFS, DOR and DCR, safety/tolerability, PK, and host immunogenicity. **Results:** As of Sep 25, 2024, 54 pts were enrolled in Part A1, 19 in Part A2, 12 in Part B, and 7 in Part C. In the efficacy evaluable analysis set, ORR was 0% in Parts A1, A2, and C, and 70% (7/10; all confirmed PRs, one unconfirmed CR) in Part B. In Parts A1, A2, B, and C, confirmed DCR was 49.0%, 33.3%, 100.0%, and 57.1%, respectively. TEAEs occurred in the majority of pts (Table). The most common treatment-related TEAEs were pyrexia (10.0% [8/80]), chills (5.0% [4/80]), and anemia (5.0% [4/80]) in the monotherapy cohorts, and anemia (75.0% [9/12]), decreased WBC (66.7% [8/12]), decreased neutrophils, and decreased platelets (58.3% [7/12], each) in the combination cohort. Treatment-related serious TEAEs occurred in 2.5% (2/80; pyrexia and asthenia in a single pt each) of pts in the monotherapy cohorts and 8.3% (1/12; febrile neutropenia) in the combination cohort. There were no BGB-A445 or tislelizumab-related TEAEs leading to treatment discontinuation or death. The most common imAE was rash (2.5% [2/80] in the monotherapy cohort; 33.3% [4/12] in the combination cohort). No Gr ≥3 imAEs or IRRs were reported. **Conclusions:** BGB-A445 alone or in combination with tislelizumab and chemotherapy was generally well tolerated across all doses in pts with advanced NSCLC, HNSCC, and NPC, and showed preliminary antitumor activity. Clinical trial information: NCT04215978. Research Sponsor: BeOne Medicines Ltd.

Safety.

	Part A1 NSCLC (N=54)	Part A2 HNSCC (N=19)	Part B NPC (N=12)	Part C NSCLC and PD-L1 ≥50% (N=7)
Any treatment-emergent AE	47 (87.0)	16 (84.2)	12 (100.0)	7 (100.0)
Gr ≥3	17 (31.5)	5 (26.3)	11 (91.7)	3 (42.9)
Serious	21 (38.9)	4 (21.1)	2 (16.7)	4 (57.1)
Leading to death	4 (7.4)	2 (10.5)	0 (0)	0 (0)
Leading to treatment discontinuation	8 (14.8)	3 (15.8)	2 (16.7)	0 (0)
Any treatment-related treatment-emergent AE	28 (51.9)	7 (36.8)	12 (100.0)	3 (42.9)
Gr ≥3	1 (1.9)	0 (0)	11 (91.7)	0 (0)
Any immune-mediated AE	6 (11.1)	1 (5.3)	6 (50.0)	1 (14.3)
Infusion-related reactions	6 (11.1)	3 (15.8)	3 (25.0)	1 (14.3)

Pts with multiple adverse events (AEs) are counted once. All AEs are listed as n (%).

Phase 1b dose extension study of a next-generation anti-CD47 monoclonal antibody IMC-002 combined with lenvatinib in patients with advanced hepatocellular carcinoma (HCC).

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Background: IMC-002 has shown significant preclinical efficacy and safety, which are attributed to its unique binding site and distinct mechanism of action. These preclinical findings strongly support its clinical development as a cancer therapeutic. Phase 1a trial confirmed its superior safety and tolerability. Here we present initial results from the phase Ib trial, focusing on safety, efficacy, PK, and biomarker. **Methods:** Eligible pts had advanced HCC that progressed following at least 1 prior systemic therapy and ECOG PS ≤1. IMC-002 was administered at 20 mg/kg Q3W in combination with Lenvatinib, continuing until disease progression. Tumor assessments were conducted every 6 weeks using RECIST 1.1 and iRECIST. A target-mediated drug disposition (TMDD) PK model incorporating FcRn recycling was developed to predict PK values for Q3W dosing and evaluated for consistency with observed data. Immunohistochemistry (IHC) images of CD47 expression were analyzed using Lunit SCOPE uIHC, an AI-based platform capable of distinguishing staining positivity and cell types at the single cell level. **Results:** A total of 13 pts with refractory HCC received IMC-002 in combination with Lenvatinib. Most patients had received prior anti-PD-(L)1 therapy (11 pts) and had an ECOG PS of 1 (9 pts). Among the 10 pts evaluable for efficacy, the ORR was 30%, and the DCR was 70%. The median TTP was 8.3 months. AI-driven analysis of CD47 membrane specificity, using a subcellular model, revealed that samples with a high proportion of non-membrane-specific cells were associated with poor clinical outcomes (ORR 0%, DCR 33%). In contrast, samples with a low proportion demonstrated improved responses (ORR 60%, DCR 80%). We confirmed that 96.3% of the observed concentrations of IMC-002 in Phase 1b not only fell within the 90% prediction percentiles of PK model developed for Q3W dosing schedule but also demonstrated steady-state achievement (after cycle 2 of Q3W) and consistent C_{trough} exposure above the MEC (> 24 μg/mL). All TRAEs were grade 1-2 (100%), with 92% occurring during cycle 1. TRAEs reported in more than one patient included skin rash and transient vitreous floaters. Anemia was observed in only one patient, while no cases of neutropenia, thrombocytopenia, or treatment-related SAEs were reported. **Conclusions:** IMC-002, when combined with Lenvatinib at a dose of 20 mg/kg Q3W, demonstrated a promising efficacy and safety profile. AI-driven biomarker analysis identified potential predictive value, supporting the need for further investigation in larger clinical trials. Clinical trial information: NCT05276310. Research Sponsor: ImmuneOncia Therapeutics Inc.

Tumor response by CD47 non-specific cell proportion.

Cohort	Non-specific cell proportion Mean (±SD)	ORR	DCR
A	0.24 (±0.05)	0%	33%
B	0.05 (±0.05)	60%	80%
p-value	0.00	0.03	0.14

Cohort A: High proportion (≥15%) of 'non-specific' cells; Cohort B: Low proportion (<15%) of 'non-specific' cells.

Safety and efficacy of QLS31905 in patients with advanced solid tumors: Updated data from phase 1 study.

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Background: QLS31905 is a Claudin18.2/CD3 bispecific antibody. Here we report the updated data of a phase 1 study of QLS31905. **Methods:** This multicenter phase 1 trial (NCT05278832) recruited patients (pts) with advanced solid tumors who had progressive disease or were intolerable to or inapplicable of standard therapy. In dose-escalation stage adopting accelerated titration and interval 3+3 design, pts regardless of Claudin18.2 status were administered QLS31905 via intravenous infusion in 11 sequential single doses (0.5, 1.5, 5, 15, 45, 100, 200, 350, 500, 800, 1200 μg/kg qw or q2w) with priming dose from 350 μg/kg. In dose-expansion stage, Claudin18.2-positive (≥1% tumor cells) pts were recruited. The primary endpoint was dose limiting toxicities (DLT) and maximum tolerated dose (MTD) in dose-escalation stage, and was objective response rate (ORR) in dose-expansion stage. **Results:** As of Jul 26, 2024, 31 pts were included from 0.5 μg/kg qw to 1200 μg/kg q2w in dose-escalation stage, and 48 pts were included in five cohorts (100~200 μg/kg qw and 350~800 μg/kg q2w) in dose-expansion stage. The 1200 μg/kg q2w cohort is ongoing. There were 43 (54.4%) pts with gastric or gastro-esophageal junction (G/GEJ) cancer and 26 (32.9%) with pancreatic adenocarcinoma (PAC). Over half of (61.8%) pts had received ≥2 lines of prior treatment. No DLT occurred. MTD was not reached. Treatment-related adverse events (TRAEs) occurred in 79 (100%) pts, of whom 34 (43.04%) were ≥grade 3. The most common ≥grade 3 TRAEs (≥3%) were lymphocyte count decreased (21.5%), γ-glutamyl transferase increased (3.8%), neutrophil count decreased (3.8%), cytokine release syndrome (CRS [3.8%]), and anemia (3.8%). CRS occurred in 17 (21.52%) pts including two pts with grade 3 and one with grade 4, and all recovered. Two pts (2.53%) discontinued treatment due to TRAEs of abdominal pain and CRS, respectively. No TRAE leading to death occurred. In 33 Claudin18.2-positive pts in 350~1200 μg/kg q2w cohorts, six pts (three with G/GEJ cancer and three with PAC) had partial response. ORR was 18.18% (95% confidence interval [CI]: 6.98%, 35.46%), disease control rate (DCR) was 87.88% (95% CI: 71.80%, 96.60%), median progression-free survival (PFS) was 4.21 months (95% CI: 2.99, 5.55), and median overall survival (OS) was 9.53 months (95% CI: 7.69, not evaluable). Among the Claudin18.2-positive pts in 350~1200 μg/kg q2w cohorts, ORR, DCR, median PFS, median OS was 15.79%, 89.47%, 4.40 months, 9.20 months in 19 pts with G/GEJ cancer, and was 25.00%, 91.67%, 3.94 months, not reached in 12 pts with PAC, respectively. QLS31905 exposure was generally linear with the administered dosage. There was no tendency of accumulation after multiple administrations. **Conclusions:** QLS31905 was safe and tolerable, and showed encouraging efficacy in Claudin18.2-positive pts with gastrointestinal tumors. QLS31905 is worthy of further exploration in combined therapy in phase 2 trials. Clinical trial information: NCT05278832. Research Sponsor: None.

Epigenetic and phenotypic signatures of T-cell response to blinatumomab in pediatric relapsed and refractory B-ALL.

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Background: By forming an immunological synapse between T cells and tumor antigen, bispecific T cell engagers (BiTEs) like blinatumomab have shown great promise in treating B-cell acute lymphoblastic leukemia (B-ALL). However, many relapsed and refractory (R/R) patients fail to achieve long-term survival, with 40% not surviving past 24 months. Prolonged T cell activation with blinatumomab therapy may lead to changes in differentiation that leave the T cell population unable to elicit a sustained anti-tumor response. A deeper understanding of the dynamics of the T cell compartment in R/R B-ALL patients will lead to improved treatment strategies and optimized patient selection for blinatumomab therapy. **Methods:** To characterize T cell persistence and response in this context, we assessed memory and exhaustion phenotypes in blinatumomab-treated T cells isolated from 10 R/R pediatric B-ALL patients treated with blinatumomab. CD8+ T cells were isolated from peripheral blood and bone marrow samples and analyzed for memory and exhaustion phenotypes via flow cytometry. Absolute lymphocyte counts were measured and linked to the sample flow cytometry data to assess expansion and contraction of T cell memory subsets throughout the course of therapy. Whole genome enzymatic methyl sequencing was performed on post-treatment PD-1 High and PD-1 Low CD8 T cells to determine the multipotency of the patient T cell compartment after blinatumomab treatment. **Results:** After 7 days of continued blinatumomab infusion, patient T cells demonstrated a significant expansion of terminally differentiated and effector memory T cells. Notably, we observed that non-responders had a high tumor burden at the start of the therapy and possessed a large population of naïve CD8 T cells that failed to expand. These CD8 T cells exhibited a significant increase in expression of TIM-3 and PD-1 compared to responders after the 7-day infusion. Methylation analysis of post-treatment CD8 T cells showed decreased methylation of exhaustion regulators IKZF1 and CD300a in non-responders compared to the responders. Additionally, *in vitro* treatment of T cells with blinatumomab induced T-cell exhaustion in a target-dependent manner. **Conclusions:** Blinatumomab therapy in pediatric B-ALL patients induced variable epigenetic and phenotypic changes to the T cell compartment indicative of exhaustion, corresponding to differences in T cell expansion and persistence between patients. Our study is the first to link epigenetic changes in exhaustion regulators with response variability in blinatumomab-treated patients. Furthermore, our findings highlight a potential role of baseline T cell composition and tumor burden in determining therapeutic outcomes. These insights provide a novel framework for improving patient stratification and treatment strategies to mitigate T cell exhaustion in blinatumomab therapy. Research Sponsor: American Lebanese Syrian Associated Charities (ALSAC), St. Jude Children's Research Hospital.

PD-1 blockade in combination with bevacizumab and nab-paclitaxel for second-line treatment in cancer of unknown primary (Fudan CUP-002): A prospective, single-arm phase II study.

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Background: Cancer of unknown primary (CUP), a heterogeneous tumor characterized by histologically confirmed metastases with undefined primary, accounts for 2-5% of all malignancies. Our previous study, Fudan CUP-001, confirmed that site-specific first-line treatment improves progression-free survival (PFS) in patients with CUP compared to empirical treatment. However, no evidence-based standard of care currently exists for second-line treatment of CUP. We conducted the Fudan CUP-002 study by Simon's two-stage design to evaluate the efficacy and safety of co-administration of F520 injection (anti-PD-1 antibody), bevacizumab, and nab-paclitaxel in patients with CUP who have progressed after first-line treatment. **Methods:** In this prospective, single-arm phase II study (ClinicalTrials.gov, NCT04848597), patients with previously treated CUP received intravenous F520 injection at a dose of 200 mg and bevacizumab 7.5 mg/kg every 3 weeks for up to 2 years, and intravenous nab-paclitaxel 125 mg/m^2 administered on day 1 and day 8 every 3 weeks for up to 8 cycles. The primary endpoint was confirmed objective response rate (ORR) by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The secondary endpoints included PFS, overall survival (OS), disease control rate (DCR), and safety. **Results:** Between June 2, 2021, and January 10, 2025, a total of 48 eligible subjects were enrolled in the study. In the overall population, the median age was 60 (range: 29 to 72) years, with 31 males (64.6%) and 17 females (35.4%). At the data cutoff on January 10, 2025, the median follow-up was 27.1 months (95% CI, 20.2 to 37.2) and 3 (6.3%) cases continued treatment. The ORR was 54.2% (95% CI, 40.3 to 67.4), and the DCR was 95.8% (95% CI, 86.0 to 98.9), as assessed by BICR per RECIST version 1.1. The median PFS was 16.7 months (95% CI, 12.6 to not available (NA)), with the 12- and 24-month PFS rates at 68.6% and 38.5%, respectively. The median OS was 24.6 months (95% CI, 14.6 to 29.5), and the 12- and 24-month OS rates were 72.5% and 53.0%, respectively. The median duration of response (DoR) was 22.5 months (95% CI, 12.5 to NA), with the 12- and 24-month DoR rates at 78.9% and 47.5%, respectively. Treatment-related adverse events (TRAEs) of any grade were reported by 46 (95.8%) patients. Hematologic toxicity (43, 89.6%) and liver injury (25, 52.1%) of any grade were the most frequently reported TRAEs, and grade 3-4 TRAEs were observed in 25 (52.1%) patients. Grade 3-4 immune-related adverse events (irAEs) occurred in 8 (16.7%) participants, with pneumonitis (2, 4.2%) and endocrine disorders (2, 4.2%) being the most common. **Conclusions:** Second-line PD-1 blockade in combination with bevacizumab and nab-paclitaxel is an effective and well-tolerated treatment regimen for patients with CUP. Clinical trial information: NCT04848597. Research Sponsor: Clinical Research Plan of SHDC.

Comprehensive analysis of NSAIDs use and oncological outcomes in non-small cell lung cancer patients treated with immune checkpoint inhibitors.

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Background: The effect of non-steroidal anti-inflammatory drugs (NSAIDs) on immune checkpoint inhibitors (ICIs) efficacy in non-small cell lung cancer (NSCLC) remains controversial. Although the COX-2/PGE2 pathway, a primary target of NSAIDs, has been implicated in diminished immunotherapy response, direct clinical association with NSAIDs and ICIs in real world has yet to be established. This study aims to evaluate the impact of NSAIDs use—considering types, duration, and timing—on ICI efficacy, alongside its effects on PGE2 and immune cell profiles. **Methods:** We included stage III-IV NSCLC patients receiving PD-1/PD-L1 antibodies in 5 centers. Blood and tumor samples were collected in perspective cohort. NSAIDs were categorized based on selectivity (non-selective COX inhibitors, selective COX-2 inhibitors) and chemical structure (salicylates, propionate derivatives, others). PGE2 and cytokines were measured in blood by ELISA. RNA sequencing data were obtained from databases. Tumor tissues were collected for immunohistochemical staining of immune cells. Multivariate Cox and logistic regression were used in analyses of progression-free survival (PFS) and objective response rate (ORR). **Results:** 883 patients were included, with 140 NSAIDs users and 743 non-users. 196 patients were enrolled prospectively with samples. Multivariate analysis showed that NSAIDs use was significantly associated with improved PFS (HR 0.67, 95% CI 0.51-0.88, P = 0.005) and ORR (OR 1.87, 95% CI 1.29-2.72, P = 0.001). Subgroup analyses indicated that non-selective COX inhibitors, salicylates, long-term use, and pre-ICI initiation were correlated with better outcomes. In contrast, selective COX-2 inhibitors, propionate derivatives, others, short-term use, and post-ICI initiation showed no effect on PFS or ORR. Blood analyses indicated that NSAIDs significantly lowered PGE2 levels, particularly salicylates and long-term use. Higher PGE2 was associated with worse outcomes. For immune cells, RNA sequencing revealed that COX-2 and mPGES-1 were significantly correlated with neutrophil enrichment and neutrophil-related cytokines. Single-cell RNA-seq showed high expression of COX-2 and mPGES-1 in neutrophils. Analysis of samples confirmed that NSAIDs use was associated with reduced neutrophils and neutrophil-related cytokines in blood and less neutrophil infiltration in tumor. **Conclusions:** NSAID use is an independent predictor of improved PFS and ORR in NSCLC patients receiving ICIs. Specifically, non-selective COX inhibitors, salicylates, long-term use, and pre-ICI initiation are associated with better clinical outcomes. NSAID use may enhance ICIs efficacy by reducing serum PGE2, which could serve as a predictive biomarker. Furthermore, NSAIDs decrease neutrophils in both blood and tumor, potentially contributing to the improvement in ICI efficacy. Research Sponsor: Basic Research Funds for Central Universities; National Natural Science Foundation of China; Shaanxi Province "Sanqin Scholars" Innovation Team Support Program; Shaanxi Province Health and Medical Research Innovation Team Support Program.

Preliminary monotherapy efficacy of novel immune checkpoint blockade GV20-0251 (anti-IGSF8) in advanced melanoma patients with primary resistance to anti-PD1.

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Background: GV20-0251 is an AI-designed, first-in-class, cross-species reactive, Fc-attenuated IgG1 antibody that targets the novel cancer immune checkpoint IGSF8 which is broadly expressed across solid tumors. In syngeneic tumor models, anti-IGSF8 alone or with anti-PD1 inhibits tumor growth by increasing cytotoxicity and infiltration of natural killer cells (NK) and antigen cross-priming by dendritic cells which in turn activates T cells. **Methods:** The phase 1 portion of this first-in-human, phase I/IIa study (NCT05669430) was conducted across multiple U.S. centers. The study utilized a standard 3+3 design to evaluate the safety, pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary efficacy of GV20-0251, and to establish a preliminary recommended phase 2 dose (RP2D). **Results:** Forty-two patients with advanced solid tumors (median age 61 years, median 4 prior treatment lines) were enrolled across six dose levels (0.5, 1, 3, 6, 10, and 20 mg/kg) and two schedules (D1/D8 Q3W and D1 Q3W). GV20-0251 demonstrated favorable safety and tolerability across all doses and schedules with no dose-limiting toxicities, and 10 and 20 mg/kg D1 Q3W were selected as the preliminary RP2D. Treatment-related adverse events occurred in 55% of patients, predominately grade 1/2, with a single grade 3 event of pneumonitis. The most common treatment-related AEs were fatigue and rash (12% each), with no dose-dependent trends. Full target occupancy and half-life of 26 days with linear PK were observed at ≥10 mg/kg, without significant serum cytokine elevation or anti-drug antibody signals. Among 38 efficacy-evaluable patients, 17 had cutaneous melanoma, all of whom progressed on prior anti-PD1 therapy and 16 progressed on prior anti-CTLA4 therapy. Among the 9 melanoma patients with primary resistance to anti-PD1, confirmed partial response (PR) was achieved in 3 (33%) patients and tumor shrinkage was observed in an additional 3 patients. Notably, responses were observed in 2 patients with liver metastases, which are typically refractory to immunotherapy. Although no responses were seen in the melanoma patients with acquired resistance to anti-PD1 (n = 8) or in patients with other tumor types (n = 21), potentially due to the lower frequency of IGSF8 protein expression in these tumors, tumor shrinkage was observed in one non-small cell lung cancer (n = 4) and one cervical cancer (n = 1) patient. Preliminary immunohistochemistry analyses of trial patient biopsies suggest IGSF8 high tumors have low anti-PDL1 at baseline, and GV20-0251 treatment increases tumor-infiltrating NK and T cells. **Conclusions:** GV20-0251 demonstrated a favorable safety profile in heavily pretreated patients with advanced solid tumors and showed promising monotherapy efficacy in cutaneous melanoma patients with primary resistance to anti-PD1. Clinical trial information: NCT05669430. Research Sponsor: GV20 Therapeutics.

Prophylactic infusion of allogeneic double-negative T cells as immune modulators to prevent relapse in high-risk AML patients after allo-HSCT: A phase I trial.

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Background: Our previous study demonstrated that double-negative T cells (DNTs) hold potential for treating relapsed or refractory acute myeloid leukemia (r/r AML) following allogeneic hematopoietic stem cell transplantation (allo-HSCT). In a first-in-human Phase I trial (ChiCTR-IPR-1900022795), we reported a complete response (CR) rate of 50% (5/10) with a favorable safety profile. This Phase I/II study aims to evaluate the safety and efficacy of off-the-shelf allo-DNTs in preventing relapse in AML patients following allo-HSCT. **Methods:** Six high-risk AML patients undergoing allo-HSCT were enrolled and assigned to two dosage groups: 1×10^8 DNTs/kg and 1.5×10^8 DNTs/kg. Each patient received three infusions at one-month intervals without prior lymphodepleting chemotherapy. The median time from transplantation to the first infusion was 3.1 months. Primary endpoint was the occurrence of adverse events and dose-limiting toxicities, while the secondary endpoint was cumulative incidence of relapse (CIR). GMP-grade DNTs were expanded ex vivo from healthy donor PBMCs and cryopreserved in liquid nitrogen until infusion. **Results:** As of January 20, 2025, with a median follow-up of 17.55 months post-HSCT, four of six patients (66.7%) remained in MRD-negative CR, with the longest recurrence-free survival exceeding 17 months. The two relapsed patients both carried high-risk genetic mutations (TP53 mutation) and were MRD-positive prior to transplantation. They succumbed at 11.4 and 14.2 months post-HSCT respectively. Donor-derived DNTs were detectable in peripheral blood shortly after each infusion, peaking at 1–4 days and persisting for up to 28 days. In two patients with MRD-negative CR, infused DNTs remained detectable for up to 360 days post-infusion. Elevated levels of IFN-γ, IL-6, and IL-10 post-infusion indicated immune activation. Importantly, no dose-limiting toxicities, neurotoxicity, cytokine release syndrome greater than Grade 2, or graft-versus-host disease were observed. In contrast to the two relapsed patients, MRD-negative CR patients showed expanded levels of CD4+, CD8+, and DNT cells, particularly those with the effector memory T cell phenotype. Both the infused DNTs and the recipient's CD4+ and CD8+ T cells in these patients secreted higher levels of granzymes A and K. To investigate the interaction between CD8+ T cells and allo-DNTs in MRD-negative CR patients, co-culture experiments were conducted. CD8+ T cells exhibited an increase in the secretion of granzyme B and IFN-γ within 3–4 days. Transcriptome sequencing and multi-cytokine analyses revealed strong immune activation. **Conclusions:** The dual ability of DNTs to suppress GvHD while preserving the graft-versus-leukemia effect, along with its potential for off-the-shelf availability, makes it a transformative therapy in the post-transplant setting. Clinical trial information: NCT05858814. Research Sponsor: National Natural Science Foundation of China; # U23A20453, 82270223 and 82170209; Anhui Provincial Key Research and Development Project; # 2022e07020015; Anhui Health Research Project; # AHWJ2022a011; Anhui Provincial Department of Education Scientific Research Project; 2023AH010079; Anhui Provincial Natural Science Foundation; 2308085J09; the Fundamental Research Fund for the Central Universities; YD9110002047.

Targeting cancer leptomeningeal metastasis with allogeneic chimeric antigen receptor γδ T-cell therapy.

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Background: Leptomeningeal metastasis (LM) occurs in 1–10% of patients with advanced solid tumors during disease progression. LM significantly worsens prognosis due to the rapid onset and progression of symptoms associated with elevated intracranial pressure. Currently, no therapies specifically targeting LM have been approved. Here, we report our clinical observations from two patients treated with intrathecal infusion of allogeneic B7H3-targeted CAR-γδT cells(QH104). **Methods:** This is an open-label, single-arm clinical study designed to evaluate the safety and efficacy of QH104 in patients with LM originating from B7H3-positive solid tumors(NCT06592092). Eligibility criteria included a diagnosis of LM from any B7H3-positive solid malignancy. QH104 was administered as a single dose of 3×10^7 cells via lumbar puncture or Ommaya reservoir infusion. Treatment-emergent adverse events were graded using CTCAE v5.0 and ASTCT criteria. Efficacy was assessed using the RANO-LM criteria. **Results:** As of January 2025, two female lung adenocarcinoma patients were enrolled. They had previously received treatments targeting LM, including intrathecal chemotherapy and oral EGFR tyrosine kinase inhibitors. No adverse events higher than grade3 were reported. One patient experienced a transient episode of absence seizures on Day 1 after cell infusion, which was considered treatment-related. At the Day 30 assessment post-infusion, both patients had stable disease, with a reduction or complete elimination of tumor cells in the CSF and improvement in clinical symptoms associated with LM. CSF component analysis demonstrated the persistence of CAR-γδ T cells for one week post-infusion. CSF cytokine analysis revealed increased levels of interleukin-5, -6, -9, -13, and -22, TNF-α and IFN-γ post-infusion compared to baseline. No significant increases in CAR-γδ T cells or cytokines were detected in peripheral blood. **Conclusions:** Our initial clinical experience with the first two patients with leptomeningeal metastasis (LM) provides preliminary evidence supporting the safety and efficacy of B7H3-targeted CAR-γδT cell immunotherapy in this patient group. A longer follow-up period and a larger patient cohort are necessary for a comprehensive evaluation of therapeutic efficacy and response durability. Clinical trial information: NCT06592092. Research Sponsor: National Natural Science Foundation of China; 82272953; The National Key Research and Development Program of China.

Patients' baseline character, administration routes and treatment evaluation.

	Diagnosis	Sex	Age	Genetic mutation	B7H3 Score	B7H3+ CAR -γδT cells infused	Administration route	Treatment response at Day 30
Patient 01	Lung adenocarcinoma with LM	F	53	EGFR 21 exon L858R mutation	70	3×10^7	Lumbar puncture	Stable disease (CSF cytology: remain positive CNS imaging: Stable Symptoms assessment score:6 to 4)
Patient 02	Lung adenocarcinoma with LM	F	58	EGFR 21 exon L858R mutation	40	3×10^7	Ommaya reservoir	Stable disease (CSF cytology: turned negative CNS imaging: Stable Symptoms assessment score:4 to 2)

Safety and efficacy of non-viral aPD1-MSLN JL-lightning–CAR-T in advanced malignant mesothelioma in a phase I trial.

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Background: CAR-T cells face challenges in solid tumors, including weak in vivo proliferation, immunosuppressive tumor microenvironments (TME), and limited tumor infiltration. We firstly developed an innovative non-viral JL-Lightning-CAR-T fast process to enhance CAR-T stemness, in vivo expansion, and persistence. The autologous non-viral aPD1-MSLN JL-Lightning-CAR-T cells were manufactured in just 30 hours, targeting mesothelin (MSLN) and secreting anti-PD-1 antibodies to counteract the immunosuppressive TME and improve the efficacy of solid tumor treatment. Here, we report the safety and preliminary efficacy of this novel CAR-T therapy in advanced malignant pleural mesothelioma (MPM) in a first-in-human phase I pilot study (ClinicalTrials.gov: NCT06249256). **Methods:** A single-arm, open-label, dose-escalation study was designed and enrolled MPM patients who had failed standard therapies and had confirmed MSLN and PD-L1 expression on tumors by IHC. Patients received a single dose of non-viral aPD1-MSLN JL-Lightning-CAR-T cells following lymphodepletion (Flu 30 mg/m^2/day, Cy 300 mg/m^2/day) for 2-3 days. The dose escalation was designed as DL1 (0.5-0.6$\times$10^6/kg) and DL2 (0.8-1.0$\times$10^6/kg). Adverse events were evaluated using CTCAE v5.0, and clinical responses were assessed by mRECIST 1.1 or RECIST 1.1. CAR expression was analyzed by qPCR, and anti-PD-1 antibodies were detected by MSD. **Results:** Patients: Seven advanced MPM patients were enrolled and received single dose CAR-T cell infusion. Efficacy: In DL1 (0.5-0.6$\times$10^6/kg), one patient achieved partial response (PR) with a disease control rate (DCR) of 75% (3/4). In DL2 (0.8-1.0$\times$10^6/kg), all of three patients achieved objective response (ORR 100%, 3/3), with one patient achieving complete response (CR) at 3 months and maintaining it for over 9 months. Pharmacokinetics: Anticipated CAR-T cell expansion and anti-PD-1 antibodies increase detected in circulation. CAR-T Cmax reached up to 47,307 copies/μg, detectable for over 3 months. Anti-PD-1 antibody Cmax reached up to 376,938 pg/ml, detectable for over 6 months. Tmax for MSLN-CAR-T and anti-PD1 nanobody occurred between Day 7 and Day 14 post infusion. IFN-γ and IL-6 levels also increased during this period. Safety: In DL1, CRS was observed in 1 of 4 patients (Grade 1), with no ICANS or DLT. In DL2, CRS was observed in 2 of 3 patients (Grade 3-4), with no ICANS. Grade 3 immune-mediated pneumonia occurred in 2 of 3 patients in DL2, managed by clinical intervention strategies. All patients experienced Grade 3-4 hematologic toxicity, reversible with supportive care. **Conclusions:** Non-viral aPD1-MSLN JL-Lightning-CAR-T cells demonstrated robust proliferative capacity, manageable safety profile, and significant anti-tumor potential, offering a promising therapeutic approach for advanced MPM patients. Clinical trial information: NCT06249256. Research Sponsor: None.

Phase I trial of personalized AI-identified TCR-transduced T cell therapy in advanced solid tumors.

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Background: TCR-T cell therapy shows promise in treating solid tumors but is limited by the need for personalized TCR identification. We developed TCR-XFinder, a deep learning model using a 3-stage transfer-learning strategy, to rapidly identify personalized tumor-reactive TCRs within 10 days after tumor tissue acquisition. This study reports the first-in-human phase I trial of KSX01, a TCR-transduced T cell therapy identified by TCR-XFinder. **Methods:** We conducted a phase I, dose-escalation study (NCT06150365) to evaluate the safety and efficacy of KSX01 in patients with advanced solid tumors. Tumor tissues were subjected to single-cell RNA sequencing and TCR sequencing to identify tumor-reactive TCRs using TCR-XFinder. These TCRs were validated and transduced into autologous T cells, which were expanded and infused back into patients. Patients received preconditioning with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) for 3 days, followed by intravenous infusion of KSX01 TCR-T cells at two dose levels ($5\times10^9 \pm 30\%$ and $1\times10^{10} \pm 30\%$ cells). Safety was assessed by monitoring adverse events and cytokine release syndrome (CRS). Efficacy was evaluated by RECIST v1.1 criteria. **Results:** Four patients with advanced solid tumors (alveolar soft part sarcoma, epithelioid sarcoma, colon cancer, and clear cell renal cell carcinoma) were enrolled. KSX01 TCR-T cells were well-tolerated at both dose levels, with no dose-limiting toxicities (DLTs) observed. All patients experienced Grade 3–4 pancytopenia, which was expected following lymphodepletion. One patient developed Grade 2 CRS, resolved with tocilizumab. No Grade 3 or higher AEs related to KSX01 were noted. At the first tumor assessment (Day 28), all patients showed disease control, with one patient achieving a partial response (PR) and a 46% reduction in target lesion size. Another patient achieved PR with second infusion at higher dose. qPCR analyses confirmed the infiltration and long-term anti-tumor effect of infused TCR-T cells. A transient post-infusion increase in interferon-γ (IFN-γ), interleukin-6(IL-6), IL-10, IL-4, tumor necrosis factor-α (TNF-α), and CRP levels was observed in all patients. While the C_{max} and T_{max} values varied among cytokines, the first T_{max} for 80% of cytokines and CRP occurred within the first week post-infusion. Re-biopsy of tumor lesions showed infiltration of infused TCR-T with persistent cytotoxic function and ameliorate the microenvironment for the endogenous tumor-reactive T cells. **Conclusions:** The first-in-human phase I trial of KSX01 TCR-T cell therapy demonstrated promising safety and efficacy in patients with advanced solid tumors. TCR-XFinder enabled rapid identification of personalized tumor-reactive TCRs, supporting the clinical feasibility of this approach. Further studies are warranted to explore optimal dosing and combination strategies to maximize clinical benefit. Clinical trial information: NCT06150365. Research Sponsor: National Natural Science Foundation of China; 82272953; The National Key Research and Development Program of China.

Artificial intelligence (XGBoost) in predicting outcomes among CAR-T therapy patients: The impact of malnutrition and comorbidities using the National Inpatient Sample (2020-2022).

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Background: Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized hematologic malignancy treatment but remains costly, with limited access and complications like prolonged hospitalization, sepsis, and mortality. Malnutrition, common in cancer patients, worsens these outcomes. Despite AI's growing role in oncology, its use in risk stratification for malnourished CAR-T recipients is underexplored. This study leverages the National Inpatient Sample (NIS) 2020-2022 to develop AI-driven models predicting length of stay (LOS), mortality, and sepsis, incorporating the Charlson Comorbidity Index and other factors. **Methods:** Using the NIS database, adult CAR-T therapy patients were identified with ICD-10 codes. Key variables included demographics (age, gender, race/ethnicity, income), clinical factors (Charlson Comorbidity Index, sepsis, admission type), and hospital characteristics (size, teaching status). AI models (XGBoost, Random Forest, Neural networks) were trained on the 2020 dataset and validated on 2020-2022 data. Hyperparameter tuning via grid search was performed to optimize model performance. LOS was modeled as a continuous outcome, while mortality and sepsis were classified as binary outcomes. Data preprocessing included handling missing values, one-hot encoding of categorical variables, and standardizing continuous variables. SHapley Additive exPlanations (SHAP) were used to interpret feature importance. **Results:** The study analyzed 1,912 CAR-T hospitalizations over three years, with 11.5% identified as malnourished. AI models demonstrated strong predictive performance, with XGBoost (RMSE: 3.5 days, $R^2 = 0.82$) for LOS, Random Forest (AUC: 0.91) for mortality, and Neural Networks (AUC: 0.87) for sepsis. Malnutrition significantly worsened outcomes, increasing LOS by 14.2 days ($p < 0.001$) and mortality risk by 3.2-fold ($p < 0.001$). Patients with Charlson Comorbidity Index scores ≥ 3 had 9.8-day longer LOS and 2.9-fold higher mortality risk ($p < 0.001$). Racial disparities were evident, with Black patients at 25% higher risk of prolonged LOS and Hispanic patients at increased risk of sepsis ($p < 0.05$). Malnourished patients in nonteaching hospitals with high comorbidity burdens had the worst outcomes, emphasizing the need for targeted interventions in high-risk populations. **Conclusions:** AI-driven models incorporating malnutrition and Charlson Comorbidity Index accurately predict LOS, mortality, and sepsis in CAR-T patients. Early identification and management of malnutrition and comorbidities, particularly in racially diverse populations, are critical to improving outcomes. Future research should focus on prospective validation and AI integration into clinical workflows to mitigate disparities. Research Sponsor: None.

A novel cellular immunotherapy using vaccine generated neoantigen-specific effector T cells.

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Background: Cellular immunotherapy languished in obscurity until genetically engineered chimeric antigen receptor T cells were shown to effectively treat B lymphocyte cancers. Genetic studies also revealed that some cancer cell mutations produce neoantigens, which are consistent with historical studies demonstrating that cancer cell vaccination generates neoantigen specific immune responses in rodents and humans. Vaccination leads to an increase in neoantigen-specific T cells in lymphoid tissue that are released into the blood, which carries them to sites of disease activity, e.g., cancer tissue. TVAX Biomedical hypothesized that the natural power of the patient's immune system could be exploited using a novel neoantigen-specific cellular immunotherapy. **Methods:** Patients are vaccinated with their own attenuated cancer cells plus an immunologic adjuvant, e.g. GM-CSF, to increase the number of circulating neoantigen primed T cells. Patients are leukapheresed to collect the T cells. The collected T cells are exposed to activation and proliferation stimulating agents to generate the neoantigen-specific effector T cells that are used for treatment. TVAX is currently testing this treatment paradigm for efficacy and safety in newly diagnosed (MGMT-negative) glioblastoma patients when they have minimized immunosuppression and minimal residual disease, TVI-AST-008. **Results:** For this novel cellular immunotherapy to be effective, T cell mediated immune responses must be generated in vaccinated patients. Delayed type hypersensitivity skin testing, a method for detecting T cell mediated immunity in humans, showed reactions in patients with leukemia, brain, breast, colon, lung, kidney, melanoma, ovarian, prostate and sarcoma (data to be presented). Multiple autologous vaccinations led to detectable responses in all patients. The combination of cancer cell/immunologic adjuvant vaccination plus neoantigen-specific T cellular immunotherapy has been shown to be highly effective against a wide range of cancer types in preclinical studies and to be effective against the least immunogenic cancers. **Conclusions:** The possibility that neoantigen-specific T cells could effectively treat some human cancers has been documented through studies with tumor infiltrating lymphocytes (TILs). However, TIL efficacy is limited to a small number of (hot) cancers. Preclinical model studies demonstrated that neoantigen-specific effector T cells enter cancer tissue, initiating a cascade of T cell mediated immunologic events that ultimately leads to killing of cancer cells by cytotoxic T cells and cytokine activated accessory cells. The benefit of the vaccine enhanced neoantigen-specific effector T cell therapy (TVAX Immunotherapy) is that it expands the range of human cancers that could be safely and effectively treated. Clinical trial information: 05685004. Research Sponsor: NIH Grant, Office of Orphan Products.

Engineering iPSC-derived mesenchymal stem cells (i MSCs) to secrete IL-7/IL-15 for modulation of the tumor microenvironment in a "cold" ovarian tumor model.

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Background: We previously discovered that bone marrow derived Mesenchymal stromal cells (BM-MSCs) migrate to the stroma of numerous cancers and their metastases, forming tumor-associated fibroblasts (TAFs) and can be modified to secrete proteins within the tumor microenvironment (TME). MSCs have not been utilized extensively in cancer therapy due to their immunosuppressive properties, limited replicative capacity, and variable quality depending on the source. **Methods:** Here, we report the characterization of induced mesenchymal stromal cells (iMSCs) derived from pluripotent stem cells (iPSCs), which were uniquely generated from adult skin fibroblasts using a transient mRNA transfection technique. Notably, iMSCs demonstrated superior proliferative capacity under both normoxic and hypoxic conditions, while preserving their trilineage differentiation potential. Comprehensive molecular profiling, including RNA sequencing, single-cell mass cytometry (CyTOF), and Luminex assays, revealed strong phenotypic and functional similarities between iMSCs and BM-MSCs. Crucially, no evidence of sarcoma formation was observed in NSGS mice following intraperitoneal, subcutaneous, or intravenous administration of iMSCs, highlighting their robust safety profile. We engineered a DNA cassette into these cells to enable constitutive superphysiological expression of interleukin(IL)-7 and IL-15, expressed as either individual molecules (P2A) or a single fused molecule (FUS). Both, P2A and FUS iMSCs demonstrate the capacity to drive T cell proliferation autonomously in co-culture experiments. **Results:** IL7/IL15-modified iMSCs induced tumor cell death in a triple co-culture system comprising iMSCs, the ovarian cancer cell line ID8, and human PBMCs. In a syngeneic mouse model of ovarian cancer (ID8 cells in C57BL/6 mice), intraperitoneal administration of P2A or FUS-iMSCs resulted in reduced tumor burden and extended survival. Immunohistochemical and flow cytometric analyses revealed massive infiltration of activated T cells, macrophages, and other immune cells into the tumor microenvironment (TME) in both FUS or P2A groups, but not in unmodified iMSC controls, or in PBS injected animals. The TME in P2A- and FUS-treated mice showed enrichment in tumoricidal M1-type macrophages, with no detection of exhausted or regulatory T cells, in contrast to controls. **Conclusions:** IL7-IL15-secreting iMSCs migrate into solid tumors, induce massive immune cell infiltration into the TME and enhance antitumor immunity in a syngeneic mouse model of cancer. These cytokine-producing iMSCs represent a potentially promising anticancer immunotherapy by converting “cold” into “hot” tumor microenvironments. Research Sponsor: Eterna Therapeutics, Inc.

Universal solid tumor therapy with CD5-deleted, DSG2-directed CAR-T cells.

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Background: CAR-T cell therapy has been curative for many patients with refractory, progressive hematologic cancers, resulting in several FDA approvals. However, this therapy has not been successful for solid cancers, reflecting the need for suitable antigen targets for each disease and solutions to immunological barriers in solid tumors. Here, we have identified the desmosomal cadherin, desmoglein 2 (DSG2), as an effective CAR-T cell therapy target in epithelia-derived solid tumors. DSG2 contributes to cell proliferation, migration, and other emerging tumor-promoting pathways, resulting in its upregulation in nearly all solid cancers and correlating with poor prognosis. Moreover, we explored CRISPR-Cas9-mediated elimination of the inhibitory receptor CD5 to enhance in vivo CAR-T cell expansion and solid tumor efficacy. **Methods:** DSG2-directed CAR-T cells were generated from human T cells using a scFv derived from a murine hybridoma targeting the extracellular domain of DSG2 in a 3rd generation CAR design with CD28, 4-1BB, and CD3ζ signaling domains. CD5 elimination employed electroporation of complexed gRNA-Cas9 ribonucleoprotein (RNP). DSG2 expression was characterized in human cancers and cell lines and CAR-T cell activity was examined in vitro by cytokine production and target cell cytolysis. In vivo efficacy studies employed cancer xenografts in NSG mice treated with CAR-T cells. Safety studies employed a human DSG2 transgenic mouse treated with syngeneic murine CAR-T cells for clinical, serum biomarkers, and histopathological evaluation. **Results:** In vitro studies revealed recognition and lysis of solid cancer cell lines and effector cytokine production. Administration of DSG2-directed CAR-T cells eliminated metastatic cell-derived xenografts, patient-derived xenografts, and orthotopic tumors derived from various solid cancers, including colorectal, pancreatic, lung, prostate, breast, and liver. Moreover, elimination of CD5 enhanced the expansion of DSG2-directed CAR-T cells in vivo, resulting in curative efficacy at sub-therapeutic CAR-T cell doses. Safety studies revealed no toxicity in any human DSG2 transgenic mouse tissues. **Conclusions:** These studies reveal the robust antitumor activity of DSG2-directed CAR-T cells in solid tumors, which is enhanced by CD5 deletion, without toxicity in a human transgenic mouse model. Thus, CD5-deleted DSG2-directed CAR-T cells are a promising therapeutic approach that may be safe and effective for all solid cancers. Research Sponsor: Kleberg Foundation; U.S. Department of Defense; W81XWH-19-1-0263; U.S. Department of Defense; W81XWH-22-1-0207; DeGregorio Family Foundation; U.S. National Institutes of Health; 1R21 CA267087; U.S. National Institutes of Health; 1R21 CA286339; The Courtney Ann Diacont Memorial Foundation and Lorraine and David Swoyer; U.S. National Institutes of Health; T32 GM008562; U.S. National Institutes of Health; T32 CA236736.

Mayhem under the microscope: T cell cytotoxicity and serial killers captured in situ.

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Background: Developing a deeper understanding of the dynamics of immune cell-mediated cytotoxicity is critical to advancing immunotherapy and cell therapy. The results from the multidisciplinary effort reported here include numerous measurements and movies of immune cell-mediated cytotoxicity with striking examples of serial killing, foraging, path-tracking, triple killing events, measurements of cytokine gradients at tumor margins, and other dynamics. Some cytotoxic events revealed peak apoptotic signatures just minutes after T Cell engagement. **Methods:** In vitro studies of immune cell killing are traditionally performed using time-lapse imaging and biochemical assays, but these methods are often limited by spatial and temporal resolution, throughput, and the ability to extract the dynamics of cellular interactions. This study integrates high-resolution and high-speed laser scanning confocal microscopy with artificial intelligence (AI), and machine learning (ML) approaches to provide a high-resolution data-driven analysis of immune cell killing dynamics in vitro. In these studies, we use human CAR T cells with an anti-cd19.28z and Burkitt Lymphoma. **Results:** We have engineered a perfusion-enabled 3D culture system integrated microscopy to assess cellular dynamics for extended periods of time. Perfusion culture maintains the interstitial flow of liquid culture media, clearing the microenvironment of toxic metabolites and reactive oxygen species. This platform uses a Liquid-Like Solids (LLS) to mimic the transport dynamics of a capillary bed. Integrated microscopy allows in situ quantification of spatiotemporal cytokine concentrations, immune cell tracking, immune cell killing dynamics, and invasion dynamics. Cytokine on and off-rates were referenced alongside measured bead fluorescence intensities and positions to fit spatiotemporal reaction-diffusion models out to a 1,600 um radius. Fast-scanning confocal microscopy facilitated in-situ observation of the evolutionary dynamics of tumor progression. In-situ cytokine measurements revealed local IL-8 concentrations reached a maximum value of 2 ng ml-1 after 10 hours. A cellular production rate was estimated at 2 molecules cell-1 s-1. **Conclusions:** T Cell cytotoxicity is shown to be incredibly heterogeneous spanning from minutes to hours. The platform developed in this study demonstrates a powerful method for real-time, high-resolution imaging of cancer-immune interactions within a controlled 3D environment. By leveraging in situ fast-scanning fluorescence microscopy, the platform enables precise quantification of spatiotemporal cytokine concentrations, T cell motility, proliferation, cytotoxic activity, and tumor invasion patterns. Research Sponsor: None.

Impact of stromal-targeting antitumor CAR T cells in solid tumors.

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Background: While chimeric antigen receptor (CAR) T cells have shown tremendous success in hematological malignancies, but such efficacy has not been achieved in the setting of solid tumors. One of the hurdles to CAR T cells therapy in solid tumors is the presence of physical stroma and cancer associated fibroblasts (CAFs), which inhibit the entry of activated T cells to the tumor sites. Membrane bound protein Leucine-rich repeat containing 15 (LRRC15) has been shown to be highly expressed on CAFs in many solid tumors including pancreatic cancer as well as directly expressed on tumors of mesenchymal origin including sarcomas, glioblastomas and melanomas. LRRC15 has very limited expression in normal tissues. The goal of the current study was to explore the impact of stromal targeting antitumor (STAT) in solid tumors using LRRC15-directed CAR T cells. Herein we demonstrate that CAR T cells directed to tumor stroma can eradicate solid tumor. **Methods:** LRRC15-directed CAR T cells were validated in *in vitro* assays that included specific lysis, cytokine secretion, and proliferation. STAT CAR T cells were administered intravenously into NSG mice after engrafted with osteosarcoma SaOS2 and pancreatic PANC1 tumor cell lines as well as patient derived tissues (PDXs). The efficacy of STAT CAR T cells was also assessed in syngeneic mouse model engrafted with murine OS F420 and pancreatic KPC tumor cell lines. Tumor was harvested from mice at various timepoints and analyzed for LRRC15 expression as well as for the presence of T cells. **Results:** LRRC15-directed CAR T cells specifically lysed SaOS2 cells. Upon stimulation with SaOS2 cell line, LRRC15-directed CAR T cells resulted in robust expansion and secreted cytokines including IL2, IFN-ɣ, GM-CSF and TNFα. The LRRC15-directed CAR T cells were able to eliminate tumor in NSG mice xenografted with SaOS2 cell line as well as OS PDX. LRRC15-directed CAR T cells significantly increased the survival of mice. Next, we sought to test the efficacy of LRRC15-directed CAR T cells in NSG mice engrafted with $LRRC15^-$ tumor/$CAFs^+$ cell line and PDX. We showed that the NSG mice injected with the $LRRC15^-$ PANC1 cell line acquired stroma with CAFs positive for LRRC15 within 2-3 weeks. LRRC15-directed CAR T cells were able to significantly inhibit the progression of both PANC1 tumors as well as PDAC PDX in NSG mice. In syngeneic mouse model, LRRC15-directed CAR T cells resulted in tumor regression of both $LRRC15^+$ sarcoma F420 and $LRRC15^-$ pancreatic KPC tumors. **Conclusions:** To our knowledge this is the first study demonstrating targeting stroma in solid tumors using STAT CAR T cells. LRRC15-directed CAR T cells showed antitumor efficacy in mouse models engrafted with $LRRC15^+$ as well as $LRRC15^-$ tumors. Collectively, we show that targeting $LRRC15^+$ CAFs in the tumor with CAR T cells has the potential to inhibit solid tumor progression as well to circumvent the challenge of limited penetration of T cells into the tumor site by disrupting the stroma. Research Sponsor: None.

Association of lymphopenia rescue and CA19-9 levels with overall survival following IL-15 superagonist N-803 and PD-L1 t-haNK chemo-immunotherapy for 3rd line or greater metastatic pancreatic cancer.

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Background: Lymphopenia and high CA19-9 levels are associated with poor prognosis in pancreatic cancer patients. N-803 (ANKTIVA), an IL-15 superagonist is the first FDA approved molecule with a mechanism of action of rescuing lymphopenia by proliferating lymphocytes (NK and T cells). In QUILT-88, a Phase 2 multi-center study (NCT04390399), participants with 2nd line or greater locally advanced or metastatic pancreatic cancer (mPC) received N-803 and PD-L1-targeted high-affinity natural killer (PD-L1 t-haNK) cell therapy in combination with low-dose chemotherapy as $\geq 3^{rd}$ line therapy. The absolute lymphocyte count (ALC), CA19-9 level, and correlation with overall survival (OS) was assessed. **Methods:** Patients (n = 84) received low-dose SBRT and low-dose chemotherapy in combination with N-803 and PD-L1 t-haNK cells to orchestrate responses of the innate and adaptive immune system, a paradigm change in the treatment of mPC. The association between OS and ALC $<$ or $\geq$ median 1.045×10^9 cells/L and CA19-9 $<$ or $\geq$ median 4079.6 U/mL at baseline was assessed. **Results:** Median OS for 3^{rd} line patients (n = 43) was 6.2 months (95% CI 5.0 - 7.1;) and for all patients $\geq 3^{rd}$ to 6^{th} line patients (n = 84) was 5.7 months (95% confidence interval [CI] 4.3 – 6.4). OS was positively associated with both higher ALC and lower baseline CA19-9 levels. OS was significantly higher for participants (median OS: 7.1 months) with ALC $\geq 1.045 \times 10^9$ cells/L and CA19-9 $<$ 4079.6 U/mL than for those participants (median OS: 3.1 months) with ALC $< 1.045 \times 10^9$ cells/L and CA19-9 $\geq$ 4079.6 U/mL (HR 3.6, $p < 0.001$). Higher ALC count was associated with prolonged OS over the course of the study. Grade 3 or higher TEAEs occurred in 95% of patients and were largely chemotherapy-associated. **Conclusions:** The multimodal chemo-immunotherapy protocol to induce immunogenic cell death resulted in OS that exceeded 6 months for both 3^{rd} and $\geq 5^{th}$ line patients, exceeding OS achieved by other therapies in this setting by ~2 months. It is notable that both favorable baseline ALC/CA19-9 and on-study higher ALC was associated with prolonged survival, given N-803's ability to increase both NK and CD8+/CD4+ T cells, the first FDA approved agent that proliferates lymphocytes in the face of lymphopenia. These findings support further investigation of this novel therapeutic regimen that includes PD-L1 t-haNK, and N-803 that, as an IL-15 superagonist, may be able to overcome lymphopenia and improve prognosis. Clinical trial information: NCT04390399. Research Sponsor: ImmunityBio, Inc.

Predictors and clinical outcomes of CMV reactivation in CAR-T therapy: A systematic review.

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Background: Cytomegalovirus (CMV) reactivation is a common complication in immunocompromised patients, particularly those undergoing chimeric antigen receptor T-cell (CAR-T) therapy. CMV reactivation has been linked to increased morbidity and mortality due to immune dysregulation, relapses, and treatment-related toxicity. This systematic review investigates the predictors and outcomes of CMV reactivation in CAR-T recipients, focusing on survival, relapses, and non-relapse mortality (NRM). **Methods:** A systematic review was conducted following PRISMA guidelines to compare characteristics and outcomes between CMV reactivation (R) and non-reactivation (NR) groups. A comprehensive search of PUBMED, EMBASE, and CENTRAL identified 172 studies, of which only four met the inclusion criteria after screening. A descriptive statistical analysis was performed to calculate frequencies and percentages. **Results:** Among 462 patients with CAR-T therapy, 114 (24.7%) experienced CMV reactivation. The median time from CAR-T therapy to CMV reactivation was 20 days (Range: -1 to 73), with an incidence of CMV disease with end-organ damage at 1.73%. Most patients received axicabtagene ciloleucel (71%) and had lymphoma (88%). Our analysis identified a higher proportion of patients receiving BCMA-targeted CAR-T therapy (7% vs. 2.9% in NR) and a greater prevalence of prior allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the R group (35% vs. 7% in NR). Severe CRS (Grade $\geq$3) was more common in the R group (11.4% vs. 8.6%), as was severe ICANS of $\geq$3 (37.7% vs. 26.7%). Immunosuppressive therapy use, including steroids (56% vs. 42.8%) and combination therapy with tocilizumab and anakinra (12% vs. 5%), was significantly higher in the R group. Outcomes varied across studies, with Lin et al. and Khawaja et al. reporting higher one-year mortality in R vs. NR groups (57% vs. 23%, P = .001; 53% vs. 38%). Khawaja et al. also noted higher NRM (48% vs. 33%). Chen et al. identified CMV reactivation (HR 2.3, 95% CI: 1.2–4.5, P = .02) as an independent mortality predictor, with relapse rates of 71.4% in R and 41.2% in NR. **Conclusions:** CMV reactivation is a significant complication in CAR-T therapy, linked to worse outcomes, including increased mortality, relapse, and NRM. Predictors include BCMA-targeted CAR-T therapy, prior allogeneic HSCT, severe CRS/ICANS, and associated treatments. Targeted CMV monitoring, prophylaxis, and immunosuppressive strategies are essential for mitigating reactivation risks and improving outcomes in CAR-T recipients. Research Sponsor: None.

Validation of an optimized tissue-agnostic genome-wide methylome enrichment assay to predict clinical outcomes in patients treated with pembrolizumab.

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Background: Recent work from the INSPIRE study (PMID38393391) suggests that kinetics of cell-free DNA (cfDNA) methylation profiles reflect immunotherapy treatment response in solid tumors. Here we provide validation data of a tissue-agnostic, genome-wide methylation enrichment assay based on cell free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq) designed for clinical use, to determine response to immunotherapy. **Methods:** This study utilizes samples and clinical data from the INSPIRE study, a single-institution investigator-initiated phase II study of pembrolizumab in multiple solid tumors given every 3 weeks (NCT02644369). A prior published analysis of cfMeDIP used TCGA to develop a classifier and demonstrated an association of response to immunotherapy. In contrast, in this analysis, a novel quantitative and highly specific measurement of ctDNA was estimated using a generative machine learning model trained on differentially methylated regions identified from a large cfMeDIP methylome atlas from individuals with and without cancer. In a blinded validation analysis, Firth's logistic regressions were used to test differences in objective response (ORR) and clinical benefit rate (CBR) defined as complete or partial response or stable disease $>$ / = 6 cycles between patients with a decrease in ctDNA from baseline to cycle 3 of treatment, and those with an increase in ctDNA. Sensitivity for no objective response, specificity for objective response, and positive and negative predictive values (PPV and NPV) were summarized. Cox regressions and log-rank tests were used to evaluate differences in progression-free survival (PFS) and overall survival (OS) between the two groups. **Results:** The analysis included 64 unique patients with a median follow up of 18.43 months (a total of 128 samples), including head & neck (n = 9), triple negative breast (n = 10), ovarian (n = 11), melanoma (n = 7), and other mixed solid tumor types (n = 27). A decrease in ctDNA was associated with significantly better objective response than an increase [odds ratio (OR) 33.89 (4.07, 44426.47), p = 0.0001], 58% sensitivity, 100% specificity, 100% PPV and 35% NPV. Significantly better CBR [OR 10.17 (2.74, 55.74), p = 0.0002] was also observed. A decrease in ctDNA was associated with significantly better PFS [hazard ratios (HR) 0.28 (0.15, 0.49) p $<$ 0.0001] and OS [HR 0.42 (0.24, 0.76) p $<$ 0.003]. **Conclusions:** A clinical tissue-agnostic, genome-wide methylome enrichment approach using cfMeDIP-seq accurately predicts clinical outcomes in patients treated with pembrolizumab in multiple advanced solid tumors. This test provides relative quantification of methylated ctDNA to predict response to immmunotherapy and does not require tumor tissue. This analysis highlights potential generalizability across tumor types in response monitoring. Clinical trial information: NCT02644369. Research Sponsor: Adela, Inc; Merck.

Personalized tumor-informed circulating tumor DNA as predictor of progression risk after long-term responses to immunotherapy in advanced non-small-cell lung cancer.

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Background: Immune checkpoint inhibitors (ICIs) have remarkably improved survival in advanced non-small-cell lung cancer (NSCLC), with about 30% ~ 40% of patients achieving long-term responses. However, biomarkers for predicting progression remain undefined. Circulating tumor DNA (ctDNA) has demonstrated its ability to predict recurrence in resected NSCLC, but its potential to forecast progression following prolonged responses to ICIs requires investigation. **Methods:** CR1STAL study is a multicenter, prospective cohort study investigating ctDNA surveillance to monitor progression risk in advanced NSCLC treated with first-line ICIs (NCT05198154). Patients with advanced NSCLC with long-term responses, defined as a PFS of about 1 year, were enrolled. Peripheral blood samples were collected alongside radiographic evaluations. ctDNA was detected using a personalized tumor-informed assay. Somatic variants were identified using a targeting 1,021 genes, followed by the design of individualized target-capture. ctDNA-positive was defined as the detection of ctDNA at any time during surveillance. The primary endpoint was PFS, defined as the time from enrollment until progression or death. Secondary endpoints included OS and ORR. Exploratory endpoints included the association between ctDNA features and survival, and comparison to other biomarkers. **Results:** We analyzed 199 sample from 42 NSCLC patients. The median age was 60.5 years with 88.1% male, and 64.3% at stage IV. The median number of sample collections was 4, with a median follow-up time of 24.7 months. ctDNA was detected in 54.8% of patients (23/42), with 82.7% of patients (19/23) showing ctDNA-positive occurring within 2 years of ICIs treatment. A total of 23 PFS events were observed. The ctDNA-positive group showed significantly worse PFS compared to the negative group (HR: 7.65, $p < 0.001$), with a positive predictive value of 90.0% and a specificity of 88.2%. Additionally, ctDNA-positive provided a median lead time of 6.6 months prior to radiological progression. ctDNA-positive significantly associated with poorer OS (HR: 68.42, $p = 0.003$) and lower ORR (60.9% vs 89.5%, $p = 0.036$). 18 exhibited clonal mutations. Compared to the ctDNA-negative group, the patients with clone had significantly worse PFS (HR: 9.38, $p < 0.001$) than those with subclone (HR: 4.16, $p = 0.063$). The ctDNA positivity rate was 84.6% in cases of local progression, 80.0% in distant metastases with brain exhibiting lower positivity rates. Additionally, peripheral CEA showed inferior predictive value for PFS (HR: 1.76, $p = 0.303$) than ctDNA. **Conclusions:** ctDNA has emerged as a promising biomarker for predicting progression risk of ICIs in advanced NSCLC patients with long-term responses. ctDNA surveillance enables earlier detection of progression and supports treatment adjustments through adaptive therapy. Clinical trial information: NCT05198154. Research Sponsor: None.

Novel dynamic circulating biomarkers for predicting therapeutic efficacy of PRaG regimen in advanced refractory solid tumors.

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Background: Common biomarkers for predicting the efficacy of immune checkpoint inhibitors (ICIs), such as programmed death-ligand 1 (PD-L1) expression, face notable challenges with tumor tissue sampling and the inability to enable dynamic monitoring. Circulating T lymphocyte subset classification and cytokines offers a promising alternative, reflecting T cell functionality and predicting ICI responses. The PRaG regimen, combining PD-1 inhibitors, radiotherapy, and granulocyte-macrophage colony-stimulating factor (GM-CSF), has shown efficacy in patients with metastatic or refractory solid tumors unresponsive to standard therapies. This study seeks to develop an efficacy evaluation model by intergrating dynamic peripheral blood lymphocyte subsets and cytokines, based on comprehensive analysis of clinical data from the PRaG studies. **Methods:** Data from the PRaG 1.0 (ChiCTR1900026175), PRaG 2.0 (NCT04892498), and PRaG 3.0 (NCT05115500) studies were analyzed to evaluate the objective response rate (ORR) by RECIST 1.1. Machine learning models, including linear, sequential, attention-based, and hybrid models, were employed to predict disease progression. These models utilized dynamic peripheral blood data from thirty-five lymphocyte subsets and seven cytokines, collected across treatment cycles. Model efficacy was further validated using independent data from two additional PRaG studies (NCT05790447 and NCT06112041). **Results:** As of November 30, 2023, 132 patients were included in the study, with a median age of 63 years. Patients over 65 accounted for 41.7%, and 60.4% had more than five metastatic sites. Patients with an ECOG score of 2-3 made up 59.7% of the cohort. The ORR was 20.13%, and the disease control rate was 48.19%. Dynamic monitoring of peripheral blood features across treatment cycles facilitated the development of an LSTM-HeterGNN model, which integrates long short-term memory (LSTM) networks with heterogeneous graph neural networks (heterGNN). This model outperformed ten other models, achieving a ROC AUC of 0.818. Independent validation further demonstrated robust performance, with a ROC AUC of 0.801. **Conclusions:** This study underscores the potential of the PRaG regimen as an effective salvage therapy for advanced solid tumors after the failure of standard treatments. The LSTM-HeterGNN model, leveraging dynamic peripheral blood biomarkers, provided precise efficacy predictions, surpassing traditional models. These findings lay the groundwork for dynamic treatment monitoring and optimization. Larger sample sizes are required to further validate the model's generalizability. Research Sponsor: None.

An exploratory study to predict the efficacy and prognosis of immunotherapy for extensive-stage small cell lung cancer based on peripheral blood dynamic immune profiles.

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Background: The high-dimensional classification information of peripheral blood mononuclear cells can provide abundant efficacy and prognosis-related data. However, in the field of immunotherapy for extensive-stage small cell lung cancer (ES-SCLC), the biomarkers that can predict the efficacy and prognosis need to be explored and clarified. **Methods:** Cytometry by Time-Of-Flight (CyTOF) was applied to the dynamic monitoring of immunotherapy using clinical resources such as dynamic peripheral blood from ES-SCLC patients. By labeling the following proteins: CD45, CD3, CD4, CD8, CD25, CD127, CD45RA, CD45RO, CCR7, TCRγδ, CD19, CD66b, CD14, CD56, CD16, CD11c, CD123, HLA-DR, CD38, CD57, CXCR3, CCR6, CCR4, CXCR5, CD95/Fas, LAG-3, Tim-3, CTLA-4, PD-L1, PD-1, CD278/ICOS, and TIGIT, this study performed high-dimensional fine-phenotyping of peripheral blood immune cells from ES-SCLC patients. We further explored the dynamic immune profile of peripheral blood that could predict the efficacy and prognosis of immunotherapy in combination with efficacy assessment and survival indicators. **Results:** 81 dynamic peripheral blood samples (baseline, after two cycles of treatment[C2], and progressive disease) were collected from ES-SCLC patients who received first-line immunotherapy combined with chemotherapy (n = 20) and chemotherapy alone (n = 7) in this study. In the immunotherapy group, a high percentage of senescent CD4+TEM/CD4+TEM at baseline (P = 0.029) was significantly associated with longer PFS. High TIGIT expression at baseline (P = 0.016) was significantly associated with shorter PFS. In addition, PD-1 (CD4+TCM, P = 0.017; Naive CD4+T, P = 0.031; pDCs, P = 0.031; NK, P = 0.007; Early NK, P = 0.007; Late NK, P = 0.02) and TIGIT (CD8+TEM, P = 0.046; NK, P = 0.038) expression levels at baseline in multiple cell subpopulations were significantly negatively correlated with OS. In contrast, the above peripheral blood immune profile was not a predictor in the chemotherapy group. In the immunotherapy group, peripheral blood dynamic monitoring showed that increased γδT cell percentage after treatment was significantly associated with longer PFS and OS (PFS, P = 0.035; OS, P = 0.032). Increased CD4+ TEM and CD4+ TCM percentage after treatment was significantly associated with shorter PFS and OS (CD4+ TEM: PFS, P = 0.021, OS, P = 0.036; CD4+ TCM: PFS, P = 0.01; OS, P = 0.014). Meanwhile, CTLA-4 and ICOS expression in total cells at progressive disease was significantly higher than C2, suggesting that it might be related to immunotherapy resistance. In the chemotherapy group, the above peripheral blood dynamic immune profile did not predict the efficacy and prognosis of chemotherapy. **Conclusions:** Dynamic peripheral blood immune profile can predict the efficacy and prognosis of immunotherapy in ES-SCLC. Research Sponsor: None.

Longitudinal tumor-informed cfDNA whole genome sequencing to capture residual disease during neoadjuvant immune checkpoint inhibition in resectable gastro-esophageal cancer.

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Background: Although circulating tumor DNA (ctDNA) detection represents a promising approach to capture minimal residual disease (MRD), the clinical performance of ctDNA MRD during neoadjuvant immune checkpoint inhibition (ICI) remains understudied. Here we employ a tumor-informed whole genome sequencing (WGS) approach to capture residual disease and link ctDNA dynamics with pathologic response and clinical outcomes. **Methods:** WGS was performed on tumor (n = 28), matched WBC (n = 28), and longitudinal plasma samples (baseline, post-ICI cycle 1, post-ICI cycle 2 and pre-op; n = 97) from 28 patients with resectable gastroesophageal cancer treated with neoadjuvant ICI and chemoradiation prior to surgical resection (NCT03044613). Tumor-specific single nucleotide variants were identified from tumor and WBC datasets, from which a high confidence candidate variant set was used to determine the presence of ctDNA through a random forest machine learning model. ctDNA status and tumor fraction (TF) were determined based on the level of signal compared to a reference population of noncancerous donor plasma samples (n = 80). Serial ctDNA TF dynamics were correlated with overall (OS) and recurrence-free survival (RFS) in comparison to a tumor-naïve targeted NGS gene panel liquid biopsy approach. **Results:** Twenty-four of the 28 patients (86%) with evaluable specimens had ctDNA detected in a least one timepoint: 22 of 25 (88%) evaluable patients had ctDNA detected at baseline, 20 of 25 (80%) evaluable patients had ctDNA detected post-ICI cycle 1, 18 of 26 (69%) evaluable patients had ctDNA detected post-ICI cycle 2, and 5 of 21 (24%) evaluable patients had ctDNA detected at the pre-op timepoint. In contrast, the tumor-naïve targeted NGS approach detected 13 of 30 (43%), 12 of 30 (40%), 11 of 30 (37%) and 5 of 25 (20%) patients at baseline, post-ICI cycle 1, post-ICI cycle 2 and pre-op respectively. A ctDNA TF peak was detected at either the post-ICI cycle 1 or cycle 2 timepoint for 50% of the patients. A 50% reduction in ctDNA TF at the post-ICI cycle 2 timepoint showed a sensitivity of 80% and specificity of 69% for prediction of complete pathologic response, which was improved compared to the tumor-naïve liquid biopsy approach and importantly showed a significantly higher evaluable rate (86% vs 62% for tumor-informed and tumor-naïve respectively). Similar trends were observed between major pathologic response and ctDNA TF. A dramatic reduction of ctDNA TF ($\geq$65%) at the pre-op timepoint predicted longer OS and RFS (log-rank p = 0.0035 and p = 0.0032 respectively). **Conclusions:** Tumor-informed cfDNA whole genome sequencing analyses showed reliable and sensitive detection and quantification of ctDNA during neoadjuvant ICI and adds to the body of evidence supporting the clinical utility of ctDNA residual disease in interpreting clinical outcomes. Research Sponsor: Bristol-Myers Squibb; U.S. National Institutes of Health; CA121113; Cancer Research Institute.

Plasma extracellular vesicles as biomarkers of primary versus acquired resistance to immune checkpoint inhibitors (ICI) in patients (pts) with solid tumors.

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Background: Plasma extracellular vesicles (pEVs) have emerged as promising biomarkers in the field of oncology. They can be obtained through minimally invasive methods, and hold the potential to help differentiate the clinically relevant subgroups of primary (PR) vs acquired resistance (AR) to ICI treatments. We hypothesized that individual pEV-derived protein cargo, or combinations thereof, associate with PR vs AR to ICI. **Methods:** A cohort of patients was derived from the Immune Resistance Interrogation Study (IRIS; NCT04243720), with plasma collected at the time of progression on ICI in advanced or adjuvant settings (n = 69; n = 44 primary resistance [PR], n = 25 acquired resistance [AR]). Plasma-derived extracellular vesicles (pEVs) were isolated using serial ultracentrifugation and characterized per ISEV guidelines. All samples were analyzed using OLink Immuno-Oncology proteomics to evaluate 92 proteins. Statistical analyses included the Mann–Whitney U test, binary logistic regression, and log-rank tests. Primary and acquired resistance were defined according to trial protocol. **Results:** A total of 57 out of 69 samples (n = 37 PR, n = 20 AR) generated evaluable proteomics data. Of the 92 proteins analyzed, 11 were significantly overexpressed in AR compared to PR (ADGRG1, CD28, FGF2, IL10, IL12RB1, IL2, IL33, IL4, MCP3, PD-L2, PTN) ($p < 0.05$), with IL10 and IL33 showing the strongest associations ($p< 0.01$). When stratified by cancer type, 9/11 proteins were over-expressed in AR vs PR among melanoma pts (n = 39; ADGRG1, CD28, FGF2, IL10, IL33, IL4, MCP3, PD-L2, PTN) ($p < 0.05$), whereas only IL12RB1 ($p < 0.01$) was overexpressed in HNSCC pts (n = 16). Analysis of 5 proteins most strongly associated with AR (IL10, IL33, IL4, MCP3, CD28) yielded a sensitivity of 70% and specificity of 95% for AR vs PR, with a positive and negative predictive value of 88% and 85%, respectively; AUC 0.853 ($p < 0.001$; 95% CI 0.742-0.963). **Conclusions:** In summary, 11 pEV-derived proteins from blood samples at progression on ICI independently statistically associated with AR vs PR, and a combination of 5 of them generated a highly accurate predictive model for AR. Immuno-modulatory cytokines IL10 and IL33 held the strongest associations, known to activate signaling cascades implicated in ICI resistance through the JAK-STAT and NF-Kappa-B/MAPK pathways, respectively. Differentially expressed proteins may signify distinct mechanisms of ICI escape. Despite requiring validation, our results highlight the potential of pEV-derived proteins as predictive biomarkers for ICI resistance in solid tumors. Future studies of pEV proteomics in the pre-treatment setting, as well as exploring other cargo such as RNA, may provide additional insights into the biology of resistance, and discover minimally invasive clinically relevant biomarkers. Clinical trial information: NCT04243720. Research Sponsor: BMO Chair in Precision Genomics, Dr. Lillian Siu.

Precision medicine research on chemo-immunotherapy combination treatment for locally advanced or metastatic non-small cell lung cancer based on deep plasma proteomics.

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Background: For locally advanced or metastatic non-small cell lung cancer (NSCLC) patients lacking specific genetic mutations, chemotherapy combined with anti-programmed death-1/programmed death-ligand 1 immunotherapy has become standard first-line treatment with enhanced therapeutic efficacy and prolonged survival. However, 40-50% of patients do not benefit from chemo-immunotherapy and develop resistance. Currently, there is a lack of predictive biomarkers for the efficacy of combined therapy in NSCLC, and research on the regulatory mechanisms and drug targets is insufficient, either. We leveraged an advanced proteomics platform to profile serum in NSCLC patients, aiming to identify chemo-immunotherapy biomarkers and uncover resistance mechanisms. **Methods:** This study collected pre-treatment plasma samples from 103 patients with locally advanced or advanced NSCLC receiving chemo-immunotherapy. These samples were analyzed using a deep proteomics platform that integrates antibody arrays and mass spectrometry. Patients were classified into "responders" (R, complete/partial response or stable disease $>$ 6 months) and "non-responders" (NR, progressive disease or stable disease $\leq$6 months) based on treatment efficacy. Differentially expressed serum proteins were identified between the groups, and weighted gene co-expression network analysis (WGCNA) was applied. Cox survival analysis was conducted on prognosis-related modules, leading to the identification of key proteins associated with treatment efficacy and survival. **Results:** Through our high throughput blood proteomics platform, a total of 1,397 proteins were detected. The median progression-free survival was 9 months, and the median overall survival was 32 months. A total of 175 differentially expressed proteins were identified between the R and NR groups. WGCNA identified 12 distinct modules, with ME4 associated with poor prognosis, enriched in inflammation, gene activation, and apoptosis suppression pathways, while ME8 correlated with favorable prognosis and ERK1/ERK2 cascade regulation. In the NR group, upregulated proteins associated with poor prognosis included erythropoietin receptor (HR: 1.41, $p < 0.01$), fibrinogen gamma chain (HR: 1.90, p: 0.03), Fc alpha receptor (HR: 2.63, $p < 0.01$), and prion protein (HR: 1.30, p: 0.04). In contrast, upregulated proteins in the R group linked to favorable prognosis were insulin-like growth factor-binding protein 2 (HR: 0.77, p: 0.02), keratin 19 (HR: 0.61, p: 0.02), and retinol-binding protein 4 (HR: 0.74, p: 0.03). **Conclusions:** Through in-depth proteomics analysis, this study systematically characterized the plasma proteomic landscape of patients undergoing chemo-immunotherapy, identifying potential novel biomarkers, and providing new insights to optimize clinical decision-making. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-Young2023-0125.

T-cell exhaustion and pre-existing T-cell immunity in circulation as predictive biomarkers for immunotherapy in NSCLC patients.

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Background: Pre-existing cancer-antigen specific T-cells describe the endogenous adaptive immunity before any treatment that may represent a valuable novel predictive biomarker for ICI. In a recent publication we have shown a positive correlation of pre-existing cancer-antigen specific $CD8^+$ T-cells with the response to ICI. Here, we analyze the major differences of exhausted T-cells between pre-existing positive ($PreI^+$) and pre-existing negative immunity ($PreI^-$) NSCLC patients as well as, between different stages of the disease. **Methods:** Blood was collected from 82 patients with NSCLC, 38 with stage III and 44 with stage IV, before ICI therapy. PBMCs were isolated with *Ficoll* density gradient centrifugation from patients and 15 healthy donors (HD). PreI was calculated by detecting endogenous IFNg expressing cells with FACS after in-vivo co-cultures of PBMCs with mixes of hTERT, MAGEA1, NY-ESO-1 και Survivin cancer-associated antigens. T-exhausted signatures were detected by multi-color flow cytometry using antibodies against CD3, CD4, CD8, PD-1 and TCF1. **Results:** 47% (18/38) of patients with stage III disease and 41% (18/44) of stage IV had peptide specific T-cells ($PreI^+$ patients). Survival analysis revealed better OS only in stage III $PreI^+$ compared to $PreI^-$ patients (Log-rank = 0.04), while for stage IV (p=0.081) there was only a trend. The percentages of CD8 T-cells that were $PD\text{-}1^+TCF1^+$(p=0.030) and $PD\text{-}1^+TCF1^-$(p=0.041) were higher in patients compared to HD, and additionally both T-cell populations harbored higher levels of PD-1 protein expression (p=0.003 and p=0.032 for stage III) as it was shown with mean fluorescence intensity (MFI). Moreover, low percentages of $PD\text{-}1^+TCF1^+$ ware associated with longer survival (p= 0.037) only in stage III patients. By subgrouping stage III patients, we observed that all patients with $PreI^+$ harboring low percentages of exhausted $PD\text{-}1^+TCF1^+$ were alive at the end of the follow up. **Conclusions:** Combinatorial analysis of Pre-existing tumor-antigen specific immunity and the status of T-cells before initiation of ICI in stage III NSCLC could serve as a good predictive factor of response. The study is ongoing. Research Sponsor: None.

Effect of fusobacterium nucleatum on NF-κB/HIF-1α/CCL20 pathway and M2 macrophages infiltration in esophageal squamous cell carcinoma.

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Background: Esophageal squamous cell carcinoma (ESCC) is one of the most common digestive malignant tumor with the highest mortality rate in China.Recent studies have shown that Fusobacterium nucleatum (F. nucleatum) can attenuate the efficacy of immunotherapy in ESCC patients through various mechanisms.One of them is recriuting more M2-like macrophages through tumor-derived cytokines such as CCL20. **Methods:** From January 2022 to June 2023, a total of 30 patients with ESCC from 4th Hospital of HeBei Medical University were enrolled.All of the pateints did not apply any neoadjuvant therapy before and received radical resection.Real-time reverse transcriptase - PCR(RT-PCR) were performed to examine the expressions of F. nucleatum in tumor tissues.According to the CT values,the level of the F. nucleatum infection could be seperated in two groups - positive group and negative group. Immunohistochemistry (IHC) staining were used to examine the expressions of CCL20、CD206 and HIF-1α in both groups. Immunofluorescence(IF) was characterised CD206 on $CD68^+$ macrophages.In addition,transwell assay was carried on to quantify macrophages migration ability in vitro.At last,Western blot was used to determine the expression level of CCL20, HIF-1α and p65/p-p65 on ESCC cells. **Results:** F. nucleatum DNA positivity was significantly associated with higher expression of CCL20, HIF-1α and accumulation of $CD68^+CD206^+$ macrophages.IHC showed that the expression of CCL20 and HIF-1α were higher in F. nucleatum positive tumor tissue. After coculture with F. nucleatum and Eca109 cells in vitro, CCL20 and HIF-1α production by ESCC cells were accelerated.Transwell assay showed using siCCL20, CCL20-Nab or siCCR6 could decline the macrophages invasion level caused by CCL20. Otherwise, siHIF-1α could lowered the CCL20 expression level caused by F. nucleatum.In addition,Western blot revealed NF-κB pathway was highly activated in Fn educated Eca109 cells.Using BAY11-7082 could decline both CCL20 and HIF-1α level triggered by F. nucleatum. **Conclusions:** Fusobacterium nucleatum promotes esophageal squamous cell carcinoma progression via NF-κB/HIF-1α/CCL20 pathway-mediated migration of M2-like macrophages into the tumour micro-environment and deteriorates the suppression of the local immune micro-environment within the tumor.Such bacteria may be a biomarker to predict the efficacy of immunotherapy in ESCC.
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Monitoring PD-L1 expression in cancer-associated macrophage-like cells as predictor of clinical outcomes in metastatic cancer patients treated with PD-L1 immunotherapies.

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Background: Studies have described the efficacy of immunotherapies (IMT) utilizing programmed death 1 receptor and its ligand (PD-L1) for treating solid tumors. However, many patients (pts) fail to respond to IMT, necessitating better predictive biomarkers for improved stratification. Poor IMT responses are often attributed to the dynamic nature of PD-L1 likely changing after chemotherapy or radiation, but typically quantified by static immunostaining. Recent studies have described PD-L1 upregulation in giant phagocytic stromal cells, i.e. Cancer associated macrophage-like cells (CAML), circulating macrophages that engulf tumor before entering circulation and may predict IMT responses. We conducted a pilot study to monitor the peripheral blood of n = 111 metastatic cancer pts undergoing systemic treatment with IMT in combination with other therapies, to evaluate CAML PD-L1 prior to & post IMT induction with clinical correlation at 2 years. **Methods:** In a prospective pilot study of n = 111 metastatic cancer pts, breast (n = 42), lung (n = 46), renal cell (n = 10), prostate (n = 5), esophageal (n = 5) & colon (n = 3), all starting new lines of systemic chemotherapy in combination with IMT (pembrolizumab [n = 69], nivolumab [n = 23], Durva [n = 4], or atezolizumab [n = 13]) for new recurrent metastasis (n = 45) or with previously treated progressive metastatic disease (n = 66). We isolated CAMLs from 7.5 ml baseline (T0) blood using the LifeTracDx PD-L1 test and scored PD-L1 as high or low. If possible, a follow-up sample (T1) was taken (~56 days) after IMT induction. Pts' progressive free survival (PFS) and overall survival (OS) hazard ratios (HRs) were analyzed by censored univariate analysis based on RECIST v1.1 over 2 years. **Results:** T0 PD-L1 CAML data was available for 78% (n = 86/111) of pts, with 34% (n = 29/88) having high CAML PD-L1 which was not correlated with improved PFS (HR = 0.99, p = 0.9416, CI = 0.6-1.6) or OS (HR = 1.1, p = 0.9472, CI = 0.6-1.8). T1 PD-L1 CAML data was available for 74% (n = 82/111) of pts, with 44% (n = 36/82) having high CAML PD-L1, which significantly correlated with improved PFS (HR = 3.1, p = 0.0002, CI = 1.8-5.5) & OS (HR = 6.6, $p < 0.0001$, CI = 3.4-12.7). In comparing CAML PD-L1 change post IMT, it was found that consistently low PD-L1 at T0 & T1 had the poorest responses, median PFS (mPFS) = 4.9 months & median OS (mOS) = 7.2 months. In contrast, consistently high PD-L1 at T0 & T1 had better responses, mPFS = 8.4 months & mOS = 18.3 months. Further, pts who increased in CAML PD-L1 after IMT had the best OS response rates, mPFS = 3.8 months & mOS = 20.9 months. **Conclusions:** We utilized a cancer agnostic blood-based biopsy to monitor PD-L1 changes in circulating tumor immune cells and predict clinical benefit to PD-L1 IMTs in several cancer types. While this initial pilot study appears to stratify pts with better IMT responses, larger validation studies are needed. Research Sponsor: Creatv MicroTech.

The classification of uncertain histologies based on cfDNA fragmentomic analysis in patients with uncommon cancers screened for NCI-MATCH.

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Background: The NCI Molecular Analysis for Therapy Choice (NCI-MATCH) was a precision medicine trial that assigned targeted treatments to patients independent of histology. We sequenced > 2500 NCI-MATCH ctDNA samples of uncommon histology (excludes colon, breast, non-small cell lung, and prostate) using the TruSight Oncology 500 (TSO500) v2 ctDNA assay. We generated a probabilistic model from ctDNA fragment sizes to assign histology to patient samples designated as "not otherwise specified (NOS)" in pathology reports. **Methods:** Fragmentomics data were computed by binning the segment-level data to each exon, followed by Shannon entropy calculation. The Least Absolute Shrinkage and Selection Operator (LASSO) algorithm was then used to build the histology classifier for each of 29 histologies (n = 1614 samples of known histology) using a 9:1 random training and validation separation for validation accuracy estimation. The 9:1 training/validation was repeated 10 times. During each training/validation step, another 10-fold cross validation within the training set was used to find the best hyperparameter. The final model was re-trained on total samples which combined 29 classifiers and final predicted histology was determined using a winner-take-all approach. Mutation data was generated by Illumina's DRAGEN TSO500 ctDNA analysis pipeline and annotated using the OncoKB knowledge base. **Results:** The fragmentomics-based classification model achieved 98.2 validation accuracy across 1614 evaluable samples. The accuracy was increased to 99.6% on a subset of samples (n = 1413) with high confidence prediction defined as prediction probability > 0.5. The model was further used to classify 232 samples with NOS histology. Although there were no ground truth cases, those where a histology was predicted with high confidence were closely aligned with their broader annotations. For example, among 37 pancreatic cancer (excluding Islets) NOS patient samples, 18/19 high-confidence predictions were adenocarcinoma of the pancreas. The model was further explored on female reproductive system cancer NOS, which includes several rare histologies with limited or no representation in the prediction model. In this analysis, 17/23 high-confidence predictions were designated as ovarian epithelial cancer (OEC) or related histologies. Interestingly, one oncogenic *BRCA2* mutation (p.T1388fs) was detected in a predicted ovarian epithelial cancer sample. **Conclusions:** The validation accuracy was high in this exploratory analysis of uncommon histologies. High-confidence prediction was achieved for adenocarcinoma of the pancreas although prediction confidence was lower in OEC or related histologies . This study may support an expanded role for large cfDNA targeted panels beyond the identification of clinically actionable mutations to the classification of tumor histologies. Research Sponsor: National Cancer Institute.

A molecular biomarker for longitudinal monitoring of therapeutic efficacy in a real-world cohort of advanced solid tumors treated with immune checkpoint inhibitors.

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Background: Clinical validation studies have shown that early dynamic changes in circulating tumor DNA (ctDNA) tumor fraction (TF) can predict clinical outcomes. Yet few studies have evaluated the clinical value of longitudinal monitoring throughout the course of treatment. Here we evaluate longitudinal changes in ctDNA TF and clinical outcomes in an advanced real-world pan-cancer cohort of patients (pts) treated with immune checkpoint inhibitors (ICIs). **Methods:** The cohort included deidentified pts from the Tempus clinicogenomic database with stage IIIB or IV solid tumors who underwent ctDNA NGS and were treated with an FDA-approved ICI +/- chemotherapy (CT). Pts had a pre-treatment baseline liquid biopsy (T0) and ≥1 on-treatment sample Ti within 21-180 days of ICI. xM for treatment response monitoring estimates TF via an ensemble algorithm that incorporates variant and copy number information. Response status was determined at each on-treatment timepoint Ti relative to T0. Pts were classified as a Molecular Responder (MR) if TF < 1% at T0 and Ti or if TF decreased by ≥ 50% from T0 to Ti; otherwise, they were classified as a Molecular Non-Responder (nMR). Pts with TF < 0.09% at T0 and Ti were classified as ctDNA not detected. The longitudinal cohort included pts with ≥2 on-treatment timepoints, further classified based on the most frequent classification across each Ti as longitudinal MR, longitudinal nMR and longitudinal ctDNA not detected. If no classification was dominant, the most recent classification was used. Real-world overall survival (rwOS) was defined from T1 to death and assessed by log-rank test. **Results:** The full cohort of 84 pts with > 10 solid tumors included 34.5% (n = 29) NSCLC and 16.7% (n = 14) SCLC. The majority of pts (59.5%, n = 50) received ICI+CT, (64.0% first-line [1L]), and 40.5% (n = 34) ICI-only (35.3% 1L). rwOS was longer for 53 MRs vs. 18 nMRs (median not reached vs. 7.0 months, P < 0.005); 13 pts had no ctDNA detected. The longitudinal subcohort of 35 pts was 31.4% (n = 11) NSCLC, 20.0% (n = 7) prostate cancer, and 14.3% (n = 5) SCLC; 45.7% (n = 16) ICI+CT (56.3% 1L), 54.3% (n = 19) ICI-only (31.6% 1L). On average, pts had 3 on-treatment liquid biopsies, with a median time between on-treatment samples of 91 days. Twelve pts were longitudinal nMRs (10 MR or ctDNA not detected at T1), 18 longitudinal MRs, and 5 longitudinal no ctDNA detected. There were 6 death events in the longitudinal nMRs, 3 in the longitudinal MRs (all > 18 months after T1), and no death events in the longitudinal no ctDNA detected group. Longitudinal MRs had longer rwOS than longitudinal nMRs (median 37.4 months vs 8.7 months, P < 0.005). **Conclusions:** Longitudinal nMR was associated with worse survival compared to longitudinal MR. Longitudinal, molecular biomarker dynamics may be a useful clinical treatment decision tool for monitoring treatment response to ICI therapy. Research Sponsor: Tempus AI.

Predictive imaging of the immunotherapy and radioimmunotherapy response by immunoPET via a new target (CD103) and innovative protein formats in preclinical NSCLC.

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Background: Immune checkpoint immunotherapies (ICI) have transformed cancer treatment, but patients have varied responses and potential risks of autoimmune disease. To improve ICI, we need to identify biomarkers to select responding patients and research new approaches. To this, resident memory T cells (TRM) LT $CD8^+$ $CD103^+$, have been identified as a promising tumor-specific biomarker for studying therapeutic efficacy involving ICI. Internal radiotherapy appears to be a promising approach. Our objective is to develop new therapeutic approaches combining radiotherapy and ICI (radioimmunotherapy) using $CD8^+CD103^+$ immunoPET imaging as a predictive biomarker of efficacy. **Methods:** After developing and characterizing a new CD103 radiotracer and validating the dual ^{18}F PET-Scan imaging for $CD8^+$ and $CD103^+$ in C57BL/6 mouse models, we implanted mice subcutaneously with MC38 and othotopically syngenetically with LLC. We evaluated the efficacy of radioimmunotherapy vs ICI and the predictive effect of TRM in this syngeneic orthotopic model. To this, we implanted two syngeneic NSCLC cell lines, either LLC for a cold tumor or CMT167 for a warmer tumor. We performed double imaging prior to treatment with [^{18}F]-CD8 mutated FcRn and [^{18}F]-CD103 minibody on 2 consecutive days. We treated our mice 3 times, 3 days apart, with the first dose of either cold Avelumab or [^{177}Lu]-Avelumab (8MBq). The second and third doses were cold Avelumab. We performed double post-treatment imaging with [^{18}F]-CD8 mutated FcRn and [^{18}F]-CD103 minibody on 2 consecutive days, as well as ex vivo analyses and a survival study. **Results:** There was a trend towards improved survival in [^{177}Lu]-Avelumab treated mice vs Avelumab treated mice but more markedly in the immunogenic model (30d vs 21d). The impact on tumor growth was assessed by comparing the two treatment groups with untreated mice. Radioimmunotherapy induced a significant decrease in overall tumor growth compared with mice treated with ICI (0.45 ccm vs 0.68 ccm, $*p < 0.05$ turkey's multiple comparison test) in the immunogenic model. In the cold tumor model, there was a significant difference in the tumor size ratio before and after treatment, for mice treated with radioimmunotherapy vs ICI (12.96 vs 26.08, $***p < 0.001$ Uncorrected Fisher's LSD). An increase in immune infiltration was validated by PET and flow cytometry for the immunogenic model (pre-treatment: 5.00%ID/cc max, versus post-treatment 8.23%ID/cc max for CD8, $*p < 0.05$ two way-Anova). More heterogeneous results were observed in the cold tumor model. **Conclusions:** Radio-immunotherapy reduces tumour growth and stimulates the immune system by circulating LT_{CD8}. The dual ^{18}F PET-Scan imaging for $CD8^+$ and $CD103^+$ offer a promising non-invasive visualization of tumor-infiltrating $CD103^+$ TRMs. We need to correlate $LT_{CD8+\ /CD103+}$ infiltration with therapeutic response. Research Sponsor: None.

Ultrasensitive ctDNA profiling to identify long-term survivors in phase I immunotherapy trials.

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Background: Patients (pts) included in early clinical trials (ECT) typically show a median overall survival of 8-10 months (PMID: 18042834 and 21975023), with long-term survivors (LTS) rarely encountered. While prognostic scores have been developed to identify short-term survivors (STS) in ECT, predictors of LTS remain largely unexplored. Ultrasensitive circulating tumor DNA (uctDNA) serves as a reliable surrogate for tumor burden (Toledo R *et al*, ASCO 2024), and may provide insights into LTS. This study aims to identify key determinants of LTS. **Methods:** A case-control study was conducted on pts treated at VHIO's phase I unit between 2013 and 2023, as part of the institutional translational study RIO360. Pts with an overall survival (OS) $>$ 3 years after C1D1 were classified as LTS and compared to STS with OS $<$ 1 year, matched for age, sex, stage, prior immunotherapy (IO), and ECOG. Clinical, histopathological, uctDNA, and treatment outcomes were collected. uctDNA analysis was performed prior to C1D1 and throughout treatment (every 3 to 4 weeks) in the subset of patients treated with IO. Comparisons between LTS and STS were performed using univariate binomial generalized linear models. **Results:** Of 1282 pts, a total of 117 pts (9.1%) were classified as LTS (median OS 5.2 years) and compared with 117 matched STS pts (median OS 0.6 year). The most common tumor types among LTS were HNSCC (18%), melanoma (10%), and breast (9.1%), while in STS were colorectal (27%), breast (12%), and melanoma (11%). Treatment with 3+ prior lines was more common in STS (45%) than LTS (24%) ($p = 0.002$). Visceral metastases were present in 59% LTS and 77% STS ($p = 0.010$). Higher neutrophil count and dNLR were associated with STS ($p < 0.05$). LTS had lower mean uctDNA at baseline (7.5 vs 10.9 ppm; $p < 0.001$). Two consecutive uctDNA decreases were observed in 92% of LTS pts, while 80% of STS pts showed two consecutive uctDNA increases ($p < 0.001$). **Conclusions:** In ECT, predictors of long-term survival include the absence of visceral metastasis, less prior treatment exposure, low baseline uctDNA levels, and early decreases in uctDNA. This study further explores uctDNA dynamics during treatment, with detailed findings to be presented. Research Sponsor: BBVA.

Ultrasensitive ctDNA monitoring to reveal early predictors of immunotherapy success in advanced cancer.

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Background: The potential of immune checkpoint inhibition (ICI) therapy is constrained by the inability to predict patient response. Circulating tumor DNA (ctDNA) has emerged as a promising tool for real-time response tracking and early prediction of therapeutic outcomes. However, the clinical utility of ctDNA-based liquid biopsy faces a critical challenge: reliable detection in low-shedding tumors and during dramatic therapeutic responses when ctDNA levels approach the analytical threshold. We overcome this technical limitation, achieving the precise longitudinal monitoring needed to optimize ICI therapy. **Methods:** We analyzed longitudinal plasma samples from 43 patients with treatment-refractory metastatic cancers spanning 8 distinct groups, composed primarily of GI (n = 17) and gynecological cancers (n = 6). Patients underwent a median of 1 previous line of therapy (range 0-8). Using NeXT Personal, an ultra-sensitive personalized liquid biopsy approach, we tracked up to 1,800 patient-specific somatic variants per case across 250 plasma samples. This methodology achieves exceptional analytical sensitivity, detecting circulating tumor DNA at levels as low as 1-3 parts per million (PPM). **Results:** ctDNA was detected across five orders of magnitude (2.0-239,315 PPM, median LOD: 1.76 PPM), with 31% of positive signals falling in the ultrasensitive range below 100 PPM. Early molecular response, measured by $>$ 50% ctDNA reduction or sustained ctDNA negativity from baseline to first follow-up (median 23 days), strongly predicted improved progression-free survival (PFS) (HR = 0.22, 95% CI 0.07-0.70, p = 0.006), representing a 3-fold increase in 1 year PFS rates. Achievement of durable molecular complete response (dmCR), defined as sustained ctDNA clearance $>$ 120 days, emerged as a powerful predictor of PFS, with dmCR patients maintaining 100% progression-free status at 12 months compared to 63% in non-dmCR patients (HR = 0.10, 95% CI 0.01-0.92, p = 0.017). This survival advantage persisted at 18 months with 80% PFS in dmCR patients versus 21% in non-dmCR patients. **Conclusions:** Early ctDNA kinetics predict long-term ICI outcomes across multiple advanced cancer types. The ability to detect ultra-low ctDNA levels proved critical for accurate minimal residual disease assessment, even in this heavily pretreated cohort. These results establish high-sensitivity ctDNA monitoring as an essential tool for precise, real-time evaluation of immunotherapy response to guide clinical decision-making. Clinical trial information: NCT02478931. Research Sponsor: Personalis.

Role of pelareorep in activating anti-tumor immunity in PDAC.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is highly lethal cancer with limited immunotherapeutic options. Pelareorep (pela) is an intravenously delivered unmodified reovirus containing a double stranded RNA genome that has been studied as an immunotherapeutic in multiple cancers including breast, anal, colorectal and pancreatic. We previously reported high tumor response rates in first-line metastatic PDAC patients treated with pela combined with gemcitabine, nab-paclitaxel and atezolizumab. We report here the immunologic effects of pela in a cohort of first-line metastatic PDAC subjects treated with pela plus chemotherapy and atezolizumab and the correlation of these effects with tumor response. **Methods:** To examine its effects on pancreatic cancer, a phase 1/2 Simon 2-stage platform study (GOBLET) was performed that included patients with first-line locally advanced/metastatic unresectable PDAC. Anti-reovirus T cell activity was assessed by interferon gamma secretion (ELISPOT). Changes in the expression of plasma proteins were analyzed by Olink Response panels. T cell receptor sequencing (TCR-seq; ImmunoSEQ Assay, Adaptive Biotechnologies) was performed on tissue collected prior to the start of therapy and on blood from baseline through 3 treatment cycles to identify TILs expansion. Tumor responses were scored according to the modified RECIST v1.1 criteria. **Results:** Increases in anti-reovirus T cell activation as determined by ELISPOT after cycle 3 of therapy were observed in 6/8 subjects. Three subjects with maximum responses ($>$ 300 spots) showed $>$30% decreases in tumor volume. Significant changes in plasma proteins as determined by Olink included PD-L1, CXCL9, CXCL10, CXCL11 and IFN-γ. Pre-treatment tumor tissue was used to identify the TIL clonal populations prior to therapy. Increased TIL clones in the blood pre-treatment was associated with tumor responses. Pela treatment increased the expansion of pre-existing and new TIL clones in the blood after one cycle of treatment. Sustained increases in pre-existing TIL clonal populations in the blood through cycle 3 of therapy were observed in subjects who exhibited reductions in tumor volume. **Conclusions:** These findings, while preliminary, demonstrate that pela induces not only anti-reovirus T cells but also activates innate and adaptive anti-tumor immunity in PDAC subjects treated with chemotherapy and atezolizumab. Tumor responses are associated with both the presence of TIL clones in the blood prior to treatment and the expansion of pre-existing TILs in the blood on treatment. These findings provide additional insights into the immunologic mechanisms by which pela-based therapy may provide clinical benefit in patients with metastatic PDAC. Research Sponsor: None.

ctDNA features of acquired resistance to immunotherapy in advanced NSCLC.

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Background: Acquired resistance to systemic therapies, including immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs), is a major clinical challenge in advanced non–small cell lung cancer (NSCLC). While mechanisms of resistance to targeted therapies are well-documented, the genomic alterations associated with resistance to immunotherapy remain poorly understood. Circulating tumor DNA (ctDNA) profiling offers a non-invasive approach to identify real-time genomic changes driving resistance, providing novel insights into the underlying biology of immunotherapy failure. **Methods:** We performed a prospective ctDNA sequencing study in 57 advanced NSCLC patients from two cohorts: STING (n = 30, NCT04932525) and COPE (n = 27, NCT04258137). Plasma samples were collected before treatment initiation and at disease progression following objective response to anti–PD-1 therapy or TKIs. ctDNA analysis was conducted to detect emergent genomic alterations, evaluate tumor mutation burden (TMB), and quantify circulating tumor fraction (TF). **Results:** The study included 57 patients, with a median age of 62 years [IQR: 54.5–70], and 54.4% (31/57) were male. At disease progression, 64.9% (37/57) of patients exhibited emergent ctDNA alterations associated with secondary resistance, independent of therapy type. Among these, 70% (26/37) harbored multiple newly arising mutations. In the non–oncogene-addicted NSCLC cohort receiving anti–PD-1 therapy (n = 30), 56.6% (17/30) exhibited emergent resistance alterations, with 76.5% (13/17) harboring multiple mutations. Frequently observed aberrations included mutations in NOTCH1/3 (n = 3), KEAP1 (n = 3), KMT2B (n = 2), POLE (n = 2), SETD2 (n = 2), TYRO3 (n = 2), STK11 (n = 2), TSC2 (n = 1), TGFBR2 (n = 1), PTPN11 (n = 1), SPEN (n = 1), STAG (n = 1), CDH1 (n = 1), and CTNNB1 (n = 1). The median progression-free survival (mPFS) was 7.0 months [95% CI: 5.0–10.3]. In the anti-EGFR TKI cohort (n = 13), 84.6% (11/13) displayed emergent ctDNA alterations, including mutations in EGFR (n = 2), PIK3CA (n = 2), and MET (n = 1). The mPFS was 8.6 months [95% CI: 6.7–11.2]. TMB and circulating TF did not significantly change between baseline and progression in both cohorts. **Conclusions:** This study highlights the high prevalence of emergent genomic alterations detected by ctDNA in advanced NSCLC patients developing resistance to ICIs and TKIs. In the ICI-treated cohort, mutations in NOTCH1/3, KEAP1, and STK11 emerged as significant resistance drivers, consistent with their roles in immune evasion, oxidative stress regulation, and impaired immune cell infiltration, as supported by prior studies. Notably, this is the first study investigating features of ctDNA at acquired resistance to immunotherapy using an FDA-approved assay. These findings underscore the heterogeneous and polyclonal nature of resistance to ICIs. Research Sponsor: None.

Mutation profiling of appendiceal cancer: Distinguishing tumor grades, comprehensive mutation landscape, and ctDNA as a discovery tool.

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Background: Appendiceal cancer (AC) encompasses rare tumors with varying clinical behavior. Histologic grade is a key determinant of disease biology and prognosis. This study utilized an in-house circulating tumor DNA (ctDNA) biomarker discovery pipeline to assess genetic determinants of histologic grade in AC, analyzing both peripheral blood and tumor tissue. **Methods:** Paired peripheral blood and solid tumor samples were collected from 52 patients undergoing surgery for AC (18 low-grade and 34 intermediate/high-grade). Comprehensive genomic profiling (CGP) using the TSO500 assay was performed on ctDNA, tissue-derived DNA and buffy-coat (germline)-derived DNA. Tumor-specific and germline mutations were analyzed using OncoKB, which classifies variants as oncogenic, likely oncogenic, or actionable (Level 1 therapeutic mutations with an approved therapy). The concordance of mutations between solid tumor and plasma CGP assays was assessed, categorizing variants as detected in both tumor and ctDNA, ctDNA only, or tumor only. **Results:** ctDNA exhibited 82% concordance with tumor tissue for known actionable mutations. Among 26 patients that were identified to have Level 1 therapeutic mutations, 88% (n = 23) had matching mutations in plasma. Frequently detected mutations included *KRAS (40%), GNAS (30.8%), SMAD4 (28.8%),* and *TP53 (28.8%)*. Germline analysis revealed additional variants, including *RUNX1 (71.2%), NOTCH4 (50%)*, and *BARD1* (48.1%). Tumor-specific *TP53* and SMAD4 mutations correlated with high-grade tumors; while *GNAS* was more prevalent in low-grade tumors. Germline analysis identified *NOTCH3* and *SPEN* mutations predominantly in high-grade tumors, suggesting that inherited determinants may determine tumor grade (23.5% each). Plasma samples exhibited lower variant allele frequencies, limiting sensitivity for novel biomarker discovery. Concordance analysis revealed some mutations were exclusive to solid tumors, while others were plasma-specific, highlighting the need for a multi-modal genomic assessment. **Conclusions:** Tumor *TP53, GNAS,* and *SMAD4* mutations serve as molecular classifiers for histologic grade differentiation in AC, while germline *NOTCH3, SPEN, RUNX1, NOTCH4,* and *BARD1* variants may influence histologic grade. ctDNA showed strong concordance for actionable mutations but had reduced efficacy for novel mutation discovery in the plasma samples. These findings underscore the value of integrating tumor and germline profiling for classification and treatment stratification, while refining liquid biopsy methodologies to enhance sensitivity in AC research.
Research Sponsor: None.

Investigating the association of blood-to-tissue tumor mutation burden (TMB) ratio with overall survival and intratumor heterogeneity (ITH) in advanced NSCLC.

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Background: High tumor mutation burden (TMB) measured via tissue-based next-generation sequencing (NGS) (tTMB) has been shown to predict better survival outcomes in certain cancers treated with immune checkpoint inhibitors (ICIs). With the increasing use and sensitivity of blood-based NGS, blood-based TMB (bTMB) is frequently employed as an alternative. However, the prognostic significance of bTMB relative to tTMB and its correlation with intratumoral heterogeneity remain poorly understood. **Methods:** This study included advanced-stage NSCLC patients who underwent both pre-treatment blood-based NGS (collected between October 2020 and February 2024) and tissue-based NGS. Intratumoral heterogeneity (ITH) was assessed using the mutant-allele tumor heterogeneity (MATH) approach, with blood based NGS (bMATH). The highest allele frequency (HAF) was obtained from blood-based NGS. Survival analyses were conducted using Kaplan-Meier curves and Cox proportional hazards models, focusing on the bTMB/tTMB ratio. **Results:** A total of 102 patients met the inclusion criteria, 55 of whom had complete data for bTMB, tTMB, bMATH, and HAF. The median follow-up time was 12 months. Treatment regimens included ICI combined with chemotherapy (19 patients), ICIs alone (15), targeted therapy (16), and cytotoxic chemotherapy (5), with 33 receiving first-line treatment and 22 receiving second-line or beyond. The median interval from blood NGS to treatment initiation was 20 days (IQR 8–28), and from tissue NGS to treatment initiation was 65 days (IQR 28–255). Multivariable Cox proportional hazards analysis—adjusting for gender, smoking status, stage, ECOG, regimen type, line of therapy, and numeric values of bMATH, bTMB, tTMB, and the bTMB/tTMB ratio—revealed that a higher bTMB/tTMB ratio was independently associated with inferior overall survival (OS) (HR 1.16, 95% CI 1.03–1.30, p=0.01) but showed no significant difference in progression-free survival (PFS) (HR 1.10, 95% CI 0.94–1.29, p=0.23). The cutoff for the bTMB/tTMB ratio that best stratified OS was 0.81. Patients below this cutoff experienced significantly longer OS (median OS 10 vs. 49 months, HR 0.23, 95% CI 0.05–0.96, p=0.02). Additionally, a moderate positive correlation was observed between bMATH and the bTMB/tTMB ratio (Spearman's r=0.33, p=0.02). **Conclusions:** A higher bTMB/tTMB ratio was associated with poorer overall survival in advanced-stage NSCLC, highlighting its potential prognostic value. Moreover, the moderate correlation between bMATH and bTMB/tTMB suggests an interplay between TMB and intratumor heterogeneity. Future studies are needed to confirm these findings and to explore their potential therapeutic implications. Research Sponsor: None.

Identifying peripheral cancer-associated TCR signals for the early-detection of lung cancer.

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Background: Tumor-associated antigens and neoantigens play a critical role in eliciting anti-tumor immune responses, leading to a significant amplification of tumor-specific T cell clones. Consequently, the detection of tumor-associated immune signaling in peripheral blood is expected as a promising strategy for cancer screening. Notably, due to the amplification effect of the immune response, the identification of tumor-related immune signals demonstrates higher abundance compared to the direct detection of tumor-derived molecules, such as circulating tumor DNA (ctDNA). This increased abundance allows for the extension of the screening time window, underscoring its potential for early cancer detection. The present study aims to identify lung cancer-associated T cell receptor (TCR) signatures, and develops a predictive model for to recognize lung cancer based on TCR repertoire sequencing. **Methods:** Peripheral blood samples were collected from 2,699 lung cancer patients and 3,360 healthy individuals. The TCR repertoires were profiled using a multiplex-PCR-based sequencing of the TCR-β chains. The frequency of TCR clonotypes were calculated using MiXCR tools by aligning against human TCR-β gene segments. The cancer-enriched TCR sequences were identified by comprehensively considering the distribution and frequency of clonotypes in the comparison between the lung cancers and the healthy controls. We proposed an lung cancer-enriched TCR score (LCS) to evaluate the risk for lung cancer based on the CDR3 sequences alignment. A robust machine learning model was developed integrating multiple TCR repertoire characteristics and LCS. **Results:** The UMAP clustering based on TCR repertoire features revealed distinct TCR characteristics in lung cancer patients compared to healthy individuals. 3,840 TCR clones were identified to be significantly enriched in lung cancer cases. Among these, the CDR3β 'CATSRDTGGREKLFF' was identified as the most highly enriched clone specific to lung cancer patients. Furthermore, a significantly higher LCS was observed in lung cancers ($p < 0.001$). To validate the utility of LCS, we applied the LCS measurement to an independent public TCR dataset with 382 lung cancer patients, 195 healthy individuals, and 1,034 COVID-19 cases. The external validation demonstrated that lung cancers show a significantly increased LCS compared with healthy controls ($p < 0.001$), while no significant difference in LCS between COVID-19 cases and healthy controls ($p = 0.25$). The detection performance of model using integrated TCR features and LCS demonstrated a sensitivity of 0.96 and a specificity of 0.95. **Conclusions:** Cancer-related immune signals in peripheral blood can inform the anti-tumor responses. This study identified lung cancer-enriched TCR signatures, highlighting the potential as promising biomarkers for lung cancer detection. Clinical trial information: ChiCTR2200055761. Research Sponsor: None.

Dietary compounds and patterns associated with immune checkpoint inhibitor (ICI) outcomes in advanced non-small cell lung cancer (NSCLC).

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Background: The gut microbiome is a modulator of ICI activity. Diet is among the most important factors influencing the gut microbiome. We previously showed that high fiber was not associated with outcome in NSCLC, in contrast to melanoma. However, the impact of dietary patterns and specific nutrients on ICI outcomes in NSCLC is unknown. **Methods:** At the CHUM Microbiome Centre, a nutritionist prospectively collected dietary history using a validated DHQ-II survey from 147 patients (pts) with advanced NSCLC treated with ICI alone or in combination with chemotherapy. Global dietary patterns and a systematic screen of 72 macro- and micronutrients (cut-offs defined by median) were examined for their association with progression-free survival (PFS) in univariable and multivariable cox-regression analyses. Associations between diet and immune-related adverse events (irAE) were examined. In 69 pts, shotgun metagenomic sequencing (WMS) was performed on fecal samples to determine differential abundance of bacteria using linear discriminant analyses, heatmaps, and MaAs-Lin2. **Results:** Median age was 68, 46% were male. Median follow-up was 13 months. Total caloric intake adjusted for basal metabolic rate (Mifflin-St Jeor equation using BMI and activity level) was not associated with PFS (p = 0.3). In univariable analyses, the following nutrients were associated with improved PFS: vitamin K (HR 0.62, p = 0.03), fat (HR 0.65, p = 0.04); while the following were associated with inferior PFS: starch (HR 1.61, p = 0.03), carbohydrates (HR 1.56, p = 0.04), sucrose (HR 1.62, p = 0.03), and iron (HR 1.7, p = 0.016). In a multivariable analysis examining all macro- and micronutrients and adjusting for BMI, vitamin K intake was significantly associated with improved PFS (HR 0.60, 95% CI 0.37, 0.97, p = 0.04). Fat-based diets such as keto-like diet (high fat, low starch) was associated with improved PFS in univariable (HR, 0.47, p = 0.008) and multivariable analyses (HR 0.37, 95%CI 0.2, 0.68, p = 0.001). Compared to high starch diet, western diet (high fat, high starch) was associated with increased risk of any grade irAE (24% vs 54%, respectively, p = 0.01). WMS analyses revealed biologically relevant signals; fat-based diets were associated with enrichment of favorable commensal bacteria such as *Ruminococcus lactaris*, *Butyricimonas faecihominis*, *Lachnospiraceae* spp, with low fat associated with deleterious *Veillonella atypica*. Starch-based diets were associated with high *Prevotella* spp. Sucrose-enriched diets were enriched with *Candidatus saccharibacteria*, a known sucrose-fermenting bacteria. **Conclusions:** Our results demonstrate the importance of diet on ICI outcomes in NSCLC and WMS results suggest this is mediated by the gut microbiome. Diet is a modifiable lifestyle factor which may be targeted to improve ICI activity, meriting study in a randomized trial. Research Sponsor: Terry Fox Research Institue; Institut de Cancer de Montréal.

The role of lipid-laden Kupffer cells in immunosuppression and immunotherapy response in MASLD-related hepatocellular carcinoma.

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Background: Hepatocellular carcinoma (HCC) related to metabolic dysfunction-associated steatotic liver disease (MASLD) is a rising global health burden. Despite systemic immunotherapy being the first-line treatment for advanced HCC, clinical observation shows that immune checkpoint inhibitors (ICI) offer lower benefit to patients with non-viral HCC, including MASLD-HCC. Macrophages, especially Kupffer cells (KCs), are the major PD-L1+ liver cells. With previous studies showing that more KCs are associated with poorer survival, we hypothesise that KCs in MASLD-related HCC show an immunosuppressive phenotype secondary to lipid accumulation, contributing to the poorer ICI responses in patients. **Methods:** As proof-of-concept, we characterised macrophage phenotypes and lipid accumulation in matched tumour and non-tumour tissues from HBV+ and non-viral HCC patients (n = 6 / group). We next assessed the functional consequences of lipid loading using induced pluripotent stem cell (iPSC)-derived KCs in vitro, followed by validation in KC-containing iPSC- and patient-derived HCC organoids. We evaluated lipid accumulation, paracrine signalling, transcriptomic changes, and cell-cell interactions in these organoids. **Results:** In patient samples, macrophage lipid accumulation is associated with a PD-L1 high, TREM2 high, KC-like phenotype in both non-tumour and tumour (Cohen's $d > 1.0$, power $> 99\%$). In non-viral HCC samples, lipid-laden macrophages, with an M2-KC phenotype, are enriched twofold in non-tumour (Cohen's $d > 1.0$, power = 72%) and tumour (Cohen's d = 0.3, power = 6%). Light-sheet microscopy confirmed colocalization of lipids and PD-L1+ immune cells. Exposing iPSC-KCs to free fatty acids and IL-6 suppressed antigen presentation, while enhancing phagocytosis and T-cell exhaustion ($p < 0.05$) – effects not reversed by ICI alone but alleviated when combined with tocilizumab or a CD36 inhibitor. These changes are likely independent of lipophagy or FASN-mediated fatty acid synthesis. Our HCC organoid models preserve KCs and recapitulate their immunosuppressive phenotype. scRNA-seq and CellPhoneDB analysis of HCC organoids highlighted significant KC-hepatocyte crosstalk, mediated by IL-6, SPP1, and other cytokines, corroborated by Luminex assay. **Conclusions:** These findings suggest that MASLD-associated lipid loading promotes a distinctly immunosuppressive KC phenotype, contributing to diminished ICI responsiveness in HCC. Targeting the lipid-KC axis, for instance with IL-6 blockade or CD36 inhibitors, may help restore immune competence and improve ICI-based treatment outcomes. Future studies, especially with a larger patient cohort and with our organoid platform, should determine whether lipid-laden KCs can serve as a biomarker for ICI responsiveness and further delineate the pathways driving their immunosuppressive behaviour. Research Sponsor: National Medical Research Council, Singapore; MOH-STaR21-nov-0002; National Medical Research Council, Singapore; NMRC/OFLCG/003/2018; National Research Foundation, Singapore; NRF-CRP26-2021RS-0001.

The economics of cancer immunotherapy: A five-year Medicare B expenditure analysis of checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICIs) have transformed cancer treatment, prompting a comprehensive analysis of Medicare Part B spending trends from 2018 to 2022. **Methods:** We conducted a detailed examination of Medicare Part B claims data, focusing on spending per dosage unit, total expenditure, and beneficiary utilization across multiple ICI drugs. **Results:** Our analysis revealed significant variations in ICI utilization and spending, with Keytruda (Pembrolizumab) emerging as the leading drug, totaling 4.94 billion and serving 67,022 beneficiaries in 2022. Notably, Opdivo (Nivolumab) demonstrated substantial market presence with 1.85 billion in spending and 26,957 beneficiaries. Price changes varied considerably, with Pembrolizumab experiencing a 12.9% price increase, Durvalumab rising 8.0%, and Atezolizumab increasing 10.1%. Interestingly, Libtayo showed a modest 1.5% price decrease. Other significant drugs included Tecentriq (Atezolizumab) with 777.8 million in spending and 12,812 beneficiaries, and Imfinzi (Durvalumab) with 562.7 million and 10,517 beneficiaries. **Conclusions:** Medicare Part B spending on immune checkpoint inhibitors reflects complex market dynamics, characterized by significant variations in drug pricing, beneficiary utilization, and total expenditure, highlighting the evolving landscape of cancer immunotherapy. Research Sponsor: None.

Cost trajectories and utilization patterns of eight immune checkpoint inhibitors (2018-2022).

Brand Name	Generic Name	Average Spending per Dosage Unit 2022	Annual Growth Rate in Average Spending per Dosage Unit (2018-2022)	Total Spending 2022	Total Beneficiaries 2022	Average Spending per Beneficiary 2022	Average Sales Price (ASP) 2022
Bavencio	Avelumab	$85.86	2.10%	$111,862,815	1,591	$70,310	$87.91
Imfinzi	Durvalumab	$75.86	1.60%	$562,741,221	10,517	$53,508	$77.53
Jemperli	Dostarlimab-Gxly	$216.09		$4,502,157	79	$56,989	$217.87
Keytruda	Pembrolizumab	$52.18	4.70%	$4,935,971,049	67,022	$73,647	$53.42
Libtayo	Cemiplimab-Rwlc	$27.02	0.10%	$203,832,304	3,187	$63,957	$27.45
Opdivo	Nivolumab	$28.78	4.10%	$1,849,938,540	26,957	$68,626	$29.43
Opdualag	Nivolumab and relatlimab-rmbw	$176.43		$42,513,402	680	$62,520	$180.64
Tecentriq	Atezolizumab	$79.07	1.50%	$777,758,575	12,812	$60,705	$80.79

Phase I study of hV01, a recombinant human IL-21-expressing oncolytic vaccinia virus, as monotherapy in advanced solid tumors.

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Background: Oncolytic viruses have shown an excellent safety profile and can initiate anti-tumour immunity through in-situ tumor lysis and systemic immune response, thereby gaining significant attention in cancer immunotherapy. Here, we conducted a phase I study of hV01, a genetically engineered oncolytic vaccinia virus expressing IL-21, in patients with advanced malignant solid tumors. **Methods:** This open-label, single-dose escalation study evaluated four dosing levels (range, 1×10^7 - 8×10^8 PFU) of intratumoral (i.t) injection of hV01, with a 28-day treatment cycle (NCT05914376). The primary aims were to determine the maximally tolerated dose (MTD), dose-limiting toxicities (DLTs) and safety. Treatment response was evaluated by RECIST v1.1 criteria on day 28 using a CT scan.Peripheral blood samples were analyzed for immune cell phenotypes with FACS and viral shedding with Q-PCR after the hV01 regimen. **Results:** Thirteen patients with advanced solid tumors were enrolled; most had failed multiple prior therapies. Twelve patients completed at least one treatment cycle, with three in each dosing cohort. Six of the twelve patients (6/12, 50%) achieved stable disease (SD), while the rest had progressive disease (PD), evaluated at the end of the first treatment cycle. Among the six patients with SD, one patient with pulmonary spindle cell carcinoma in the 1×10^7 PFU cohort had progression-free survival (PFS) for 138 days, and one patient with dedifferentiated liposarcoma in the 6.0×10^8 PFU cohort had a PFS for 206 days. One patient with nasopharynx cancer in the 8.0×10^8 PFU cohort achieved a partial response (PR) after four treatment cycles. No DLTs occurred during the observation period of this study. The most commonly treatment-related adverse events (TRAE) were fever and anemia, which were reported as grade 1-2 events in eleven patients (11/13, 84.6%) and six patients (6/13, 46.2%), respectively. The only grade 3 event was decreased lymphocyte count in one patient in the 6.0×10^8 PFU cohort. FACS analysis found a decrease in T cells and natural killer (NK) cells in the peripheral blood in all patients on the day following hV01 administration, and later, the levels of T cells and NK cells gradually rebounded. Notably, four patients had significantly higher (more than doubled or tripled) levels of NK cells compared to their baseline on day 15 after the hV01 regimen. **Conclusions:** Single-dosing of hV01 per treatment cycle was well tolerated and safe. hV01 i.t. injection demonstrated primary efficacy in patients with advanced tumors. The data support further study of multiple-dosing regimens and future trials evaluating the benefits of combining hV01 with other antitumor therapies. Clinical trial information: NCT05914376. Research Sponsor: Hangzhou ConVerd Co., Ltd.

Influence of salmonella-IL2 in combination with FOLFIRINOX on overall and progression-free survival in stage IV metastatic pancreatic cancer.

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Background: Salmonella-IL2 is an attenuated Salmonella Typhimurium strain carrying the human gene for IL-2. When orally administered, the bacterium colonizes tumors and locally releases IL-2, triggering immunologically-mediated tumor cell killing without untoward side effects. Salmonella-IL2 was tested in a phase 2 clinical trial in which patients with stage IV metastatic pancreatic cancer were treated with standard of care chemotherapy (SOC) combined with Salmonella-IL2. **Methods:** A Health Canada and local IRB approved, non-randomized, two-arm human study evaluated the combination of Salmonella-IL2 with standard of care (SOC) chemotherapy; Arm One patients received Salmonella-IL2 plus FOLFIRINOX (FFX). Arm Two patients received Salmonella-IL2 plus Gemcitabine/nab-Paclitaxel (GEM/nabP). Overall survival (OS), progression-free survival (PFS), safety, and biomarker data in each arm were compared to corresponding values for reference patients (SOC Controls) receiving care at the study site in the four years preceding the clinical trial (2016 to 2020). Four patients with stage IV pancreatic cancer were treated via Salspera's Expanded Access Program (EAP) using the Arm One regimen. **Results:** In total, 34 patients (30 in the trial, 4 via EAP) were enrolled: 26 received Salmonella-IL2 with FOLFIRINOX (average age 58.7 years, range 32-74, 54% born female) and eight received Salmonella-IL2 with GEM/NabP (average age 68 years, range 56-82, 54% born female). SOC Control patients comprised 37 administered FOLFIRINOX (average age 58 years; range 33-75 years; 46% born female) and 31 given GEM/nabP (average age 65.1 years; range 45-84 years; 42% born female). Patients receiving more than five doses of Salmonella-IL2 with FOLFIRINOX (n = 20) had a mPFS of 15 months vs. 5.8 months in control patients who had received only FOLFIRNOX ($p < 0.0001$, 95% CI, HR 0.3, Concordance Index 0.64). For those same compared cohorts, the mOS was 20.3 months vs. 11.5 months ($p = 0.07$, 95% CI. HR 0.59, Concordance Index 0.59). Only eight patients were enrolled in the GEM/NabP Arm thus limiting useful conclusions. Overall, 41 serious adverse events were noted and attributed to SOC chemotherapy agents but none to Salmonella-IL2. **Conclusions:** Addition of Salmonella-IL2 to FOLFIRINOX for treating stage IV pancreatic cancer is associated with increased mPFS and mOS. A multicenter, randomized, phase III trial is warranted. Clinical trial information: NCT04589234. Research Sponsor: None.

Initial safety and efficacy results from a first-in-human, phase 1/2 study of SAR445877, an anti-PD-1/IL-15 fusion protein, for patients with advanced solid tumors.

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Background: SAR445877 is a fusion protein of an PD-1 antibody combined with a detuned IL-15, designed to selectively expand and activate CD8+ T and NK cells expressing both PD-1 and IL-2/15Rβγ. Preclinical studies demonstrated the efficacy of SAR445877 in neoplastic models. Here, we present initial safety and efficacy observations from a first-in-human, dose escalation of SAR445877 monotherapy in patients (pts) with advanced solid tumors. **Methods:** This open-label, multicenter, Phase 1/2 study in adult pts with any type of measurable, advanced unresectable or metastatic solid tumors (NCT05584670) comprised two parts: dose escalation (Part 1) and dose expansion (Part 2). In Part 1, SAR445877 was administered intravenously at two dosing schedules (Q2W and QW). Pts with advanced solid tumors that do not typically respond or were resistant/refractory to immune checkpoint inhibitors (ICI), and with at least 1 measurable lesion per RECIST 1.1, were eligible. Tumor biopsy was performed at baseline and on treatment. The primary objective for Part 1 was safety. Secondary objectives included efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity. **Results:** Thirty-two pts (Q2W) and 17 pts (QW), respectively, were enrolled. Median lines of prior therapy were 3 for both schedules. The Q2W schedule was tested at 6 dose levels (DLs) and QW schedule at 3 DLs. Median exposure to SAR445877 was around 9 weeks (Q2W range: 2–55 weeks; QW range: 1–46 weeks). All pts reported at least one treatment-emergent adverse event (TEAE). Treatment-related AEs (TRAEs) were reported in 47 pts (Grade ≥3: 12 pts [Q2W]; Grade ≥3: 5 pts [QW]). Most common TRAE was cytokine release syndrome (CRS), which was mainly Grade 1 or 2. Six pts discontinued treatment due to any TEAEs. DLTs occurred in 4 pts in the Q2W cohort (n = 1 each metabolic acidosis, pneumonia, hyperbilirubinemia, and GI hemorrhage) and in 2 pts in the QW cohort (both CRS). Serious TEAEs were reported in 23 pts (Q2W) and 7 pts (QW). All toxicities were manageable/reversible, and no TEAEs leading to death were observed. Confirmed partial response was reported in 5 pts (Q2W) and in 2 pts (QW) bearing melanoma, CRC, SCC of the scalp, penile cancer, adnexal carcinoma, urothelial carcinoma, and myxofibrosarcoma, with benefits lasting > 1 year. Five of the 7 pts had progressed on prior immunotherapy. Stable disease ≥ 6 months was observed in 3 pts (Q2W) and 3 pts (QW). Antidrug antibodies (ADAs), detected in 23 pts (Q2W) and 13 pts (QW), did not correlate with clinical benefit or toxicity. A trend of dose dependent increase of cytokine (IFNγ, TNFα, IL-6, IL-8, IL-10) and chemokine (CCL2, CXCL10, MIP1α, MIP1ß) release were detected at both dosing schedules. **Conclusions:** SAR445877 monotherapy demonstrated a tolerable safety profile and promising antitumor activity in pts with advanced solid tumors unresponsive or resistant to ICI. Clinical trial information: NCT05584670. Research Sponsor: Sanofi.

SLAMF8 as a potential therapeutic target for modulating tumor-associated macrophages in colorectal cancer.

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Background: Reprogramming or repolarizing tumor-associated macrophages (TAMs) has emerged as a novel strategy in tumor immunotherapy, leveraging their remarkable plasticity. Our previous studies have demonstrated that SLAMF8, predominantly expressed in macrophages, is a promising biomarker for predicting the efficacy of immune checkpoint inhibitor (ICI) therapy in colorectal cancer (CRC). This study aims to elucidate further the regulatory role of SLAMF8 in TAMs and its influence on the tumor immune microenvironment. **Methods:** In vitro, M2 macrophage and TAM models were established to investigate the regulatory role of SLAMF8 in macrophage immunophenotypic transition and its impact on CD8+ T cell function using qRT-PCR, flow cytometry, and co-culture assays. Additionally, pathway enrichment analysis of RNA-seq data and western blotting were conducted to elucidate the underlying molecular mechanisms. In vivo, SLAMF8-specific small interfering RNA (siSLAMF8) was utilized to inhibit SLAMF8 expression in subcutaneous colorectal cancer (CRC) tumor models. Subsequent observations included tumor growth monitoring and analysis of immune cell infiltration via flow cytometry. Furthermore, two subcutaneous tumor models, one sensitive and one resistant to PD-1 therapy, were constructed to explore potential synergistic effects between SLAMF8 inhibition and anti-PD-1 treatment. **Results:** In vitro studies reveal that SLAMF8 facilitates the polarization of macrophages toward the M2 phenotype, contributing to the immunosuppressive characteristics of TAMs and dysfunction of CD8+ T cells. Inhibiting SLAMF8 in vivo significantly delayed colorectal cancer (CRC) progression. Flow cytometry analysis confirmed that the infiltration of anti-tumor TAMs (CD86+ F4/80+) and cytotoxic CD8+ T cells (IFNγ+ GZMB+ CD8+ T cells) was augmented, while the infiltration of pro-tumor TAMs (CD206+ F4/80+) and exhausted CD8+ T cells (PD1+ LAG3+ CD8+ T cells) was reduced in tumors treated with SLAMF8-specific small interfering RNA (siSLAMF8). Additionally, targeting SLAMF8 enhances the efficacy of anti-PD-1 therapy. Mechanistically, Western blotting experiments confirmed that the phosphorylation levels of key molecules in the PI3K/AKT and JAK/STAT3 signaling pathways were significantly increased in SLAMF8-overexpressing macrophages. **Conclusions:** Inhibition of SLAMF8 delays tumor growth, enhances the sensitization to ICI therapy, and reverses the immunosuppressive microenvironment by modulating TAMs via the PI3K/AKT and JAK/STAT3 pathways in CRC. These findings reveal the potential of SLAMF8 as a therapeutic target for immunotherapy focused on TAMs. Research Sponsor: National Natural Science Foundation of China; 82303970.

Preclinical development of GNTbm-38, a novel class I histone deacetylase inhibitor, while combined with anti-VEGFR TKI or anti-PD-1 Ab: Assessment of immune activation and immune memory in cancer immunotherapy.

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Background: Several clinical trials explored ICI-based combinations in MSS mCRC patients, and the promising outcomes are lacking. Histone deacetylase inhibitors (HDACis) for cancer therapy may boost antitumor immune activity, reduce immunosuppressive cells, and play a crucial role in controlling tumor progression. Therefore, rational drug combinations, containing class I HDACi or other immune-modulating drugs, may provide opportunities in immunotherapy. **Methods:** The activities of GMTbm-38 were assessed in vitro, including H3 acetylation and cancer cell growth inhibition, etc. The murine colon cancer CT-26 model was used to test antitumor efficacy in wild type and transgenic humanized PD1/PD-L1 mice. GNTbm-38 was combined with an anti-VEGFR TKI or murine/human PD1 antibody to test the antitumor synergistic effect. RNA-seq, flow cytometry, and IHC were performed to illustrate the potential mechanisms. **Results:** GNTbm-38 induced histone 3 acetylation and inhibited the cell growth of varieties of human cancer cells. By using CT-26 model, GNTbm-38 showed a superior efficacy profile in WT mice compared to immune-deficient mice. The antitumor activity related to induced immune activation and immune memory was dependent on $CD8^+$ T cell activation. Treatment with GNTbm-38 showed an increased number of intratumoral $CD8^+$ CTLs, a decreased number of MDSCs, and induced normalization of tumor vessels. GNTbm-38 substantially induced the expression of IFN-γ response genes and enhanced antigen processing and presentation signatures. GNTbm-38 acts as a TME reprogramming regulator in immunotherapy. When combined with TKI, GNTbm-38 significantly improved tumor response rate and survival rate through synergistic effect by normalizing tumor vessels, increasing tumor antigen presentation, increasing activated $CD8^+$ T cell infiltration into tumors, inducing memory T cell persistence, and inhibiting mobilization of immunosuppressive cells into tumors. Treatment with GNTbm-38 plus anti-PD-1 Ab in the CT-26 model showed greatly improved tumor response rate and survival rate with a strong synergistic effect. Furthermore, in B-hPD-1/hPD-L1 mice (humanized model) subcutaneously injected with B-hPD-L1 CT-26 cells, treatment of pembrolizumab and GNTbm-38 resulted in a 46.5% inhibition on tumor growth. Therefore, our data provided a strong rationale to explore the combination of GNTbm-38 with anti-VEGF TKI with or without ICI. **Conclusions:** Collectively, our data show that GNTbm-38 exhibits markedly superior pharmacokinetics, tolerability, and efficacy in animal models. GNTm-38 has been shown to display powerful induction of immune activation and immune memory in combination therapy with TKI/ICI against colon CT-26 cold tumor. Research Sponsor: Great Novel Therapeutics Biotech & Medicals Corporation (GNTbm).

Inhaled KB707, a novel HSV-based immunotherapy, as a monotherapy in patients with advanced solid tumor malignancies affecting the lungs: Efficacy and safety results from a phase 1/2 study.

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Background: The development of potent anti-tumor cytokines has been hindered by the systemic toxicity of intravenous administration. KB707 is a novel gene therapy designed to deliver high doses of cytokines to the local tumor microenvironment. The agent is a replication-defective herpes simplex virus type 1 (HSV-1)-based vector engineered to deliver human interleukin (IL)-12 and IL-2 with complementary anti-tumor effects. This replication-defective vector platform enables repeated dosing without significant toxicity or clinically relevant immunogenicity while allowing for localized, sustained IL-12 and IL-2 delivery to induce both innate and adaptive anti-tumor immunity. This study evaluates whether KB707 administered by inhalation will deliver efficacious dose to the lung while minimizing systemic exposure in advanced solid tumor patients with predominantly lung disease. **Methods:** KB707-02 is a Phase 1/2, open-label, multicenter, dose escalation (3+3 design) and expansion study of inhaled KB707 (NCT06228326). Eligible patients (pts) with at least one measurable lung lesion at screening and histological confirmation of advanced solid tumor malignancy in the lungs received nebulized KB707 once weekly for up to 3 weeks followed by treatment every 3 weeks. The primary objective is to assess safety and tolerability, with a secondary objective to evaluate preliminary efficacy per RECIST 1.1. **Results:** As of 08 Jan 2025, a total of 39 pts were enrolled and received at least one dose of inhaled KB707. Monotherapy dose escalation and expansion was completed. The doses evaluated were 10^8 and 10^9 PFU and the maximum tolerated dose (MTD) was not reached. Treatment-emergent adverse events have been consistent with known adverse event profiles of IL-2 and IL-12. The majority of treatment-related adverse events have been mild to moderate in severity and transient, with no Grade 4 or 5 adverse events observed. The 11 response-evaluable NSCLC pts were of advanced age (median 71 [54-77] years old) and heavily treated (4 median lines of prior therapies; all received at least 1 line of prior immunotherapy). The ORR was 27% (3/11) and DCR was 73% (8/11) with 7 out of 11 pts remaining on study. The response rate of the target lesions in the lungs was 36%. The median duration of response was not reached; treatment duration ranged from 10.3 to 33.3 weeks. **Conclusions:** KB707 administered by inhalation was safe and well tolerated. The MTD was not reached, and the monotherapy recommended Phase 2 dose is 10^9 PFU. Single agent anti-tumor effects were observed, including in heavily treated NSCLC patients. The study has been expanded to evaluate the combination of inhaled KB707 plus pembrolizumab, with or without chemotherapy, in advanced NSCLC pts. Enrollment in these combination expansion cohorts is ongoing. Clinical trial information: NCT06228326. Research Sponsor: Krystal Biotech Inc.

A generative model for the design of novel inhibitors targeting the PD-1/PD-L1 pathway.

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Background: The programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) signaling pathway plays a pivotal role in tumor immunosuppression. However, the design of de novo molecules with precise pharmacological and molecular properties remains a resource-intensive and financially demanding endeavor. It is hypothesized that generative models trained on molecular graph encodings can design novel inhibitors targeting the PD-1/PD-L1 pathway. Objective: This study aims to develop a generative model capable of designing novel, orally bioavailable inhibitors of the PD-1/PD-L1 pathway. **Methods:** A large language model was pre-trained on 1 million chemical structures derived from the ChEMBL database. Each structure was represented using the Simplified Molecular Input Line Entry System (SMILES) strings, which were further tokenized into discrete atomic and functional group-level tokens. The model employs an Average-Stochastic Gradient Descent Weight-Dropped Long Short-Term Memory (AWD-LSTM) architecture. Transfer learning was applied to fine-tune the pre-trained language model on the target chemical structures, enabling domain-specific adaptation for the desired application space. **Results:** The model demonstrated robust performance in generating chemically valid, unique, and novel inhibitors targeting the PD-1/PD-L1 pathway. It achieved a validity rate of 97%, a uniqueness rate of 96%, a novelty rate of 95%, and a diversity score of 76.04%. Additionally, the generated molecules exhibited favorable physicochemical properties, including a logarithm of the partition coefficient (LogP) of 4.52, atopological polar surface area (TPSA) of 113.06 Angstrom squared, an average of 9.62 rotatable bonds, 2.77 hydrogen bond donors, and 6.79 hydrogen bond acceptors. **Conclusions:** A generative model was developed to design novel, orally bioavailable inhibitors of the PD-1/PD-L1 pathway. This approach provides an efficient and automated tool for designing de novo molecules with precise molecular and pharmacological properties, potentially accelerating drug discovery in immuno-oncology. Research Sponsor: None.

Completed phase 1a dose escalation study of the first oral ENPP1 inhibitor RBS2418 immunotherapy in subjects with metastatic solid tumors.

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Background: ENPP1 clears cGAMP and ATP in the tumor microenvironment (TME). Its expression is associated with poor prognosis in cancer and development of metastases. ENPP1 inhibition can protect cGAMP and ATP from hydrolysis and reduce adenosine levels in the TME. These immune modulators are known to activate APCs and increase T-cell infiltration, promoting anticancer immunity. RBS2418 is a potent and selective oral first-in-class inhibitor of ENPP1. In this open-label, multi-site Phase 1a/b study, safety and efficacy of RBS2418 is being evaluated as monotherapy and in combination with pembrolizumab in advanced/metastatic solid tumors. **Methods:** The phase 1a dose escalation part comprised 100, 200, 400 and 800 mg BID dose levels of RBS2418 alone or in combination with pembrolizumab (200 mg IV q3w) in patients who have failed all approved treatments including immunotherapy using a 3+3 study design. Study objectives were to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical outcomes. Tumor and blood samples were collected to determine PK/PD and immune profiles using LC/MS, IF, IHC, TCR and RNAseq analyses. **Results:** Dose escalation is complete, andRBS2418 was safe and well tolerated at all dose levels with no DLTs (n = 24). Treatment durations range from 1 to 15 months to date, and no treatment-related grade 3 adverse effects (TRAEs) or serious AEs (SAEs) have been observed. A total of 21 grade 1 or grade 2 TRAEs were reported in 9 (37.5%) subjects; the most common TRAE was grade 1 fatigue. Median plasma concentrations of RBS2418 increased in a dose-proportional manner. Plasma and tumor concentrations of RBS2418 were maintained above the ENPP1 inhibition EC90 level in all patients and at all dose levels tested. Of 19 patients with adequate baseline tissue, pre-treatment ENPP1 and cGAS co-expression (EG+ phenotype, n = 8) in tumors correlated with RBS2418 treatment-associated immune activation and significantly improved progression-free-survival (PFS) as compared to EG- phenotype at baseline (n = 11). A switch from "cold" tumor to "hot" tumor phenotype was consistently observed in EG+ subjects. Disease control rate (DCR) was 75% (6/8) in EG+ and 9% (1/11) in EG- subjects. **Conclusions:** The Ph1a dose escalation study with oral RBS2418 alone, and with pembrolizumab has been completed. All doses were safe and well tolerated with no grade 3 TRAEs, SAEs or DLTs. RBS2418 plasma concentrations enabling full cGAMP protection was observed in all patients at all dose levels. Immune activation and clinical benefits strongly correlated with EG+ phenotype. RBS2418 achieved Phase 1a goals of safety, PK, PD, and target engagement and showed significant treatment benefits in advanced metastatic cancer patients. The results support further development of RBS2418. Phase 1b dose expansion is in progress and the first Phase 2a study has been initiated for the treatment of mCRC. Clinical trial information: NCT05270213. Research Sponsor: None.

Deep learning–powered H&E whole-slide image analysis of endothelial cells to characterize tumor vascular environment and correlate treatment outcome to immunotherapy.

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Background: Beyond their vascular function, endothelial cells (ECs) regulate tumor growth through recently described angiocrine signaling, influencing cancer progression and treatment outcomes. Here, we applied a deep learning model, which we validated using spatial transcriptomics data, to a pan-cancer dataset to analyze the EC distribution associated with the response to immuno-oncology (IO) treatments. **Methods:** An AI-powered H&E analyzer, Lunit SCOPE IO, quantifies tumor microenvironment EC density and tumor-infiltrating lymphocytes (TILs) density in cancer epithelium and stroma. We validated AI-powered cell type prediction by evaluating cell-specific gene expression through spatial transcriptomics (10x Xenium). 7,467 pan-carcinoma samples from The Cancer Genome Atlas (TCGA) were analyzed for EC distribution and overall survival (OS). From a previously described multi-center, multi-national pan-cancer cohort (Pan-IO, Shen et al JITC 2024), 1,654 patients were analyzed for IO treatment response. **Results:** We validated our AI prediction of cell types by demonstrating consistency with known cardinal gene expressions from spatial transcriptomic results, where 77.5% of AI-predicted endothelial cells (ECs) expressed VEGFR2 (compared to 6.9% in tumor cells (TCs)), while VEGFA expression was 2.8 times higher in TCs. Consistent with previous studies, EC density was highest in RCC and HCC, while lowest in pancreatic adenocarcinoma, melanoma, and cholangiocarcinoma. While EC and TIL density were not correlated pan-cancer ($r = 0.08$), exceptions were head and neck cancer ($r = 0.45$, $p < 0.001$) and pancreatic cancer ($r = 0.44$, $p < 0.001$). In the TCGA cohort, the high EC density was associated with prolonged OS (HR 0.84, $p < 0.001$). In contrast, within the Pan-IO cohort (HR 1.26, $p < 0.001$) and its lung cancer subgroup (HR 1.26, $p < 0.001$) high EC density was associated with shorter progression-free survival (PFS) on treatment with IO monotherapy. Moreover, the predictive impact of EC density varied by TIL status. In the Pan-IO cohort, EC density predicted PFS in both TIL-high (HR 1.40, $p < 0.001$) and TIL-low cancers (HR 1.33, $p < 0.001$). Among four groups divided by median values, the EC-low and TIL-high group showed the longest PFS (median PFS of EC/TIL high/low: 2.5m, high/high: 3.2m, low/low: 3.6m, low/high: 5.6m, $p < 0.001$). **Conclusions:** EC distribution varied among cancer types, and importantly high EC content strongly correlated with poor IO monotherapy response, including NSCLC. These findings support exploring immunotherapy combination strategies that include anti-endothelial approaches, which could encompass the emerging class of PD-1/VEGFR bispecifics, for tumors with high EC content. Early evidence was observed for this for HCC (Chon et al ASCO GI 2024), with a hazard ratio of 0.62 for high EC HCC for atezolizumab/bevacizumab. Research Sponsor: None.

SECN-15: A novel treatment option for patients with checkpoint inhibitor–resistant tumors by targeting Neuropilin-1 with antisense oligonucleotides.

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Background: SECN-15 is a high-affinity antisense oligonucleotide (ASO) targeting Neuropilin-1 (NRP1), a transmembrane protein that exerts a variety of protumorigenic functions by interacting with various receptors and ligands. NRP1 contributes to an immunosuppressive microenvironment, tumor growth, metastasis, and neoangiogenesis. The recent success of bispecific antibodies targeting PD-1/PD-L1 and VEGF such as ivonescimab has highlighted the potential of combining checkpoint inhibitors with anti-angiogenic approaches. Consequently, NRP1 represents a highly attractive target for treating patients with tumors that are resistant to or insufficiently responsive to checkpoint inhibitor therapies, such as gastric (GC) and breast cancer, where high NRP1 expression correlates with poor prognosis. **Methods:** NRP1-specific locked nucleic acid (LNA)-modified ASOs were identified using our OligoCreator platform. We assessed in vivo anti-tumor efficacy after systemic administration in various mouse tumor models as monotherapy and in combination with checkpoint inhibitors. Target downregulation was analyzed in tissues and in plasma by measuring soluble NRP1. Cell composition and transcriptome changes in tumors were analyzed using flow cytometry and RNA sequencing. Exaggerated pharmacology was investigated in a 28 non-GLP tolerability study in mice. In silico analyses of patient transcriptomics data were performed to prioritize indications for the upcoming Phase I/II clinical trial. **Results:** Systemic administration of NRP1-specific ASOs resulted in robust knockdown in tumors across various cell types, including macrophages and T cells. Soluble NRP1 levels were reduced in treated animals, serving as a target engagement biomarker. Tumor growth was delayed in the monotherapy setting, with several animals showing complete responses. Combining NRP1-specific ASOs with checkpoint inhibitors enhanced efficacy in models where checkpoint inhibitors alone had limited activity. Transcriptomic analysis showed upregulation of inflammatory genes and downregulation of extracellular matrix organization genes. No adverse effects were observed from persistent NRP1 downregulation in non-tumor-bearing mice. In silico analyses revealed that NRP1 expression is negatively associated with survival and increases in advanced GC stages. GC was selected as one of the priority indications for the upcoming Phase I/II clinical trial to investigate SECN-15's safety and efficacy as monotherapy and in combination with PD-1 blocking antibodies. **Conclusions:** Targeting NRP1 with ASOs is a promising therapeutic strategy for solid cancers. Combining NRP1 ASOs with ICIs significantly enhances anti-tumor efficacy, potentially overcoming current ICI therapy limitations. IND-enabling studies are underway to advance SECN-15 into clinical development. Research Sponsor: None.

Utilizing targeted intra-tumoral hyperthermia as an immunotherapy in immunogenically 'cold' tumor models.

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Background: Hyperthermia is an established adjunct in multimodal cancer treatments, with mechanisms including cell death, immune modulation, and vascular changes. Traditional hyperthermia applications are resource-intensive and often associated with patient morbidity, limiting their clinical accessibility. Gold nanorods (GNRs) offer a precise, minimally invasive alternative by leveraging near-infrared (NIR) light to deliver targeted hyperthermia therapy (THT). THT induces controlled tumor heating, promoting immunogenic cell death (ICD) and modulating the tumor microenvironment (TME) to enhance immune engagement. This study explores the synergistic potential of GNR-mediated THT with immunotherapies in immunogenically 'cold' tumors to achieve durable anti-tumor immunity. **Methods:** GNRs from Sona Nanotech Inc.™ were intratumorally injected and activated using NIR light to induce mild hyperthermia (42–48°C) for 5 minutes. Tumor responses were analyzed for cell death pathways and immune modulation. The immunogenic effects of THT were assessed alone and in combination with intratumoral interleukin-2 (i.t. IL-2) or systemic PD-1 immune checkpoint blockade. Immune cell infiltration, gene expression changes, and tumor growth kinetics were evaluated. **Results:** THT reduced tumor burden through cell death mechanisms, including upregulated ICD marked by calreticulin exposure within 48 hours. By 48 hours, CD45+ immune cell levels were increased, including increased levels of immunosuppressive M2 macrophages. While THT led to innate immune cell stimulations highlighted by gene expression upregulation in the STING cGAS pathway and enhanced M1 and dendritic cell levels, tumor regrowth was observed within six days post-treatment. To enhance THT's immunogenic effects, the therapy was combined with intratumoral interleukin-2 (i.t. IL-2) or systemic PD-1 immune checkpoint blockade. Sequential administration of i.t. IL-2 post-THT induced robust CD8+ T-cell infiltration and led to sustained tumor regression in both treated and distant tumors, accompanied by the emergence of memory T cells. However, IL-2-induced immunosuppressive T-reg populations were also sustained to tumor endpoint suggesting that therapy could be further enhanced. Additionally, PD-1 expression, which was upregulated in CD8+ T cells by THT, was targeted with systemic PD-1 inhibition, further augmenting immune engagement within the TME. **Conclusions:** These combinatory treatments demonstrated synergistic effects, promoting durable anti-tumor responses and immune memory. Collectively, GNR-mediated THT effectively reduces tumor burden and remodels the TME, potentiating systemic immunity and enhancing the impact of complementary immunotherapies. Research Sponsor: None.

Employing novel pan-cancer targets for immunotherapy in leukemias and solid tumors.

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Background: Acute myeloid leukemia (AML) and many solid tumors are difficult to treat. Tumor-associated protein targets that are the focus of cancer immunotherapy research are prone to on-target, off-tumor toxicity and antigen-negative relapse due to mutation or downregulation. Targeting cancer-specific markers less susceptible to resistance is key for safer therapies. Our research explores high mannose (Man 9) oligosaccharides and phosphatidylserine (PS) as non-protein targets. Man9 glycans are absent on healthy cells but are present in cancers like AML, breast, colon, and lung. PS, exposed during malignant transformation, is found on colon, prostate, and brain tumors. **Methods:** We have engineered trispecific T cell engagers (Man9/PS/CD3) to target Man9 and/or PS-positive cancers. We tested solid tumor cell lines (pancreatic, lung, colorectal) via flow cytometry and found that the dual affinity molecule (Man 9 x PS) had high binding to many solid tumors (Table 1). We assessed their efficacy *in vivo* and specificity using glycan microarray, and immunohistochemistry to confirm tumor specificity and predict favorable safety profiles. **Results:** Flow cytometry showed that our therapeutic molecules specifically bind to AML cells and various solid tumors while sparing healthy tissues. Glycan microarrays confirmed selective binding to abnormal glycans on cancer cells. Immunohistochemistry of FFPE tissues indicated tumor specificity and enrichment on cancer stem cells. *In vitro* studies (coculture of luciferase-transduced target cells with activated CD8+ T cells in the presence of absence of the T cell engager) demonstrated strong anti-leukemia activity against AML cell lines, with IC50 values of 5–10 pM. *In vivo* studies in human CD3 transgenic mice treated with intravenous doses of VTRU200 (Man9 x PS x CD3) showed significant therapeutic responses, based on *in vivo* bioluminescence imaging. **Conclusions:** Our data supports Man9 and PS as promising non-protein targets for pan-cancer immunotherapy. The dual targeting approach with T cell engagers reduces on-target, off-tumor toxicity and antigen-negative relapse, advancing a first-in-class Man9 x PS x CD3 trispecific T cell engager. We have also designed and validated a bispecific (Man9 x PS) chimeric antigen receptor (CAR) and research is ongoing for CAR-T therapy for pancreatic cancer. With IND-enabling studies underway, we aim to advance this breakthrough immunotherapy for AML and other cancers, targeting an IND submission within 18 months. Research Sponsor: Vitruviae; Alex's Lemonade Stand Foundation; Hyundai Hope on Wheels; National Cancer Institute.

Cell type	Man9/PS positivity (%)	Sample size
Mouse AML (cell line)	75-80	2
Human AML (cell line)	54-100	9
Human adult AML (primary)	35-98	8
Human pediatric AML (primary)	31-87	7
Human pediatric ALL (primary)	80-97	3
Human MM (cell line)	88-99.9	2
Human DLBCL (cell line)	56-93	3
Human pancreatic cancer (cell line)	46-95	3
Human colorectal cancer (cell line)	66-98	2
Human lung cancer (cell line)	82	1

Prevalence of the HPV, EBV, and TTV viral RNA in the plasma of patients with solid and hematologic neoplasms and the detection of a specific immune signature.

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Background: Epstein–Barr virus (EBV) and human papillomavirus (HPV) are considered human oncoviruses. In contrast, the torque teno virus (TTV) is not associated with any disease but its detection in circulation is associated with the status of the immune system. In this study, we examine the prevalence of active EBV, HPV and TTV viral RNA in patients treated for solid tumors or hematologic neoplasms. In addition, we compared differential expression of selected immune and inflammatory biomarkers between Virus positive (V+) and Virus negative (V-) cases using peripheral blood cell-free RNA (cfRNA). **Methods:** cfRNA was extracted from the peripheral blood of 581patients with a diagnosis of hematologic neoplasms and 558 patients with solid tumor. cfRNA was sequenced by NGS using a targeted RNA panel of 1600 genes and the viral RNA of TTV, EBV and HPV. Two thirds of the samples were used for training and one third for testing machine learning (ML) system (Bayesian/Random Forest) and exploring the presence of specific inflammatory profiles distinguishing V+ from V- patients. **Results:** RNA testing was selected to ensure that only active and proliferating viruses were detected. We detected TTV in 52/1139 (4.6%), EBV in 251/1139 (22%), and HPV in 68/1139 (6.0%). TTV with EBV codetection was observed in 11 samples (1%), and with HPV in 4 patients (0.4%). Co-detection of EBV with HPV was observed in 13 patients (1.1%). Using 90 biomarkers in ML algorithm can reliably distinguish V+ from V- with AUC of 0.725 (CI: 0.658-0.791) in the testing set. Significantly higher levels of B-cell markers are noted in V+ patients. PD-L1 mRNA was significantly ($P < 0.001$) higher in V+ patients, which suggests that these patients may be more responsive to checkpoint immune therapy. CD70 is also detected at high level in V+ patients ($P < 0.0001$). Upon comparing between the V+ groups (TTV, EBV, and HPV), there was no statistical difference between the three groups after adjusting for multiple testing. However, some difference in cytokine levels was noted between TTV-positive patients and HPV-positive patients. CD36, IFNA2 and IL17A were higher in TTV-positive cases as compared with HPV-positive cases (P-value 0.0003, 0.005 and 0.004, respectively). **Conclusions:** Globally, detectable active viruses in plasma of patients with cancer is relatively high (29%) and this detection is associated with a specific immune/inflammatory "activation" signature characterized by transcriptomic upregulation of PD-L1 and CD70 and increase in B-cells. There is no specific signature that distinguishes between the V+ subgroups [TTV vs EBV vs HPV]. However, transcriptionally, CD36, IFNA2 and IL17A upregulation distinguished TTV+ and HPV+ cases, a phenomenon that may indicate HPV ability to initiate an immunosuppressive tumor microenvironment. Research Sponsor: None.

Phase 1 trial of HCB101, a novel Fc-based anti-SIRPα-CD47 fusion protein, in subjects with advanced cancers.

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Background: CD47-targeting agents face challenges, including "on-target, off-tumor" toxicities affecting red blood cells, limited efficacy, and manufacturing complexities. Clinical holds and discontinued trials highlight these difficulties. These issues have constrained their therapeutic potential and broadened the need for better solutions. HCB101 is an engineered human SIRPα fused to human IgG4 crystallizable fragment (Fc) protein developed using the proprietary FBDB platform, blocks the signal of the SIRPα-CD47 pathway, enhancing macrophage-mediated phagocytosis. Preclinical studies show HCB101's potent antitumor activity across solid tumors and hematological malignancies. HCB101's safety profile in repeat-dose cynomolgus monkey toxicity studies revealed acceptable red blood cell or platelet abnormalities, supporting its potential as a best-of-the-kind SIRPα-CD47 directed immunotherapy. **Methods:** This Phase 1, open-label, dose-escalation trial evaluates HCB101's safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity in advanced solid tumors or non-Hodgkin lymphoma (NHL) in the US, Taiwan, and mainland China. Eligible adults have treatment-refractory cancers, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. The 3+3 dose-escalation Bayesian Optimal Interval (BOIN) design assesses dose-limiting toxicities (DLTs) in the first 28-day cycle. Secondary endpoints include objective response rate (ORR), duration of response, and progression-free survival. Exploratory endpoints include CD47 receptor occupancy (RO), correlating response, and immune cell infiltration (NCT05892718). **Results:** 32 participants (median age 61 years; 74% male) enrolled across 7 escalating cohorts (0.08–5.12 mg/kg, QW). Patients had a median of 4 prior regimens. 68% had solid tumors, and 32% had NHLs. HCB101 was well tolerated, only 1 DLT reported at 2.56 mg/kg dose level (G3 platelet decrease). The most common treatment related AEs were anemia (17%), all grade 1or 2, that did not require blood transfusion or other treatments. HCB101 systemic exposure increased in a dose-dependent manner. Preliminary efficacy showed 29% stable disease (6 patients) in 21 evaluable patients, with 2 patients have SD $>$ 16 wks, and 1 patient has SD $>$ 23 wks. Doses $\geq$1.28 mg/kg achieved $\geq$90% CD47 RO in peripheral T cells. **Conclusions:** HCB101 demonstrated an acceptable safety profile and preliminary antitumor activity in heavily pretreated advanced cancer patients. These findings support its further clinical development, including expansion cohorts to evaluate efficacy in specific tumor types or in combination with other agents. Clinical trial information: NCT05892718. Research Sponsor: None.

Role of p57 in cGAS-STING-mediated innate sensing and immunotherapy response in hepatocellular carcinoma.

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Background: Hyperactivation of cell cycle programs in cancer cells suppresses the antitumor immune response. The endogenous cyclin-dependent kinase inhibitor p57 is an important tumor suppressor and a potential therapeutic target for hepatocellular carcinoma (HCC). However, the role of p57 in modulating antitumor immunity to HCC remains unclear. **Methods:** We examined p57 expression in HCC patient samples prior to treatment with immune checkpoint inhibitors (ICIs) through immunohistochemistry (IHC). Multiple mice tumor models were constructed to explore the role of p57 on the recruitment of $CD8^+$ T cells in the tumor immune microenvironment. Through performing transcriptome sequencing, we analyzed the differential genes and activation pathways induced by p57 overexpression; through Real-Time Quantitative Polymerase Chain Reaction (RT-qPCR), western blot (WB) , Enzyme-Linked Immunosorbent Assay (ELISA), IHC, immunofluorescence (IF) , Flow Cytometry (FCM) and other molecular experimental methods, we verified the molecular mechanism of increasing $CD8^+$ T infiltration and elevating PD-L1 caused by p57 overexpression; Through constructing mice model and giving different treatments, we explored the anti-tumor efficacy of p57 overexpression combining with ICIs. **Results:** We found that patients with p57 expression had a higher disease control rate, correlating with the number of tumor infiltration $CD8^+$ T cells. Using mouse models, we discovered that p57 promoted $CD8^+$ T cells infiltration and that $CD8^+$ T cells were required for p57 to function as a tumor growth suppressor. Furthermore, through RNA-sequencing analysis and the multiplex assay *in vitro* and *in vivo*, we found that p57 induced chromosomal instability and subsequently stimulates cGAS-STING-type I IFN signaling, leading to upregulation of the chemokines CCL5 and CXCL10, which promoted $CD8^+$ T cell infiltration into the tumor microenvironment. Meanwhile, p57 also elevated the expression of PD-L1 on the surface of HCC cells. Moreover, combining p57 overexpression with anti-PD-1 treatment synergistically inhibited tumor growth *in vivo*. **Conclusions:** Our studies demonstrated that p57 may serve as a new biomarker for ICIs efficacy and that increasing p57 expression is a potential therapeutic strategy for improving the efficacy of immunotherapy in HCC patients. Research Sponsor: National Natural Science Foundation of China.

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

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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. for patients (pts) resistant to or refractory to PD-1/PD-L1 treatments, showing superior T/DC cell activity and in vivo anti-tumor efficacy compared to a combination of TIM-3 and PD-1 antibodies in preclinical studies. Here, we report the dose escalation and dose expansion results of LB1410 as monotherapy in patients with advanced solid tumors (Keyplus-001). **Methods:** Eligible patients were ≥18 years old with ECOG PS 0-1 and advanced solid tumors. Dose cohorts ranged from 0.001 mg/kg to 20 mg/kg IV Q2W: 0.001 mg/kg-1 mg/kg in an accelerated titration design, and 3 mg/kg - 20 mg/kg using a traditional 3+3 design. Selected dose levels were expanded in patients with advanced clear cell renal cell carcinoma (ccRCC) and cervical cancer (CC). The primary objective was safety, including dose-limiting toxicities (DLTs). Secondary/exploratory objectives included efficacy, pharmacokinetics (PK), and immunogenicity. **Results:** As of January 15, 2025, a total of 79 patients received LB1410 at doses ranging from 0.001 mg/kg to 20 mg/kg as of January 15, 2025. The median age was 59 years, and 70% of patients were male. All enrolled patients had multiple organ metastases or multiple metastases in a single organ and were heavily pretreated with anti-tumor therapies. Of the patients, 76.9% (60/79) had solid tumors that had failed standard therapies and were resistant or refractory to anti-PD-1/PD-L1 treatments. Treatment-related adverse events (TRAEs) occurred in 63.3% of patients. The most common TRAEs (≥10%) included anemia (24.1%), proteinuria (12.7%), increased alanine aminotransferase (11.4%), increased aspartate aminotransferase (11.4%), hyponatremia (10.1%), increased blood lactate dehydrogenase (10.1%), and weight loss (10.2%). Grade 3 TRAEs occurred in 7 patients, including 3 with hypokalemia, 2 with hypertension, 1 with hyponatremia, 1 with proteinuria, and 1 with pulmonary embolism. No dose-limiting toxicities (DLTs) were observed. On- treatment scan was available for 66 patients. The observed overall response rate (ORR) per RECIST 1.1 was 3/66 (4.5%), with 3 confirmed partial responses (PRs) in patients with ccRCC and CC. The disease control rate (DCR) was 45.5% (30/66). In patients with ccRCC, the ORR was 16.7% (1/6), and the DCR was 66.7% (4/6). In patients with CC, the ORR and DCR were both 66.7% (2/3). Of the 27 patients with stable disease, 3 had stable disease for nearly 12 months, and 2 of them are still receiving ongoing treatment in the study. **Conclusions:** LB1410 has a manageable safety profile and demonstrates potential efficacy at tolerable doses in heavily pretreated patients, particularly those with immune-oncology (IO)-refractory or resistant ccRCC and CC. Clinical trial information: NCT05357651. Research Sponsor: L&L Biopharma Co., Ltd., Shanghai, China.

Effect of KROS 101, a small molecule GITR ligand agonist, on T effector cells, T reg cells and intratumoral CD8 T cell cytotoxicity.

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Background: A small molecule was identified that stabilizes the trimerization of the glucacorticoid-induced tumor necrosis factor receptor (GITR) ligand which then leads to the trimerization of GITR and magnified signaling of GITR. GITR signaling of T cells results in T effector cell expansion and T reg reduction. An antagonist to the GITR ligand was also indentified which stabilizes the GITR ligand dimer formation preventing trimerization. **Methods:** Binding of KROS 101 to the GITR ligand was assessed and the binding region of GITR ligand to KROS was determined with targeted deletion of GITR. T cell suppression studies were performed with T cell proliferation assays and T cell cytotoxicity assays with glioblastoma target cells using patient derived PBMCs. Double humanized GITR/GITRL mice bearing B16-F10-LUC2 tumors were treated with KROS 101 or controls. Tumor-infiltrating lymphocytes were analyzed by flow cytometry and tumors assessed. **Results:** KROS 101 agonist binds to GITRL with high affinity with a K_D of 340nM by Surface Plasmon resonance. T cell suppression assay showed KROS 101 had peak proliferative induction of T effector cells at 25 uM concentration to 52% increase in proliferation, and peak proliferation induction of T effector cells with 1:1 ratio of T reg cells at 50uM concentration to 80% increase in proliferation of T effectors. KROS 101 treated T cell show enhanced effetor function and selectively target glioblastoma and cancer stem cells in vitro. KROS 101 enhances tumor immune infiltration by Increasing CD3+ T Cells, CD8+ T Cells, and M1 Macrophages While Reducing Tregs and Myeloid Cells *in vivo.* KROS 101 enhances cytotoxicity by increasing IFNγ and TNFα While Reducing TIGIT and TIM3 in CD4+ and CD8+ T Cells I*n Vivo*. **Conclusions:** KROS 101 is a GITR ligand agonist that increases T cell proliferation and increased cytotoxicity and reduces the T reg population more effectively than TRX 518 which is a therapeutic GITR antibody that was in clinical trial. Research Sponsor: None.

Machine learning–driven approaches for predicting T-cell–mediated immunity and beyond.

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Background: Recognition of peptides presented by the major histocompatibility complex (MHC) through the T cell receptor (TCR-pMHC) is crucial for T cell function, influencing disease conditions such as cancer, infections, and autoimmune disorders. Despite previous attempts, predictive models of TCR-pMHC specificity remain challenging. **Methods:** Inspired by recent breakthroughs in protein structure prediction achieved by deep neural networks, we explored structural modeling using AlphaFold 3 (AF3)-based AI-enabled computation as a potential avenue for predicting TCR epitope specificity. **Results:** We show that a specialized version of the neural network predictor AlphaFold can generate models of TCR-pMHC interactions, effectively distinguishing valid peptide epitopes from invalid ones with increasing accuracy. Strongly immunogenic epitopes could be identified and selected for vaccine development through in-silico high-throughput processes. Higher-affinity and specificity T cells could also be computationally designed to achieve improved efficacy and safety profiles for T cell therapy. An accurate TCR-pMHC prediction model is expected to significantly benefit T-cell-mediated immunotherapy and facilitate advanced drug design. **Conclusions:** Overall, precise prediction of T-cell immunogenicity holds substantial therapeutic potential, enabling the identification of peptide epitopes associated with tumors, infectious agents, and autoimmune diseases. Although much work remains before these predictions could achieve widespread practical utility, deep learning-based structural modeling represents a promising path toward the generalizable predictions of TCR-pMHC interactions and beyond. Research Sponsor: None.

Phase 1 study of DK2^{10} (EGFR), a tumor-targeted IL2 x IL10 dual immunocytokine, in advanced cancer patients: Dose escalation, immune activation, and safety results.

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Background: IL-2 induces anti-tumor immunity and toxicity, predominantly vascular leak syndrome (VLS), leading to edema, hypotension, organ toxicity, and therapy-inhibiting regulatory T cell (Treg) accumulation. DK2^{10} (EGFR) couples wild-type IL-2 to a high affinity variant of EBV IL-10 via an scFv that binds to epidermal growth factor receptors. The IL-10 component was designed to block IL-2 mediated cytokine release syndrome (CRS) and VLS while retaining T cell activation and proliferation and limiting Treg expansion. We report the clinical and pharmacodynamic results from the dose escalation in 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 3 times per week 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 every 3 cycles thereafter. RECIST 1.1 tumor responses were evaluated every 9 weeks. **Results:** 35 pts (14 RCC, 6 NSCLC, 9 CRC, 5 PDAC, 1 SCC) were enrolled. Median age was 63 yrs (range 35-80). Treatment-related AEs (TRAEs; any grade) in ≥ 10% pts were injection site reactions (63%), fever (40%), fatigue (31%), nausea (23%), anemia (17%), chills (17%), eosinophilia (14%), CRS (14%), diarrhea (11%); the majority were G1-2. G3 TRAEs included fatigue (n = 4), anemia (n = 3), syncope (n = 3) and single events of acute kidney injury, cellulitis, hypoalbuminemia, and lymphopenia. No DLTs were observed. While MTD was not exceeded, a dose proportional induction of IFNγ was observed through 8 mg but not at 16 mg. Therefore, higher doses were not explored, and a 12 mg dose level was introduced for dose optimization. No appreciable increase in IL-6, TNF-a, or IL-1β was seen other than 1 subject at 4 mg with G2 CRS and elevated IL-6. IFNγ and IL-5 were concomitantly induced proportional to dose level and reached saturation between levels 3 and 4, consistent with pK exposure of DK2^{10} (EGFR). Sustained IL-5 associated eosinophilia was observed and correlated with drug concentration but did not require intervention. IL-2 and IL-10 induction led to sustained elevation of IL-2Ra and IL-18, respectively. 33% of evaluable patients had a best ORR of SD. **Conclusions:** DK210 (EGFR) demonstrates strong IL-2 activity shown by IL-5 driven eosinophilia, shed IL-2Ra, T and NK cell proliferation and expansion but not Treg accumulation. These effects have been decoupled from IL-2 driven toxicity, confirming the hypothesis of the balancing effect of IL-10. These data support further evaluation in combination with T cell engagers, T cell therapeutics, and kinase inhibitors. Clinical trial information: NCT05704985. Research Sponsor: Deka Biosciences.

PCT1:CO-STIM TCR T-cells to overcome the hostile tumor micro-environment and target triple-negative breast cancer.

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Background: Adoptive T-cell therapy has demonstrated impressive efficacy in hematoligical cancers but the solid tumor micro-environment presents a unique challenge. However, recently TCR-T cell therapy has shown benefit in difficult-to-treat solid tumors and selection of specific tumor targets and control of the tumor micro-environment can unlock the broader potential of T cell therapy. Triple-negative breast cancer (TNBC) is a difficult-to-treat tumor as it lacks classical targets for hormone and antibody-based therapies. It harbors a highly immune-suppressive microenvironment and rarely responds to immune-checkpoint inhibitors. We sought to identify a novel target to make TNBC amenable for adoptive T-cell therapy with T-cell receptor (TCR)–engineered cells and applied a unique next-generation gene-engineering approach to make T-cells overcome the hostile microenvironment. **Methods:** (i) Discovery of TNBC-restricted target: We applied *in silico* analyses of >500 TNBC samples and >1,500 healthy tissues and validated findings with qRT-PCR and immune stainings of >300 TNBC samples as well as 40 healthy tissues. (ii) Discovery and selection of PCT1 TCR: We enriched ROPN1-specific TCRs from naïve repertoires and assessed specificity, sensitivity and performed preclinical safety studies. (iii) Development of TCR:CO-STIM technology to overcome immune suppression: we designed a panel of murine TCRs harboring different intracellular co-stimulatory domains, thereby providing additional stimulation to T cells aimed to overcome immune suppression in solid cancer. We tested their ability to extend anti-tumor durability in a murine melanoma model, performed comprehensive permutations to enable stable expression of fully human *TCR:CO:STIM* and applied it to multiple TCR specificities. **Results:** For TNBC, we identified that Ropporin (ROPN1), a protein expressed homogeneously in >90% of TNBC and persistent across disease stages but absent from healthy tissues, as an ideal target. We identified 13 clonal TCRs directed against 9 different ROPN1 epitopes. The lead TCR, termed *PCT1 TCR*, demonstrated high sensitivity and specificity towards ROPN1$^+$/HLA-A2$^+$ cell lines and patient-derived organoids in 3D. Our *TCR:CO-STIM* technology significantly improved duration of response in a murine model and improved T cell fitness. Notably, when repeatedly challenged with ROPN1$^+$/HLA-A2$^+$ TNBC cells, *PCT1:CO-STIM*, but not *PCT1* TCR T-cells, could resist up-regulation of T-cell exhaustion markers and retained tumor-killing capacity for 3-10 extra rounds of stimulation. Importantly, *PCT1:CO-STIM* did show any signs of tonic signaling nor crossreactivity nor alloreactivity towards any major HLA-I allele. **Conclusions:** *TCR:CO-STIM* technology has shown enhanced activity of a selective and specific TCR targeted at ROPN1 and we are progressing *PCT1:CO-STIM* to the clinic for the treatment of TNBC. Research Sponsor: None.

First-in-human mRNA CAR therapy: Correlative biomarker analysis from the MT-302 phase 1 study targeting TROP2 in patients with advanced epithelial tumors.

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Background: Outcomes for patients with epithelial cancers, including breast, lung and gastrointestinal tumors, remain poor particularly in advanced stages. MT-302, an mRNA-based chimeric antigen receptor (CAR) therapy, seeks to address this unmet need by reprogramming myeloid cells in vivo to recognize and kill TROP2-expressing tumors, recruit immune cells into tumor and induce systemic anti-tumor responses. Its CAR construct combines an anti-TROP2 scFv with truncated CD89 and becomes functionally active only upon association with FcRγ-expressing myeloid cells, ensuring precise immune engagement. Delivered as an off-the-shelf, repeatable intravenous treatment without the need for preconditioning, MT-302 overcomes the logistical and technical challenges of traditional cell and CAR therapies. MT-302 is being evaluated in a Phase 1, multicenter, open-label dose-escalation study (NCT05969041) in adults with advanced epithelial cancers expressing TROP2. Here, we present a correlative biomarker analysis from the first-in-human MT-302 study. **Methods:** Tumor biopsies and peripheral blood samples were collected pre- and post-dose. Biomarkers were evaluated utilizing advanced technologies including immunohistochemistry (IHC), Xenium and Hyperion imaging, flow cytometry, Chromium single-cell sequencing, T cell receptor sequencing and Meso Scale Discovery (MSD). These methods assessed TROP2 expression on cancer cells, TROP2 CAR expression within immune cells, systemic pharmacodynamic effects, immune cell infiltration and tumor microenvironment changes. **Results:** Results showed robust TROP2 CAR expression in circulating myeloid cells within hours of dosing. In tumor biopsies, CAR-positive myeloid cells co-localized with TROP2-expressing cancer cells. Post-dose tumor biopsies exhibited an increase in antigen presentation markers and pro-inflammatory signaling compared to baseline. MT-302 elicited systemic interferon-driven chemokine responses and reprogrammed the tumor immune microenvironment, promoting effector T cell recruitment. T cell receptor sequencing confirmed the emergence of novel T cell clones, consistent with adaptive immunity activation. Baseline IHC confirmed high TROP2 expression in enrolled patients, correlating with pharmacodynamic activity and immune reprogramming. **Conclusions:** This Phase 1 study provides the first evidence of successful delivery of mRNA-CAR therapy in humans. These biomarker findings demonstrate that MT-302 selectively engages myeloid cells and induces robust innate and adaptive anti-tumor pharmacodynamic responses, providing support for further investigation of MT-302's potential as a transformative treatment for patients with TROP2-expressing epithelial cancers. Clinical trial information: NCT05969041. Research Sponsor: None.

AI-driven biomarker prediction in oncology: Enhancing pathological image analysis with EXAONEPath.

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Background: Hematoxylin and eosin (H&E)-stained whole-slide images (WSIs) are fundamental in cancer diagnosis, providing critical insights into tumor morphology and the tumor microenvironment. Traditionally, biomarker assessment has relied on manual pathological evaluations, which are prone to human error and limited in scalability. Subtle biomarker expressions that evade visual detection further challenge conventional methods. **Methods:** We developed EXAONEPath, an artificial intelligence (AI) model trained on approximately 73,000 pan-cancer H&E-stained WSIs, to predict key cancer biomarkers. The model was evaluated across three major biomarker prediction tasks: Tumor Mutation Burden (TMB) Prediction in Lung Adenocarcinoma (LUAD): Using the TCGA-LUAD cohort, the model was trained (n=373), validated (n=47), and tested (n=47). Cross-institutional validation was conducted on Samsung Medical Center (SMC) (n=341) and an in-house dataset (n=254). EGFR Mutation Prediction in LUAD: The TCGA-LUAD dataset was split into training (n=382), validation (n=48), and test (n=48) sets. Additional validation was performed on the SMC LUAD cohort (n=341). Microsatellite Instability (MSI) Prediction in Colorectal Adenocarcinoma (CRC): A combined TCGA-STAD/TCGA-READ dataset was used for training (n=432), validation (n=55), and testing (n=54). The model was further validated on the SMC CRC cohort (n=974). **Results:** EXAONEPath demonstrated a strong predictive performance: TMB in LUAD: AUROC scores of 0.77 (TCGA), 0.81 (SMC), and 0.76 (in-house). EGFR Mutation in LUAD: AUROC scores of 0.78 (TCGA) and 0.84 (SMC). MSI in CRC: AUROC scores of 0.92 (TCGA) and 0.86 (SMC). **Conclusions:** EXAONEPath advances AI-driven pathological image analysis by automating biomarker prediction with high accuracy and cross-institutional robustness. Its strong performance in predicting clinically relevant biomarkers, including TMB, EGFR mutations, and MSI, highlights its potential for integration into precision oncology workflows. Future research will focus on expanding biomarker applications and enhancing cross-institutional generalizability for broader clinical impact. Research Sponsor: None.

Systemic antitumor virotherapy: Pre-clinical evaluation of tumor targeting, efficacy, and safety of lead candidate (CLD-401).

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Background: Systemic antitumor virotherapies are a promising modality of cancer immunotherapy. However, challenges include quick virus clearance from the bloodstream and potential off-target toxicity. To overcome these limitations, we have developed a novel strain called RT vaccinia virus which can be enveloped by an extracellular membrane during the manufacturing process and become resistant to human-complement. Our RTNova program, using extracellular enveloped RT (envRT) vaccinia viruses, focuses on generating potent systemic virotherapies with improved survival in circulation, tumor-specific targeting and enhanced therapeutic efficacy. **Methods:** The RT virus was genetically engineered to improve tumor selectivity and increase resistance to complement-mediated inactivation. The virus's ability to kill cancer cells was tested using the NCI-60 panel. The resistance of envRT vaccinia virus against human humoral immunity and its rapid spread were assessed ex-vivo. Targeting, biodistribution, therapeutic efficacy, and safety profile of selected envRT was evaluated in multiple animal models. **Results:** Out of several genetically modified RT Vaccinia viruses, we selected the one with three knockouts (3KO): TK (Thymidine kinase), A46R (immunomodulator), and VGF (Vaccinia virus growth factor). These genetic modifications significantly improved tumor-selective amplification and safety profile while maintaining therapeutic efficacy. The 3KO RT virus demonstrated strong oncolytic activity against more than 60 different human cancer cell lines NCI-60. Additionally, the 3KO RT virus was genetically engineered with CD55-domain fused with viral envelope A33R. This chimeric protein is designed to be expressed specifically in the extracellular envelope of the viral particle to robustly protect the envRT and viral progeny from inactivation by human complement. Targeting and biodistribution studies revealed that RT virus targeted all tumors after intravenous administration followed by significant tumor-selective amplification and spreading. In multiple immunocompetent mouse models, including metastatic lung cancer, RT virus demonstrated excellent tumor killing, and expression of selected therapeutic payload. **Conclusions:** We have developed a new scalable process to manufacture extracellular enveloped antitumor virotherapies and identified the first lead candidate from RTNova Platform, designated as CLD-401. This candidate, CLD-401, demonstrates promising therapeutic efficacy and safety in preclinical models. It effectively addresses the challenge of targeting and treating metastatic lung cancer by delivering Immunotherapeutics directly to disseminated tumors. Research Sponsor: None.

The predictive value of BRCA mutation on survival of cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis of phase III randomized clinical trials.

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Background: Immune checkpoint inhibitors (ICIs) have significantly enhanced survival for various types of cancers; however, resistance has limited the number of patients who can benefit from these regimens. Therefore, additional biomarkers are necessary to hopefully overcome resistance. Currently, the role of BRCA Mutation in ICI therapy remains poorly understood and controversial. **Methods:** We systematically searched PubMed, Web of Science, and Cochrane for phase III randomized clinical trials (RCTs) comparing ICI with placebo or standard-of-care cancer treatment stratified by BRCA mutation status as wildtype or mutant type up to 19 November 2024 regardless of cancer type or stage. The included phase III trials must report at least one of the following: Progression-free survival (PFS) or overall survival (OS); the meta-analysis was conducted using RevMan 5.4 pooling hazard ratio (HR) with 95% confidence intervals (CI) with a p-value of < 0.05 considered significant. **Results:** We conducted a meta-analysis of six phase III RCTs involving 3,328 patients: three trials investigated ovarian cancer, two investigated prostate cancer, and one investigated breast cancer. The analysis revealed that ICIs significantly improved both OS and PFS for patients with BRCA mutation, with HR of 0.61 (95% CI, 0.46 – 0.81, p = 0.0008) and 0.64 (95% CI, 0.47 – 0.89, p = 0.008), respectively. Furthermore, for patients with wildtype BRCA, the analysis revealed that using ICIs significantly improves PFS with HR of 0.81 (95% CI, 0.72 – 0.90, p = 0.0001). However, ICIs did not significantly improve overall survival, with HR of 0.94 (95% CI, 0.84 – 1.06, p = 0.33). **Conclusions:** The use of ICIs in cancer patients with BRCA mutation is associated with significant improvement in PFS and OS; however, in patients with wildtype BRCA, the use of ICIs showed only significant improvement in PFS with no significant improvement in OS. Research Sponsor: None.

Monotherapy of envafolimab in patients with high tumor mutational burden advanced solid tumors: Results from a phase II clinical trial.

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Background: Tumor mutational burden (TMB) has emerged as a predictive biomarker of immune checkpoint blockade response in cancers. Envafolimab, a humanized single-domain anti-PD-L1 antibody subcutaneous administration (s.c.), has been approved in China for the treatment of advanced solid tumors with MSI-H. The study is to explore the potential anti-tumor activity in patients with TMB-high (TMB-H) in China. **Methods:** The study consists of two parts. Part 1 is to explore the association of single agent envafolimab activity with tissue TMB (tTMB) measured by Onco500 assay in patients with advanced solid tumors. Part 2 will further evaluate the efficacy of envafolimab in advanced solid tumor patients base on the cutoff of TMB value identified from Part 1. Envafolimab is administrated s.c. at 400 mg every 4 weeks until disease progression, adverse events, or other reasons causing treatment discontinuation. Efficacy and safety are assessed in all patients who received at least one dose of envafolimab. tTMB is assessed by a central lab using SimcereDx Onco500 assay (Jiangsu Simcere Medical Device Co., Ltd, China). The primary endpoint was objective response rate (ORR) assessed by independent review committee per RECIST v1.1 criteria. **Results:** As of Nov 15, 2024, a total of 70 patients with advanced cancers (colorectal cancer [9,12.6%], cervical cancer and soft tissue sarcoma [8 each; 11.4%], and other 18 tumor types) have received envafolimab in Part 1. 30 (42.9%) patients had received ≥3 systemic therapies (median 2; range 1-19). Median follow-up time was 31.2 months (range: 0.6-36.8). 49 (70%) patients had at least one treatment-related adverse events (TRAEs), and 6 (8.6%) had grade 3 or 4 TRAEs. The most common TRAEs were anemia and alanine aminotransferase increased (9 each; 12.9%). Grade 2 decreased appetite was the only TRAE resulting in treatment discontinuation. No treatment-related death reported. TMB≥13 mut/Mb with Onco500 panel was selected as the threshold of TMB-H based on the clinical data and previous comparison of platforms for determining TMB value in patients. Key efficacy outcomes are presented (Table). ORR and DOR were higher in patients with tTMB ≥13mut/Mb (33.3% and 20.2m) than patients with tTMB < 13mut/Mb (4.3% and 3.8m). **Conclusions:** tTMB could be a useful predictive biomarker for response to envafolimab in patients with pre-treated advanced solid cancer. The Part 2 of this study is ongoing (NCT04891198). Clinical trial information: NCT04891198. Research Sponsor: None.

	tTMB≥13 mut/Mb (n = 24)	tTMB<13 mut/Mb (n = 46)
Objective response rate, n (%) [95% CI]	8 (33.3) [15.6-55.3]	2 (4.3) [0.5-14.8]
Complete / partial response	1 (4.2) / 7(29.2)	0 (0) / 2 (4.3)
Stable disease / progressive disease	2 (8.3) / 9 (37.5)	16 (34.8) / 24 (52.2)
Median DoR, months (95% CI)	20.2 (4.4-NE)	3.8 (NE-NE)
Median PFS, months (95% CI)	2.8 (1.8-8.7)	1.9 (1.8-3.6)
Median OS, months (95% CI)	13.2 (5.7-NE)	12.7 (7.4-18.2)

A phase 1 study of fixed-dose regimens of serplulimab, an anti-PD-1 antibody, in patients with advanced solid tumors.

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Background: Serplulimab is a recombinant humanized IgG4 monoclonal antibody targeting PD-1. A two-cohort phase 1 study was conducted to evaluate the safety of serplulimab monotherapy in patients with advanced solid tumors (NCT03468751). Findings from the dose-finding cohort has been previously reported at the 2022 ASCO Annual Meeting (No. e14560). Here we present results from the dose expansion cohort, in which fixed-dose regimens were evaluated. **Methods:** This multicenter phase 1 study enrolled patients with locally advanced or metastatic solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy is available. In the dose expansion cohort, patients received intravenous serplulimab at 200 mg Q2W, 300 mg Q3W, 400 mg Q4W, or 600 mg Q6W. The primary endpoints were adverse event profile and maximum tolerated dose (MTD). Secondary endpoints included pharmacokinetic (PK), immunogenicity, pharmacodynamics (PD), and efficacy. **Results:** As of data cut-off on Jan 5, 2024, 37 patients received at least one dose of serplulimab at 200 mg Q2W (n = 9), 300 mg Q3W (n = 9), 400 mg Q4W (n = 10), or 600 mg Q6W (n = 9). All patients were Asian, 70.3% male; median age was 60.0 yrs (range 33–88). Patients had head and neck cancer (n = 10, 27.0%), esophageal cancer (n = 6, 16.2%), colorectal cancer (n = 4, 10.8%) or other types of tumor. Most patients had metastatic disease (64.9%). All patients had prior systemic cancer treatment, including 4 (10.8%) with prior immunotherapy; 51.4% had ≥ 3 prior lines of therapy. All 37 patients were included in safety, PK, and PD analyses; 35 response-evaluable patients were included in efficacy analysis. No dose-limiting toxicity was reported, and MTD has not been determined. Treatment-related adverse events (TRAEs) were observed in 19 patients (51.4%), including 7 (18.9%) reporting grade ≥ 3 TRAE. TRAE incidence was similar across regimen groups. Following multiple infusions, the geometric mean $t_{1/2}$, ss was from 341.1–751.3 h, and geometric mean CL_{ss} was 0.006–0.009 L/h. Treatment-emergent anti-drug antibody (ADA) was detected in 7 (18.9%) patients. No difference in safety or PK was noted between ADA-positive and -negative patients. Profiles of PD-1 receptor occupancy in circulating $CD3^+$ T cells and interleukin-2 stimulation ratio were similar across dose groups, suggesting dose-independent functional blockade. Six patients (300 mg Q3W, 4; 400 mg Q4W, 2) achieved partial response, resulting in an ORR of 17.1%. Among the responders, 12-month duration of response rate was 66.7% (95% CI confidence interval, 19.5–90.4). Median progression-free survival was 2.3 months (95% CI, 1.9–5.1). **Conclusions:** Fixed-dose regimens of serplulimab showed favorable safety, PK, and PD characteristics and preliminary anti-tumor activity, supporting its further investigation. Clinical trial information: NCT03468751. Research Sponsor: Shanghai Henlius Biotech, Inc.

Consolidative camrelizumab following definitive concurrent chemoradiotherapy with involved-field irradiation in locally advanced esophageal squamous cell carcinoma: A single-arm phase 2 trial.

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Background: Definitive concurrent chemoradiotherapy (dCCRT) is considered the standard treatment for esophageal squamous cell carcinoma (ESCC). The PACIFIC study demonstrated that consolidation durvalumab significantly improves overall survival (OS) in patients with stage III non-small cell lung cancer (NSCLC) after dCCRT. However, the efficacy of consolidation immunotherapy in ESCC still remains unclear. We conducted a clinical trial to evaluate the efficacy of camrelizumab in patients with unresectable, locally advanced ESCC following dCCRT. **Methods:** This single-arm, phase 2 study enrolled patients with locally advanced ESCC. All participants received dCCRT with involved-field irradiation (IFI). Patients were treated with camrelizumab within 1 to 42 days after completing dCCRT. Camrelizumab was administered intravenously over 30 minutes every 2 weeks for up to 12 months. The primary endpoint was progression-free survival (PFS). Secondary endpoints included disease control rate (DCR), objective response rate (ORR), duration of response (DoR), overall survival (OS), and safety. **Results:** Thirty-five patients were enrolled between April 2020 and November 2023. Data from 32 patients were analyzed. As of December 22, 2024, the median follow-up was 25.1 months (IQR 5.5–56.8). Twelve patients experienced disease progression, and seven patients died. The DCR was 59.4%. The median PFS and OS were not reached. The 1- and 2-year PFS rates were 81.3% and 60.6%, respectively. The 1- and 2-year OS rates were 96.9% and 81.0%, respectively. The most common adverse events were grade 1-2. No grade 4 or 5 adverse events were reported. Pneumonia occurred in 31.3% of patients, all of whom experienced grade 1-2. **Conclusions:** Consolidative camrelizumab following definitive concurrent chemoradiotherapy with IFI shows promising efficacy and manageable toxicity in patients with unresectable locally advanced ESCC. Clinical trial information: NCT04286958. Research Sponsor: None.

Efficacy of low-dose nivolumab in advanced cancers: A retrospective analysis from medical oncology clinic in Eastern India.

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Background: Immunotherapy with PD-1/PDL1 blocking monoclonal antibodies has improved survival across several malignancies at different stages of these malignancies. But in Low- & middle-income countries, only 1-3% of cancer patients can access the standard dose of Immunotherapy. In this study, we aim to assess the response to low dose (LD) of Immunotherapy (nivolumab) across a broad range of malignancies. **Methods:** The study is a retrospective descriptive study. A total of 104 patients with advanced cancers were included in the study. Patients received a lower dose of Nivolumab (20/40 mg), ones in a 2-weekly-4weekly schedule, with treatment continued until disease progression or intolerable toxicity Their demographics, clinical profile, response to therapy, and adverse events were analyzed. **Results:** Male to female ratio was 5:1. The median age of patients was 49 years (range - 15 years to 78 years) and 70% patients were ECOG-PS 1-2 30% were ECOG-PS 3-4. Overall 56 patients were diagnosed with Squamous cell carcinoma (SCC) Head&neck, 15 had Renal cell carcinoma (RCC), 14 had Malignant melanoma, 5 had lung cancer, 4 with Hepatocellular carcinoma (HCC), 2 each of Gynecological cancer, Gall bladder cancer & CUP and 1 each of stomach cancer, Urinary bladder malignancy (HGUC), & Lymphoma. The most common metastatic sites were Lungs (46%) > Bone(27%) > Liver(15%). A total of 73 patients were included for assessment (received ≥2 cycles of Nivolumab). The overall response rate (ORR) was 39.7% and the Disease control rate (DCR) was 54.7%. Median PFS was 4 months (range - 1month to 26months) with Median OS being 11 months (range - 3months to 30months). Grade 3-4 adverse events were seen in 21/104(20%), the most common being dermatological (8/21) followed by anemia (7/21) and endocrinal AEs (4/21). **Conclusions:** Low-dose Nivolumab showed good response rates in advanced malignancies with manageable toxicities even in poor general condition. The cost of therapy was 1/5th to 1/10th of the standard dose of Nivolumab, highlighting its potential as a cost-effective alternative in resource-limited settings. Research Sponsor: None.

Response and survival analysis.

Charectiristics	N=73
Response rates	
CR	**5**
PR	**24**
SD	11
PD	33
ORR	**39.7%**
DCR	54.7%
Survival analysis	
mPFS	4 months
mOS	11.5 months

Immune related liver toxicity, management, and outcomes in ICI treated patients with advanced or metastatic cancers.

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Background: The impact of hepatic immune-related adverse events (HirAEs) and their management (mgmt) on clinical outcomes in patients receiving immune checkpoint inhibitors (ICI) has not been fully examined. We aimed to evaluate the association between HirAEs, their mgmt, and overall survival (OS) in ICI-treated cancer patients. **Methods:** Data were drawn from the Flatiron Health Research Database, an EHR-based database representing 280+ U.S. community oncology practices. Adults with advanced non-small cell lung cancer (aNSCLC), advanced melanoma (aMel), or metastatic renal cell carcinoma (mRCC) who initiated ICI between 1/1/16 - 12/31/20 were included and followed from ICI initiation to death, loss to follow-up, or end of the study period (12/31/2021). CTCAE Grade 2 or higher HirAEs and mgmt actions (immunosuppression using corticosteroids or other immunosuppressants, ICI-regimen holds, ICI-regimen discontinuations) and hospitalizations were curated from unstructured data. Cox regression was used to evaluate the association between HirAEs, their mgmt (both as time-varying covariates) and OS adjusting for baseline characteristics such as line of therapy and corticosteroid use. The earliest HirAE per patient was examined in OS analysis. **Results:** The study included 529 aNSCLC, 557 aMel, and 431 mRCC patients. For aNSCLC, aMel, and mRCC, respectively, 23.4%, 41.5%, and 30.9% experienced at least one HirAE, with a median time to onset of 59, 60, and 63 days. Among all HirAEs, elevated liver enzymes were the most common (72.9% in mRCC to 76.6% in aMel), followed by hepatitis (8.3% in aNSCLC to 12.6% in aMel). Immunosuppression was used to treat HirAEs in 47.6%, 57.6%, and 38.3% of aNSCLC, aMel, and mRCC patients with HirAEs. In aNSCLC, aMel, and mRCC, respectively, median survival was 12.7, 52.2, and 25.5 months and HirAEs were associated with a higher risk of all-cause mortality than no HirAEs [HR (95%CI): 1.8 (1.3-2.2); 1.4 (1.0-1.8); 1.3 (1.0-1.8)]. In mRCC, ICI-regimen holds and discontinuations were associated with a higher risk of all-cause mortality than immunosuppression alone (HR$\geq$4.0; P$\leq$0.05). In aNSCLC, HirAEs that led to hospitalization were associated with a higher risk of all-cause mortality regardless of HirAE mgmt (HR: 6.2; P $<$ 0.01). In aMel HirAE mgmt was not associated with OS. **Conclusions:** ICI-related HirAEs were associated with higher mortality in aNSCLC, aMel, and mRCC. HirAE mgmt impacted OS differently across cancer types, highlighting the need for tailored, timely, and multidisciplinary mgmt strategies in the ambulatory care setting, especially for cancers with poorer prognosis. Research Sponsor: Bristol Myers Squibb.

Baseline autoimmune diseases and characteristics of solid tumor patients on immune checkpoint inhibitor (ICI) therapy enrolled in a prospective study of immune-related adverse events (irAEs): SWOG S2013 (I-CHECKIT).

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Background: I-CHECKIT is a prospective observational study whose primary objective is to develop and independently validate a risk prediction model for the development of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher non-hematological irAEs in patients with solid tumors during the first year of treatment with ICI. **Methods:** Any patient initiating ICI per their treating oncologist and National Comprehensive Cancer Network guidelines was eligible to participate in this study. Eligibility criteria were unrestrictive and included participants with active autoimmune disease, decreased performance status, and any stage of cancer. One important exclusion criterion was planned receipt of ICI with chemo, biological or targeted therapy. Hormonal therapy and palliative radiation were allowed. The study is close to accrual in May 2024. Here we describe baseline participant characteristics. **Results:** Of a total of 2084 enrolled participants, 62 were ineligible. Community based NCORP sites enrolled the majority (n= 1,181, 56%) of participants. Participants were also enrolled from SWOG Latin American sites and Veteran Affairs (VA). 31% (n=656) had skin cancer (melanoma 90%, squamous 5% and Merkel cell 2.9%), 29% (n=604) had lung cancer and 12% (n=256) had kidney cancer. 17% (n=346) received combination ICI. The median age was 69.9 years. 64% were male, 90% (n=1866) were white, 8% (n=165) Hispanic/Latino, 5% (110) black, and 1% (16) Asian. 12% had performance status (PS) 2 or greater. 67% of the participants were overweight or obese. 9% (n=180) of the participants had active autoimmune disease such as rheumatoid arthritis, Type I diabetes, hypothyroidism, psoriasis, Crohn's, ulcerative colitis. 3% (n=54) had a history of autoimmune disease not currently requiring treatment. **Conclusions:** The I-CHECKIT observational study enrolled participants representative of a real-world population, as most of the participants were from community practices such as NCORP. Most participants had melanoma, resulting in a higher proportion of white participants. 9% of this population had baseline active autoimmune disease, a population excluded in initial clinical trials, highlighting the broader use of ICI in daily clinical practice. Clinical trial information: NCT04871542. Research Sponsor: NIH/NCI/NCORP grant UG1CA189974.

Baseline characteristics.

Age	All No (%)	Single ICI No (%)	Combo ICI No (%)	Skin No (%)	Lung No (%)
61-65 years	301 (14)	244 (14)	57 (16)	94 (14)	91 (15)
66+ years	1324 (64)	1119 (64)	205 (59)	372 (57)	430 (71)
PS					
0-1	1822 (88)	1523 (88)	299 (87)	607(93)	500(83)
2 and +	258 (12)	211 (12)	47 (14)	48 (7)	101 (17)
Active Autoimmune	180 (9)	153 (9)	27 (8)	54 (8)	51 (8)
Hypothyroidism	113 (9)	97 (9)	16 (8)	28 (8)	34 (8)
Type I Diabetes	15 (1)	10 (1)	5 (1)	5 (1)	4 (1)
Psoriasis	11 (1)	9 (1)	2 (1)	3 (0)	3 (0)

Immune related kidney toxicity, management, and outcomes in ICI treated patients with advanced or metastatic cancers.

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Background: The impact of kidney immune-related adverse events (KirAEs) and their management (mgmt) on clinical outcomes in patients receiving immune checkpoint inhibitors (ICI) has not been fully examined. We aimed to evaluate the association between KirAEs, their mgmt, and progression-free survival (PFS) and overall survival (OS) in ICI-treated cancer patients. **Methods:** Data were drawn from the Flatiron Health Research Database, an EHR-based database representing 280+ U.S. oncology practices. Adults with advanced non-small cell lung cancer (aNSCLC), advanced melanoma (aMel), or metastatic renal cell carcinoma (mRCC) who initiated ICI between 1/1/16 - 12/31/20 were included and followed from ICI initiation to death, loss to follow-up, or end of the study period (12/31/21). CTCAE Grade 2 or higher KirAEs and mgmt actions (immunosuppression using corticosteroids or other immunosuppressants, ICI-regimen holds, ICI-regimen discontinuations) and hospitalizations were curated from unstructured data. Cox regression was used to evaluate the association between KirAEs, their mgmt (both as time-varying covariates) and PFS and OS adjusting for baseline characteristics such as line of therapy and corticosteroid use. The earliest KirAE per patient was examined in survival analyses. **Results:** The study included 513 aNSCLC, 463 aMel, and 451 mRCC patients. For aNSCLC, aMel, and mRCC, respectively, 21.1%, 29.6%, and 33.9% experienced at least one KirAE, with a median time to onset of 70, 84, and 128 days. Nephritis ranged from 2.1% of KirAEs in aNSCLC to 4.6% in aMel. Elevated creatinine was the most common KirAE (23.6% in mRCC to 29.1% in aNSCLC), followed by acute kidney injury (20.5% in mRCC to 28.4% in aNSCLC). Immunosuppression was used to treat KirAEs in 67.6%, 80.3%, and 67.3% of aNSCLC, aMel, and mRCC patients with KirAEs. In aNSCLC, aMel, and mRCC, respectively, median OS was 17.1, 58.6, and 33.7 months, median PFS was 7.8, 8.9, and 9.5 months, and patients with KirAEs had longer PFS than those without KirAEs [HR (95%CI): 0.65 (0.51-0.83); 0.74 (0.57-0.97); 0.67 (0.53-0.84)]. In aNSCLC, KirAEs were associated with shorter OS [1.31 (0.98-1.74); P = 0.06]. In all cancers, KirAEs that occurred during hospitalization or led to hospitalization were associated with shorter OS (HR$\geq$2.84; P $<$ 0.02). KirAE mgmt was not associated with OS or PFS. **Conclusions:** Results suggest that while KirAEs might indicate an intensified immune response, their management and impact on survival vary across cancer types and call for cancer-specific strategies for early identification and management of KirAEs in the ambulatory care setting.
Research Sponsor: Bristol Myers Squibb.

Hepatotoxic adverse events with immune checkpoint inhibitors: Real world pharmacovigilance study using FAERS database.

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Background: Immunotherapy with immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment. With their increasing use, it is important to track and manage potential adverse events (AEs) . One such AE of ICI therapy is immune-mediated liver injury (ILICI). We aim to review the real-world data on ILICI using FDA Adverse Event Reporting System (FAERS) database. **Methods:** We queried FAERS using a search-by-product strategy on 22nd January 2025 and retrieved 224889 adverse events from 2013-2024. We employed 5 ICIs in the analysis (Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, and Ipilimumab). Descriptive statistics were carried out, and disproportionality analysis was done by calculating the reportable odds ratio (ROR) with 95% confidence intervals (CI). ROR was considered significant when the lower limit of the 95% CI was > 1. RORs were calculated for all hepatic events in general and Autoimmune Hepatitis (AIH), Drug-induced liver injury (DILI), Vanishing bile duct syndrome (VBDS), Primary biliary cholangitis (PBC), and Venooccluisve disease (VOD). **Results:** Total AEs from all included ICIs were 224889 and Hepatobiliary AEs constitute 9.2% of all AEs across all ICIs. ROR for any hepatic event is highest with Durvalumab i.e., 17.97 (16.08,20.08) in general as compared to the rest of the ICIs. AIH was seen highest with Ipilimumab with a ROR of 48.0 (43.1, 53.5); DILI with Pembrolizumab with a ROR of 5.8 (5.3, 6.4) (Overlapping CI); VBDS and PBC with Pembrolizumab with a ROR of 7.93 (4.9, 12.8) and 7.91 (4.46,14.03) respectively. Atezolizumab showed the highest ROR of 6.15 (3.6, 10.4) for VOD. (Table) **Conclusions:** This is the largest real-world study demonstrating specific hepatotoxic AEs with ICIs. Our results show varying patterns of hepatotoxicity with ICIs. Knowing these patterns will help us make better decisions in treating patients with ICIs. Research Sponsor: None.

Baseline characteristics, hepatic AEs and outcomes.

Baseline characteristic	Pembrolizumab (n= 67603)	Nivolumab (n=79283)	Atezolizumab (n=28521)	Durvalumab (n=13303)	Ipilimumab (n= 36179)
ROR for any hepatic event (95% CI)	8.24 (7.66,8.87)	7.46 (6.95, 8.01)	7.94 (7.08, 8.89)	17.97 (16.08, 20.08)	11.47 (10.54, 12.48)
ROR for AIH	21.34 (18.9, 24.0)	27.3 (24.8, 30.1)	22.3 (18.7, 26.5)	22.3 (18.7, 26.5)	48.0 (43.1, 53.5)
ROR for DILI	5.8 (5.3, 6.4)	3.74 (3.34, 4.19)	5.3 (4.61,6.29)	5.3 (4.61, 6.29)	5.04 (4.37, 5.82)
ROR for VBDS	7.93 (4.9, 12.8)	4.37 (2.41, 7.94)	0.5 (0.03, 8.8)	1.1 (0.15, 7.86)	2.61 (0.84, 8.1)
ROR for VOD	2.22 (1.2, 3.9)	3.79 (2.5, 5.6)	6.15 (3.6, 10.4)	0.44 (0.06, 3.12)	2.08 (0.9, 4.63)
ROR for PBC	7.91 (4.46,14.03)	3.37 (1.5, 7.5)	0.78 (0.04, 12.5)	1.51 (0.21, 11.1)	2.46 (0.6, 9.8)

Hepatic AEs included in the ROR calculation with these agents are Drug-Induced Liver Injury (DILI), Autoimmune hepatitis (AIH), Vanishing bile duct syndrome (VBDS), Veno-occlusive disease (VOD), Primary biliary cholangitis (PBC).

Impact of body mass index on immunotherapy outcomes and complications in solid tumor patients: A real-world evidence analysis.

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Background: Obesity alters immune function by modifying cytokine profiles and altering immune cells. Body mass index (BMI) influences cancer outcomes, including response to therapy. Several studies have shown that patients (pts) with a higher BMI respond better to immunotherapy (IT). This study assesses the impact of BMI on IT outcomes, admission risk, and major complications in pts with solid tumors. **Methods:** We utilized TriNetX, a global data platform from 104 healthcare institutions, to analyze outcomes in cancer pts on IT. Patients were categorized into two groups: BMI < 25 (n = 8,460) and BMI ≥ 25 (n = 13,631). Propensity Score Matching balanced groups for age, sex, race, comorbidities, smoking status, and alcohol use. Pts aged 18–65 years with solid tumors who received ≥1 IT dose were included with a 1-year follow-up. IT regimens included PD-L1, PD-1, or CTLA-4 antibodies. Cancers analyzed: esophagus, bladder, stomach, endometrium, melanoma, lung, kidney, head and neck, and breast. Outcomes included: ICU admissions, hospital admissions, mortality, heart failure, ischemic stroke/transient ischemic attack (TIA), venous thromboembolism (VTE), myocardial infarction, polyneuropathy, pneumonitis/pneumonia, and acute kidney injury (AKI). Risks were assessed using 1-year event-free survival and survival analysis. **Results:** After 1:1 PSM, the two groups each consisted of 8,460 pts, with balanced baseline variables. Post-matching, the mean age was ~52.5 ± 9 years, 56.0% were White, and 54.7% were female. A BMI < 25 was found to be a predictor of increased risk for multiple adverse outcomes. The 1-year risk-free survival was significantly lower in pts with BMI < 25 compared to those with BMI ≥ 25 for ischemic stroke/TIA (94.6% vs. 95.9%, log-rank $P < 0.01$), ICU admissions (83.3% vs. 89.05%, $P < 0.01$), hospital admissions (37.5% vs. 48.1%, $P < 0.01$), mortality (64.01% vs. 80.62%, $P < 0.01$), heart failure (84.3% vs. 87.6%, $P < 0.01$), and pneumonitis/pneumonia (79.1% vs. 84.9%, $P < 0.01$). However, there was no significant difference in the incidence of VTE, myocardial infarction, polyneuropathy, or AKI ($P > 0.05$). We performed several sensitivity analyses using different BMI cutoff groups and compared outcomes to the BMI < 25 group. In these balanced comparisons, we found similar trends except for an increased incidence of polyneuropathy in BMI ≥ 35 compared to BMI < 25 (1-year risk-free: 89.2% vs. 91.6%, $P < 0.01$) and in BMI ≥ 40 compared to BMI < 25 (1-year risk-free: 89.0% vs. 91.4%, $P < 0.01$). **Conclusions:** Our study provides real-world evidence on the types of complications experienced by pts with BMI < 25 when treated with IT for different types of solid tumors. It also explains, at least partly, the improved outcomes and tolerability observed in pts with higher BMI receiving IT. Based on our findings—such as the increased risk of hospital admissions and pneumonitis—we postulate that pts with low BMI may have a stronger inflammatory reaction to IT, leading to a higher incidence of complications. Research Sponsor: None.

Final analysis of a multicenter, open-label, phase 2 study evaluating the efficacy and safety of tislelizumab (TIS) in combination with fruquintinib (F) in patients (pts) with selected solid tumors.

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Background: Immunotherapy in combination with antiangiogenic agents has shown promising antitumor activity compared with either agent alone. We report efficacy and safety data from the final analysis of the phase 2 BGB-A317-Fruquintinib-201 trial evaluating the programmed cell death-1 antibody TIS combined with the selective vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 inhibitor F in pts with advanced solid tumors. **Methods:** This was an open-label, multicenter, two-part study with a safety run-in followed by dose-expansion. Eligible pts were adults with advanced or metastatic unresectable gastric cancer (GC), microsatellite stable colorectal cancer (MSS CRC), or locally advanced surgery-/radiotherapy-ineligible and programmed death ligand-1–positive (PD-L1+; defined as PD-L1 ≥1%) stage IIIB/IV non-small cell lung cancer (NSCLC). F 5 mg daily (3 weeks on, 1 week off) plus TIS (300 mg IV Q4W) was administered as second-line therapy for pts with GC, third-line therapy for pts with MSS CRC, and first-line therapy for pts with PD-L1+ NSCLC. The primary outcome measure was overall response rate (ORR) per RECIST v1.1. Secondary endpoints included other efficacy measures and safety. **Results:** The median study follow-up was 11.6 months (mo; range, 0.4-32.8). A total of 84 pts were enrolled (GC, n=31; MSS CRC, n=31; PD-L1+ NSCLC, n=22). One study treatment component-related death was reported in the GC cohort and 1 in the PD-L1+ NSCLC cohort. The recommended phase 2 dose was established at F 5 mg daily (3 weeks on, 1 week off) in combination with TIS with no observed dose-limiting toxicities. Efficacy and safety are reported in the Table. Any-grade treatment-emergent adverse events (TEAEs) occurred in 83 (98.8%) pts; proteinuria (32.1%), hypoalbuminemia (27.4%), and hypothyroidism (25.0%) were most common. 9/32 (10.7%) pts had grade ≥3 immune-mediated AEs. **Conclusions:** Despite the limited sample size, TIS+F demonstrated moderate antitumor activity in pts with advanced solid tumors, with manageable safety observed in pts with GC and MSS CRC. Further investigation of TIS+F is warranted in the GC and MSS CRC settings. Clinical trial information: NCT04716634. Research Sponsor: BeOne Ltd.

	GC (N=31)	MSS CRC (N=31)	PD-L1+ NSCLC (N=22)
ORR, n (%)	4 (12.9)	3 (9.7)	9 (40.1)
Disease control rate, n (%)	23 (74.2)	23 (74.2)	15 (68.2)
Clinical benefit rate, n (%)	10 (32.3)	12 (38.7)	13 (59.1)
Median progression-free survival, mo (95% CI)	4.6 (3.4, 7.4)	4.6 (3.6, 7.2)	15.6 (1.8, NE)
Median overall survival, mo (95% CI)	10.5 (5.2, 14.6)	10.0 (4.7, 15.2)	NR (6.0, NE)
Median duration of response, mo (95% CI)	NR (5.6, NE)	11.9 (3.7, NE)	NR (7.7, NE)
Grade ≥3 TRAE, n (%)	10 (32.3)	12 (38.7)	14 (63.6)
Serious TRAE, n (%)	3 (9.7)	3 (9.7)	9 (40.9)
TEAE leading to discontinuation of any study treatment, n (%)	5 (16.1)	3 (9.7)	7 (31.8)

CI, confidence interval; NE, not evaluable; NR, not reached.

Effects of UCHL1 on tolerogenic DC maturation and promotion of mregDC-Treg crosstalk to nullify anti–PD-L1 therapy.

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Background: Immune-checkpoint blockade (ICB) therapies have revolutionized cancer treatment, but such immunotherapy regimens fail in a subset of patients. Dendritic cells (DCs) are a heterogeneous group of professional antigen-presenting innate immune cells that activate adaptive immunity and determine the efficacy of immunotherapies. While they can also be hijacked by tumour-mediated factors to contribute to immune tolerance and tumor progression. However, little is known about the molecular mechanisms that drive the tolerogenic maturation of DCs in the tumor microenvironment (TME). **Methods:** We enrolled 85 patients with advanced hepatocellular carcinoma (HCC) exhibiting varying response to immunotherapy, and profiled the tumor ecosystems using a single-cell transcriptomes sequencing (scRNA-seq) and mass cytometry by time of flight (CyTOF) for 10 patients, and plasma protein level quantification, conducted both pre-treatment and post-treatment across all patients. We integrated our in-house data and 6 additional published scRNA-seq cohorts of 83 donors to generate a comprehensive landscape of cellular dynamics underlying different responses to immunotherapy. We verified the prognostic value in our in-house tumor microarray (TMA) of 342 patients. **Results:** UCHL1 overexpression nullifies anti-PD-L1 therapy by driving conventional DC transformation into mature DC enriched in immunoregulatory molecule (mregDC) via tolerogenic maturation and promoting mregDC and regulatory T (Treg) cell crosstalk, thereby restrains $CD8^+$ T anti-tumor immunity. Mechanistically, UCHL1 enhances glycolysis and lactate accumulation in TME by stabilizing HIF-1α, which further promotes SREBP2 activation and nuclear translocation in DC. We verified the positive correlations of UCHL1 with HIF-1α/VEGFα/LAMP3/FOXP3 in 342 patients with HCC. Genetic ablation or pharmacological inhibition of UCHL1 all reduce the mregDC and Treg accumulation, restore the immuno-surveillance of tumour-infiltrating lymphocytes, and safeguard anti-tumour immunity and efficacy of anti-PD-L1 therapy in mouse models. **Conclusions:** UCHL1 hijacks tolerogenic DC maturation and promotes mregDC-Treg crosstalk to nullify anti-PD-L1 therapy. Genetic ablation or pharmacological inhibition of UCHL1 unleash the immuno-surveillance of tumour-infiltrating lymphocytes, and safeguard the anti-tumor immunity. Plasma level of UCHL1 predicts the efficacy of anti-PD-L1 therapy in patients with HCC. Clinical trial information: NCT04649489. Research Sponsor: None.

A phase 1b/2, open-label study of selective Axl, Mer and CSF1R inhibitor adrixetinib (Q702) in combination with intravenous pembrolizumab in patients with selected advanced solid tumors: Results of a phase 1 study (QRNT-008).

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Background: Adrixetinib (Q702) is an orally administrated novel Axl/Mer/CSF1R tyrosine kinase inhibitor for which the primary mechanism of action of tumor regression is through immune-stimulating effects. The safety profile, pharmacokinetics (PK) and efficacy data for Q702 in combination with pembrolizumab are presented. **Methods:** QRNT-008 (NCT05438420) is an ongoing Phase 1b/2 multicenter, open-label, dose escalation and expansion study in patients with advanced esophageal, gastric/GEJ, hepatocellular, and cervical cancers who have progressed on prior anti-PD-1/PD-L1 treatment. The Part 1 dose escalation was guided by a mTPI design to determine the Part 2 dose of Q702 in combination with pembrolizumab. Patients received Q702 (week on/off dosing regimen) orally at 100 mg or 120 mg doses in combination with pembrolizumab (200 mg Q3W) intravenously in 42-day cycles. **Results:** As of the data cutoff (December 19th, 2024), 29 patients received Q702 plus pembrolizumab across 2 dose levels: 7 patients at 100 mg and 22 patients at 120 mg. The median number of prior lines of systemic therapy was 4 (range 1-7). Of the 29 patients (3 esophageal; 11 gastric; 2 GEJ; 9 hepatocellular; 4 cervical) who received Q702 across all doses, there were no treatment discontinuations due to the treatment-related AEs (TRAEs). Most common TRAEs ≥10% were AST increase (51.7%), ALT increase (41.3%), CPK increase (37.8%) and LDH increase (34.5%). One patient dosed at 120 mg experienced 1 DLT (G3 skin rash and G3 diarrhea). Adrixetinib PK analyses showed dose dependent increase of AUC_{0-last} and C_{max}. Overall response assessment (RECIST 1.1) included 1 confirmed complete response (CR) in a patient with metastatic gastric cancer (GC) and 6 patients with stable disease (SD) across multiple tumor types. Among 6 SD patients, 1 GC and 1 hepatocellular cancer (HCC) patient continued treatment for ≥24 weeks. **Conclusions:** Preliminary data from QRNT-008 study showed that selective Axl/Mer/CSF1R inhibitor Q702 plus pembrolizumab has a manageable safety profile. The Part 2 dose of Adrixetinib is confirmed at 120 mg. Preliminary anti-tumor activity in patients previously treated with anti-PD-1 supports further development of the combination. Clinical trial information: NCT05438420. Research Sponsor: Qurient Co., Ltd.

Outcomes of conversion surgery after immune checkpoint inhibitor-based combination therapy in initially unresectable hepatocellular carcinoma: A retrospective cohort study.

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Background: Hepatocellular carcinoma (HCC) has a high incidence rate and is often asymptomatic in its early stages. Combination therapies using immune checkpoint inhibitors (ICIs) have demonstrated survival benefits and high objective response rates, offering hope for conversion surgery in patients with initially unresectable HCC. We aimed to investigate the oncological outcomes of conversion surgery compared to those with continuing systemic treatment alone in patients who responded well to ICIs-based therapy, as well as the surgical outcomes associated with conversion surgery. **Methods:** We consecutively enrolled patients diagnosed with HCC between January 1, 2019 and April 1, 2024. These patients received treatment with ICIs combined with either anti-VEGF antibodies or tyrosine kinase inhibitors. Tumor response and resectability were assessed every 2 months. Patients who responded positively and met the criteria for conversion surgery were included. **Results:** Among 613 patients with initially unresectable HCC, 136 achieved conversion and met the surgical resection criteria during combination therapy. The median follow-up time was 26.9 and 42.5 months for the surgery and non-surgery groups, respectively. The median PFS was 29.1 months in the surgery group versus 11.2 months in the non-surgery group ($P < 0.0001$, hazard ratio [HR] = 0.40 [0.25–0.63]). The median OS was 50.8 months in the surgery group, compared to 25.8 months in the non-surgery group ($P < 0.0001$, HR = 0.27 [0.15–0.47]). The median RFS was 18.7 months in the surgery group. Multivariate Cox regression analysis indicated that conversion surgery was independently associated with improved OS and PFS ($P < 0.001$), and continuing the original treatment post-surgery significantly influenced OS and RFS. **Conclusions:** Conversion surgery after meeting the surgical criteria during immunotherapy provides significant prognostic benefits for patients with initially unresectable HCC, demonstrating high safety and R0 resection rates. For those specifically selected based on their response to immunotherapy and undergoing conversion surgery, promptly resuming the original treatment after surgery is necessary. Our results emphasize the importance of continuing immunotherapy post-conversion surgery to prevent recurrence in patients who respond to immunotherapy. Research Sponsor: None.

Phase I/II study of the EP4 antagonist vorbipiprant combined with anti-PD-1 immunotherapy: Safety and efficacy results in metastatic gastrointestinal non-colorectal cancers.

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Background: Novel combination strategies are being explored to enhance the effectiveness of immune checkpoint inhibitors (ICIs). Prostaglandin E2, through its receptor 4 (EP4), is a major contributor to immunosuppression in the tumor microenvironment. In a dose-response phase I/II study, the EP4 antagonist vorbipiprant (CR6086) combined with PD-1 blockade was well tolerated and showed promising efficacy in refractory mismatch-repair-proficient/microsatellite stable metastatic colorectal cancer (CRC) (Pietrantonio et al, Clin Cancer Res 2024). Here we report the results from a study extension in non-colorectal gastrointestinal (GI) cancers with the vorbipiprant dose selected for further development in combination with immunotherapy. **Methods:** Twenty-seven adult patients (pts) with metastatic non-colorectal GI cancers, ECOG PS $\leq$1, and $\geq$1 prior treatment line were included in 3 cohorts (9 pts each): gastric cancer (GC) with PD-L1 Combined Positive Score (CPS) $\geq$5 (cohort A), GC with PD-L1 CPS $<$ 5 (cohort B), and GI cancers other than CRC and GC (cohort C). Pts receive oral vorbipiprant (90 mg twice daily) plus iv balstilimab (3 mg/kg every 2 weeks) until disease progression, unacceptable toxicity or death. Primary endpoints are safety and disease control rate (DCR) per RECIST 1.1. Secondary endpoints include objective response rate, progression-free and overall survival (ORR, PFS, OS). Exploratory endpoints include tissue and blood biomarkers. **Results:** At a cutoff date of November 20, 2024, enrolment is completed. In cohort C, we enrolled: 5 BTC, 2 pancreatic and 2 ampullary cancer patients. Overall, median age was 61 (interquartile range: 55-68) years, similar among cohorts; 70% were men, with a slightly higher prevalence in Cohort A; the median number of prior treatment lines was 3 (IQR: 2-4) overall and in gastric cohorts, and 2 (IQR: 2-3) in other GI cancers cohort. Prior ICIs were administered in 44%, 22% and 11% in Cohort A, B and C, respectively. No treatment-related serious or grade $>$ 3 adverse events were reported. Promising activity was observed. In cohort A, 3 pts had a partial response (PR), 2 of them still ongoing and 2 lasting more than 6 months; in addition, 1 pt had stable disease (SD). In cohort B, 4 pts had SD, 1 of them still ongoing and 2 lasting more than 6 months. In cohort C, 1 pt with pancreatic cancer had a PR, still ongoing for $>$ 6 months; in addition, 1 BTC patient had SD. Median PFS and OS were: 4,5 and 9,7 months in Cohort A, 1,8 and 6,8 months in Cohort B, 2,0 and 4,5 months in Cohort C. Responses occurred irrespective of MSI/MMR status and prior exposure to ICIs. **Conclusions:** Vorbipiprant combined with PD-1 blockade was well tolerated and showed signs of activity in non-colorectal GI cancers, thus confirming a broader spectrum of activity on top of the results in MSS CRC. Clinical trial information: NCT05205330. Research Sponsor: Rottapharm Biotech.

Bispecific innate cell engager (ICE) AFM24 in combination with atezolizumab in patients with advanced/metastatic *EGFR*-expressing non-small cell lung cancer (NSCLC) without driver mutations: Initial results from a phase 2a study.

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Background: Novel treatments are needed for patients with advanced/metastatic NSCLC without actionable driver mutations who progress after prior therapies including checkpoint inhibitors (CPI) and platinum-based chemotherapy. AFM24 is a tetravalent, bispecific ICE that binds CD16A on NK cells and macrophages and EGFR on solid tumors, redirecting and enhancing the innate and possibly the adaptive immune response. The *EGFR*-wildtype (*EGFR*-WT) NSCLC expansion cohort of the Phase 1/2a study (NCT05109442) is evaluating the combination of AFM24 and atezolizumab. **Methods:** AFM24 is given weekly at 480 mg intravenously (IV) in combination with 840 mg atezolizumab IV fortnightly to patients with advanced or metastatic *EGFR*-WT NSCLC who progressed on ≥1 prior line of therapy, including at least a platinum doublet and a CPI. The primary endpoint is overall response rate (ORR) by RECIST v1.1 by Investigator assessment. Secondary endpoints include safety, pharmacokinetics, and immunogenicity. Treatment is given in 28-day cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal of consent. **Results:** As of 15 January 2025, 43 patients received AFM24 and atezolizumab for a mean (range) duration of 19.6 (1–78) weeks. Median (range) age is 67 (40–79) years; 72% male; all patients had an ECOG performance status of 0 (14%) or 1 (86%). Median (range) number of prior lines is 2 (1–7). All patients had discontinued their previous CPI treatment due to progressive disease. The combination was well tolerated with no unexpected toxicities; infusion-related reactions, the most common adverse events (AE), were reported in 54% of patients (28 Grade 1–2, 4 Grade 3). Most common ≥G3 treatment-related AEs were ALT/AST elevations in 2 patients, all fully resolved. The 35 response-evaluable patients showed an ORR of 23% (8 responses: 1 complete response, 7 partial responses), tumor shrinkage in 46% (16/35) and a disease control rate (DCR) of 77%. Of the 8 responders, 6 had never achieved an objective response on prior CPIs. Preliminary median progression-free survival (PFS) is 5.5 months (95% CI 2.9–7.4), with 29% of patients still on treatment. **Conclusions:** AFM24 in combination with atezolizumab shows promising clinical efficacy in patients who failed prior treatment including platinum-based chemotherapy and CPI. Patients showed a tolerable and well-managed safety profile. A considerable DCR of 77%, with some long, sustained responses was observed. Confirmed responses were achieved in patients who had not responded to prior CPI. This combination treatment approach could offer a promising chemotherapy-free alternative to patients who have exhausted the available therapeutic options and could provide a strategy to overcome resistance to prior CPI. Clinical trial information: NCT05109442. Research Sponsor: Affimed GmbH.

Combination of bispecific innate cell engager (ICE) AFM24 with atezolizumab in patients with advanced/metastatic non-small cell lung cancer (NSCLC) with *EGFR* kinase domain mutations (*EGFR*mut): Initial results from a phase 2a study.

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Background: Immune checkpoint inhibitor (ICI) monotherapy has shown limited activity against advanced *EGFR*mut NSCLC. However, combinatorial approaches may enhance the clinical outcomes and are under evaluation. AFM24 is a tetravalent, bispecific ICE that binds CD16A on NK cells and macrophages and EGFR on solid tumors, redirecting and enhancing immune responses towards EGFR-expressing tumors. Atezolizumab, an anti-PD-L1 antibody, has been approved in patients with various solid tumors. The *EGFR*mut NSCLC expansion cohort of this Phase 1/2a study explores a possible synergistic effect of AFM24 in combination with atezolizumab in heavily pretreated patients with NSCLC *EGFR*mut (NCT05109442). **Methods:** AFM24 is given weekly at 480 mg intravenously (IV) in combination with 840 mg atezolizumab IV fortnightly to patients with advanced or metastatic *EGFR*mut NSCLC who progressed on ≥1 prior line of therapy, including ≥1 prior TKI. The primary endpoint is overall response rate (ORR) by RECIST v1.1 by Investigator assessment. Secondary endpoints include safety, pharmacokinetics, and immunogenicity. Treatment is given in 28-day cycles until disease progression, intolerable toxicity, investigator discretion, or patient withdrawal of consent. **Results:** As of 15 January 2025, 28 patients received AFM24 and atezolizumab for a mean (range) duration of 21.7 (2–65) weeks. Median (range) age is 65 years (32–83); 67.9% were female. All patients had received prior *EGFR*-specific TKI, 82% had received platinum-based chemotherapy and 75% 3rd gen TKIs. Patients received a median (range) of 3 (1–8) prior lines of treatment. The combination was well tolerated with no new or unexpected toxicities observed compared to each single agent. The most common treatment-related adverse events (TRAE) were infusion-related reactions in 64% of patients (19 Grade 1–2, 1 Grade 3). 9 patients had ≥G3 TRAEs, the most common being neutropenia/neutrophil count decrease, with no associated infections. No other immune TRAEs were reported. The 22 response-evaluable patients achieved an ORR of 23% (1 CR, 3 PRs, 1 unconfirmed PR), a DCR of 64% and tumor shrinkage in 50% of patients. Responses were deepening over time in 3 patients. With a median follow-up of 9 months, the median PFS was 5.5 months (95% CI 1.9–not-evaluable). 6 (27%) patients have received treatment for over 10 months. **Conclusions:** AFM24 combined with atezolizumab demonstrated encouraging clinical efficacy in patients with *EGFR*mut NSCLC who had exhausted prior lines of therapy. Treatment showed a well-managed safety profile. This approach potentially offers a feasible, chemotherapy-free therapeutic option for the *EGFR*mut NSCLC patients who have progressed to prior TKIs and platinum-based chemotherapy and warrants further evaluation. Clinical trial information: NCT05109442. Research Sponsor: None.

Primary efficacy and safety results of BAT1308, a PD-1 inhibitor, + chemotherapy ± bevacizumab in phase 2 trial for persistent, recurrent, or metastatic cervical cancer.

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Background: BAT1308 is a fully humanized and high-affinity anti-PD-1 IgG4κ antibody. Previous phase 1 study demonstrated BAT1308 had a promising efficacy in patients with advanced cervical cancer. Here we present the primary safety and efficacy results in phase 2 study for BAT1308 combined with platinum-based chemotherapy ± bevacizumab as first-line therapy for PD-L1–positive persistent, recurrent, or metastatic cervical cancer. **Methods:** In this multicenter, single-arm, open-label, phase 2 study, eligible patients were ≥18 to ≤75 years of age with PD-L1 CPS ≥1, FIGO Stage IVB cervical cancer, who did not receive prior systemic anti-tumor therapy for persistent, recurrent or metastatic cervical cancer and not amenable to curative treatment. Patients received BAT1308 (300 mg Q3W for up to 24 months) plus platinum-based chemotherapy (paclitaxel 175 mg/m^2 + cisplatin 50 mg/ m^2 or carboplatin AUC 5) and, per investigator discretion, bevacizumab (15 mg/kg). The primary endpoint was safety. The major secondary endpoint was objective response rate assessed by investigator according to RECIST 1.1. **Results:** As of January 7, 2025, a total of 29 patients were enrolled, with a median age of 53 years (range 32-69), 20 (69.0%) patients had ECOG performance status of 1, 15 (50.7%) patients with PD-L1 CPS ≥ 10, 24 (82.8%) patients had squamous-cell carcinoma, 17 (58.6%) patients received previous neoadjuvant or adjuvant chemotherapy or chemoradiotherapy with a paclitaxel + platinum regimen, 7 (24.1%) patients had previous untreated metastatic disease at trial entry. Bevacizumab was used by 23 (79.3%) patients in this phase II study. All 29 subjects received combination therapy. 27 subjects completed at least one efficacy assessment. The ORR was 74.1%, with a confirmed ORR of 70.4%. The complete response rate was 11.1%, and the disease control rate was 100%. Currently, 16 subjects remain on treatment. Among those who discontinued the study, 8 withdrew informed consent, 4 experienced disease progression, and 1 died. The 6-month, 9-month, and 12 -month PFS rates were 83.4%, 78.8%, and 78.8% respectively. The median PFS has not yet been reached. The most common adverse events were anemia (82.8%), white blood cell decreased (51.7%), alopecia (51.7%), thrombocytopenia (48.3%), and neutropenia (44.8%). Grade 3 and above adverse events occurred in 72.4% of 29 patients, and ≥ Grade 3 irAEs observed in 3 (10.3%) patients. Serious adverse events occurred in 44.8% of the patients. **Conclusions:** BAT1308 combined with platinum-based chemotherapy ± Bevacizumab as first-line therapy showed durable anti-tumor activity and manageable safety profile for PD-L1-positive (CPS ≥ 1) persistent, recurrent or metastatic cervical cancer. These data are consistent with the earlier results and provide support for further studies. Clinical trial information: NCT06123884. Research Sponsor: Bio-Thera Solutions, Ltd.

Neoadjuvant serplulimab with concurrent chemoradiotherapy in resectable esophagogastric junction adenocarcinoma: Phase 2 updated results.

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Background: This study evaluated the efficacy and safety of neoadjuvant Serplulimab combined with concurrent chemoradiotherapy for locally advanced resectable esophagogastric junction (EGJ) adenocarcinoma. **Methods:** Eligible patients with resectable EGJ (cT3-4 or N+M0) adenocarcinoma received neoadjuvant Serplulimab (300 mg) plus SOX (oxaliplatin 130 mg/㎡; TS1 40-60 mg) for the first cycle, followed by Serplulimab with concurrent chemoradiotherapy (oxaliplatin 100 mg/㎡, TS1 40-60 mg; radiotherapy dose 45 Gy/ 25 fractions) during the second and third cycles. Surgery was performed 6-8 weeks after chemoradiotherapy. Tissue and blood samples were collected for genetic analysis. Primary endpoints included pathological complete response (pCR) and major pathological response (MPR). **Results:** From March 2023 to November 2024, 24 patients were enrolled and 19 patients underwent radical resection. The R0 rate was 100%. pCR rate was 26.3%, MPR rate was 36.8%. T downstaging rate 78.9%, ypN0 89.5%. The median DFS was not reached. Microsatellite stable status was 100%. PD-L1 CPS expression: <1 (5.3%), 1-5 (42%), >5 (52.6%), >10 (31.6%). PD-L1 expression was associated with pathological response, with MPR rates of 57.1% for CPS ≥ 5 and 14.3% for CPS <5. Minimal residual disease positivity (MDR+) before enrollment was 68.7%, and 6 MRD+ patients converted to MRD- after neoadjuvant therapy. Grade ≥ 3 adverse events occurred in 33.3% of patients, with manageable treatment-related adverse events. **Conclusions:** Neoadjuvant Serplulimab with concurrent chemoradiotherapy showed promising efficacy for locally advanced resectable EGJ adenocarcinoma. Improved R0 and ypN0 rate may change the surgical procedure in the future. Follow-up will assess correlations between biomarkers and outcomes. Clinical trial information: NCT05918419. Research Sponsor: None.

Niraparib plus PD-1 inhibitor for patients previously treated with immune checkpoint inhibitor for solid tumors with homologous recombination repair gene mutation (IMAGENE): A phase II basket study.

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Background: Prior clinical trials have established the effectiveness of poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) or immune checkpoint inhibitor (ICI) monotherapy in patients with cancer characterized by mutations in homologous recombination repair (HRR) genes. This trial aims to evaluate the efficacy and safety of PARPi and PD-1 inhibitor in patients with HRR gene-mutated solid tumors previously treated with ICIs. **Methods:** IMAGENE is an open-label phase II basket study evaluating the efficacy and safety of niraparib and PD-1 inhibitor in patients with HRR gene-mutated cancers that have shown resistance to one or more standard therapy including ICIs. HRR mutation status was evaluated by circulating tumor DNA (ctDNA) or tumor tissue DNA. The primary endpoint was confirmed objective response rate (cORR) per investigator assessment. Patients were treated on a 21-day cycle with niraparib (200 mg orally daily) and nivolumab/pembrolizumab (240 mg/body intravenously every 2 weeks or 3 mg/kg every 3 weeks, respectively). **Results:** Of 47 enrolled patients, 22 were enrolled based on HRR gene alteration detected in ctDNA. The most common tumor type was gastric cancer (36.2%), followed by bladder cancer (BC, 25.5%), and renal cell carcinoma (RCC, 12.8%). As of data cutoff (September 30, 2024), the median duration of follow-up was 31.7 weeks. The median number of prior treatment line was 6.5 (1 to 20). In total, the cORR was 4.4% (90% CI, 0.8 to 13.3), with a disease control rate (DCR) of 55.6% (90% CI, 42.3 to 68.3). Notable DCRs were observed in patients with RCC (83.3%) and BC (80.0%). The median duration of response and progression-free survival (PFS) were 35.0 weeks (90% CI, 20.0 to 50.0) and 11.6 weeks (90% CI, 7.0 to 13.6), respectively. At data cutoff, 28 patients (62.2%) had died, with 12-month overall survival (OS) rate of 41.7% (90% CI, 29.1 to 53.8). Interestingly, *BRCA1/2*-mutated patients had significantly shorter OS compared to those with other HRR gene mutations ($p = 0.0096$). The three most common treatment-emergent adverse events (TEAEs) were nausea (31.1%), vomiting (31.1%), and anaemia (26.7%). Grade ≥3 TEAEs were reported in 18 patients (40.0%), with the most common being anaemia (17.8%). TEAEs led to treatment regimen discontinuation in one patient, and there were no deaths due to TEAEs. **Conclusions:** Niraparib combined with PD-1 inhibitor showed modest activity even in heavily pretreated patients with HRR gene-mutated cancers who progressed on ICI therapy. Furthermore, patients with specific cancer type had promising benefit from this combination therapy, warranting further investigation in specific populations. Clinical trial information: jRCT2051210120. Research Sponsor: The Japan Agency for Medical Research and Development; 21ck0106656h0001; Takeda Pharmaceutical Co., Ltd.

Stereotactic radiotherapy plus immunotherapy and influence on prognosis in driver-gene–negative non-small cell lung cancer patients with brain oligo-metastases.

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Background: This study seeks to elucidate the therapeutic benefits of integrating stereotactic radiotherapy (SRT) with immunotherapy for treating brain oligo-metastases (BMs) in patients with non-small cell lung cancer (NSCLC). **Methods:** In this retrospective real-world study, patients with driver-gene-negative NSCLC and 1-3 BMs were enrolled to evaluate the therapeutic benefits of combining SRT with immune checkpoint inhibitors (ICIs) and chemotherapy. The primary endpoint was overall survival (OS). Secondary endpoints included intracranial progression-free survival (iPFS), progression-free survival (PFS), and the response of intracranial lesions. **Results:** Based on chemotherapy (CT), 65 patients underwent SRT+ICIs therapy, 47 patients underwent SRT, and 44 patients underwent ICIs. For patients with with $>$ 500 mm^3 BMs, SRT + ICIs + CT significantly improved the OS (22.1 vs. 13.5 vs. 18.5 months, p = 0.012), iPFS (17.5 vs. 7.8 vs. 11.8 months, p $<$ 0.001), PFS (11.3 vs. 7.6 vs. 5.3 months, p = 0.019), and iORR (56.3% vs. 20.3% vs 28.9%, p = 0.001) compared to SRT+CT or ICIs + CT therapy. In the sub-group of patients of symptomatic BMs, SRT + ICIs + CT significantly improved the OS (24.7 vs. 14.7 vs. 17.5 months, p = 0.012), iPFS (13.7 vs. 9.8 vs. 11.8 months, p = 0.046), and iORR (34.5% vs. 13.8% vs 23.7%, p = 0.027) compared to SRT + CT or ICIs + CT therapy as well. Concurrent SRT with ICIs (time interval $<$ 2 weeks) significantly improved the OS (28.2 vs. 15.4 months, p = 0.01), iPFS (25.8 vs. 12.1 months, p = 0.014), and iORR (63.2% vs. 37.0%, p = 0.017) when compared to sequential SRT with ICIs. Combined therapy did not increase the incidence of any grade of central nervous system and immune-related adverse events. **Conclusions:** Based on chemotherapy, the combination of concurrent SRT and ICIs improve the prognosis of driver-gene-negative NSCLC with BMs without increasing the occurrence of adverse events. Furthermore, it demonstrates increased effectiveness for treating larger and symptomatic intracranial lesions, specifically those $>$ 500 mm^3 in volume. Research Sponsor: None.

Data on patient outcomes.

	All Patients				Sub-Group in Lesions > 500 mm^3				Sub-Group in Symptomatic Brain Metastases				SRT+ICIs+CT Sub-Group		
Median, months	SRT+ ICIs+CT (n=65)	SRT+CT (n=47)	ICIs+CT (n=44)	p-Value	SRT+ ICIs+CT (n=44)	SRT+CT (n=28)	ICIs+CT (n=17)	p-Value	SRT+ ICIs+CT (n=38)	SRT+CT (n=38)	ICIs+CT (n=21)	p-Value	Concurrent (n=31)	Sequential (n=34)	p-Value
OS	23.0	14.2	18.7	0.033	22.1	13.5	18.5	0.012	24.7	14.7	17.5	0.012	28.5	15.4	0.01
iPFS	15.3	8.5	13.0	0.002	17.5	7.8	11.8	< 0.001	13.7	9.8	11.8	0.046	25.8	12.1	0.014
PFS	9.8	6.7	8.0	0.072	11.3	7.6	5.3	0.019	8.9	6.7	5.7	0.13	12.2	9.0	0.009
iORR	48.8%	24.5%	49.0%	0.01	56.3%	20.3%	28.9%	0.001	34.5%	13.8%	23.7%	0.027	63.2%	37.0%	0.017
iDCR	83.3%	75.5%	76.5%	0.46	85.4%	62.1%	72.2%	0.063	22.2%	17.2%	12.7%	0.61	92.1%	76.1%	0.05

SRT, stereotactic radiotherapy; ICIs, immune checkpoint inhibitors; CT, chemotherapy; OS, overall survival; iPFS, intracranial progression free survival; PFS, progression free survival; iORR, intracranial overall response rate; iDCR, intracranial disease control rate.

A randomized controlled study of tislelizumab combined with concurrent chemoradiotherapy in the treatment of locally advanced cervical cancer and the predictive value of T lymphocyte subsets for efficacy.

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Background: Concurrent chemoradiotherapy (CCRT) has been the standard of care for locally advanced cervical cancer (LACC) for over 20 years. However, 30-40% of treated patients have recurrence or progression within 5 years. **Methods:** A total of 53 patients with LACC who were treated in the First Affiliated Hospital of Guangxi Medical University from May 2023 to November 2024 were prospectively collected and randomly divided into the CCRT group (N = 26) and the CCRT+T group (N = 27). The treatment plan was as follows: 200 mg of tislelizumab was intravenously infused on the first day of radiotherapy, once every 3 weeks, for 1 year or until disease progression or intolerable toxicity, whichever occurred first. Chemotherapy involved single-agent cisplatin at a dose of 40 mg/m^2. External irradiation used 6MV-X-ray intensity-modulated radiotherapy with a dose of 45-50Gy/25f. Simultaneously, peripheral blood T lymphocyte subsets were detected in the enrolled patients before and at the end of radiotherapy. The primary endpoint of the study was the objective response rate, and secondary endpoints included toxicity, PFS and OS. **Results:** Follow-up was completed by January 2025, with a median follow-up time of 13.7 months (5.2-20.5 months) in the CCRT group and 11.2 months (5.9-20.6 months) in the CCRT+T group. The CCRT+T group had higher complete response (CR) and objective response rates (ORR) compared to the CCRT group, with CR rates of 44.4% versus 19.2% (p = 0.035) and ORR rates of 100% versus 84.6% (p = 0.046). The patients with CR were subjected to logistic regression analysis. The results of univariate and multivariate analysis showed that CD4+T cell percentage (p = 0.034) and tislelizumab use (p = 0.038) were significantly associated with CR. However, no statistical difference was observed in the OS (p = 0.414) and PFS (p = 0.716) between the two groups, as shown by the Kaplan-Meier survival curves. After treatment, the CCRT+T group had increased levels of total T cell percentage, CD4+T cell percentage, CD4/CD8, double positive T lymphocyte subset percentage, absolute T lymphocyte count, absolute CD4+T lymphocyte count, and B lymphocyte (CD19) compared to the CCRT group. Notably, the double positive T lymphocyte subset percent (p = 0.025) and absolute CD4+T lymphocyte count (p = 0.047) showed significant increases. There was no significant difference in the incidence of acute adverse reactions between the two groups ($P > 0.05$). **Conclusions:** CCRT+T demonstrated superior short-term efficacy in treating LACC compared to CCRT, although long-term efficacy necessitates further follow-up observation. The combination of tislelizumab and CCRT in the treatment of LACC can improve the levels of T cell subsets, with tolerable acute toxic and good safety. CD4+T cell percentage and tislelizumab use may be associated with CR. Research Sponsor: None.

PD-1 inhibitors combined with radiotherapy and GM-CSF, sequentially followed by IL-2 regimen in advanced refractory solid tumors: A prospective, multicenter clinical trial.

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Background: Low frequency of durable responses in patients treated with immune checkpoint inhibitors demands for taking complementary strategies in order to boost immune responses against cancer. Our previous PRaG1.0 trial also demonstrated that PD-1 inhibitors in combination with radiotherapy and granulocyte macrophage-colony stimulating factor (GM-CSF) could improve clinical response in patients with advanced refractory solid tumors (ChiCTR1900026175). In an effort to further enhance efficacy, we conducted this PRaG2.0 trial (ClinicalTrials.gov: NCT04892498) and optimized the PRaG1.0 regimen by incorporating interleukin-2 (IL-2). **Methods:** The PRaG 2.0 regimen was administered to patients with advanced refractory solid tumors who lacked or were unable to tolerate standard-of-care treatments. A treatment cycle consisted of radiotherapy (5 or 8Gy×2-3f) delivered for one metastatic lesion, PD-1 inhibitor dosing within one week after completion of radiotherapy, GM-CSF 200μg subcutaneous (SC) injection once daily for 7 days, and then sequentially followed by IL-2 2million IU SC once daily for 7 days. PRaG 2.0 regimen was repeated every 21 days for at least 2 cycles until no appropriate lesions for irradiation or reached the tolerance dose of normal tissues. Patients who could not continue radiotherapy and had not yet developed progression disease (PD) allowed PD-1 inhibitors to be continued as maintenance therapy until PD or unacceptable toxicity but no more than one year. The endpoints were Progression-Free Survival (PFS), objective response rate (ORR) and overall survival (OS). **Results:** As of 31st October 2024, 66 patients were enrolled in the study. The median Progression-Free Survival (PFS) was 4.3 months, and the median overall survival (OS) was 10.3 months. The objective response rate (ORR) was 22.7%, and the disease control rate (DCR) was 56.1% according to RECIST version 1.1. Treatment-related adverse events (TRAE) experienced in 57 (86.4%) patients, with 6 patients (9.1%) experiencing Grade ≥ 3 TRAEs. We found that in the period prior to disease progression, the absolute count of Treg cells increased compared to baseline, while the percentage of CD8+PD-1+/CD8+ cells decreased compared to baseline. **Conclusions:** The PRaG 2.0 trial demonstrates that PD-1 inhibitors in combination with radiotherapy, GM-CSF, and IL-2 could be a potential treatment regimen for patients with advanced refractory solid tumors. The decrease in the CD8+PD-1+/CD8+% ratio and the increase in the absolute count of Treg cells may suggest potential tumor progression in patients. Clinical trial information: NCT04892498. Research Sponsor: None.

Phase 1 study of recombinant interleukin 15 in combination with nivolumab and ipilimumab in subjects with refractory cancers.

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Background: Combining immune checkpoint inhibitors with cytokine therapies holds promise in cancer immunotherapy. Recombinant human interleukin-15 (rhIL-15) increases circulating CD8+ T cells and natural killer (NK) cells. This Phase 1 study evaluated the safety (NCI-CTCAE v5.0), tolerability, and preliminary efficacy (RECIST v1.1 and iRECIST) of rhIL-15 with nivolumab and ipilimumab. Safety data for rhIL-15/ipilimumab and rhIL-15/nivolumab doublets were reported earlier (O'Sullivan et al., AACR 2019). Here, we present updated triplet dose-escalation results and correlative analyses. **Methods:** This open-label, non-randomized Phase 1 trial employed a 3+3 dose-escalation design to determine the MTD/RP2D of rhIL-15 SQ (administered on days 1-8 and 22-29, cycles (C) 1-4 only) combined with fixed doses of nivolumab (240 mg IV on days 8, 22, 36) and ipilimumab (1 mg/kg IV on day 8) in 42-day cycles in patients with advanced, refractory cancers. Correlative analyses assessed effects on circulating T cell subsets, PD-1/PD-L1 expression, and immune cell activation in tumor tissue (using multiplex immunofluorescence, immunohistochemistry and flow cytometry). **Results:** Thirty-one patients (median age: 56 years, range: 24-81) were enrolled and evaluable for safety and response. The most prevalent cancer types were sarcoma, pancreatic, and colorectal cancers (n = 5 each). The MTD/RP2D was established at 1 μg/kg/day SQ rhIL-15, with a manageable safety profile. Common treatment-related adverse events (TRAE) included injection site reactions (74%), fever (65%), and chills (65%). Grade 3/4 lymphopenia was seen in 13% of patients (4 of 31). Confirmed partial response (cPR) was measured in 1/31 patients (3%); the patient had cholangiocarcinoma and was treated at dose level 1 (DL1, 0.5 μg/kg/day rhIL-15) and the response lasted through cycle 16. Stable disease (SD) occurred in 17/31 patients (55%, median: 2 cycles, range: 1-10), including durable SD (10 cycles at DL1) in salivary gland squamous cell carcinoma. Nine patients had progressive disease as a best response. Four patients did not have tumor measurements after C1 or did not complete C1, including 3 with clinical disease progression and one with grade 3 TRAE. NK cells and γδ-T cells increased in blood, but increases did not correlate with tumor infiltration measured on C1D42. CD8+ T cells increased modestly in blood and tumor without correlation to either clinical benefit, increased PD1+CD3+ lymphocytes, or PD-L1+ tumor cells on C1D42. **Conclusions:** These data suggest the addition of rhIL-15 to the combination of ipilimumab and nivolumab is safe, elicited a pharmacodynamic response from the immune system in blood but not tumor, and did not improve overall response rate. Clinical trial information: NCT03388632. Research Sponsor: U.S. National Institutes of Health.

Effect of AdAPT-001 on checkpoint inhibitor resistance in solid tumors.

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Background: Checkpoint inhibitors (CIs) have revolutionized cancer treatment, but most patients do not respond to them because of primary or secondary resistance. Introduction or reintroduction of CIs to resistant patients is relatively contraindicated because of the likelihood of an unfavorable harm-benefit profile. An intensive search is on for therapies that sensitize resistant tumors to CI therapy. AdAPT-001 is an oncolytic adenovirus armed with a transforming growth factor beta (TGFβ) trap that eliminates the immunosuppressive cytokine, TGFβ. Clinical data demonstrate that AdAPT-001 reverses the tumor immune evasion phenotype and improves the efficacy of immune checkpoint therapy, increasing response rate and progression-free survival (PFS) in CI refractory angiosarcoma. **Methods:** Patients with CI-refractory solid cancers of any type including sarcomas, melanoma, and breast cancer who received AdAPT-001 with a concurrent checkpoint inhibitor. Response was assessed every 8 weeks using RECIST 1.1. Treatment beyond progression was allowed for patients clinically benefiting, and if progression was confirmed on the next assessment then the first assessment meeting PD criteria was considered the date of progression. PFS on AdAPT-001 + CI was compared to duration of treatment on the most recent previous regimen including a CI before study enrollment. **Results:** Among all patients who were treated with a CI in a previous line of therapy (Prior CI) before being treated with AdAPT-001 + CI, the 6-month PFS rate was 17% (3/18) with Prior CI and 33% (6/18) with AdAPT-001 + CI, and the 12-month PFS rate was 0% (0/18) with Prior CI and 17% (3/18) with AdAPT-001 + CI. Particular activity was seen in angiosarcoma, where all patients progressed within 3 months on Prior CI and 75% (3/4) had PFS $>$ 11 months with AdAPT-001 + CI. Treatment with AdAPT-001 was well tolerated and no new safety signals emerged. **Conclusions:** CI treatment is not an option for many patients because of primary or secondary resistance to them and the potential for harm without benefit. The data from this P2 clinical trial strongly suggests that AdAPT-001 circumvents resistance to CIs in multiple tumor types, improving PFS when compared to the patient's prior CI regimen. In addition, AdAPT-001 may prevent the development of CI-induced autoimmune toxicities. P3 clinical trials in sarcoma and hepatocellular carcinoma are planned. Clinical trial information: NCT04673942. Research Sponsor: None.

Duration of treatment on a previous CI regimen compared to subsequent PFS with AdAPT-001 + CI.

Subject ID	Months on prior CI regimen	PFS (months) with AdAPT-001 + CI	PFS Change (months)
1	3.0	11.4	+8.4
2	3.0	2.0	-1.0
3	1.9	13.0	+11.1
4	2.7	12.0	+9.3
Median	2.8	11.7	+8.9

Efficacy and toxicity of nivolumab and ipilimumab in rare cancer brain metastases: A multi-center basket trial analysis (NCI/SWOG S1609).

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Background: Outcomes of patients with brain metastases (BM) treated with single or dual checkpoint inhibitors have been previously evaluated, showing similar intra-cranial and extra-cranial response rates and overall survival (OS). However, prior research has primarily focused on common tumor types such as melanoma and lung cancer. We report outcomes in patients with BM from the largest basket trial for rare cancers (N=684 evaluable patients) to evaluate efficacy and toxicity. **Methods:** Patients were treated with nivolumab (NIVO, 240 mg Q2W) and ipilimumab (IPI, 1 mg/kg Q6W) in the federally funded SWOG S1609 DART trial (NCT02834013), conducted across >1000 sites. The protocol and consent were reviewed and approved by SWOG, the NCI, the NCI central institutional review board, and institutional review boards of participating sites. Efficacy and toxicity were assessed in patients with and without BM at enrollment. Progression-free survival (PFS), and OS were estimated using Kaplan-Meier methodology. Tumor response was evaluated per RECIST v1.1, toxicities were assessed using CTCAE v5.0. Hazard ratios (HR) with 95% confidence intervals (CI) and P-values were calculated to compare outcomes. **Results:** Similar response rates were observed in patients without BM (11%, n=707) compared to 10% in those with BM at enrollment (n=20). PFS and OS were comparable between patients with and without BM at enrollment (HR=1.29 [0.81-2.07], P=0.28; HR=1.36 [0.81-2.27], P=0.24, respectively). Grade ≥3 CNS treatment-related toxicity occurred in 3% of patients without BM versus 5% in those with BM (P=0.43). Similarly, Grade 5 treatment-related toxicity was observed in 2% of patients without BM compared to 5% in patients with BM (P=0.31). Among 18 patients with BM with progression, intra-cranial progression only was seen in 1 (5.5%) patient, while extra-cranial disease progression only in 12 (66.7%); 5 (27.8%) patients experienced concurrent intra- and extra-cranial disease progression. **Conclusions:** In this unique cohort of patients with rare tumors and BM receiving dual checkpoint inhibitor therapy, similar response rates and survival outcomes were observed in patients with or without BM at enrollment. No significant differences in CNS or non-CNS toxicity were noted. Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819. Clinical trial information: NCT02834013. Research Sponsor: None.

Clinical outcomes and cox regression analysis.

Outcome	No BM (n=707), n (%)	BM (n=20), n (%)	P-value
Best RECIST Response			0.76
Confirmed CR/PR	81 (11.5)	2 (10)	
Unconfirmed CR/PR	22 (3.1)	0 (0)	
Clinical benefit (SD >6 mo)	97 (13.7)	3 (15)	
SD <6 mo or censored	123 (17.4)	1 (5)	
Progression/Failure	384 (54.3)	14 (70)	
PFS, HR (95% CI)			
Univariate	1.22 (0.77-1.93)		0.39
Multivariate	1.29 (0.81-2.07)		0.28
OS, HR (95% CI)			
Univariate	1.23 (0.75-2.02)		0.41
Multivariate	1.36 (0.81-2.27)		0.24

Clinical factors and prognostic outcomes of hyperthyroidism induced by immune checkpoint inhibitor therapy.

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Background: Hyperthyroidism is a recognized but less frequent immune-related adverse event (iRAE) associated with Immune Checkpoint Inhibitor (ICI) use. While its occurrence has been documented, gaps remain in understanding the underlying risk factors, and its impact on patient outcomes. This study seeks to provide clarity on these aspects and guide improved management strategies. **Methods:** Data were obtained from the TriNetX research network for patients with cancers where ICI is used. Inclusion criteria encompassed patients aged 18 years or older treated with ICIs (e.g., pembrolizumab, nivolumab, atezolizumab, cemiplimab) between January 1, 2013, and December 31, 2024. Patients with a history of thyroid disorders or Levothyroxine use were excluded. Competing risk analyses evaluated the likelihood of hyperthyroidism versus death up to 12 months after ICI use and the likelihood of beta-blocker usage after diagnosis. Cox proportional hazards modeling was used to identify significant covariates associated with hyperthyroidism, including age, sex, cancer type, comorbidities, and ICI type. Backwards batchwise elimination was employed to retain only significant variables. **Results:** Among 39,749 patients receiving ICIs, 2.3% developed hyperthyroidism within 12 months after treatment. In patients with hyperthyroidism, 31.3% initiated metoprolol, 9.5% initiated propranolol, and 6.0% initiated atenolol for symptom management. The mortality rate in the group was 32.1% based on the cumulative incidence. An increased risk of hyperthyroidism was associated with endometrial cancer (HR: 1.44; 95CI: 1.23-1.69; $p < 0.0001$), non-Hodgkin lymphoma (HR: 1.42; 95CI: 1.09-1.84; $p = 0.010$), and kidney cancer (HR: 1.34; 95CI: 1.25-1.63; $p = 0.001$). Conversely, patients with colon cancer (HR: 0.74; 95CI: 0.55-0.98; $p = 0.038$) had a lower chance of developing hyperthyroidism. Among all ICIs, atezolizumab (OR: 1.32; 95% CI: 0.82–2.13; $p = 0.25$) showed the strongest trend toward hyperthyroidism, followed by durvalumab (OR: 1.24; 95% CI: 0.75–2.05; $p = 0.39$), pembrolizumab (OR: 1.23; 95% CI: 0.81–1.87; $p = 0.34$), and nivolumab (OR: 1.22; 95% CI: 0.80–1.86; $p = 0.37$). In contrast, cemiplimab (OR: 0.61; 95% CI: 0.17–2.16; $p = 0.44$) showed a lower likelihood of causing hyperthyroidism. **Conclusions:** ICI-induced hyperthyroidism, while less common, has a significant impact on patient outcomes, including mortality. Identifying high-risk cancer subtypes and implementing proactive management, including beta-blocker therapy for symptom control, are critical steps to mitigate adverse effects and improve patient care. Personalized management and early intervention, particularly for high-risk groups, are essential to improving patient outcomes. Research Sponsor: None.

2621 Poster Session

Quantum mechanics–based multi-tensor AI/ML discovery and validation of actionable and mechanistically interpretable whole-transcriptome predictors of survival in response to immunotherapy from real-world clinical trial data.

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Background: Prediction in cancer remains limited, and 90% of drugs continue to fail trials and post-market validation. The entire multi-ome affects the disease. Previously, we developed quantum mechanics-based multi-tensor AI/ML to overcome the limitations of typical AI/ML, e.g., neural networks and deep learning, in small-cohort, noisy, high-dimensional, multi-omic clinical data [doi: 10.1073/pnas.0530258100, 10.1145/3624062.3624078]. We have demonstrated the algorithms in the discovery and validation of whole-genome and -chromosome predictors of survival and response to treatment in, e.g., brain, lung, ovarian, and uterine cancers [doi: 10.1063/1.5142559, 10.1200/JCO.2024.42.16_suppl.10043]. **Methods:** Here, we use the algorithms to discover two whole-transcriptome predictors of OS in response to atezolizumab PD-L1 inhibitor immunotherapy in a 348-patient, multi-center, single-arm, bladder cancer clinical trial, and validate the predictors in the 401-patient bladder cancer cohort in the Cancer Genome Atlas (TCGA). **Results:** The algorithms discovered the two predictors in the open-source, pre-atezolizumab, locally advanced or metastatic disease profiles of the 348 patients alone. By incorporating the patient labels, both predictors were found to outperform the best indicator of response to the treatment to date, i.e., the tumor mutation burden (TMB): The Cox proportional hazards model ratios, i.e., the corresponding relative risks, of 2.7 and 1.7, and concordance indices, i.e., accuracies, of 0.70 and 0.63, of each predictor, are greater than the ratio, of 1.3, and index, of 0.61, of TMB (Wald P-values=2.0×10^{-7} and 8.2×10^{-3} vs. 2.1×10^{-5}). The maximum Kaplan-Meier median OS difference of the two predictors together, of 22 months, is greater than that of TMB, of 16 months (log-rank P-values=3.6×10^{-11} vs. 1.7×10^{-4}). One predictor is additionally correlated with the objective response rate (ORR), and the other – with the tissue of advanced or metastatic disease (Kruskal-Wallis P-values=9.8×10^{-4} and 2.2×10^{-3}). Both predictors are similarly correlated with the OS of the 401 TCGA bladder cancer patients. Both are statistically independent of the imbalanced variations in the patient demographics, e.g., race, or the tissue batches, e.g., pre- vs. post platinum-based chemotherapy. By using the transcript labels, the predictors were interpreted in terms of known and new disease mechanisms and drug targets to sensitize the tumors to the treatment. **Conclusions:** Our multi-tensor AI/ML discovered and validated two whole-transcriptome predictors of OS in response to atezolizumab that outperform TMB. This further suggests that quantum mechanics-based algorithms can be used to derive predictors that are consistent across studies and over time. Research Sponsor: None.

Phase II trial of neoadjuvant nivolumab and SOX in resectable gastric/gastroesophageal junction cancer: Therapeutic response and biomarker correlations.

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Background: Neoadjuvant immunotherapy produces a major pathologic response (MPR) in 40% of patients with locally advanced gastric cancer (LAGC). Herein, we conducted a phase prospective clinical study to investigate markers related to the response to neoadjuvant immunotherapy. **Methods:** Patients with locally advanced gastric or gastro-esophageal junction cancer (cT3-4N+M0,CY0,P0) were enrolled and received either 3 preoperative and 3 postoperative cycles of nivolumab (360 mg, IV, d1, Q21d) plus SOX regimen (oxaliplatin 130 mg/m^2, IV, d1 with oral S-1 40-60mg, bid, d1-d14, Q21d) therapy, followed by 11 cycles of nivolumab monotherapy. The primary endpoint was the pCR rate, while the mPR, 3-year-DFS and 3-year-OS as the second endpoint. This clinical trial was registered at Clinicaltrial.gov (NCT05739045). In addition, tissue samples from patients before and after preoperative therapy were performed scRNA-seq to explore the changes of tumor microenvironment during the therapy and biomarkers associated with therapy response. **Results:** Forty-six patients were enrolled from November 2022 to March 2023, with a median age of 66 years (range, 34-74), and 38 (82.60%) were male. There were 28 (60.87%) patients with PD-L1 CPS $\geq$5. The study achieved its primary endpoints, with a pCR rate of 21.74% and an MPR rate of 41.30%. Among the 46 patients who underwent D2 gastrectomy, the 1-year OS rate was 97.83% and 1-year DFS rate was 95.65%. Single-cell RNA sequencing of 131 tumor samples obtained from 46 patients with LAGC at multiple time points during neoadjuvant therapy showing that the expression of MHC-II was upregulated in malignant cells in the pre-sensitive group. In a retrospective cohort of 226 patients treated with neoadjuvant immunotherapy, MHC-II-positive patients exhibited significantly higher rates of pCR and mPR compared to MHC-II-negative patients. Furthermore, 30 MHC-II-positive GC patients were prospectively enrolled to receive neoadjuvant immunotherapy, showing pCR and mPR rates of 36.67% and 66.67%, respectively. Mechanistically, we observed that T cell-induced IFN-γ signaling predominated in the tumor microenvironment of the sensitive group before treatment. This signaling pathway induces MHC-II expression in tumor cells, thereby enhancing the T cell-mediated antitumor immune response during neoadjuvant immunotherapy. In addition, MHC-II expression in tumor cells can be detected via IHC and commercially available antibodies in standard pathology laboratories, making it a potential biomarker to guide the selection of appropriate GC patients for neoadjuvant immunotherapy. ClinicalTrials.gov registration: NCT05739045. **Conclusions:** Our study illuminates the role of MHC-II expression in tumor cells in modulating the response to immunotherapy in gastric cancer. Clinical trial information: NCT05739045. Research Sponsor: None.

Delineation of immunotherapeutic predictive versus prognostic transcriptional programs to identify SLC22A5-centric carnitine metabolism-driven resistance to anti-PD-L1 treatment in advanced non–small-cell lung cancer.

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Background: Prognostic factors indicate the natural course of a disease regardless of treatment, whereas predictive factors determine the likelihood of response to specific therapies. Distinguishing between predictive and prognostic factors is essential for separating treatment-specific outcomes from the inherent progression of cancer, thereby guiding clinical decision-making. We aim to dissect the predictive and prognostic transcriptional programs underlying the efficacy of anti-PD-L1 versus chemotherapy in advanced non-small cell lung cancer (NSCLC) to uncover mechanisms specific to immunotherapy resistance. **Methods:** Clinical and baseline tumor transcriptomic data were collected from two randomized controlled trials comparing atezolizumab with docetaxel: OAK (n=697, discovery cohort) and POPLAR (n=192, validation cohort). Transcriptional program scores for each biological process and metabolic pathway from the Reactome database were calculated using gene set variation analysis for each patient. Cox regression and P-value for interaction tests were conducted to differentiate predictive versus prognostic effects of transcriptional programs. Tumor microenvironment and cell-cell communication underlying immunotherapy resistance were explored using bulk and single-cell transcriptomic data. **Results:** Transcriptional programs in the OAK discovery cohort were divided into four categories associated with different predictive effects specific to atezolizumab or docetaxel. Carnitine metabolism was the most prominent process contributing to atezolizumab-specific resistance, while porphyrin metabolism drove docetaxel-specific resistance. SLC22A5, the only high-affinity carnitine transporter, was upregulated in atezolizumab-resistant patients. The predictive effect of SLC22A5-centric carnitine metabolism for resistance to atezolizumab rather than docetaxel was confirmed in the POPLAR validation cohort. Integrative analyses of bulk and single-cell transcriptomes revealed that cancer cell-specific SLC22A5 expression induced M2 macrophage polarization and decreased CD8+ T cell infiltration via carnitine uptake, thus forming an immunosuppressive microenvironment. **Conclusions:** Our study elucidates the distinction between predictive and prognostic factors in advanced NSCLC from a metabolic perspective. Cancer cells uptake of carnitine via SLC22A5 mediates resistance to anti-PD-L1 treatment. Combining inhibition of SLC22A5-centric carnitine metabolism with anti-PD-L1 agents might be a promising strategy to reverse immune escape in advanced NSCLC. Keywords: Predictive, Prognostic, Non-small cell lung cancer, Carnitine metabolism, Resistance. Research Sponsor: National Natural Science Foundation of China; 82373307; Natural Science Foundation of Guangdong Province; 2024A1515013214; the China Postdoctoral Science Foundation; 2024M753780; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

Biomarkers associated with outcomes from OPTIMIZE-1: CD40 agonist mitazalimab with mFOLFIRINOX in patients with untreated metastatic pancreatic cancer.

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Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has a 5-year overall survival (OS) rate of less than 5% and remains a leading cause of cancer related mortality. Mitazalimab, a human CD40 agonistic IgG1 antibody, activates CD40 signaling in myeloid cells, enhancing tumor sensitivity to chemotherapy and licensing dendritic cells to prime and activate tumor-specific T cells. The OPTIMIZE-1 Phase 1b/2 trial evaluated the safety and efficacy of mitazalimab combined with mFOLFIRINOX (mFFX) in treatment *naïve* mPDAC patients (pts) (Van Laethem 2024). This combination therapy has shown promising clinical efficacy compared to historical controls with a median OS of 14.9 months, median duration of response of 12.6 months, median progression free survival of 7.7 months, and an overall response rate of 54.4 % (42.1% confirmed) (Geboes, 2024). **Methods:** Patients received mitazalimab on day 1 (priming dose), followed by a 2-week regimen starting with mFFX on day 8 and mitazalimab on day 10. Associations between survival benefits and both baseline and on treatment biomarkers (RNAseq data from tumor biopsies and longitudinal circulating tumor KRAS (ctKRAS) data) were assessed in patients from the full analysis set (n = 57) treated with 900 μg/kg mitazalimab. **Results:** Differential gene expression analysis (DGEA) identified a fibrosis-related gene signature (including genes involved in extracellular matrix (ECM) remodeling) that correlated with improved OS (p = 0.002). Conversely, a distinct gene signature linked to chemoresistance mechanisms involved in the inactivation and secretion of mFFX components was associated with shorter OS. Comparing DGEA of three on-treatment biopsies from patients with partial response to baseline samples revealed treatment-induced tumor changes. These analyses identified upregulation of genes involved in myeloid cell biology and regulation of T cell responses, along with downregulation of immunosuppressive genes. Longitudinal data analyses revealed that ctKRAS clearance was reached by 72% of pts and was significantly associated with longer OS. Molecular response was also associated with longer OS and predicted radiological response with 76.7% accuracy (sensitivity 72.7%, specificity 81.0%). Further, molecular progression was significantly associated with OS and predicted radiological response with 62.8% accuracy (sensitivity 71.4%, specificity 58.6%). **Conclusions:** A potentially predictive fibrosis-related gene signature, directly linked to mitazalimab's mode of action, was associated with improved OS. Biomarker correlations further suggest a mitazalimab-driven contribution to clinical benefits in the OPTIMIZE-1 trial. These encouraging results will inform the planned randomized confirmatory trial of mitazalimab in combination with mFFX in mPDAC. Clinical trial information: NCT04888312. Research Sponsor: Alligator Bioscience AB.

2625 Poster Session

Tumor mutational burden, PD-1, negative Wnt/β-catenin regulators, and positive MHC class II antigen presentation regulators as predictors of longer survival after immune checkpoint inhibitors across cancers: A comprehensive analysis of 400 immunity biomarkers.

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Background: Immune checkpoint inhibitors (ICIs) have become a standard treatment, yet no universal biomarker consistently predicts prolonged survival across cancer types. While multiple biomarkers have been proposed, they have not been systematically compared or evaluated in a tumor-agnostic manner. This study comprehensively investigates the impact of 397 immunoregulatory transcripts and other factors on survival in patients with cancer treated with ICIs. **Methods:** The Profile-Related Evidence Determining Individualized Cancer Therapy (PREDICT, NCT02478931) study enrolled 514 patients, including 217 treated with ICIs. The study analyzed the effect of bulk tumor transcriptomic expression of 397 immunoregulatory factors plus microsatellite instability [MSI], tumor mutational burden [TMB], and PD-L1 immunohistochemistry (total = 400 biomarkers) along with cancer type on overall survival (OS) and progression-free survival (PFS) following ICI therapy. Transcriptome expression was categorized into three groups based on percentile ranks compared to 735 controls spanning 35 histologies: "High" (75–100th percentile), "Intermediate" (25–74th percentile), and "Low" (0–24th percentile). Hazard ratios (HRs) for OS and PFS were estimated using a Cox regression model. Storey's q-value correction accounted for multiple testing, and a multivariable analysis was performed to explore novel biomarkers and different TMB cutoffs (10 [mutations/mb], 16, 20, and continuous). **Results:** In the 217 ICI-treated patients (median age: 61.2 years; women: 56.2%), the most common ICI was anti-PD-1 therapy (83.4%, N = 181), and the median TMB was 5.0 mut/mb. MSI was detected in 9 patients (4.1%). In multivariable analysis adjusting for age, sex, significant markers ($q < 0.05$) and co-inhibitory checkpoints ($p < 0.1$ in univariate analysis), and TMB (with different cutoffs and as a continuous variable), high expression of CIITA, KREMEN1, and PD-1 (but not PD-L1), as well as higher TMB (≥10 mut/mb, ≥16 or ≥20 or continuous), were independently associated with longer OS ($p \leq 0.05$). In the PFS analysis, high KREMEN1 expression and higher TMB (≥16 or ≥20 or continuous but not ≥10 mut/mb) also independently correlated with longer PFS. Cancer type was not independently correlated with outcome. **Conclusions:** Our comprehensive biomarker analysis identified novel factors associated with ICI efficacy. In addition to confirming the predictive role of TMB, the study highlights CIITA, a regulator of MHC class II expression that enhances tumor antigen presentation, and KREMEN1, a suppressor of Wnt/β-catenin signaling that preserves antitumor immunity, as well as the PD-1 checkpoint, as predictive biomarkers for ICI therapy across cancers. Clinical trial information: NCT02478931. Research Sponsor: U.S. National Institutes of Health; P30 CA023100; U.S. National Institutes of Health; 5U01CA180888-08; U.S. National Institutes of Health; 5UG1CA233198-05.

Impact of *Helicobacter pylori* infection on molecular alterations and immune dynamics in gastric cancer.

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Background: *Helicobacter pylori* (HP) infection, a major risk factor for gastric cancer (GC), modulates tumor immunity. Evidence indicates that *H. pylori* infection status correlates with the efficacy of immune checkpoint inhibitors (ICI), with varying outcomes in *H. pylori*-positive (*HPP*) and -negative (*HPN*) patients. This study investigated the impact of HP infection on splicing alterations to elucidate its role in shaping immune responses and the tumor immune microenvironment (TIME), immune checkpoint molecule expression, transcriptional profiles in GC. **Methods:** Tumors and adjacent normal tissues were collected from 24 patients with GC, comprising 39 tumor samples from *HPP* patients, 27 samples from *HPN* patients, and 13 and 10 normal samples of each, respectively. RNA sequencing was performed on these tissues and whole blood RNA from six patients (four *HPP* and two *HPN*) to analyze the alternative splicing (AS) events, the transcriptional profiles, and immune-related gene expression. Differential gene expression (DGE) and enrichment analyses were conducted, and immune cell fractions were evaluated using CIBERSORTx. **Results:** DGE analysis revealed that *HPP* tumors were enriched in genes related to cell cycle regulation, whereas *HPN* tumors were enriched in immune response pathways, including those involved in leukocyte activation, chemokine signaling, and immune effector processes. Additionally, *HPN* tumors showed higher expression of immune checkpoint molecules, such as CD160 ($p = 0.016$), PDCD1LG2 ($p = 0.0082$), and BTLA ($p = 0.025$). Immune cell profiling demonstrated increased proportions of gamma-delta T cells ($p = 0.0077$), resting dendritic cells ($p = 0.0002$), and neutrophils ($p = 0.016$), reflecting enhanced immune activation and a favorable ICI response. In contrast, *HPP* tumors were enriched in cell cycle-related pathways, suggesting a proliferative phenotype. *HPP* tumors also exhibited higher levels of M0 macrophages ($p = 0.0039$) and CD276 expression ($p = 0.0082$), indicative of an immunosuppressive TIME. AS analysis identified increased intron retention (IR) events in *HPP* tumors, particularly in genes associated with RNA processing and extracellular matrix remodeling. These alterations may contribute to immune evasion and tumor progression. In the peripheral blood, *HPP* samples exhibited upregulation of tripartite motif family genes, which are implicated in immune modulation. **Conclusions:** This study demonstrated that *HP* infection significantly affects the TME and gene expression profiles of GC. *HPP* tumors are characterized by increased M0 macrophage populations, CD276 expression, and IR events that contribute to immunosuppression and tumor progression. In contrast, *HPN* tumors exhibit greater immune activation and checkpoint molecule diversity. These findings highlight the potential role of HP status in shaping the immune landscape of GC and influencing responsiveness to ICI. Research Sponsor: None.

Levels of immune responses in tertiary lymphoid structures of non-small cell lung cancer (NSCLC) and association with survival.

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Background: Tumor-infiltrating tertiary lymphoid structures (TLSs) are thought to have anti-tumor activity and are believed to indicate a favorable prognosis in cancer patients. However, the prognostic value of TLSs in non-small cell lung cancer (NSCLC) is unknown. **Methods:** RT-qPCR analysis of the reactive Th-cell subsets and fluorescence activated cell sorting (FACS) analysis of the cell composition in tumor and paired controls. Histological evaluation of the co-localization of tumor-associated $CD20^+$ B cells, $CD4^+$ T cells and DC-$LAMP^+$ mature dendritic cells (DCs) within TLSs, and statistically analysis of the relationship between TLSs and overall survival. **Results:** The results indicated high levels of immune responses in tumour microenvironment ofNSCLC, which that high levels of Th-CXCL13, Th1, Tfh and Treg cell immune responses were the main reactions in tumor tissue of NSCLC, followed by weak Th2 and Th17, suggesting high levels of immune responses in tumor microenvironment of NSCLC. Tumor-associated TLS is a complete and mature lymphoid follicle-like structure containing T cells, B cells and APCs in tumor of NSCLC. Six-color MIHC staining indicated tumor-associated TLSs were complete and mature lymphoid follicle-like structures containing T cells, B cells and antigen presenting cells (APCs), and tumor-associated TLSs. Architectural analysis showed that $CD20^+$ B cell clusters were localized in the local tumour microenvironment, and were mainly colocalized with $CD4^+$ T cells, $CD68^+$ macrophages, $CD11c^+$ DCs and DC-$LAMP^+$ mature DCs, which indicated the formation of mature TLSs. One of the primary functions of TLS is to support the survival of incoming lymphocytes. The vast majority of the evaluated tumour-associated TLSs in NPC represented mature secondary-follicle-like TLSs, as indicated by the presence of both $CD21^+$ FDC and $CD23^+$ GC-B cells. Understanding and analyzing the phenotypes of these TABs was important for interpreting the local immune response. We used six-color MIHC staining (CD10, CD20, CD38, CD138, CD27 and DAPI) to approximate six different TABs in whole tissue sections of NPC. These molecules were expressed to varying degrees in all paraffin sections, and MIHC showing that $CD38^+$ plasmablast cells and $CD138^+$ plasma cells were primarily located at the tumor interstices or margins, which indicated improved survival outcome. In conclusion, this is the first research of applying multiple complementary strategies to map the biological function and clinical relevance of those cells in the TLSs of NSCLC. **Conclusions:** Our findings provide insights into the potential role of TLSs in the adaptive anti-tumor immune response, with implications for the development of biomarkers and therapeutic targets. Research Sponsor: None.

Clinical significance of the CGRP pathway gene expression in advanced solid tumors: A sub-analysis of MONSTAR-SCREEN-2.

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Background: Calcitonin gene-related peptide (CGRP), a neuropeptide associated with pain perception, has emerged as a therapeutic target for migraine. Recent studies have reported that the CGRP pathway is associated with suppression of anti-tumor immunity and poor prognosis in patients (pts) with solid tumors via induction of CD8+ T cell exhaustion by sensory nerves. However, clinical significance of the CGRP pathway genes in oncology including the impact for the efficacy of immune checkpoint inhibitors (ICIs) remains elusive. Herein, we evaluated the landscape of the CGRP pathway gene expression and their association with efficacy of ICIs by mRNA expression level of the CGRP pathway genes in advanced solid tumors from the SCRUM-Japan MONSTAR-SCREEN-2, a nationwide molecular profiling project. **Methods:** Pts with advanced solid tumors were enrolled; tumor tissues were profiled using whole exome/transcriptome sequencing (MI Profile, Caris Life Sciences, Phoenix, AZ, USA). The association between the expression profiles of the CGRP pathway genes (*CALCA* encoding CGRP, *CALCRL* and *RAMP1* encoding CGRP receptors) and the efficacy of ICI monotherapy was analyzed. **Results:** Among 2,768 pts enrolled as of March 2024, mRNA expression data of baseline tissue samples were available in 1,475 pts across 36 cancer subtypes: most common subtypes were colorectal adenocarcinoma (n = 352) and esophagogastric adenocarcinoma (EGAC, n = 192). mRNA expression of the CGRP pathway genes were observed across diverse cancer types. One hundred and fifty-eight pts were treated with ICI monotherapies: most common subtypes were urothelial carcinoma (UC, n = 41), EGAC (n = 30) and head and neck squamous cell carcinoma (HNSCC, n = 30). The low *RAMP*1 mRNA expression group tended to have a better objective response rate (ORR) and significantly better progression-free survival (PFS) than the high mRNA expression group (ORR: 29.3% vs 15.2%, P = 0.056, PFS: 5.1 vs 2.7 months, hazard ratio [HR]: 0.68, 95% CI: 0.47-0.98, P = 0.04). Among the patients with UC and HNSCC, the low *RAMP1* mRNA expression group tended to have a better PFS than the high mRNA expression group (UC: 3.5 vs 6.0 months, HR: 0.69, 95% CI: 0.34-1.39, P = 0.3, HNSCC: 1.5 vs 6.0 months, HR: 0.67, 95% CI: 0.30-1.51, P = 0.3). **Conclusions:** High RAMP1 mRNA levels were associated with worse therapeutic efficacy of ICI, highlighting the potential of CGRP pathway as a resistance mechanism and a treatment target. Clinical trial information: UMIN000043899. Research Sponsor: SCRUM-Japan Funds.

Predication of clinical outcomes of advanced cutaneous squamous cell carcinoma to PD1 inhibition directly from histopathology slides using inferred transcriptomics.

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Background: Metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) not amenable to local therapy is treated with programmed death (PD)-1 inhibitors, namely Cemiplimab . While response rates are relatively high at approximately 45%, no predictive biomarkers for PD-1 inhibition have been validated in advanced CSCC subjecting some patients, especially older, to unnecessary immune-related adverse events (irAE). We present a retrospective analysis of ENLIGHT-DP, a novel biomarker for response to PD-1 inhibition in advanced CSCC, calculated directly from histopathological slides. **Methods:** We retrospectively examined high resolution hematoxylin and eosin (H&E) slide scans from archived tumor-tissue samples of advanced CSCC patients treated with Cemiplimab to generate an individual prediction score to PD-1 inhibitors using ENLIGHT-DP. This is composed of two main steps: (I) prediction of individual mRNA expression directly from H&E slides using the digital pathology-based DeepPT algorithm (II) use these values as input to ENLIGHT, a transcriptomics-based precision oncology platform for prediction of response to cancer therapies. We then unblinded clinical outcomes and assessed the predictive values of ENLIGHT-DP. **Results:** We evaluated 39 cases of advanced CSCC (tumors from various origins) at a median age of 81 years old (range 57-100). Of them, 32 cases (82%) were initially treated with surgery or radiotherapy with curative intent, but ultimately suffered disease progression. The objective response rate (ORR) was 69%, median progression free survival (PFS) was 11 months (CI 95% 10.4-17.6) and 6 patients (15%) suffered from severe irAE necessitating treatment cessation. ENLIGHT-DP was predictive of response with ROC AUC = 0.67. Using a binary threshold for classification, calibrated on previous lung and head and neck cohorts, ENLIGHT-DP displays promising biomarker characteristics: 81.8% PPV, 66.6% sensitivity and 4.0 OR ($p = 0.04$) for matched vs. unmatched patients. ENLIGHT-DP successfully stratified PFS with HR 0.02 (CI 95% 0.0005-0.96, $p = 0.05$). Importantly, omitting cases in which ENLIGHT-DP was calculated on samples which were taken more than 6 months prior to Cemiplimab therapy (i.e., during diagnostic excisions) did not influence the results. No other patient characteristics (e.g., age, stage, co-morbidities, previous treatments) were associated with outcomes. **Conclusions:** ENLIGHT-DP demonstrates high predictive values for clinical outcomes of PD-1 inhibition in advanced CSCC, relying solely on easily accessible archived H&E slides. Research Sponsor: Pangea Biomed.

Evaluation of AI-assisted PD-L1 CPS scoring in immunostained pan-organ tumor whole-slide images.

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Background: PD-L1 inhibitors have shown remarkable results in oncology, yet many patients fail to respond, underscoring the importance of reliable assessment of PD-L1 expression for patient selection. PD-L1 scoring, especially the Combined Positive Score (CPS), is hindered by inter-observer variability, complex staining patterns, and technical discrepancies across platforms and antibody clones. These challenges may impact therapeutic decisions. Artificial intelligence (AI) offers a solution by standardizing PD-L1 evaluation. This study evaluates Diadeep PD-L1 CPS AI solution designed to provide reproducible and robust PD-L1 scoring across diverse tumors and conditions. **Methods:** AI performance was validated on 142 formalin-fixed, paraffin-embedded samples spanning multiple tumor types (GI, head and neck, breast, uterine cervix) and sourced from four centers, reflecting diverse staining protocols (22C3 and QR001 clones; BenchMark ULTRA and Omnis/Dako platforms). The routine scores were available for these cases. A Gold Standard was established through independent retrospective scoring by three blinded senior pathologists, which allowed to compute the intraclass correlation coefficient (ICC). The scoring was followed by collegial discussions to resolve discordant cases and ensure medical consensus. After a washout period, pathologists re-evaluated the cases with the AI assistance. AI-computed scores and routine manual scores were evaluated and compared by using the Gold Standard as a reference and the organ-specific recommended cut-offs. **Results:** The AI assistance improved interobserver agreement among pathologists, with the ICC increasing from 0.62 to 0.74. This effect was particularly pronounced for challenging cases with CPS < 20 ($n = 91$), where ICC improved from 0.19 to 0.62, underscoring the AI's value in reducing variability near clinical decision thresholds. Moreover, the AI-based scoring tool demonstrated superior accuracy (88%) compared to routine manual scoring (75%) in classifying PD-L1 expression based on clinical cutoffs. Sensitivity was significantly higher with AI (96% vs. 78%, $p < 0.001$), while the positive predictive value was comparable (88% vs. 87%), indicating an improved ability to detect true positive cases. **Conclusions:** This study highlights the potential of an AI-driven tool to enhance PD-L1 scoring by significantly improving accuracy and reducing inter-observer variability, particularly in cases near clinical decision thresholds where consistency is critical. By delivering reliable and reproducible results, the AI algorithm addresses key challenges in PD-L1 evaluation, ensuring more precise patient stratification for immunotherapy. Beyond accuracy, the integration of such tools into clinical workflows could optimize patient selection and improve therapeutic outcomes, offering oncologists greater confidence in treatment decisions. Research Sponsor: None.

Validation of ENLIGHT, an AI predictor of immune checkpoint blockade (ICB) response and resistance, across the treatment span.

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Background: Advanced computational AI algorithms, such as ENLIGHT and DeepPT (Med 2023, Nature Cancer 2024), represent a promising approach to identify predictive biomarkers for cancer therapeutics. Evaluation of ICB response prediction via these algorithms through the full span of pre-treatment, on-treatment, and at progression time points provides a dynamic perspective of response prediction abilities. **Methods:** A post-hoc analysis of two pan-cancer clinical trials was performed: i) BIO2 is a biobanking protocol of ICB-naïve patients (pts) treated with pembrolizumab (NCT02644369); and ii) The IRIS study (NCT04243720) which enrolled pts who have progressed immediately post ICB. In BIO2, complete, partial response or stable disease for >6 months was classified as responders (R), the rest as non-responders (NR). In IRIS, acquired and primary resistance were defined according to trial protocol. ENLIGHT matching scores were calculated using either transcriptomics from NGS (EMS-NGS), or transcriptomics imputed directly from H&E slides using DeepPT (EMS-DP). The predictive value of EMS was compared to PD-L1 IHC, tumor mutational burden (TMB) and tumor infiltrating lymphocytes (TILs) abundance by IHC, and its trajectory across timepoints was studied. **Results:** 76 pts from BIO2 (23:53, R:NR), and 37 pts from IRIS (18:19, AR:PR), comprising of 14 tumor types, were analyzed. We first established the value of ENLIGHT as a predictive biomarker using the BIO2 pre-treatment samples. EMS-NGS was a superior predictive biomarker compared with PD-L1 IHC, TMB and TIL abundance, while EMS-DP was comparable (Table). The EMS-NGS scores of responders were significantly higher than non-responders pre-treatment (medians: 0.92 vs. 0.62, p = 1.4e-4). Analyzing the trajectory of the EMS-NGS scores across two additional timepoints reveals that while the scores of non-responding patients remained low (median: 0.62, 0.69, 0.67 for pre-, on–treatment and post-progression, respectively), it is higher among responders (median: 0.92, 0.78 for pre- and on–treatment, respectively). Finally, EMS-NGS was higher among pts with acquired vs primary resistance in IRIS (medians: 0.75 vs 0.59, p = 0.17). **Conclusions:** In two pan-cancer cohorts, EMS-NGS outperformed conventional biomarkers in predicting ICB response. EMS-DP was comparable to conventional biomarkers and could be calculated directly from H&E slides in a fast, low-cost manner. EMS-NGS values were concordant with response or resistance throughout the ICB treatment course, reflecting the level of the tumor's vulnerability to ICB inhibition. Further validation of ENLIGHT in larger ICB-treated pts is warranted given these promising results. Clinical trial information: NCT02644369, NCT04243720. Research Sponsor: BMO Chair in Precision Genomics, Dr. Lillian Siu.

	ROC AUC (p)	Sensitivity	PPV (cf 30% baseline response rate)	F1 Score
EMS-NGS	0.74 (0.0003)	61	48	54
EMS-DP	0.64 (0.02)	57	45	50
PD-L1 IHC	0.7 (0.003)	70	40	51
TMB	0.64 (0.03)	39	69	50
TILs	0.6 (0.065)	39	52	44

Effect of elevated expression of *LILRB4* and *TSC22D3* on survival in lung cancer.

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Background: HER2/neu mutations or amplifications, present in up to 23% of non-small cell lung cancers (NSCLCs), activate STAT3, promoting inflammation and suppressing adaptive immune responses. Elevated systemic inflammation-immune index (SII) in small cell lung cancer (SCLC) correlates with reduced response to PD-1/L1 immune checkpoint inhibitors (ICIs), leading to worse overall survival (OS) and progression-free survival (PFS). These findings highlight the need to mitigate inflammation in lung cancers to enhance ICI response and improve survival. Biomarker studies can identify genes that differentiate inflammatory and immune pathways, offering therapeutic insights. **Methods:** To identify genes regulating the HER2/neu oncogene, HER2/neu-overexpressing mice were crossed with genetically Diverse Outbred (DO) mice. The resulting DO F1 offspring were monitored for HER2/neu-expressing tumor onset and growth. Tumor phenotypes were associated with mouse haplotypes to identify quantitative trait loci (QTL) on chromosomes (chr) 2, 6, and X linked with aggressive HER2/neu tumors. Of the 35 candidate genes harboring protein-coding changes, homologous genes on human chr 1, 10, and X were analyzed using Caris Life Sciences datasets of NSCLC and SCLC: 25,143 primary NSCLC; 12,365 metastatic NSCLC; 621 primary SCLC; and 971 metastatic SCLC where primary biopsies are those taken from the lung and metastatic biopsies from sites other than the lung. Patient cohorts stratified by gene expression (top vs. bottom 50%) were correlated with OS, ICI response, and time on pembrolizumab or atezolizumab treatment (TOT). **Results:** Several homologous candidate genes correlated with lung cancer survival in both NSCLC and SCLC. Notably, high expression of *LILRB4*, a macrophage-specific checkpoint molecule, was associated with improved survival (HR 0.66–0.84, $p < 0.001$) across all lung cancer types and sites. Additionally, elevated *TSC22D3*, a glucocorticoid receptor-activated gene regulating anti-inflammatory pathways, including *LILRB4* expression, was positively associated with OS in metastatic NSCLC (HR 0.82, $p < 0.00001$) and SCLC (HR 0.77, $p < 0.001$). Expression of *LILRB4* and *TSC22D3* further enhanced survival in ICI-treated patients (SCLC: HR 0.72; NSCLC: HR 0.82; $p < 0.001$). In NSCLC, high *LILRB4* expression conferred an 18% improved TOT with pembrolizumab (HR 0.858, $p < 0.0001$). **Conclusions:** *LILRB4* and *TSC22D3* are key genes linked to improved survival outcomes in both SCLC and NSCLC, likely through their roles in mitigating inflammation. Their association with enhanced ICI responses underscores their potential as therapeutic targets. Future research will evaluate the relationship between *LILRB4* and *TSC22D3* expression and HER2/neu status in NSCLC and validate protein-level correlations in positive cells. Our long-term goal is to determine the therapeutic potential of *LILRB4* and *TSC22D3* in SCLC, NSCLC and HER2/neu-positive NSCLC. Research Sponsor: U.S. National Institutes of Health; 7R01CA278818-02.

Tertiary lymphoid structures and their association with immune checkpoint inhibitor response and survival outcomes in patients with non-small cell lung cancer.

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Background: Immune checkpoint inhibitor (ICI)-based therapy is currently the first-line treatment for patients with lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) without actionable mutations. However, the commonly utilized biomarkers, including PD-L1 protein expression and tumor mutation burden, are not sufficiently accurate to predict the treatment response from ICI in this patient population. As tumor microenvironment (TME) and tertiary lymphoid structure (TLS) play a significant role in antitumor immunity, we explore these immunophenotypic factors to determine the potential biomarkers in patients with LUAD or LUSC. **Methods:** We evaluated all patients with LUAD or LUSC from three publicly available data and two novel retrospective cohorts for transcriptomic-based immune TME subtype classification (immune-hot vs. immune-cold) and TLS signature, along with associated clinical and genomic data. Those with other histological subtypes of non-small cell lung cancer or those who harbored *EGFR* mutations or *ALK* rearrangements were excluded from our study. The cellular decomposition within tumor samples was calculated using the deconvolutional Kassandra algorithm. Survival analysis was evaluated using log-rank test and multivariate Cox regression adjusted by PD-L1 status, KEAP1/STK11/KRAS/TP53 mutational status, immune TME subtype, and TLS signature. All statistical analyses were performed using Python. **Results:** A total of 514 patients were included from five cohorts, with 272 and 505 having genomic and transcriptomic data, respectively. 59% of patients with LUAD or LUSC exhibited an immune-cold phenotype, which correlated with adverse overall survival (OS) and progression-free survival (PFS) than immune-hot phenotype in LUAD. However, the ICI response rates were similar in both groups. Superior PFS and ICI response rates were observed in patients with high TLS signatures ($>$ 88th percentile) in LUAD, even after multivariate adjustments. Immune signatures that were positively associated with ICI response included the infiltration and trafficking of T and NK cells for LUAD and B-cell percentage for LUSC. In contrast, $CD8^+$ T-cell abundance did not correlate with ICI response. The presence of *KEAP1* or *STK11* mutations also did not affect the response rates but were associated with shorter OS and PFS. **Conclusions:** Transcriptomic-based immune-hot TME and high TLS signature may serve as novel predictive and prognostic biomarkers in patients with LUAD, while the presence of *KEAP1* or *STK11* mutations only offered prognostic values. Further prospective studies are warranted to expand to other treatment combinations with PD-(L)1 inhibitors. Research Sponsor: None.

CCR8 positive Tregs and their correlation with immunotherapy response in advanced non-small cell lung cancer (NSCLC).

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Background: Regulatory T cells (Tregs) expressing the chemokine receptor CCR8 are pivotal modulators of the tumor immune microenvironment. CCR8 has recently emerged as a promising therapeutic target due to its selective expression on activated Tregs in the tumor microenvironment and its role in promoting immunosuppression. This study investigates the prognostic and therapeutic implications of CCR8-positive Tregs in non-small cell lung cancer (NSCLC), focusing on their impact in relation to tertiary lymphoid structure (TLS) status. **Methods:** A validated 6-plex multiplex immunofluorescence (mIF) panel was used to analyze tumor samples from NSCLC patients treated with immune checkpoint blockers (ICB) in the BIP precision medicine study (ClinicalTrials.gov: NCT04389143). Markers included CD4, CD8, CD20, FoxP3, PanCK, and CCR8, alongside DAPI staining to assess immune contexture (infiltrated, excluded, desert), TLS status, and CCR8/FOXP3 double-positive Tregs. Clinical outcomes, including progression-free survival (PFS) and objective response rate (ORR), were analyzed in 50 responders and 50 non-responders. Findings were validated using transcriptomic data from the POPLAR (NCT01903993) and OAK (NCT02008227) studies, which evaluated atezolizumab versus docetaxel in advanced NSCLC. Kaplan-Meier curves, hazard ratios, and Cox regression models were used for survival analyses. **Results:** CCR8-expressing Tregs were significantly enriched in infiltrated tumors, showing a 1.5-fold increase compared to excluded tumors ($p = 0.057$), a 3.3-fold increase compared to desert tumors ($p = 0.001$), and a 1.8-fold increase in TLS-positive tumors compared to TLS-negative tumors ($p = 0.003$). These findings highlight that activated Tregs co-infiltrate with CD8 T cells and other immune cell types. This enrichment was confirmed in samples from the POPLAR and OAK studies using transcriptomic analyses (3-fold increase, $p = 2e\text{-}16$). Due to their correlation with overall immune cell infiltration, the presence of CCR8-positive Tregs was significantly associated with better survival (HR 0.45, $p < 0.001$) across the entire patient cohort. However, when stratified for TLS-positive tumors, the presence of activated Tregs was associated with diminished objective response rate and progression-free survival suggesting a negative impact of these immunosuppressive cells on response to ICB. **Conclusions:** This study provides the first evidence linking CCR8-positive Tregs with immunotherapy resistance in NSCLC, particularly in TLS-positive tumors. These findings parallel observations in TLS-positive sarcomas, where Treg abundance predicted poor outcomes (Italiano et al., *Nature Medicine*, 2022). This study supports the exploration of CCR8-targeted therapies to deplete immunosuppressive Tregs and enhance the efficacy of immunotherapy in TLS-positive NSCLC. Research Sponsor: None.

Biological determinants of immune exclusion in non-small cell lung cancer: An analysis of the precision medicine BIP study.

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Background: Immune exclusion has been associated with resistance to immunotherapy in NSCLC. However, its biological determinants remain largely unknown. Instead of relying on preclinical models, high-throughput profiling of patient samples using spatial transcriptomics (ST) and multiplex immunofluorescence (m-IF) offers a powerful approach to dissect immune profiles and uncover key drivers of immune response and resistance. **Methods:** Tumor samples collected from NSCLC patients enrolled in the BIP precision medicine study (NCT02534649) prior to initiation of ICI therapy and divided into Discovery and Validation cohorts (n = 148 and 117, respectively). Response to treatment was assessed as per RECIST criteria. Multiplex immunohistochemistry (mIHC) with CD8 and panCK markers was used to classify tumors as desert, excluded or inflamed through pathologist assessment (PA) and image analysis ST using the NanoString GeoMx Whole Transcriptome Atlas compared gene expression profiles between inflamed and excluded tumors Spatially resolved T-cell receptor (TCR) profiling assessed clonal diversity and repertoire to evaluate T-cell functionality. m-IF was used for proteomic validation. **Results:** In both the training and validation cohorts, excluded tumors demonstrated lower objective response rates (ORR), progression-free survival (PFS), and overall survival (OS) compared to inflamed tumors (Table 1), independent of PD-L1 expression in multivariate analysis. ST identified marked overexpression of HLA-A/B (MHC class I) and CD74 (involved in MHC class II processing) in inflamed tumors versus excluded tumors, underscoring their crucial roles in antigen presentation. These results were validated by m-IF. Spatially resolved TCR profiling demonstrated higher Gini coefficients and lower Shannon entropy in excluded tumors, indicating a more oligoclonal TCR repertoire dominated by fewer T-cell clones. These findings suggest impaired antigen recognition and restricted T-cell diversity in excluded tumors. **Conclusions:** Our classification approach using mIHC and IA offers a practical, and clinically actionable biomarker for predicting response to ICI therapy. Immune exclusion, prevalent in NSCLC, is associated with resistance to ICI and characterized by reduced expression of key antigen presentation molecules such as HLA-A/B and CD74 and a restricted TCR repertoire highlighting the need for novel strategies to overcome this immune barrier. Research Sponsor: None.

	Phenotype	Objective Response Rate (ORR)	PFS (Median, Months)
Discovery	Inflamed (n=32)	**58%**	**12.8** (95% CI: 6.16-NA)
	Excluded (n=65)	**38.7%**	**4.1** (95% CI: 2.4-10.3)
	Desert (n=51)	**20%**	**2.8** (95% CI: 1.9-6.9)
Validation	Inflamed (n=40)	**57.5%**	**11.3** (95% CI: 4.6-NA)
	Excluded (n=30)	**43.3%**	**6.1** (95% CI: 3.4-14.9)
	Desert (n=47)	**31.9%**	**4.4** (95% CI: 2.3-7.2)

The predictive role of TRAIL gene expression in immune checkpoint inhibitor (ICI)-treated patients (pts).

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Background: Despite FDA-approved molecular biomarkers such as PD-L1 levels, tumor mutation burden (TMB), and microsatellite instability (MSI) status, only ~30% of matched cancer pts respond to ICI. TRAIL, a protein product of TNFSF10 gene, is a member of the TNF superfamily involved in regulating immune responses and inducing apoptosis when bound to either Death Receptor 4 or 5 (DR4/5) especially in cancer cells. While TRAIL has been studied for its prognostic roles in cancer, its predictive value for pts treated with ICI remains unclear. This study investigates the association between TRAIL expression and outcomes in ICI-treated pan-cancer pts. **Methods:** RNA expression levels of TRAIL were assessed in a cohort of 217 pan-cancer pts treated with ICIs at the University of California San Diego (UCSD) Moores Cancer Center. RNA transcripts were normalized using an internal housekeeping gene profile of 735 tumors and 35 histologies. Transcript abundances were percentile-ranked (0–100) and categorized as high (≥75th percentile) or low (< 75th percentile). Associations between TRAIL expression and overall survival (OS) and progression-free survival (PFS) were analyzed. Statistical significance was defined as p-value ≤ 0.05. **Results:** Among the 217 ICI-treated pts, the median age was 61.9 years, and 56.2% were female. The most common cancer types were colorectal (24.9%), breast (8.8%), ovarian (8.3%), pancreatic (7.4%), and lung (6.5%) cancers. FDA-approved ICI biomarkers favorable rates were PD-L1 ≥1% in 40.1%, TMB-high (≥10 mut/Mb) in 11.5%, and MSI-high in 4.8%. Based on the ICI type used, 91.7% received anti-PD-(L)1 while 7.8% received anti-CTLA-4 with anti-PD-1. Pts with high TRAIL expression (24%) had similar PD-L1, TMB, MSI profiles (p > 0.05). Pts with high levels of TRAIL expression achieved better OS (HR = 0.41, 95%CI:0.25-0.69, p = 0.0004) and PFS (HR = 0.67, 95%CI:0.47-0.96, p = 0.027). After adjusting for age, sex, cancer type, PD-L1 IHC level (≥1% vs. < 1%), TMB (≥10 mut/Mb vs. < 10mut/Mb), MSI status (stable vs. unstable), KRAS, TP53 and CDKN2A/B alteration status and immune checkpoints genes expression, overall survival remained significantly associated with better survival in TRAIL high pts compared to TRAIL low pts (HR = 0.38, 95%CI:0.19-0.76, p = 0.006). However, no difference was found between both groups in regard to progression-free survival (HR = 0.68, 95%CI:0.42-1.10, p = 0.11). **Conclusions:** High TRAIL expression is associated with improved overall survival in ICI-treated pan-cancer pts, independent of cancer type or other predictive biomarkers. These findings suggest TRAIL as a potential biomarker for ICI benefit. Larger studies in diverse and real-world settings are warranted to validate these findings. Research Sponsor: None.

Randomized phase II trial evaluating the combination of TG4001, an HPV16 therapeutic vaccine, and avelumab (ave) in patients (pts) with immunotherapy-naïve recurrent and/or metastatic (R/M) HPV16-positive cervical or anogenital cancer.

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Background: Human papillomavirus (HPV) is a small DNA virus associated with cervical, anogenital (AG) cancers and squamous cell carcinoma of the head and neck. TG4001 is a therapeutic vaccine based on modified vaccinia virus Ankara with insertion of modified non-oncogenic HPV-16 E6 and E7 antigens and interleukin-2 as adjuvant. The phase I trial of TG4001 combined with ave showed a favorable safety profile (Borcoman E. et al, 2023). **Methods:** Pts with R/M cervical and anogenital cancer and who were checkpoint inhibitors naïve were randomized independent of PD-L1 expression between ave plus TG4001 or ave alone. Pts were required to have no more than one prior line of therapy for R/M disease and no liver involvement. Primary endpoint was PFS. Subgroup analysis (cervical, anal, other genital cancer) was preplanned in the protocol. **Results:** 90 pts were randomized between June 2021 and April 2024. 49 (54%), 27 (30%) and 14 (16%) pts had cervical, anal, and other genital cancers, respectively. Patients' demographics were well balanced between the 2 arms. Median PFS (mPFS) was 3.0 and 2.8 months (mo) in the experimental and control arm, respectively (HR=0.87 [90%CI: 0.59-1.29], p=0.28). In the cervical cancer subgroup, mPFS was 4.3 and 2.1 mo in the experimental and control arm, respectively (HR=0.58 [90%CI: 0.33-1.01], p=0.053). Overall Response Rate (ORR) in the whole population was 15.2% (7/46pts) in the experimental arm and 13.6% (6/44pts) in the control arm. In the cervical cancer subgroup ORR was 20% (5/25pts) in the experimental arm and 8.3% (2/24pts) in the control arm. There were no new safety signals. Three pts (6.5%) in the experimental arm and 2 pts (4.5%) in the control arm presented grade 3 or 4 treatment-related AEs. Translational analysis including immunogenicity results will be presented. **Conclusions:** TG4001 combined with ave did not improve PFS over ave alone in the whole patient population. Preplanned subgroup analysis in cervical cancer showed a positive efficacy signal in the combined arm. Avelumab was provided by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Clinical trial information: NCT03260023. Research Sponsor: None.

Induction of neoantigen-specific immune responses by VB10.NEO in combination with atezolizumab in heavily pretreated patients with advanced solid tumors: Final analysis of the phase 1b VB N-02 trial.

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Background: VB10.NEO, a personalized DNA-based neoantigen vaccine, was evaluated with atezolizumab in a Phase 1b trial to assess safety, clinical activity, and immune responses in heavily pretreated patients with advanced solid tumors. The NeoSELECT platform enriches for clonal neoantigens by analyzing RNA and circulating tumor DNA, incorporating frameshift antigens and single nucleotide variants. **Methods:** This open-label, dose-escalation trial investigated VB10.NEO across three dose levels (3, 6 and 9 mg) combined with atezolizumab (1200 mg Q3W). Eligible patients had advanced or metastatic solid tumors, sufficient tumor material for vaccine manufacturing, at least 10 identified tumor neoantigens, and measurable disease. Immune responses were assessed using ELISpot assays (in vitro stimulation and ex vivo), T cell receptor sequencing, and flow cytometry. Endpoints included safety, immune response, and antitumor activity per RECIST v1.1. **Results:** At study completion (October 2024), 26 patients (median age 61 years, range 28–72; 62% female) received at least one dose of VB10.NEO. Median prior therapy lines for advanced disease were three (range 1–6), and 54% had prior immunotherapy, including checkpoint inhibitors. Tumor types included head and neck squamous cell carcinoma (15%), triple-negative breast cancer (15%), and others (31%; most were tumors with low tumor mutational burden). The majority (69%) of evaluable patients had low or negative PD-L1 expression. Injection site reactions (15%) and fatigue (12%), mainly Grades 1–2, were the most common adverse events. A dose-limiting Grade 3 transient blood pressure increase occurred in the 9 mg cohort. No treatment-related serious events or deaths occurred. Across all dose levels, VB10.NEO induced robust and durable neoantigen-specific immune responses. In vitro stimulated ELISpot assays detected vaccine-induced T cell responses in 85% (11/13) of evaluable patients and in 58% of evaluated neoantigens, while *ex vivo* ELISpot demonstrated responses in 22% (4/18) of patients and 5% of evaluated neoantigens. T cell receptor sequencing showed persistent T cell clone expansion in 9/11 patients, indicating durable immune responses. Putative neoantigen-specific clones were detected in 6/7 analyzed patients, with persistent expansion in 4. All patients achieving stable disease (34.8%, 8/23) exhibited neoantigen-specific immune responses. **Conclusions:** VB10.NEO combined with atezolizumab demonstrated a favorable safety profile while eliciting robust, durable immune responses across all dose levels, even in heavily pretreated patients with advanced solid tumors. The potential correlation between immunogenicity and clinical benefit supports further exploration in earlier treatment settings. Clinical trial information: NCT05018273. Research Sponsor: Nykode Therapeutics in collaboration with Roche/Genentech.

An open-label single-center investigator-initiated exploratory clinical study in patients with refractory or recurrent solid tumors: R-ISV-FOLactis trial.

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Background: Soft tissue sarcomas (STSs) are a highly complex group of tumors and the treatment still remains a challenge. Immunotherapy has become a powerful clinical strategy, especially the application of therapeutic tumor vaccine. Hypofractionated radiotherapy (HFRT) can serve as an in situ vaccine and provide durable local control. We also develop a bifunctional engineered Lactococcus lactis (FOLactis) which expresses an encoded fusion protein of Fms-like tyrosine kinase 3 ligand and co-stimulator OX40 ligand to conduct in situ vaccination (ISV). In this study, we establish a novel R-ISV-FOLactis strategy, which refers to the combination of HFRT, intratumoral (IT) injection of FOLactis and synergetic anti-PD-1 therapy, to further enhance efficacy and realize the activation of the whole immunity cycle. **Methods:** This study is an open-label, single-center trial aimed at patients with advanced STSs who are unresponsive or intolerable to previous standard treatment. Patients will be treated with HFRT, the IT injection of FOLactis and PD-1 inhibitors. The primary endpoint is the objective response rate (ORR) of target lesions at 3 month and 6 month. The secondary endpoint includes the disease control rate (DCR) of target lesions, progression-free survival (PFS), overall survival (OS), etc. **Results:** This study started from July 2022 and ended in December 2023, involving 30 eligible patients with solid tumors and 16 of them are patients with STSs. The ORR and DCR of all target lesions after three months are 27.6% and 93.1% respectively, and in sarcomas, the ORR and DCR are 11.1% and 88.9%. We calculate the ORR and DCR of target lesions after six months, which are 56.3% and 100% respectively, and in sarcomas, these are 41.7% and 100%. Systemic median PFS are 2.87 months. Median PFS of target lesions has not been reached. Among the evaluable target lesions, 6-month EFS is 50% in sarcomas (6/12) and 50% in all patients (8/16). We test the level of cytokines before and after the first treatment and find that the changes in the percentage of CD8+ T cells, CD103+CD8+ T cells and CD39+CD8+ T cells have significance. Moreover, in sarcomas, PFS is relevant to the level of CD103+CD8+ T cells before treatment, CD39+CD8+ T cells after treatment, NK cells before treatment and immature DC cells after treatment. The most common treatment-related adverse events (TRAEs) are fever (83.3%), lymphocytopenia (53.3%), hypocalcemia (30%), neutrophilia (26.7%) and nausea (26.7%). Grade≥3 TRAEs occur in 11 patients, including lymphocytopenia (30%), fever (6.7%), leukopenia (3.3%), anemia (3.3%) and cardiac insufficiency (3.3%). **Conclusions:** The R-ISV-FOLactis strategy demonstrates its efficacy among patients with advanced STSs and induces certain anti-tumor immunity. The ISV of "FOLactis" may provide a promising option in the treatment of recurrent or refractory solid tumors. Clinical trial information: ChiCTR2200060660. Research Sponsor: None.

First-in-human study of ZGGS15, a dual-specific antibody targeting LAG-3 and TIGIT, as monotherapy in patients with advanced solid tumors.

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Background: ZGGS15 is a novel humanized bispecific antibody of anti LAG-3 and TIGIT. It could reverse Treg inhibition of T cells and NK cells, and kills tumor cells by restoring the function of T cells and NK cells. In non-clinical studies, ZGGS15 showed synergistic anti-tumor effects with the anti-PD-1 antibody. We conducted a Phase 1 dose escalation and expansion study to assess tolerability, safety, and efficacy of ZGGS15 as monotherapy in patients with advanced solid tumors. **Methods:** In the dose-escalation phase, a standard "3+3" design, with an accelerated titration for the starting dose. Total of 6 dose levels, from 0.3 to 30 (0.3, 1, 3, 10, 20, 30) mg/kg administered by the intravenous infusion, once every three weeks, in patients with advanced solid tumors who had failed to the available standard treatments. The first treatment cycle (21 days) was defined as the dose-limiting toxicity (DLT) observation period. The study assessments included tolerability, safety, preliminary efficacy, etc. and tumor responses were assessed by RECIST1.1 and iRECIST criteria. **Results:** As January 8 2025, a total of 22 patients (9 males and 13 females), with a median age of 59 years, participated in the dose escalation from 0.3 to 30 mg/kg and completed the DLT observation. Of the 22 patients, 11 (50.0%) received at least 3 prior lines of therapies, and eight (36.4%) had previously treated with PD-1 or PD-L1 inhibitors. No DLT events were observed. TRAEs occurred in 20 (90.1%) patients, with only one patient (4.5%) experienced a Grade 3 TRAE of lymphocyte count decreased, and no Grades 4 or 5 TRAEs were reported. Among the 17 patients who had at least one post-baseline tumor scan, six had achieved stable disease (SD) with a disease control rate (DCR) of 35.3%. In the subgroup of 8 patients with lung adenocarcinoma, 5 (62.5%) had achieved SD, including two patients who had $\geq$ 2 prior lines of treatments and maintained SD over 36 weeks. **Conclusions:** The results showed that ZGGS15 was well tolerated and had a very good safety profile. It is anticipated that when in combination with other anti-cancer therapies, e.g., an anti-PD-1 or PD-L1 antibody, for advanced solid tumors, ZGGS15 may provide synergistic anti-tumor effects and further enhance treatment benefits. Clinical trial information: NCT05864573. Research Sponsor: Suzhou Zelgen Biopharmaceuticals. Co., Ltd.

Adverse events profile of novel agents targeting immune checkpoints beyond PD-1/PD-L1 and CTLA-4 in solid tumors: A meta-analysis.

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Background: PD-1, PD-L1, and CTLA-4 blockade are standard therapies in multiple solid tumors, and novel agents targeting alternative co-stimulatory and co-inhibitory immune checkpoints are under development. Immune checkpoint inhibitors are well known to cause immune-related adverse events (irAEs) and multiple studies reported the accurate incidence of irAEs from PD-1, PD-L1, and CTLA-4 blockade. With the increasing investigation and anticipated approval of novel immunotherapy agents, understanding their toxicity profiles is critical. **Methods:** We systematically searched PubMed/MEDLINE, EMBASE, and Web of Science for clinical trials published up to December 1st, 2024. Studies evaluating the safety of agents targeting co-inhibitory checkpoints (B7-H3, CD47, TIGIT, LAG-3, and TIM-3) or co-stimulatory checkpoints (OX40, 4-1BB, CD27, ICOS, GITR, CD70, and CD40) in solid tumors were included. Incidence rates of grade 1-5 (G1-5) and grade 3-5 (G3-5) treatment-related adverse events (trAEs) and irAEs were extracted. Toxicity data were derived from phase 2 and 3 trials, as well as phase 1/2 trials with safety information reported at the recommended phase 2 dose. Random-effects meta-analysis was used to pool odds ratios (ORs) from two-arm studies evaluating the addition of LAG-3 or TIGIT blockade to control-arm therapy, and proportional meta-analysis was conducted to analyze AE incidence across immunotherapy subtypes. **Results:** A systematic review identified 27 clinical trials with 40 cohorts comprising 3,946 patients and evaluating 10 immune checkpoints (B7-H3, LAG-3, TIGIT, CD47, OX40, CD137. TIM-3, CD40, CD27, CD40, ICOS). Meta-analyses showed that the addition of LAG-3 blockade to either PD-1 blockade-based therapy or placebo was associated with increased G3-5 trAEs (OR 1.79, 95% confidence interval [CI]: 1.26–2.54, p = 0.001), G3-5 adrenal insufficiency (OR 8.43, 95% CI: 1.04 - 68.37, p = 0.046), G1-5 adrenal insufficiency (OR 4.81, 95% CI: 1.81-12.78, p = 0.002) and arthralgia (OR 2.07, 95% CI: 1.29-3.30, p = 0.002). The addition of TIGIT blockade to PD-L1 blockade-based therapy was associated with increased G1-5 rash (OR 2.32, 95% CI: 1.01–5.34, p = 0.048) (other outcomes will be shown). Proportional meta-analysis revealed varying irAE patterns across agents: G5 trAEs (0.9-2.9%), G3-5 pneumonitis (0.5-5.5%, highest in TIM-3 blockade), G3-5 colitis (0.2-5.4%, highest in LAG-3 blockade), G3-5 hepatitis (1.5-5.5%, highest in TIM-3 blockade), G3-5 rash (0.8%-18.4%, highest in CD40 agonists), G3-5 adrenal insufficiency (1.7-8.4%, highest in TIGIT blockade) (details of all outcomes will be presented). **Conclusions:** This study highlights the distinct toxicity profiles of novel immunotherapy agents, providing essential safety data to support clinicians as these therapies move toward anticipated clinical approval. Research Sponsor: None.

JAK inhibitor for the treatment of steroid refractory and life-threatening immune-related adverse events secondary to immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICIs) boost anti-tumor immune responses but carry the risk of off-target effects, manifesting as immune-related adverse events (irAEs). Approximately 20% of irAEs are refractory to steroids, requiring subsequent immunosuppressive therapies, while a smaller subset presents with fulminant reactions requiring multiple agents simultaneously. Although biologics like TNF and IL-6 inhibitors are often used, their targeting of single inflammatory pathways may be insufficient to resolve irAEs in these critical scenarios. We conducted a prospective study to assess the safety and efficacy of oral JAK inhibitors, molecules capable of rapidly modulating multiple inflammatory cytokine signals, in managing steroid-refractory or life-threatening irAEs. **Methods:** The MIRAE Biobank is a prospective cohort study of cancer patients treated with ICI at the Jewish General Hospital in Montreal, Canada. Patients with steroid refractory subjects with grade $>$ 3 irAE or persistent grade 2 toxicity despite optimal therapy, as well as life-threatening irAEs in the first-line setting treated with JAK inhibitors were extracted from the database and their clinical data was summarized. Among those who survived at least 30 days post-JAK inhibitor, we compared characteristics of responders and non-responders. Responders were defined as resolution of the irAE to grade $<$ 1 and $<$ 10mg prednisone equivalents without any relapses during a 30-day period. **Results:** In this series, 29 patients were treated with JAK inhibitors for refractory or life-threatening irAEs. Mean age was 69 years, 34.5% were women, 82.8% received anti-programmed cell death protein-1 (PD-1) antibodies alone, and 13.8% patients were treated with the combination of anti-cytotoxic T lymphocyte antigen-4 and anti-PD-1 antibodies. Cancer types were primarily melanoma (10, 34.5%) and lung cancer (6, 20.7%). Primary irAEs for which JAK inhibitors were initiated included myocarditis (n=11), colitis (n=4), arthritis (n=4), hepatitis (n=4), encephalitis (n=2), pneumonitis (n=2), myasthenia gravis (n=1) and sicca (n=1). JAK inhibitors were used as second- (refractory to steroids alone), third- or fourth- or more line in 9, 11 and 9 patients, respectively. Median duration of JAK inhibitor exposure was 30.5 days. Among the 24 patients who survived at least 30 days, 17 (71%) responded after a median of 11 days from initiation of the JAK inhibitor. Interestingly, this included 6/8 patients with myocarditis, 4/4 with arthritis and 2/3 with colitis. Of those who responded to JAK inhibitor, 11/18 were steroid refractory and 6/6 were life-threatening cases requiring simultaneous treatment with steroids. **Conclusions:** This preliminary data suggests that JAK inhibitors may be effective at treating various types of steroid-refractory and life-threatening irAEs. Research Sponsor: Arthritis Society Canada; #23-313.

Albumin-myosteatosis gauge as a prognostic biomarker in patients treated with immune checkpoint inhibitors.

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Background: Although immune checkpoint inhibitors (ICIs) have heralded a new era in cancer treatment, many patients do not respond, underscoring the need for biomarkers. The albumin-myosteatosis gauge (AMG) is a recently developed integrated measure of myosteatosis and serum albumin levels, reflecting systemic inflammation and malnutrition. Herein, we investigate the prognostic value of AMG in patients with advanced cancer treated with ICIs. **Methods:** A total of 308 patients with advanced cancer treated with ICIs were included. Skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) were measured from computed tomography images obtained at the level of the L3 vertebra. The AMG was calculated by multiplying SMD by albumin and expressed as an arbitrary unit (AU). Survival outcomes were assessed using Kaplan-Meier survival curves and Cox regression models. **Results:** The median age (interquartile range) was 63 (55-70), and 198 (64.3%) were male. Non-small cell lung cancer (NSCLC) was the most common primary cancer (28.2%), followed by renal cell carcinoma (RCC) (20.8%) and melanoma (20.2%). Regarding AMG, the cutoff values were determined to be 109.38 AU for males and 102.11 AU for females. Multivariable analyses revealed that lower AMG values were independently associated with decreased OS (HR: 1.43; 95% CI: 1.08-1.90; p=0.012) and PFS (HR: 1.39; 95% CI: 1.07-1.79; p=0.011) compared to the AMG high-group. **Conclusions:** Our findings suggest AMG, an easily accessible novel biomarker, is an independent prognostic factor for survival in patients with advanced cancer treated with ICIs. Prospective studies are required to validate these findings and evaluate the role of AMG measurement in aiding treatment choices. Research Sponsor: None.

Tumor flare reactions secondary to T-cell engaging immunotherapies: A study from the French REISAMIC registry.

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Background: Tumour flare reactions (TFR) were recently reported in patients receiving T-cell engagers (TCE) and require further investigations. This study aims to investigate incidence, predictive factors, and outcomes of pts with TFRs related to TCE. **Methods:** This observational cohort study is nested in the French academic pharmacovigilance register, Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie (REISAMIC, CNIL number 2098694v0). All patients treated at Gustave Roussy (France) with TCE, for all tumor indications except acute leukemia, were included. The main objectives were to determine the incidence, predictive factors, associated clinical and biomarker profiles, as well as the outcomes of patients. TFRs were clinically defined with transient worsening of tumor symptoms including tumor pain, effusions, or compressive symptoms, mimicking tumor growth but without reflecting disease progression. Statistical analyses included log-rank tests and Cox regression models. **Results:** Overall, 222 TCE-treated patients were included, median [range] age: 53 [5 - 87] years; male-to-female ratio: 1.44, median prior lines of therapies was 3 [2-9]. Of them, 147 (66.2%) had solid tumors, including prostate cancer (n=51), high-grade serous ovarian carcinoma (n=28), and small-cell lung cancer (n=24), and 75 (33.8%) had hematologic malignancies, primarily multiple myeloma (MM, n=35) and diffuse large B-cell lymphoma (DLBCL, n=31). Common TCE targets included CD3/CD20 (n=40), CD3/KLK2 (n=36), CD3/BCMA (n=35), CD3/DLL3 (n=28), and CD3/B7-H4 (n=27). TFRs occurred in 54 pts (24.3%), with higher TFR frequency in solid tumors (34.0%) than lymphomas (12.1%) and none in MM. Median TFR onset was 1 day [1–8]. Symptoms of TFRs were pain (92.6%), compression syndrome (22.2%), and effusion (7.4%). Severity of TFRs was grade 3–4 in 68.5% of cases. No TFR-related deaths occurred. TFRs management included corticosteroids (35.2%), opioids (61.1%), paracentesis (7.4%), JJ stenting (3.7%) and tocilizumab (3.7%). TFRs correlated with transient increases of CRP (182 vs. 69 mg/L; p=0.0002) and LDH (316 vs. 225 U/L; p=0.04). Patients with TFRs were more frequently exposed to cytokine release syndrome (p=0.0001). Predictors included tumor serous localization (p=0.052) and a higher CD4+/CD8+ ratio in blood (p=0.048). In solid tumors pts; TFRs were associated with higher response rates (18.0% vs. 6.3%; p=0.013) and disease control rates (72.0% vs. 49.5%); PFS (2.83 vs. 2.76 months; p=0.865) and OS (9.92 vs. 9.72 months; p=0.539) were comparable regardless of TFRs. **Conclusions:** TFRs related to TCE are clinically significant adverse events, primarily observed in solid tumor pts. TFRs may indicate a unique pattern of antitumor response distinct from progression. Better recognition and management of TFRs should help to optimize tolerability of TCE therapies. Research Sponsor: Gustave Roussy.

Evaluating the role of exercise in modulating immunity and immunotherapy outcomes in cancer: A systematic review.

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Background: Immunotherapy has become a key cancer treatment, improving survival and reducing side effects. However, its effectiveness can be influenced by immune system function, overall health, and treatment-related side effects. Exercise, known for its health benefits, may also modulate immune responses and enhance immunotherapy outcomes. Despite promising evidence, the impact of exercise on immune function and cancer treatment remains insufficiently understood. This review aims to assess the role of exercise in modulating immunity and improving immunotherapy outcomes in cancer patients. **Methods:** A systematic review was conducted following PRISMA guidelines, with a comprehensive search of PubMed, Cochrane Library, EMBASE, and ClinicalTrials.gov for studies published from 2010 to 2025. Eligible studies included randomized controlled trials (RCTs), non-randomized trials, pilot studies, and systematic reviews investigating exercise interventions on immune function and immunotherapy in cancer. Key outcomes included changes in immune markers, immune function, and quality of life. Data were extracted and analyzed using standardized protocols. **Results:** Eight studies, involving 1,172 cancer patients across various types (lymphoma, CLL, melanoma, NSCLC, breast, ovarian, prostate), were included. Exercise modalities studied included aerobic exercise, resistance training, cycling, yoga, and mind-body practices like qigong. Findings consistently showed positive effects of exercise on immune function and treatment outcomes. Two studies reported that exercise mobilized T cells and NK cells, enhancing immune responses. Another two demonstrated improved efficacy of immunotherapeutic agents such as rituximab. Additionally, three studies indicated that exercise improved physical fitness, body composition, and overall quality of life. **Conclusions:** This review provides evidence that exercise may enhance immune responses and improve outcomes in cancer immunotherapy. While exercise appears to be a beneficial adjunctive therapy, the optimal type, intensity, and duration remain unclear. Further large-scale, high-quality trials are needed to define effective exercise regimens and explore their impact on immunotherapy across various cancer types. The study is registered in PROSPERO: CRD42024627822. Research Sponsor: None.

Safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HLX301, a bispecific antibody targeting PD-L1 and TIGIT, in patients with advanced solid tumors.

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Background: Immune checkpoint proteins PD-L1 and TIGIT are important components of cancer-related T cell immunosuppression. HLX301 is a humanized, bispecific IgG1 antibody targeting PD-L1 and TIGIT that showed anti-tumor activity in preclinical studies. A phase 1/2 first-in-human study was conducted to evaluate HLX301 monotherapy in patients with advanced solid tumors (NCT05102214). Here we report findings from the dose escalation part (phase 1a). **Methods:** This multicenter study enrolled patients with locally advanced or metastatic solid tumors who had failed or were intolerant to standard therapy, or for whom no standard therapy was available. Phase 1a evaluated doses of 0.25-15 mg/kg IV Q2W. Primary endpoints included safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD). Secondary endpoints included PK, PD, and immunogenicity. **Results:** As of Oct 27, 2023, 9 patients were enrolled (0.25 mg/kg, 3; 1 mg/kg, 3; 2.5 mg/kg, 1; 5 mg/kg, 2). Patients were all White, 55.6% female, median age 72.0 yrs; 88.9% had metastatic disease; all had ECOG PS of 0 (44.4%) or 1 (55.6%). All patients had prior systemic cancer treatment, including 3 (33.3%) treated with PD-(L)1 blockade; 5 (55.6%) patients had $\geq$ 4 prior lines of therapy. All patients were included in DLT, safety, and PK analyses. Median duration of HLX301 treatment was 10.3 weeks. One patient (11.1%) in the 5 mg/kg cohort reported DLT (grade 3 cytokine release syndrome [CRS]). MTD was not determined. All patients experienced at least one treatment-emergent adverse event (TEAE). TEAEs leading to death occurred in 3 (33.3%) patients, none of these adverse events (AEs) were related to HLX301. Six (66.7%) patients experienced at least one treatment-related adverse event (TRAE). TRAE of grade $\geq$ 3 was reported in 1 patient (11.1%; grade 3 CRS), who was also the only patient for whom TRAE led to treatment discontinuation. Treatment-related immune-related AEs occurred in 4 (44.4%) patients and treatment-related infusion-related reactions (IRRs) in 2 (22.2%). TRAEs occurring in $\geq$ 2 patients included IRR (22.2%) and arthralgia (22.2%). HLX301 exhibited linear PK over 0.25-5 mg/kg after single infusion and very limited accumulation after multiple infusions. Mean PD-L1 and TIGIT receptor occupancy in peripheral $CD3^+CD8^+$ cells reached saturation at 5 mg/kg. Anti-drug antibody was detected in 7 patients (77.8%). Among 8 efficacy-evaluable patients, 1 (5 mg/kg cohort) achieved partial response and 2 achieved stable disease; objective response rate and disease control rate per RECIST 1.1 were 12.5% and 37.5%, respectively. **Conclusions:** HLX301 showed an acceptable safety profile with preliminary anti-tumor activity. These findings could support further clinical investigation. Clinical trial information: NCT05102214. Research Sponsor: Shanghai Henlius Biotech, Inc.

Solid tumor–specific patterns of immune-related adverse events due to immune checkpoint inhibitor.

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Background: Immune checkpoint inhibitors (ICIs) are the backbone of therapy for several solid tumors; however, they have a unique toxicity profile that may limit treatment. The objective of this systematic review was to identify differences in type and frequency of immune-related adverse events (irAEs) across solid tumors. **Methods:** Using PubMed, we identified registrational phase 2 and 3 clinical trials of ICI-based therapy (i.e., single agent immunotherapy (single I/O), single I/O plus chemotherapy, single I/O plus kinase inhibitor, double immunotherapy combination (double I/O), double I/O plus chemotherapy) for first-line and second-line unresectable disease for which irAEs (dermatologic, endocrine, gastrointestinal, hepatic, renal, pulmonary) were specified for the following tumor types: melanoma, non-small cell lung (NSCLC), esophageal, colorectal (CRC), biliary tract (BTC), hepatic (HCC), renal (RCC), urothelial, endometrial, head and neck (H&N). Odds ratio (OR) were used to analyze effect size. All analysis performed on Microsoft Excel. **Results:** 105 trials (n = 32,896 patients) were identified with the most commonly studied regimens being those that were PD-1 or PD-L1-based. While endocrinopathies were the most frequent irAE (~15-20%) with first-line single I/O, one tumor type was not more likely than the other to develop endocrinopathies. Interestingly, patients with melanoma and RCC treated with first-line single I/O were significantly more likely to develop gastrointestinal irAE compared to those with NSCLC, CRC, HCC, urothelial, and H&N with OR of 3.41 – 30.64 and 2.96 – 26.60, respectively. Second-line single I/O led to increased frequency of irAE and greater variation in the predominant irAE for a given tumor type – four tumor types (melanoma, NSCLC, gastric, H&N) had dermatologic irAE as most frequent, five (esophageal, CRC, HCC, urothelial, endometrial) had endocrine irAE, and two (BTC, RCC) had gastrointestinal irAE. Overall odds of developing irAE were greater with double I/O than with single I/O in the first-line setting and more pronounced in the second-line. For example, in melanoma, OR for endocrine irAE was 2.55 (95% CI 1.27 – 5.10) in first-line and 17.03 (95% CI 8.04 – 36.05) in second-line and for hepatic irAE was 4.41 (95% CI 1.55 – 12.50) in first-line and 7.63 (95% CI 2.45 – 23.78) in second-line. The addition of chemotherapy or kinase inhibitor did not significantly alter irAE frequency across tumor types. In fact, there were fewer irAEs in some tumor types with addition of kinase inhibitor in first-line unresectable disease compared to single I/O alone; for example, OR for dermatologic irAE with kinase inhibitor compared to single I/O alone was 0.36 (95% CI 0.18 – 0.70) for melanoma and 0.22 (95% CI 0.08 – 0.59) for RCC. **Conclusions:** irAE profiles vary across tumor type, treatment regimen, and line of therapy and do not necessarily correlate with the primary tumor site. Research Sponsor: None.

Impact of immune checkpoint inhibitor (ICI)-associated autoimmune hemolytic anemia (AIHA) on mortality in cancer patients: A retrospective analysis.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but can cause serious immune-related adverse events; including rare yet severe autoimmune hemolytic anemia (AIHA) . This study evaluates the impact of ICI-associated AIHA on mortality in patients with solid cancers. **Methods:** A retrospective analysis using the TriNetX database examined patients with solid cancers treated with ICIs. Patients were defined using ICD-10 codes and grouped into those who developed AIHA after ICI use and those who did not. Baseline characteristics, including cancer diagnosis, ICI medications, and comorbidities, were compared between groups using TriNetX's built-in t-tests and z-tests to calculate p-values. Confounding variables were adjusted with 1:1 propensity score matching. Primary outcomes were 30- and 60-day mortality; secondary outcomes included transfusions and hospitalizations. Outcomes were evaluated using measures of association, Kaplan-Meier log-rank tests, and a Cox proportional hazards model. **Results:** Among 106,388 ICI-treated patients, 352 developed AIHA. After matching (352 per group), the AIHA group had a significantly higher 30-day mortality (15.25% vs. 5.14%; OR 3.493, 95% CI: 1.898-5.803, $p < 0.0001$) and 60-day mortality (22.87% vs. 6.86%; OR 4.195, 95% CI: 2.479-6.54, $p < 0.001$). Transfusions (OR 4.085, 95% CI: 2.897-6.525, $p < 0.0001$) and hospitalizations (OR 1.865, 95% CI: 1.525-2.837, $p < 0.0001$) were also significantly higher in the AIHA group. Hazard ratios (HR) confirmed significant mortality risks in AIHA group at 30 days (HR: 3.16, 95% CI: 1.849-5.402, $p < 0.0001$) and 60 days (HR: 3.673, 95% CI: 2.324-5.805, $p < 0.0001$) (table 1). HRs for transfusion and hospitalization were 4.309 (95% CI: 2.975-6.241, $p < 0.0001$) and 2.049 (95% CI: 1.692-2.48, $p < 0.0001$), respectively. **Conclusions:** This study highlights the clinical impact of ICI-associated AIHA, which is linked to higher mortality at 30 and 60 days, as well as increased transfusion and hospitalization rates. Although rare, ICI-associated AIHA is a potentially fatal complication. Clinicians should maintain a high level of suspicion for AIHA in patients on ICIs, as early recognition and intervention may improve outcomes. Research Sponsor: None.

Primary Outcomes	HR	95 % Confidence Interval	P-Value
Mortality within 30-days*	3.16	(1.849,5.402)	< 0.0001
Mortality within 60-days*	3.673	(2.324,5.805)	< 0.0001
Transfusion	4.309	(2.975,6.241)	< 0.0001
Hospitalization or emergency services	2.049	(1.692,2.48)	< 0.0001

Improved survival with sodium-glucose cotransporter-2 inhibitors and immune checkpoint inhibitors in metastatic solid tumors.

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Background: Immune checkpoint inhibitors (ICI) are used in the first-line setting for the treatment of many advanced solid tumor malignancies. Patients with type 2 diabetes mellitus (T2DM) have decreased response rates to ICI, and poor glycemic control is associated with worse outcomes in patients with cancer. Further adjunctive therapies increasing the efficacy of ICI in these patients are needed. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as effective antihyperglycemic medications with concomitant cardiovascular benefits. SGLT2i have been approved by the Food and Drug Administration for use in patients with DM and congestive heart failure (CHF). Pre-clinical studies have demonstrated the potential benefit of SGLT2i in slowing tumor growth in-vitro and in-vivo; however, there is a lack of clinical data regarding SGLT2i use in patients with advanced malignancy receiving ICI. **Methods:** We performed a retrospective, matched cohort study of patients with stage IV malignancy and T2DM or CHF, who were treated with ICI using the Epic Cosmos dataset (2013–2024). Ten different solid tumor types, five ICI, and three SGLT2i were analyzed. Among 4,808 patients treated with ICI, 282 had at least one overlapping cycle of ICI and SGLT2i. 1:1 propensity score matching was conducted to balance baseline covariates including cancer type, comorbidities, age at diagnosis, and sex. Kaplan-Meier curves were generated to examine survival differences and Cox proportional hazards models were used to estimate hazard ratios (HR). The primary outcome was overall survival (OS) for the entire matched cohort and sub-groups by cancer, ICI, and SGLT2i types. **Results:** Patients who received ICI and SGLT2i had significantly improved OS compared to those who received ICI alone (HR = 0.62, 95% CI: 0.49-0.79). Among cancer types, significant improvements in survival were observed in patients with renal cell carcinoma (RCC, HR = 0.48, 95% CI: 0.27–0.84) and non-small cell lung cancer (NSCLC, HR = 0.60, 95% CI: 0.37–0.96). Among ICI types, ipilimumab + nivolumab (HR = 0.35, 95% CI: 0.15–0.79) and pembrolizumab (HR = 0.49, 95% CI: 0.32-0.74) showed a significant improvement in survival when used with SGLT2i. There was no statistically significant difference in OS amongst the three SGLT2i types. **Conclusions:** In this retrospective, matched cohort study we observed encouraging improvements in OS in patients with T2DM or CHF receiving SGLT2i in addition to ICI across multiple solid tumor types. Patients with RCC and NSCLC derived the greatest benefit. Patients treated with either ipilimumab + nivolumab or pembrolizumab had the best responses to therapy. SGLT2i may be beneficial as adjunctive therapies in patients with advanced malignancy receiving ICI. However, further prospective studies to validate our observations and determine potential underlying mechanisms are needed. Research Sponsor: None.

Prognostic value of host genetic variants determining Bifidobacterium abundance in the lactose metabolism pathway for immunotherapy efficacy.

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Background: The potential predicative and therapeutic value of *Bifidobacterium* in immune checkpoint inhibitors (ICIs) treatment has been widely studied. However, the value of its genetic determinants on the prognosis of ICIs treatment remains unclear. **Methods:** we examined the associations of 11 single nucleotide polymorphisms (SNPs) located at host genes determining *Bifidobacterium* abundance with the outcomes of ICIs treatment in 370 eligible cancer patients. **Results:** Cox regression analysis revealed that rs3739020 TT carriers experienced significantly extended OS (*P*-value = 0.003, adjusted HR = 0.46, 95%CI = 0.27-0.77) compared with GG+TG carriers. The *LCT* haplotype analysis showed that the lactose poor metabolizers exhibited significantly poorer OS (*P*-value = 0.002, adjusted HR = 0.45, 95%CI = 0.27-0.74) than the extensive or intermediate metabolizers. In polygenic SNP analysis, the high galactose level carriers exhibited significantly prolonged OS (*P*-value = 0.007, adjusted HR = 0.32, 95%CI = 0.14-0.73) and progression-free survival (PFS, *P*-value = 0.001, adjusted HR = 0.45, 95%CI = 0.29-0.71). All the four SNPs and the *LCT* metabolic phenotype were not associated with the occurrence of overall immune-related adverse events (irAEs). Genetically predicted *Bifidobacterium* abundance was significantly associated with an increased abundance of lactose metabolism pathway (*P*-value = 0.012, Beta coefficient = 0.549). **Conclusions:** SNPs determining *Bifidobacterium* abundance in the lactose metabolism pathway have prognostic value for immunotherapy efficacy, and the lactose extensive and intermediate metabolizers exhibited better immunotherapy efficacy. Research Sponsor: National Natural Science Foundation of China; 82204534.

The details of *LCT* metabolic phenotypes and the associations of *LCT* metabolic phenotypes with overall survival.

	LCT genotypes and their risk allele					
	rs3739020G	rs56263017C	rs55809728A	rs3739022A	HR	P
Lactose extensive metabolizer (EM, no risk allele exist)	TT	TT	GG	GG	Refernces	
Lactose inermediate metabolizer (IM, risk alleles exist in 1-3 SNPs)	TG or GG	TT	GG	GG	0.58,95% CI=0.33-0.99	0.049
	TT	TC or CC	GG	GG		
	TT	TT	AA or GA	GG		
	TG or GG	TT	GG	AA or GA		
	TG or GG	TC or CC	GG	GG		
	TG or GG	TT	AA or GA	GG		
	TT	TT	GG	AA or GA		
	TT	TC or CC	AA or GA	GG		
	TT	TC or CC	GG	AA or GA		
	TG or GG	TT	AA or GA	AA or GA		
	TG or GG	TC or CC	AA or GA	GG		
	TG or GG	TC or CC	GG	AA or GA		
	TT	TT	AA or GA	AA or GA		
	TG or GG	TC or CC	AA or GA	AA or GA		
Lactose poor metabolizer (PM, risk alleles exist in 4 SNPs)	TG or GG	TC or CC	AA or GA	AA or GA	0.33,95% CI=0.18-0.62	0.001

The patients were stratified into three *LCT* metabolic phenotypes (PMs, IMs, EMs) according to the existence of the risk alleles (rs3739020 G, rs56263017 C, rs55809728 A, and rs3739022 A) in these four *LCT/MCM6* SNPs.The lactose EMs and IMs exhibited significantly extended OS than PMs.

Early peripheral Treg expansion after SBRT combined with low-dose radiotherapy to predict subsequent immune checkpoint inhibitor responses in patients with metastatic lung or gastrointestinal cancers.

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Background: This study aims to explore the potential therapeutic advantages of combining stereotactic body radiation therapy (SBRT) and low-dose radiotherapy (LDRT) prior to immune checkpoint inhibitor (ICI) treatment for metastatic lung or gastrointestinal cancers, to induce an immune-favoring tumor microenvironment. **Methods:** Patients with metastatic cancer and three or more measurable lesions scheduled for ICI therapy were enrolled in this study. Treatment consisted of three SBRT doses of 8–10 Gy to the main target lesion and LDRT (2–3 Gy) for other lesions. Patients without evidence of disease progression within 6 months after the first dose of ICI were defined as responders, while others were classified as non-responders. Peripheral blood samples obtained before SBRT/LDRT (W0), 1 week after SBRT/LDRT but prior to ICI initiation (W1), and 4 weeks after SBRT/LDRT (W4) were analyzed using multi-color flow cytometry. This trial has been registered at cris.nih.go.kr (registration number:KCT0005879). **Results:** Among the 13 enrolled patients (lung 9, gastrointestinal 4), samples from 4 responders and 7 non-responders were analyzed initially, revealing a median progression-free survival of 22.2 months for responders and 3.1 months for non-responders. The fold change in the proportion of regulatory ($Foxp3^{+}CD25^{+}$) $CD4^{+}$ T cells (Tregs) among total $CD4^{+}$ T cells at W1 compared to W0 (Treg/CD4–$FC_{W1/W0}$) was lower in responders than in non-responders (0.66 vs. 1.22; $P = 0.08$). Furthermore, the fold change in the proportion of suppressive $Foxp3^{hi}CD45RA^{+}$ Tregs among Tregs at W1 compared to W0 (Fr.II/Treg–$FC_{W1/W0}$) was significantly lower in responders than in non-responders (0.80 vs. 1.18; $P = 0.047$). This difference was no longer evident after one cycle of ICI, as Treg/CD4–$FC_{W4/W0}$ (1.15 vs. 0.86; $P = 0.46$) and Fr.II/Treg–$FC_{W4/W0}$ (1.06 vs. 1.33; $P = 0.18$) were not significantly different between responders and non-responders. **Conclusions:** We investigated circulating T cell modulation and its potential as a biomarker which revealed early expansion of Tregs in peripheral blood after SBRT/LDRT is associated with suboptimal response to ICIs in patients with metastatic cancers. Clinical trial information: KCT0005879. Research Sponsor: None.

The impact of immunotherapy versus chemotherapy on mortality and adverse events in cancer patients hospitalized with septic shock.

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Background: Traditionally, chemotherapies have been associated with well-characterized toxicity profiles and adverse events. Meanwhile, immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, but their secondary toxicities, particularly in patients with septic shock, remain underexplored. Our study sought to evaluate the comparative risk of mortality and adverse events in patients treated with ICIs versus chemotherapy. **Methods:** Using the TriNetX Research Database, we identified cancer patients (≥18 years) diagnosed with septic shock between January 1, 2013, and December 16, 2024. Eligible cancers included malignancies of the oral cavity, pharynx, larynx, stomach, kidney, bladder, skin, head, neck, and lung. Patients treated with ICIs or chemotherapy within 6 weeks before or up to 2 weeks after septic shock diagnosis were stratified into two cohorts. Propensity score matching (1:1) adjusted for confounders. Kaplan-Meier log-rank tests analyzed outcomes. Primary outcomes were mortality at 30, 60, and 90 days. Secondary outcomes included irAEs, organ failure, and hospitalization or emergency services within 1 week to 1 month. **Results:** Through our study we identified 44,052 cancer patients diagnosed with septic shock. A total of 4,284 patients were on chemotherapy within the time of their diagnosis, while 472 patients were on ICIs. ICI use was associated with higher 30-day (HR: 1.27, 95% CI: 1.03-1.57, p = 0.02), and 90-day (HR: 1.21, 95% CI: 1.009-1.45, p = 0.03) mortality. But only a near significant difference was noted at 60-days (HR: 1.20, 95%CI: 0.99-1.45, p = 0.054). Additionally, the risk of organ failures (HR: 1.28, 95% CI: 1.11-1.48,$p < 0.001$) and hospitalization or usage of emergency services (HR: 1.35, 95%CI: 1.16-1.56, $p < 0.001$) was higher in patients treated with ICIs compared to chemotherapy. The frequency of irAEs was slightly higher in patients with ICIs, though these results were only near significant (HR: 1.155, 95%CI: 0.977-1.364, p = 0.0532). **Conclusions:** Cancer patients treated with ICIs with septic shock exhibited higher short-term mortality, organ failure rates, and hospitalization or emergency service usage compared to those receiving chemotherapy. These findings are unexpected, given the perceived safety profile of immunotherapy compared to traditional chemotherapy. Further research is warranted to better understand these risks and to develop strategies for mitigating adverse outcomes in this population. Research Sponsor: None.

	Log-Rank Test			
	HR	95% CI	P-Value	$\chi 2$
Primary Outcomes				
30-day Mortality	1.272	(1.032,1.569)	0.0231	0.233
60-day Mortality	1.203	(0.996,1.452)	0.054	3.714
90-day Mortality	1.212	(1.009,1.455)	0.039	4.262
Secondary Outcomes				
Frequency of irAEs	1.155	(0.977,1.364)	0.0532	3.737
Incidence of organ failure	1.285	(1.115,1.48)	< 0.0001	23.556
Hospitalization or emergency services	1.349	(1.165,1.562)	< 0.0001	22.937

Gut dysbiosis as a potential guide for immunotherapy (dis)continuation after 2 years in non-small cell lung cancer: A mono-institutional, multi-omic assessment.

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Background: Although most phase II and III clinical trials have set the duration of immune checkpoint blockers (ICB) for advanced non-small cell lung cancer (NSCLC) at two years, there remains uncertainty regarding the feasibility and safety of discontinuing treatment after this period. Of note, gut microbial taxonomic profiling prior to starting immunotherapy shows promise as biomarker for predicting ICB response. Here, we recommend integrating multi-omics approaches over time (24 months -mo-) to inform clinical decision-making and guide personalized treatment strategies. **Methods:** Pts completing 18 to 24 mo of ICB treatment between July 2016 and January 2023 were identified and enrolled (NCT04567446) at Gustave Roussy. Clinical factors influencing treatment (dis)continuation were assessed at 24 mo. Multi-omic analyses, including gut-based biomarkers (TOPOSCORE by whole genome sequencing), PET-FDG imaging, and ctDNA, were proposed at this timepoint. Key outcomes, including overall survival (OS) and progression-free survival (PFS) rates, were analyzed. **Results:** Among 123 advanced NSCLC pts treated for ≥18 mo, 35 (28,5%) completed 24 mo, with 31 included in the analysis (4 excluded due to PD). Of these, 68% continued ICB, while 32% stopped between 23.5 and 29.7 mo, mainly based on the physician or the patient decision. Clinical characteristics were comparable between the 2 groups (Table 1). After a median follow-up of 59.1 mo, no significant OS and PFS differences were observed between pts who discontinued and those who continued (OS p=0.9012, PFS p=0.3715). Among the multi-omic assessments performed at 24 mo, only gut-based biomarkers appeared to be conditionally associated with PFS24 rates. The proportion of long-responders (progression-free at 24 mo) was higher among those with a favorable gut composition compared to those with harmful composition (81% vs 44%, respectively, p=0.0870). **Conclusions:** Our results suggest that multi-omics approaches may help safely discontinue ICB after two years of treatment. In this context, multi-institutional validation and the implementation of a translational multi-omic algorithm, including gut-based biomarkers, could provide insight into the optimal duration of ICB therapy beyond the predefined 24-mo period. Clinical trial information: NCT04567446. Research Sponsor: None.

Clinical characteristics of the cohort (n=31).

	Cessation group	Pursuit group	
Characteristics	**N = 10**	**N = 21**	**p-value***
Gender - no. (%)			
Male	5 (50)	12 (57)	0.7366
Female	5 (50)	9 (43)	
Age years - median (range)	61 (39-68)	62 (43-77)	
ECOG performance status - no. (%)			
0-1	9 (90)	15 (71)	0.2044
2	1 (10)	6 (29)	
PD-L1 expression - no. (%)			
<1%	0	2 (13)	0.5749
≥1%-<50%	3 (30)	2 (13)	
≥50%	7 (70)	11 (73)	
unknown	-	6	
Treatment regimen - no. (%)			
		Chemoimmunotherapy	
3 (30)		2 (10)	0.1907
		Monoimmunotherapy	
7 (70)		19 (90)	
Line of treatment - no. (%)			
First	7 (70)	10 (48)	0.7332
≥ Second	3 (30)	11 (52)	

*Chi-Square test.

Validation and refinement of Society of Immunotherapy of Cancer (SITC) definitions for PD-(L)1 resistance: An analysis of more than 1,300 participants from SWOG.

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Background: New immuno-oncology (IO) agents are commonly used in patients who previously received PD-(L)1 inhibitors. In order to facilitate clinical trial interpretation and better delineate therapeutic contributions of novel IO agents, consensus definitions of PD-(L)1 single-agent and combination immunotherapy resistance were published in 2020 (PMC7174063) and 2022 (PMC10016305) by the Society of Immunotherapy of Cancer (SITC); definitions outlined in Table. Validation of these expert-derived definitions is currently lacking. Herein we analyze two SWOG trials to evaluate the proposed definitions for the advanced and adjuvant settings. **Methods:** S1609/DART (NCT02834013) was a basket trial for patients with rare cancers treated with ipilimumab (1mg/kg intravenously [IV] every 6 weeks) plus nivolumab (240mg IV every 2 weeks). S1404 (NCT02506153) included an arm where patients with high-risk resectable Stage III melanoma received adjuvant pembrolizumab (200mg IV every 3 weeks for 1 year). In both trials, overall survival (OS) was measured from study registration to death from any cause with those last known to be alive censored. OS was evaluated with Kaplan-Meier and martingale residual plots and Cox regression models. **Results:** In S1609 (advanced setting), 733 participants were analyzed: 127 (17%) were not evaluable for primary resistance due to death or off treatment before 6 weeks. Among the 570 evaluable, 366 met the SITC primary resistance definition and 204 did not. Martingale residuals plots indicated a positive association between time to progression and OS with no evidence of a threshold. With a 6-month landmark, participants with primary resistance had significantly shorter OS compared to those who did not: hazard ratio (HR)=2.84, 95% confidence interval (CI) 2.28-3.55, p<0.001. In S1404 (adjuvant setting), 626 participants were analyzed with 12 (2%) meeting the definition of early recurrence/primary resistance and 138 (22%) meeting the definition of late recurrence/secondary resistance. Using a 12-month landmark, there was no significant difference in OS between early and late recurrences (HR=0.98, 95% CI:0.35-2.70, p=0.25), however late recurrences were associated with significantly shorter OS than no recurrence (HR=7.69, 95% CI: 2.71-20.1,p<0.001). **Conclusions:** In the advanced cancer cohort, the SITC definitions were validated. In the adjuvant cohort, early recurrences were uncommon and there was no significant difference in OS between early and late recurrences suggesting a 12-month cutoff may be more appropriate than 12 weeks. Additional analyses in other patient cohorts are needed to further understand if the SITC definitions for advanced cancers validate more broadly and if data-drive refinements are needed for the adjuvant setting. Research Sponsor: US National Cancer Institute; Bristol-Myers Squibb Company.

Advanced	
Primary	Treatment > 6 weeks; no response or < 6 months
Secondary	Treatment > 6 months; response/stable > 6 months
Adjuvant	
Early/primary	< 12 weeks last dose
Late/secondary	12 weeks

PhaseX: Patient tumor avatars for evaluating anticancer therapeutics.

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Background: Current preclinical tumor platforms, such as in vitro 2D cell cultures and organoid models, fail to fully recapitulate the complexity of the tumor microenvironment, including critical components like the extracellular matrix and immune interactions. While humanized patient-derived xenograft models address some of these limitations, they are costly, low-throughput, artificial, and technically challenging to establish. PhaseX (Patient-derived hydrogel-assisted eXplants) presents a robust alternative, preserving the native TME, including cellular diversity, gene expression, and immune landscapes, for at least seven days. This study utilizes PhaseX to assess patient-specific responses to immune checkpoint blockade (ICB), chemotherapeutics, and targeted therapies while providing insights into their mechanisms of action. **Methods:** Fifteen fresh patient-derived tumor explants (PDTEs) from HNSCC patients were embedded in bioengineered hydrogel and treated ex vivo with pembrolizumab. Supernatants were collected at 2 and 4 days post-treatment for immunoassay analysis. Tumor explants were either dissociated for high-dimensional flow cytometry or processed into FFPE sections for immunofluorescence analysis at 2 and 5 days. Additionally, ten PDTEs representing various cancer types (peritoneal, colorectal, sarcoma, lung and ovarian) were used to evaluate dose-dependent responses to commonly used chemotherapeutics, including cisplatin, doxorubicin, and erlotinib. Six PDTEs were treated with plasminogen activator inhibitor-1 (PAI-1), and their post-treatment metabolic activity was assessed using the resazurin cell viability assay. **Results:** This study highlights the importance of capturing temporal dynamics in ex vivo tumor models to accurately predict pembrolizumab responses, achieving 100% sensitivity and specificity in HNSCC patients. Increased IFN-γ secretion and upregulation of chemokines (CXCL9, CXCL10, CXCL11) distinguished responders, alongside elevated cytotoxicity markers (perforin, granulysin, sFasL, sFas) contributing to cancer cell death. Responders exhibited reduced terminally exhausted CD8+ T cells ($PD\text{-}1^{+}TIM3^{+}$), allowing reinvigoration of functional CD8+ T cells, while non-responders showed elevated $Tox^{+}CD38^{+}$ levels, indicating resistance to PD-1 blockade. Spatial analysis revealed greater T cell infiltration in responders, facilitating tumor-cell interactions. Additionally, the PhaseX platform demonstrated its utility in evaluating dose-dependent responses across multiple tumor types (sarcoma, colorectal, lung, cervical) and identified patient-specific responses to PAI-1 inhibition. **Conclusions:** The PhaseX platform accurately predicts patient-specific responses for ICB, chemotherapeutics and targeted therapy across multiple tumor types. These findings establish PhaseX as a valuable tumor platform to evaluate anticancer therapeutics. Research Sponsor: None.

Examining the relationship between multi-agent immunosuppressive therapy for immune-related adverse events (irAE) and infectious complications.

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Background: Treatment of severe irAEs with multiple immunosuppressive therapies (ISTs) decreases the morbidity and mortality of these conditions. Nevertheless, the rates of and risk factors for infectious complications in this population are not known. **Methods:** We conducted a retrospective study of patients (pts) who received an immune checkpoint inhibitor (ICI) and experienced ≥1 irAE requiring treatment with corticosteroids along with at least two lines of steroid-sparing ISTs administered either concurrently or within 90 days of each other. We annotated all infections from ICI start until 90 days after IST. Opportunistic infections (OIs) were defined as herpesvirus (CMV, EBV, VZV, and HSV) and invasive fungal infections. Infection density was reported as number of infections per 1000 patient-days and graded as mild (not requiring treatment), moderate (requiring oral treatment), severe (requiring hospitalization or parenteral treatment), life threatening, or fatal. Risk factors were identified using univariable and multivariable Cox regression analysis adjusting for age at ICI initiation, sex, ICI regimen, ISTs, and steroid dose. **Results:** 175 pts (52% male, mean age: 66) with 238 irAEs and 417 ISTs were analyzed with a median follow-up of 367 days. The associated ICI regimens included αPD-1 (n = 81, 46%) and αPD-1/αCTLA-4 (n = 67, 38%). The most common irAEs were colitis (n = 67, 38%), hepatitis (n = 42, 24%), and myocarditis (n = 26, 15%). The most frequently used ISTs were mycophenolate mofetil (n = 92, 53%), infliximab (n = 77, 44%), and vedolizumab (n = 54, 31%). 103 pts (59%) developed 223 infections (median 2/pt, range: 1-8). 93 pts had 187 non-OIs. Of the 87 pts (50%) who had OI testing, 29 (33%) had 36 OIs, most commonly EBV DNAemia (n = 14, 16%) and CMV reactivation (n = 12, 14%). 6 pts had >1 OI, including 1 pt with CMV, EBV, and HSV. OI density significantly increased after starting ISTs for irAEs, but non-OI density was unchanged (Table 1). αCD20 use was associated with increased non-OI risk (HR: 10.58, 95% CI: 3.64-30.72, $p < 0.001$), while there was a trend towards increased non-OI risk with a max prednisone dose >100mg (HR: 1.74, 95% CI: 0.96-3.13, p = 0.07). In contrast, a max prednisone dose >100mg was associated with increased OI risk (HR: 2.89, 95% CI: 1.21-6.90, p = 0.017). 58 pts (33%) had severe or life-threatening infections, of whom 16 (9%) had OIs. 8 pts (5%) had fatal infections in this population. **Conclusions:** Use of multiple ISTs for severe irAEs is associated with increased rates of opportunistic infections as well as a 5% infection-related mortality rate. Patients requiring multiple lines of ISTs must be closely monitored for infectious complications, and prophylaxis should be considered when appropriate. Research Sponsor: None.

Mean OI and non-OI density per 1000 patient-days while on ICI alone vs ISTs.

	ICI	ISTs	p-value
OI	0.03	1.70	0.002
Non-OI	10.70	8.98	ns

Incidence and outcomes of immune checkpoint inhibitor (ICI) rechallenge after ICI pneumonitis: A single-center retrospective study.

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Background: Limited evidence is available on the safety and efficacy of immune checkpoint inhibitor (ICI) rechallenge following an immune-related adverse event (irAE). Pneumonitis is a potentially life-threatening irAE, and minimal data is available with regards to outcomes after rechallenge. In this single-center retrospective analysis we analyzed patients who developed ICI pneumonitis and were later rechallenged with an ICI to further investigate incidence patterns and outcomes. **Methods:** We conducted a manual chart review on a cohort of 69 patients with ICI pneumonitis at our institution from 2015 to 2024. Rechallenged cases were defined as any patient who developed ICI pneumonitis and were later trialed on the same or another ICI. Patient records were reviewed to identify demographics, clinical features, treatment, and outcomes. **Results:** Of 69 patients with ICI pneumonitis, we identified 19 that were rechallenged with an ICI. Of these, 10 were women and 9 were men. The average age was 64 years (range: 42-82). Most patients had lung cancer (42%, 8/19) followed by melanoma (32%, 6/19). The treatment intent was palliative for 74% of patients (14/19). The most common therapy was nivolumab (n = 15), however, pembrolizumab, atezolizumab, and durvalumab were also used. The initial grade of ICI pneumonitis was as follows: grade 1 (n = 2), grade 2 (n = 13), grade 3 (n = 3), and grade 4 (n = 1). Many of these patients were treated with steroids, with the average time on steroids being 136 days (range: 0-488). Additionally, the only grade 4 patient was also treated with infliximab due to steroid-refractory pneumonitis. After recovery from their pneumonitis, all patients, except for two, were rechallenged with the same ICI that they had originally been treated with. The average time to rechallenge was 149 days (range: 12-714). Ultimately, 6/19 (32%) patients had recurrent ICI pneumonitis after rechallenge, but all six eventually recovered. On grading ICI toxicity after recurrence, 60% (4/6) remained grade 2, one was downgraded from grade 3 to 2, and one escalated from grade 2 to 3. Eleven percent (2/19) of patients developed an irAE other than pneumonitis (e.g. colitis, arthritis) after rechallenge. Finally, none of the 19 patients died from complications associated with ICI therapy. **Conclusions:** The recurrence rate of ICI pneumonitis after ICI rechallenge was 32%. At initial presentation, most of these patients had lower grade (grade 1: 2/19, grade 2: 13/19) ICI pneumonitis and most cases of recurrent pneumonitis remained at their initial grade 2. These results indicate that resuming ICI therapy could be considered in select patients with mild to moderate pneumonitis. Further research is needed to investigate immunotherapy rechallenge as it remains a nuanced decision that involves assessing the potential benefits of continued tumor control against the risk of a life-threatening toxicities. Research Sponsor: None.

Clinical outcomes of patients with or without DNA repair pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study.

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Background: DNA repair deficiency is common among tumors, and emerging data suggest that genomic instability is associated with response to immuno-oncology (IO) therapies (PMID 28630051). We evaluated patients with advanced metastatic cancer across tumor types, who were treated on the IMPACT2 study (NCT02152254) and analyzed their clinical outcomes by treatment type (anti-DNA damage repair [DDR] agents, IO, or other [non-IO, non-anti-DDR]). **Methods:** Patients had tumor biopsies followed by molecular profiling in a CLIA-certified lab. All cases were discussed at Molecular Tumor Board meetings. Patients were treated on early-phase clinical trials. Progression-free survival (PFS), overall response rate (ORR), and overall survival (OS) were compared by therapy type in patients with or without DDR/MMR mutations (DDR+). **Results:** Of 829 enrolled patients, 510 had molecular profiling and received anticancer therapy: 85 were DDR+ (PS 1, 75%; med. age, 59 yrs; males 56.5%; med prior therapies 4; PDL1+ 44.9%; TMB-H 18%,) and 425 DDR- (PS 1, 88%; med. age, 60 yrs; men 47%, med. No. prior therapies 3; PDL1+ 46%; TMB-H 6.5%). Results are shown in the Table. In patients with DDR mutations, IO was associated with a higher ORR compared with "other" treatments (p=0.044); and with longer PFS compared with anti-DDR therapies (p = 0.044); no difference was noted in OS by treatment type. In the DDR-neg group, IO was associated with longer PFS (p = 0.017), and longer OS (p = 0.0004) compared with anti-DDR therapy; OS was longer in the IO group compared with "other" treatments (p = 0.029) and in the "other" treatments group compared with anti-DDR agents (p=0.006). **Conclusions:** Our data indicate the complexity of assessing outcomes in patients with various tumor types and without DDR mutations. Further work is needed to develop predictive biomarkers for IO and anti-DDR agents. Clinical trial information: NCT02152254. Research Sponsor: Steven McKenzie's Endowment for Dr Tsimberidou's personalized medicined program; Katherine Russell Dixie Distinguished Endowed Professorship for Dr Tsimberidou; Jamie's Hope for Dr Tsimberidou's personalized medicined program; NIH National Cancer Institute award number P30 CA016672 (to The University of Texas MD Anderson Cancer Center).; Tempus, Inc. for the IMPACT 2 study; Foundation Medicine, Inc for the IMPACT 2 study.

	Rx type	DDR-pos	N	Outcome	Anti-DDR vs IO	IO vs Other	Anti-DDR vs Other	DDR-neg	N	Outcome	Anti-DDR vs IO	IO vs Other	Anti-DDR vs Other
Overall response (%)	IO		34	6 (25%)	OR* 0.78; p=0.81	**OR* 20.73; p=0.044**	OR* 16.09; p=0.1		116	9 (11%)	OR* 0.34; p=0.46	OR* 2; p=0.13	OR* 0.67; p=0.79
	Anti-DDR		18	1 (16.7%)					52	0 (0%)			
	Other		33	0 (0%)					257	12 (5.9%)			
PFS, med. (95% CI)	IO		34	4.26 (2.3, 7.4)	**HR 2.01 (1.02,3.96) (p=0.044)**	HR 0.91 (0.56,1.47) p=0.69	HR 1.82 (0.95,3.49) p=0.07		116	5.42(3.02,6.61)	**HR 2.02 (1.14,3.61) p= 0.017**	HR 0.85 (0.68,1.06) p= 0.15	HR 1.71 (0.98,2.99) p=0.058
	Anti-DDR		18	2.58 (1.68, NA)					52	1.64 (1.45, NA)			
	Other		33	4.54 (3.06, 6.54)					257	3.98 (3.45, 4.57)			
OS, med. (95% CI)	IO		34	14.37 (10.22, NA)	HR 1.68 (0.82,3.42) p=0.16	HR 0.73 (0.43,1.23) p=0.24	HR 1.23 (0.62,2.42) p=0.56		116	12.46 (8.75, 20.78)	**HR 2.98 (1.62,5.48) p=0.0004**	**HR 0.76 (0.6,0.97) p=0.029**	**HR 2.27 (1.27,4.07) p=0.006**
	Anti-DDR		18	8.98 (3.48, NA)					52	4.31 (2.66, NA)			
	Other		33	10.82 (7, 16.83)					257	9.4 (8.28, 11.21)			

*OR, Odds Ratio, p values, unadjusted for multiple comparisons.

MicroRNA-based signatures of early and late immune-related adverse events to anti-PD1 treatment.

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Background: Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but are associated with toxicity in the form of immune-related adverse events (irAEs). We previously reported a genetic signature predicting anti-PD1 irAEs in a retrospective analysis of a heavily pretreated melanoma cohort, which validated in a pan-cancer cohort. Here we investigate the applicability of that signature in a prospectively collected cohort of GU, breast, and NSCLC cancer patients. We evaluated clinical and genetic differences between the original training set and this cohort and leveraged the expanded dataset to develop novel models for timing-specific anti-PD1 toxicity. **Methods:** We analyzed clinical and genetic differences in the melanoma training cohort (n=58) and the new cohort of patients, all treated with single agent anti-PD1/PDL1 therapy (n=137). Clinical and genetic differences were assessed using Fisher's exact test for categorical variables: pre-treatment, concurrent radiation, and SNP genotype across 165 loci. Kruskal-Wallis tests were used for age, toxicity timing, and severity of toxicity. Predictive genetic models were constructed using elastic net, random forest, and boosted tree algorithms and evaluated using leave-one-out cross-validation (LOOCV) metrics. Outcomes included cycle-specific toxicity (early $\leq$5 cycles, late $\geq$15 cycles). SNPs were pre-filtered for inclusion in genetic models using Fisher or Jonckheere-Terpstra p-values ($<$0.2) for relevance to outcomes. **Results:** The training and current cohort were different in their toxicity timing, with earlier toxicity onset in the new cohort (median 5 cycles vs. 20 cycles in melanoma, Kruskal p = 0.00018). Genetic analysis identified 12 significantly different SNP genotypes (Fisher $p < 0.05$) between cohorts, including mir146A rs2910164 (Fisher p = 0.0005). This SNP was associated with early toxicity overall and within data subsets. Refining our model to account for cycle-specific toxicity events significantly enhanced performance. For late toxicity ($\geq$15 cycles), the refined model achieved a LOOCV AUC of 0.793 (genetics + clinical). A newly developed early toxicity model ($\leq$5 cycles) using genetics alone demonstrated robust predictive accuracy with an AUC of 0.753. **Conclusions:** These findings emphasize the importance of defining clinical and genetic diversity in refining predictive models for anti-PD1/PDL1 outcomes. The development of an early toxicity model offers significant clinical utility. Next steps will be to use time to event (toxicity) versus cycle number. This study provides a foundation for the application of personalized genetic tools to predict the safety of ICIs for currently treated patient cohorts. Research Sponsor: U.S. National Institutes of Health; R01CA238998.

New LOOCV performance metrics in expanded PD1 data (n=234).

Outcome	Covariates	Sensitivity	Specificity	PPV	NPV	F1	AUC
Late Toxicity (>= 15 cycles)	SNPs + Clin	0.692	0.894	0.450	0.959	0.545	0.793
Early Toxicity (<=5 cycles)	SNPs Only	0.600	0.907	0.486	0.939	0.537	0.753

Overall survival according to timing of immune checkpoint inhibitors administration in patients with advanced cancer: Results from a large single-centre cohort analysis.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionised cancer treatment but are only effective in a subset of patients. Evidence of a circadian dependence of the immune system has led to retrospective studies which suggested that the time of day of ICIs infusion influences treatment response, with better outcomes for early treatment times. Previous studies are limited by small sample size and methodological bias. We performed a retrospective study in patients with advanced solid tumours treated with ICIs at a large tertiary cancer centre. **Methods:** Patients who received regimens comprising ICIs for advanced/metastatic disease between January 2018 and December 2023 were grouped according to whether they received ≥50% ("late group") or < 50% ("early group") of cycles after the median time of all treatments. The primary endpoint was overall survival (OS). Hazard ratios (HRs) for OS after multivariable adjustments for age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, cancer type and treatment were estimated using Cox models with and without time-dependent variables that allowed for group (early vs. late) assignment to change after baseline. **Results:** 2631 patients with lung cancer (45%), melanoma (23%), renal carcinoma (18%), head and neck (9%) and urothelial cancer (5%) were included. The median age was 68.2 years and 1602 (61%) were men. The median follow up was 38 months. The median infusion time was 12:49h. Median OS was 13.1 (95% confidence interval [CI] 11.8-14.4) vs. 21.4 (95% CI 19.8-24.5) months for late and early group. The late group was associated with shorter OS compared to the early group on both the standard multivariate analysis (HR 1.48, 95% CI 1.33-1.63) and the time dependent Cox model (HR 1.30, 95% CI 1.16-1.44). The association was significant for most regimens with ICIs alone (n = 1886) and for ICIs plus tyrosine kinase inhibitors (n = 163). There was no difference for regimens comprising chemotherapy (n = 582). A sensitivity analysis based on exposure at 3 months showed no difference between the groups with the standard model (HR 1.09, 95% CI 0.98-1.20) and a higher risk of death for the late group with the time dependent model (HR 1.14, 95% CI 1.02-1.26). **Conclusions:** This study suggests a benefit in OS with early administration of ICIs with a large sample size and a time-dependent Cox model which reduces the risk of immortal time bias. These findings could have a major clinical impact after small changes in the way services are provided. Exclusive morning administration for all doses in the first 3 months could be a feasible approach to minimise complexity of treatment slot allocation. Research Sponsor: None.

The impact of lymphocyte count dynamics on the predictive value of tumor mutational burden (TMB) for immune checkpoint inhibitors (ICI) outcomes in patients (pts) with cancer.

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Background: TMB has become a reliable biomarker for ICI response in several cancer types, leading to the pan-cancer FDA approval of the PD-1 inhibitor pembrolizumab in tumors with a TMB ^{3}10 mut/Mb. Lymphocyte count dynamics (lymphocyte stability LS) have been reported to be associated with both increased immune-related adverse events and improved overall survival (OS) on ICI. We aimed to investigate the role of LS as a risk stratification tool, in combination with TMB, in patients with cancer treated with ICIs. **Methods:** We identified 1215 pts from the Dana-Farber Cancer Institute, who had received ICI between 2015 and 2024. The change in relative blood lymphocyte counts was calculated between pre- (up to 30 days) and post-treatment (between 21 and 49 days). Lymphocyte counts were considered stable (LS ≥80%) if the drop in lymphocyte count did not exceed 20% after ICI-exposure. TMB was assessed from targeted panel sequencing and categorized into high and low, based on a cutoff of 10 mut/Mb. Overall survival was assessed using a multivariable Cox regression model, adjusting for several baseline characteristics. **Results:** The most prevalent cancer types were non-small cell lung cancer (n = 190), breast carcinoma (n = 160), glioma (n = 104), and melanoma (n = 100). Median TMB was 6.8 (IQR: 0–265.4). In total, 846 (69.6%) patients had LS (drop < 20%), while 369 (30.4%) did not. Higher TMB (≥10) and LS were both independently associated with better survival on ICI after adjusting for age, sex, tumor purity, line of therapy, ICI type and cancer type (HR 0.58, CI: 0.50–0.67; p < 0.001) and 0.75 (CI: 0.63–0.90; p = 0.002) respectively. Overall, patients with LS and high TMB demonstrated the longest median OS while the combination of unstable lymphocyte counts and low TMB was associated with the worst survival (Table). **Conclusions:** LS provides additional value, irrespective of TMB, in predicting response to ICI, suggesting distinct underlying immunological pathways. These findings emphasize the need for further research to validate LS and explore its integration into clinical decision-making in ICI-treated pts. Research Sponsor: None.

Results from multivariable Cox regression.

Groups	Median OS (mo)	N	HR	95% CI	P-value
Stable lymphocytes (LS ≥80%) & High TMB (Cutoff = 10)	34.27	245	Ref.	Ref.	Ref.
Stable (LS ≥80%) & Low TMB	18.99	601	1.3	1.04 - 1.63	0.019
Unstable (LS <80%) & High TMB	17.05	96	1.66	1.22 - 2.26	0.001
Unstable (LS <80%) & Low TMB	9.59	273	2.28	1.79 - 2.90	<0.001

Model is adjusted for age, sexe, tumor purity, lines of treatment, PD1/PDL1 therapy, and CTLA-4 therapy.
Abbreviations: TMB: Tumor mutational burden; LS: Lymphocyte Stability; OS: Overall Survival; mo: Months.

Association of intestinal exfoliome and Prevotellaceae with toxicity and clinical outcome during immune-checkpoint blockade.

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Background: Immune-related adverse events (irAEs) are autoimmune side effects related to ICI, varying in severity, onset and organ involvement that may be hard to differentiate from non-irAEs. Some reports have demonstrated that gut microbiota (GM) plays a role in modulating the risk of AEs. In this study, we combine gut mamalian and microbial metagenomics sequencing (MGS) to explore the influence of GM on treatment response and risk of AEs. **Methods:** NCT04567446 allowed fecal MGS at baseline and longitudinally in patients (pts) with advanced non-small cell lung cancer (), renal cell carcinoma and bladder cancer treated with ICI alone (ICI cohort, n = 542pts) or in combination with chemotherapy (CT+ICI cohort, n = 122 pts) in France and Canada. Pts who experienced severe (≥ grade 3) irAEs after ICI+/-CT were compared to those who did not, using microbial MGS parameters (Shannon diversity, TOPOSCORE, PCoA and LEfSe). Multivariate Cox regression models to analyze factors influencing overall survival (OS) included microbiota composition and the host exfoliome (i.e., mammalian eukaryotic DNA read counts within stools). **Results:** Pts with severe irAEs (10%) presented a less diverse microbiome, a lower TOPOSCORE and a distinct microbial community compared to those without severe irAEs, showing an overabundance of several members of the *Prevotellaceae* family. Interestingly, CT+ICI pts who experienced severe irAEs had the most dysbiotic microbiome, characterized by a lower alpha-diversity and TOPOSCORE, dominated by oral taxa (*Ligilactobacillus salivarius)* and tolerogenic *Hungatella* spp. and *Enterocloster spp.* Among pts screened for exfoliation, 44% presented hstool mammalian DNA than healthy subjects, showed a GM enriched with pathobionts, including the *Enterocloster* genus, and exhibited worse OS (HR 1.212, p = 0.0135) in univariate and multivariate analyses (HR 1.18, p = 0.049). Although there was no significant correlation between toxicity and exfoliation, either in CT+ICI or ICI alone, pts enriched with Prevotellaceae family appeared to exhibit the highest levels of exfoliation. **Conclusions:** Host-microbial interactions influence immunity and therefore ICI prognosis and toxicity. We found Prevotellaceae members as potential biomarkers for ICI-related toxicity. The host exfoliome is an interesting parameter that may reflect gut fitness, requiring further investigation. Clinical trial information: NCT04567446. Research Sponsor: RHU IMMUNOLIFE, RHU LUMIERE.

A Bayesian population-based framework for detecting hyperprogressive disease on cancer immunotherapies.

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Background: Hyperprogressive Disease (HPD), defined as an unexpected treatment-induced rapid increase in tumor growth rate relative to the tumor burden pretreatment growth rate, has been reported in 9% of patients receiving immune checkpoint inhibitor (ICI) therapies (Champiat et al, Clin Cancer Res (2017)). The definition of HPD used in that work was an increase in the on-treatment "Tumor Growth Rate" (TGR) by a factor of 2 or greater over the pre-treatment TGR as calculated from three consecutive CT scans: pre-baseline, baseline and on-treatment. This method of directly calculating TGR from slopes between successive tumor measurements, however, does not consider uncertainty in the CT-assessed sum of diameters (SoD) of target lesions (~8% per Zhao et al, Radiology (2009)), nor prior knowledge of the distribution of responses under ICI treatment. We sought to develop and test a Bayesian approach to HPD detection and compare its receiver operating characteristics (ROC) to the published TGR ratio threshold of 2-fold as well as the TGR ratio considered as a continuous classifier of HPD. **Methods:** We represented the prior distribution of exponential TGR (eTGR) pre-treatment based on population modeling of historical data of untreated NSCLC tumor dynamics. We then calibrated the on-ICI-treatment prior distribution based on reported rates of HPD and tumor regression. Next, we developed a Bayesian parameter estimation system to take three successive SoD assessments to calculate a patient's posterior probability of being in a state of HPD, attenuated tumor growth (ATG) or tumor regression (REG). We then simulated a cohort of 1000 virtual patients (VPs) with known state and tested the ability of the Bayesian method, the TGR ratio method, and the TGR ratio $>$ 2 method to correctly classify each VP. We additionally developed a user-friendly web-based prototype tool (https://deanbot1.shinyapps.io/GRICalc/) to solicit feedback from a potential future user community. **Results:** ROC analysis estimated the area under ROC curve (AUROC) to be 0.94 for the Bayesian method, a significant improvement in classification accuracy over the TGR ratio method (AUROC = 0.77) as well as better maximal sensitivity (Se) and specificity (Sp) than the TGR ratio $>$ 2 method (Se = 80% & Sp = 90% vs Se = 90% & Sp = 40%). **Conclusions:** We have developed a Bayesian population-based methodology and prototyped a web-based tool which under simulated conditions consistently outperformed previous methods for detecting HPD. We believe that this approach, trained on a larger patient-level dataset, can potentially support and improve clinical management and decision-making for cancer patients taking immune checkpoint inhibitor therapies. Research Sponsor: None.

Safety outcomes of intravenous immunoglobulin (IVIG) in treatment of steroid-refractory immune-checkpoint inhibitor pneumonitis.

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Background: Pneumonitis is a potentially severe adverse event of immune checkpoint inhibitors (ICIs). While the first line treatment for ICI pneumonitis is corticosteroids, there are subsets of patients who either fail to respond, deemed steroid-refractory, or who cannot be tapered off steroids, deemed steroid-dependent. In these patients, there is no clear consensus on the best approach to treatment. IVIG has emerged as a potentially efficacious treatment for its immunomodulatory effects. It is also less immunosuppressive than other potential therapies, which is beneficial in a population which respiratory infection could lead to rapid clinical decline. However, there are concerns about treatment safety, including volume overload, thrombosis, and renal injury, which can be devastating in a patient population with pre-existing respiratory compromise. In this study, we aimed to assess the safety of IVIG treatment in patients with steroid-refractory ICI pneumonitis. **Methods:** A retrospective review was conducted of patients with steroid-refractory ICI pneumonitis treated with IVIG at Johns Hopkins Hospital from 2018 to 2024. Patient characteristics, treatment features, disease severity, clinical outcomes, and development of adverse events post-IVIG including renal injury, volume overload, or thrombosis were evaluated. **Results:** A total of 31 patients were selected with steroid refractory pneumonitis treated with IVIG. Mean age at diagnosis was 68 (56-80). The most common primary tumor site was lung (n = 23) and majority of patients had stage IV malignancy (n = 19). 81% (25/31) had grade 3 or 4 pneumonitis at the time of IVIG therapy. In-hospital death occurred in 41% (13/31). Majority of in-hospital death was due to respiratory decompensation from pneumonitis and no deaths were directly related to complications of IVIG. Regarding adverse events, 9.68% (3/31) of patients developed a venous thromboembolism related to IVIG. 3.23% (1/31) developed acute kidney injury and 12.90% (4/31) developed hypervolemia in response to IVIG. **Conclusions:** IVIG was not associated with a high rate of toxicity when used in the treatment of steroid refractory ICI-pneumonitis. The increased in-hospital mortality indicates the severity of illness in this patient population. Despite this, IVIG-related adverse events were low overall. Although a small cohort, these results suggest a favorable safety profile and support further study to evaluate efficacy of IVIG as compared with other immunomodulatory agents. Research Sponsor: None.

IVIG treatment related adverse events.	
VTE related to IVIG* (%; n)	9.68 (3)
Acute kidney injury (%; n)	3.23 (1)
Volume overload (%; n)	12.90 (4)

IVIG: intravenous immunoglobulin, VTE: venous thromboembolism.
*2 of the patients died.

Vedolizumab or infliximab: Treatment option in immune checkpoint inhibitor–induced colitis.

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Background: ICI use is linked to severe gastrointestinal (GI) immune-related adverse events (irAEs), which affect morbidity and mortality and often require treatment pauses. Among these, immune-mediated colitis (IMC)—primarily associated with CTLA-4 therapy—occurs in 5.7% to 39.1% of patients receiving CTLA-4 inhibitors and 0.7% to 31.6% of those receiving PD-1/PD-L1 inhibitors; combination therapy can raise this incidence to 40.4%. IMC symptoms range from mild diarrhea to severe colitis, typically requiring urgent intervention within six to eight weeks of immunotherapy to prevent complications such as colonic perforation or sepsis. Corticosteroids are the usual first-line treatment, with TNF-alpha inhibitors (e.g., infliximab) considered when patients do not improve after three to seven days. Vedolizumab, a gut-selective $\alpha 4\beta 7$ integrin antagonist that targets gastrointestinal-homing T-lymphocytes, offers an alternative approach. Both infliximab and vedolizumab—referred to as Selective Immunosuppressive Therapies (SITs)—have shown promise, though their distinct mechanisms have led to a lack of standardized protocols and reliance on provider discretion. This study compares infliximab, vedolizumab, and combined SITs (infliximab plus vedolizumab) in managing IMC, focusing on remission rates, recurrence, and improved steroid tapering success. **Methods:** A systematic search was conducted across the PubMed database. The Meta-Analysis was conducted using R version 4.4.1 to calculate odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** A total of eight studies were included in the final analysis. In patients with immune checkpoint inhibitor–induced colitis, vedolizumab was associated with higher rates of colitis recurrence (OR = 0.32, 95% CI = 0.19–0.53) compared to infliximab. Patients receiving vedolizumab also had lower overall corticosteroid usage (mean difference in days: -18.29, 95% CI = -21.88 to -14.71) compared to infliximab recipients. There was no significant difference in remission rates between vedolizumab and infliximab monotherapy; however, higher remission was noted with combination therapy (vedolizumab plus infliximab) (OR = 0.40, 95% CI = 0.19–0.84) compared to infliximab monotherapy. **Conclusions:** Vedolizumab was associated with a higher recurrence rate of colitis but resulted in significantly lower corticosteroid usage compared with infliximab. Although remission rates were similar for both monotherapies, combination therapy (vedolizumab plus infliximab) demonstrated higher remission rates than infliximab alone. Research Sponsor: None.

TPS2668 Poster Session

A phase 1, first-in-human study of DS-2243, an HLA-A*02/NY-ESO–directed bispecific T-cell engager, in patients with advanced solid tumors.

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Background: NY-ESO-1 and LAGE-1 are homologous proteins commonly expressed in various malignancies but not in normal tissues other than the testis and placenta. Tumor types showing prevalent NY-ESO-1 and/or LAGE-1 expression include synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCLS), non-small cell lung cancer (NSCLC), and urothelial carcinoma (UC). Both NY-ESO-1 and LAGE-1 undergo intracellular proteolytic processing to generate the same highly immunogenic 9-mer NY-ESO peptide (SLLMWITQC), which is presented on the cell surface in association with HLA-A*02 major histocompatibility complex molecules. DS-2243 is a bispecific antibody and T-cell engager with an effectorless Fc region. It is designed to target HLA-A*02/NY-ESO peptide complexes on tumor cells and specific molecules on T-cells, redirecting T-cell–mediated cytotoxicity toward the tumor. **Methods:** DS2243-054(NCT06644755) is a Phase 1, first-in-human, open-label, multicenter, 2-part, dose-escalation and -expansion trial of DS-2243. Patients must be ≥18 years of age and have HLA-A*02-positive advanced or metastatic SS, MRCLS, squamous or adenocarcinoma NSCLC, or UC, and be unable to tolerate standard treatments, or have relapsed disease after or be refractory to such treatment. Patients with NSCLC or UC in dose escalation and all patients in dose expansion must have NY-ESO protein expression confirmed in tumor tissue by immunohistochemistry in a central laboratory. Further inclusion criteria include the presence of ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1) and Eastern Cooperative Oncology Group performance status of 0 or 1. The primary objective of dose escalation is to evaluate the safety and tolerability of DS-2243 and determine the maximum tolerated dose and/or recommended dose for expansion (RDE). The dose-expansion part includes 4 cohorts defined by tumor type—SS/MRCLS, squamous NSCLC, adenocarcinoma NSCLC, and UC—in which patients receive DS-2243 at the RDE. The primary objectives of dose expansion are to evaluate safety and determine the objective response rate (ORR) assessed by the investigator per RECIST 1.1. Safety endpoints include dose-limiting toxicities (dose escalation only) and treatment-emergent adverse events. Secondary outcome measures include ORR (dose escalation only), time to response, duration of response, progression-free survival (all assessed by the investigator per RECIST 1.1), and overall survival. The planned sample size is ~150 patients; enrollment is ongoing. Clinical trial information: NCT06644755. Research Sponsor: Daiichi Sankyo, Inc.

TPS2669 Poster Session

Phase 2 expansions of OR502, an antibody targeting leukocyte immunoglobulin-like receptor B2 (LILRB2) ± cemiplimab in patients with advanced solid tumors.

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Background: LILRB2 is an inhibitory receptor expressed on myeloid cells, including tumor-associated macrophages, which binds to HLA-class I proteins and is associated with poor outcomes in multiple cancers. OR502 is a humanized immunoglobulin G1 antibody that blocks LILRB2 binding to HLA-class I proteins. Preclinically, OR502 has demonstrated best-in-class reversal and prevention of myeloid cell-mediated immune suppression and restoration of T cell functions. Using OR502 to tackle immunosuppression and improve T cell-mediated responses in the tumor microenvironment (TME) is a rational for combination with checkpoint inhibitors.
Methods: This is an ongoing, first-in-human, Phase 1-2 study of OR502 ± cemiplimab in patients with advanced solid tumors (NCT06090266). The primary objectives are to evaluate the safety/tolerability and identify a dose for further clinical development. Secondary objectives include assessment of pharmacokinetics (PK), immunogenicity and anti-tumor activity. We are also assessing the effects of OR502 on the TME and associations between response and pharmacodynamic (PD) markers. Dose escalation enrolled 39 patients at OR502 doses of 100–1600 mg, once every 3 weeks (Q3W) ± standard dose cemiplimab (350 mg), using a modified toxicity probability interval-2 design. As dose escalation completed, it became clear that to satisfy the FDA's Project Optimus, adaptations were needed to provide dose-response proof and identify the minimal effective dose before proceeding with development. The protocol's adaptive elements, in conjunction with Safety Committee oversight, enabled modifications without amendment. Prior to dose-response optimization, we adapted the design in order to explore the efficacy signals from phase 1, specifically in patients with melanoma and NSCLC. Based on efficacy signals and excellent safety, PK and PD results, we selected OR502 800 mg Q3W for both expansion cohorts. Two new mini-expansion cohorts are now actively recruiting 10–20 patients each: monotherapy in patients with cutaneous melanoma and combination in patients with NSCLC. The sample size was chosen pragmatically, to exclude a response rate of ~ 10%, with a target of ~ 35%. If < 2 responses are seen in the first 10 patients, the cohort will be discontinued. All patients must have a histological diagnosis of measurable disease that has progressed with ≥ 2 lines of treatment, ≥ 12 weeks of prior PD-(L)1-based therapy, resolved prior toxicity with a 2–4 week washout, adequate organ function, ECOG ≤ 2, and no significant ascites, pleural effusion or CNS metastases, recent infections or autoimmune disease requiring steroids or immunosuppressants. Cycles 1 and 3 include serial PK sampling, while Cycles 2, 4 and beyond require only one visit on Day 1. Efficacy is assessed Q6W for 1 year, then Q6 months. Safety follow-up at end of treatment is at 120 days. Clinical trial information: NCT06090266. Research Sponsor: OncoResponse, Inc.; The Cancer Prevention and Research Institute of Texas.

TPS2670 **Poster Session**

A phase 1/2a, multicenter, first-in-human, open-label clinical trial evaluating MDX2001, a tetraspecific T cell engager-expander in patients with advanced solid tumors.

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Background: MDX2001 is a multispecific antibody recognizing CD3 and CD28 on T cells, and c-MET and TROP2 on tumors. Anti-CD3 provides the primary signal for T cell activation; anti-CD28 delivers the secondary signal for enhanced T cell activation, survival, and proliferation. Combinatorial targeting of c-MET and TROP2 by MDX2001, either on the same or different cancer cells, provides more effective engagement on tumor cells, and may better address tumor heterogenicity and the development of resistance due to antigen downregulation. *In vitro* and *in vivo* studies with MDX2001 demonstrate potent antitumor activity with no CD28-superagonist activity and minimal T cell activation in the absence of tumor cells. **Methods:** This Phase 1/2a, multicenter, first-in-human, open-label clinical trial explores intravenous MDX2001 in patients with advanced solid tumors (NCT06239194). The study design consists of Phase 1a dose escalation guided by a Bayesian Optimal Interval design with a target maximum tolerated dose toxicity rate of 30%, Phase 1b dose expansion, and Phase 2a indication expansion. Patients with non-small cell lung, renal cell, prostate, breast cancer and 10 other selected tumors known to have significant levels of TROP2 or c-MET expression are eligible for Phase 1a. In Phase 1b, patients will be randomized into 2 dose cohorts using a Bayesian Optimal Phase 2 (BOP2) design. Once a recommended Phase 2 dose (RP2D) is determined, Phase 2a will enroll patients in search of initial efficacy signals using a BOP2 design. The primary objectives of this study are to characterize the safety, tolerability, and anti-tumor activity of MDX2001 in patients with advanced solid tumors. Secondary endpoints include time to response, disease control rate, duration of response, pharmacokinetics, immunogenicity and evaluation of the relationship between baseline tumor target protein expression and clinical benefit. Patients will have radiologic tumor assessments every 8 weeks and will continue to receive treatment until disease progression per RECIST v1.1 (as assessed by the investigator), unacceptable toxicity, withdrawal of consent, another protocol-defined discontinuation criterion is met, or the sponsor terminates the study, whichever occurs first. The study will be conducted in United States, Europe, and Asia. Recruitment is ongoing. Clinical trial information: NCT06239194. Research Sponsor: None.

TPS2671 Poster Session

ARC101-P1-101: A first-in-human phase 1 study of ARC101, a next generation T cell engager (TCE), in patients with advanced solid tumors.

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Background: T-cell Engagers (TCEs) are emerging as a promising immuno-therapeutic modality in the treatment of solid tumors, demonstrating outstanding potency and a manageable safety profile. Claudin 6 (CLDN6) is an oncofetal protein that has recently emerged as a particularly attractive tumor-associated antigen (TAA) for TCE therapy because of its highly tumor-restricted pattern of expression. ARC101 is a bispecific antibody that targets CLDN6 on tumor cells with high specificity and selectivity, and CD3 on T cells. In pre-clinical models, ARC101 demonstrated potent cytolytic activity at low concentrations against a panel of CLDN6-expressing tumor cells in vitro and an ovarian cancer xenograft in vivo. **Methods:** First-in-human, multicenter, phase 1 study ARC101-P1-101 (NCT06672185) aims to determine the optimal dosing, safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor efficacy of ARC101 as monotherapy in patients with locally advanced or metastatic CLDN6 expressing solid tumors. The study will be conducted according to the Bayesian Optimal Interval (BOIN) design in two parts: Part 1 (dose escalation) and Part 2 (dose expansion). Part 1 is designed to select the Maximum Tolerated Dose (MTD), Recommended-Phase 2-Dose (RP2D) and dosing schedule of ARC101. Part 1 will start with an 'Accelerated Titration Phase', with cohorts of at least one, but no more than three patients and a fixed dose, intravenous regimen. Once a single event of clinically significant toxicity of Grade $\geq$2 occurs, the 'Standard Titration Phase' will be initiated with cohorts of at least three patients per ARC101 target dose level. Once immune-related toxicity is observed, the regimen may be changed to a 'Fractionated Step-up Dosing' IV regimen. The study design allows for backfill cohorts and intra-patient dose escalations. Part 2 will further explore the safety, PK/PD characteristics, and preliminary efficacy of ARC101 administered at the RP2D and schedule identified in Part 1 in patients with testicular and ovarian cancer. Key eligibility criteria include patients with any advanced or refractory solid tumor malignancy that expresses CLDN6 and is metastatic or unresectable. Patients must be $\geq$18 years of age and have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Patients must have received standard therapy for advanced or metastatic disease, and disease must be measurable per Response Criteria in Solid Tumors (RECIST) v1.1 or evaluable. Mandatory requirement of a pre-study tumour sample for IHC analysis will facilitate the exploratory objective of biomarker analysis, including correlating CLDN6 expression with treatment response. The study is actively enrolling participants for the dose escalation phase. Contact clinicaltrials@thirdarcbio for additional information. Clinical trial information: NCT06672185. Research Sponsor: None.

TPS2672 Poster Session

EGL-121, a first-in-human phase 1/2 trial of EGL-001 in adult patients with selected advanced and/or metastatic solid tumors.

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Background: Regulatory T cells (Tregs) play a key role in the resistance to immune checkpoint inhibitors therapy (ICI). Disarming Tregs could therefore restore/enhance anti-tumor responses and increase the number of patients benefiting from these treatments. EGL-001, a novel therapeutic agent, is designed to provide checkpoint inhibition by antagonizing the CTLA-4-CD80/86 interaction while selectively depleting intratumoral Tregs by downregulating CD25 and inhibiting IL-2 signaling specifically within these cells. This dual mechanism of action effectively unleashes potent anti-tumor immunity even in anti-PD-1 resistant models, independent of FcgR activity. In murine models, EGL-001 shows preferential distribution and persistence in the tumor until Treg get depleted/inactivated. Our data demonstrated complete anti-tumor activity of EGL-001 as a single agent across various tumor models and it overcomes resistance to anti-PD-1 treatment in many tumor models, highlighting its broad therapeutic potential. Additionally, EGL-001 effectively depletes Tregs and exhibits activity in ex-vivo human tumor samples, where other ICI showed no significant effect. In NHPs, EGL-001 was well tolerated across all tested doses, with rapid peripheral clearance preventing lymphoid tissue hyperplasia in the spleen and lymph nodes. **Methods:** A Phase I/II clinical trial (NCT06622486) is currently underway in eight sites in France and Spain to evaluate EGL-001 as monotherapy and in combination with checkpoint inhibitors in selected tumor types characterized by tumor Treg implication in induction of mechanism of resistance to ICI. The selective targeting of tumor-infiltrating Tregs could effectively improve anti-tumor immune response and limit systemic immune-related toxicities. This first-in-human, multicenter, open label Phase 1/2 study evaluates the safety, tolerability, and initial activity of EGL-001 in adult patients with selected advanced and/or metastatic solid tumors. The study consists of a Part 1 (Phase 1) dose escalation of EGL-001 administered as a single agent (from 0.3 mg/kg to 12 mg/kg), and in combination with pembrolizumab treatment, according to a BOIN design, followed by a Part 2 (Phase 2) dose expansion of EGL-001 administered at the selected doses as monotherapy and/or in combination therapy with anti-PD(L)1. Eligible patients are those who have initially benefited (secondary resistance) from an ICI treatment as monotherapy or in combination as SoC as defined by a CR, PR, or SD $\geq$3 months as best response by RECIST Version 1.1. As of January 2025, the first 3 Cohorts of EGL-001 (0.03, 0.1, 0.3 mg/kg) have been completed. EGL-001 was well tolerated with no DLTs reported. Clinical trial information: NCT06622486. Research Sponsor: None.

TPS2673 Poster Session

SUPRAME: A phase 3 trial comparing IMA203, an engineered T-cell receptor expressing T cell therapy (TCR-T) vs investigator's choice in patients with previously treated advanced cutaneous melanoma.

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Background: Frequent recurrence and limited long-term survival in unresected or metastatic melanoma after relapse from 1L treatment with a checkpoint inhibitor (CPI) highlight the critical need for new therapies that deliver deeper, more durable responses (Knight *Cancers* 2023; Switzer *JCO Oncol Pract* 2022). ACTengine IMA203 is an autologous T cell receptor (TCR)-engineered T cell therapy (TCR-T) targeting PRAME, an intracellular protein displayed as peptide antigen at high density on the surface of multiple solid tumors, including melanoma. IMA203 TCR-T demonstrated a favorable tolerability profile and durable objective responses in heavily-pretreated patients with different tumor types. In melanoma, IMA203 showed 54% confirmed ORR (14/26), 12.1 months mDOR and 6 months mPFS. mOS was not reached at a mFU of 8.6 months (Wermke et al., SMR, Oct 10, 2024). Based on these observations, a registration-enabling randomized phase 3 trial, SUPRAME, was initiated to evaluate IMA203 in 2L patients with advanced cutaneous melanoma after treatment with a CPI. **Methods:** SUPRAME (NCT06743126) is a phase 3, multicenter, open-label, randomized, actively controlled, parallel-group trial that will evaluate the efficacy, safety and tolerability of IMA203 compared to investigator's choice of treatment in patients with previously treated, unresectable or metastatic cutaneous melanoma (incl. acral melanoma). Eligible patients are ≥18yo, HLA-A*02:01-positive, with measurable disease (RECIST v1.1), ECOG PS of 0-1 and disease progression on or after at least one PD-1 inhibitor. Patients with BRAF mutation should have been treated with one prior line of BRAF-directed therapy (± MEK inhibitor) prior to initial eligibility assessment. Patients with asymptomatic stable brain or leptomeningeal metastases will be assessed for eligibility. Patients with active brain metastases or with primary mucosal, uveal melanoma and melanoma of unknown primary are excluded. The study will randomize ~360 patients 1:1. Patients in the experimental arm will undergo leukapheresis to generate the PRAME-specific TCR-T product, IMA203. Following lymphodepletion with cyclophosphamide (500 mg/m^2 x 4 days) and fludarabine (30 mg/m^2 x 4 days), 1-10x10^9 IMA203 TCR-T cells will be administered, followed by low-dose IL-2 (1mio IU daily x5 days, twice daily x5 days). Patients in the control arm will receive approved investigator's choice of standard treatment (nivolumab/relatlimab, nivolumab, ipilimumab, pembrolizumab, lifileucel (US), chemotherapy). The primary efficacy endpoint is BICR-assessed (RECIST v1.1) PFS. Secondary endpoints include OS, ORR, safety and patient-reported outcomes (EORTC QLQ-C30, EQ-5D-5L). The trial will enroll patients in the US and Europe. Clinical trial information: NCT06743126. Research Sponsor: None.

TPS2674 **Poster Session**

Autologous tumor-infiltrating lymphocytes (HS-IT101) with low-dose lymphodepletion and IL-2 infusion for the treatment of advanced solid tumors: A phase I clinical trial.

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Background: Adoptive cell therapy with tumor-infiltrating lymphocytes (TIL-ACT) has demonstrated great therapeutic potential in numerous solid tumors and has become an effective treatment for melanoma. However, high-dose lymphodepletion chemotherapy and IL-2 infusion during the treatment could cause serious safety risks, even death. The purpose of this study is to develop a TIL cell therapy product (HS-IT101) that requires low-dose lymphodepletion and IL-2 infusion to reduce safety risks and to improve clinical accessibility. Currently, the Phase I clinical trial (NCT06342336) for the treatment of advanced solid tumors with HS-IT101 has been initiated. **Methods:** HS-IT101 is an autologous non-genetically modified TIL-ACT product independently developed by Sino-cell Biomed. The tumor tissue of culture require is ≥0.05g, and the manufacture time needed is 14 days. This study is a single-arm, multi-center, open-label Phase I clinical trial of HS-IT101 for advanced solid tumors. The plan is to enroll 20 - 44 patients to explore the safety and preliminary efficacy under low-dose lymphodepletion and IL-2 infusion. Before HS-IT101 infusion, subjects will receive lymphodepletion chemotherapy consisting of cyclophosphamide (Cy) and fludarabine (Flu) for 3 - 4 days (Cy: 900/2250mg/m^2 & Flu: 90/120mg/m^2). After HS-IT101 infusion, 1/2MIU/m^2 of IL-2 will be subcutaneously injected once a day for a maximum of 3 doses. The primary endpoint is the occurrence of adverse events (AE) and serious adverse events (SAE) after HS-IT101 infusion. The secondary endpoints include the objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) in efficacy evaluation, and changes in relevant pharmacokinetic (PK) indicators. The exploratory endpoint is the change in pharmacodynamic (PD) indicators. Clinical trial information: CTR20234065. Research Sponsor: Qingdao Sino-Cell Biomedicine Co., Ltd.

TPS2675 Poster Session

A phase 1/2 study of KSQ-004EX: Autologous tumor infiltrating lymphocytes, engineered to inactivate genes encoding SOCS1 and Regnase-1, in patients with select advanced solid tumors.

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Background: The effectiveness and durability of TIL therapy may be limited by the immunosuppressive tumor microenvironment and baseline functionality of transferred T cells. Through KSQ Therapeutics' CRISPR^2 platform, a novel method for screening optimal combinatorial targets for enhancing T cell anti-tumor efficacy in vivo, SOCS1 and Regnase-1 were identified as the most potent gene editing combination. KSQ-004EX, an engineered TIL product with CRISPR/Cas9 mediated dual-inactivation of SOCS1 and Regnase-1, is anticipated to in enhance T cell tumor infiltration, persistence, and efficacy. This first-in-human clinical study (NCT06598371) evaluates KSQ-004EX in patients with melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), colorectal carcinoma (CRC), pancreatic cancer, and cervical cancer. **Methods:** The phase 1/2, single-arm, open-label study will assess the safety, tolerability, and efficacy of KSQ-004EX in patients with select advanced solid tumors. Patients with melanoma, NSCLC, HNSCC, CRC, pancreatic, and cervical cancer who have progressed following treatment with 1 to 3 lines of prior standard therapy including standard directed therapy (as applicable), are eligible. KSQ-004EX is manufactured from the patient's tumor, which is collected through surgical resection or core needle biopsy. All patients must have at least 1 measurable lesion following resection. Patients receive lymphodepleting chemotherapy with cyclophosphamide and fludarabine prior to KSQ-004EX infusion. Patients in the initial dose escalation cohorts do not receive dosing with IL-2; IL-2 dosing may be included in subsequent cohorts. Approximately 6 patients will be enrolled in Phase 1 dose escalation, in escalating dose levels. The primary objective of Phase 1 is to evaluate the safety and tolerability of KSQ-004EX. In Phase 2, patients will be enrolled in indication-specific cohorts. The primary objective of Phase 2 is to assess the anti-tumor activity of KSQ-004EX in patients with advanced solid tumors by ORR per RECIST v1.1. This is currently a single-institution study that is actively enrolling/recruiting patients. Clinical trial information: NCT06598371. Research Sponsor: KSQ Therapeutics, Inc.

TPS2676 **Poster Session**

A phase 1, first-in-human study of IB-T101, an OUTLAST CAR-T product for the treatment of CD70-positive clear cell renal carcinoma.

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Background: Relapsed or treatment-resistant clear cell renal cell carcinoma (ccRCC) poses a significant, unmet medical challenge, as patients contend with scarce therapeutic alternatives and unfavorable clinical prognoses. CD70 is expressed in the majority of ccRCC and presents an attractive target for chimeric antigen receptor T cell (CAR-T) therapy. IB-T101, an autologous CAR-T expanded under OUTLAST conditioning, targets CD70 for the treatment of ccRCC. OUTLAST conditioning has been demonstrated to result in CAR-T cells that exhibit an early memory T cell phenotype, are resistant to suppressive signals from the tumor microenvironment, and exhibit increased persistence. The effects of OUTLAST conditioning are expected to lead to superior clinical outcomes for IB-T101 CAR-T cells in the ccRCC solid tumor setting.
Methods: Here we report an in-progress phase 1, first-in-human, open label, investigator-initiated clinical trial aimed at evaluating the safety and efficacy of IB-T101 in ccRCC. Patients eligible for inclusion had previously relapsed following VEGF targeting therapies alone or in combination with an immune checkpoint inhibitor. Autologous patient T cells are transduced with a lentiviral vector encoding a CD70-targeting CAR and are CRISPR Cas9 gene edited to knock out endogenous CD70, followed by expansion under OUTLAST conditioning. Escalating doses of IB-T101 CAR-T cells ($150 - 500 \times 10^6$) will be infused following lymphodepletion. Primary endpoints of the study will assess the safety and tolerability of IB-T101. Additional objectives of the study are to assess the anti-tumor activity and the pharmacokinetics of IB-T101. Correlative assessments will include pre-treatment biopsies to assess the level of CD70 expression in the tumor. Research Sponsor: None.

TPS2677 Poster Session

Logic-gated, allogeneic Tmod chimeric antigen receptor T-cell (CAR T) therapy targeting epidermal growth factor receptor (EGFR) in advanced solid tumors with human leukocyte antigen (HLA) loss of heterozygosity (LOH): DENALI-1 trial.

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Background: Despite the success in hematologic malignancies, CAR T therapies face significant challenges in solid tumors due to the lack of tumor-specific targets that distinguish cancer from normal cells. EGFR plays a critical role in oncogenesis across several cancers and is often upregulated (TCGA 2022). While monoclonal antibodies targeting EGFR have demonstrated efficacy, these approaches are often limited by on-target, off-tumor toxicities, such as skin rash, which constrains dose escalation and efficacy (Macdonald, et al. *J Am Acad Dermatol*. 2015). A2B395 is an allogeneic, logic-gated, EGFR-targeted Tmod CAR T therapy designed to address these limitations and provide a convenient and consistent off-the-shelf option. This therapy incorporates 2 CARs: an activator targeting EGFR, and a blocker targeting HLA-A*02. The activator recognizes EGFR on both tumor and normal cells, while the blocker inhibits CAR T activity against normal cells with preserved HLA expression and decreases the risk for graft-versus-host disease (Hamburger, et al. *Mol Immunol*. 2020). To address potential host-vs-graft response, an shRNA expression module targeting B2M is included in the Tmod construct, which significantly reduces major histocompatibility complex class I levels and subsequent host immune response (DiAndreth, et al. *Clin Immunol.* 2022). Importantly, the Tmod system is modular and adaptable to multiple targets. Initial data on autologous Tmod CAR T therapy suggest reduced off-tumor toxicity and encouraging clinical efficacy (Grierson, et al. SITC 2024. Abstract 588). A2B395 represents a novel approach for EGFR-expressing solid tumors with HLA-A*02 LOH. **Methods:** DENALI-1 (NCT06682793) is a phase 1/2, open-label, nonrandomized study evaluating the safety and efficacy of A2B395 in adults. 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 via next-generation sequencing (Tempus AI, Inc.). Key inclusion criteria include histologically confirmed recurrent unresectable, locally advanced, or metastatic cancers associated with EGFR expression, including colorectal, non-small cell lung, squamous cell head and neck, triple negative breast, and renal cell cancers. Patients must have received ≥1 line of prior therapy, such as a checkpoint inhibitor, molecular targeted therapy, or chemotherapy. The primary objective of phase 1 is to evaluate safety, tolerability, and the recommended phase 2 dose (RP2D) using a Bayesian optimal interval design for dose escalation. The dose-expansion phase will confirm RP2D and collect biomarker data. Phase 2 will assess overall response rate per RECIST v1.1. Clinical trial information: NCT06682793. Research Sponsor: A2 Biotherapeutics, Inc.

TPS2678 Poster Session

A phase I study of AFNT-211, autologous CD4$^+$ and CD8$^+$ T cells engineered to express a high avidity HLA-A*11:01-restricted, KRAS G12V-specific transgenic TCR; CD8α/β coreceptor; and FAS-41BB switch receptor in patients with advanced or metastatic solid tumors.

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Background: Activating mutations in KRAS (including KRAS G12V) are well-described oncogenic drivers in solid tumors, conferring poor prognosis to patients due to a lack of effective therapies for cancers with such KRAS driver mutations. T cell receptor (TCR)-T cell therapies targeting mutant KRAS have demonstrated proof of concept in the clinic, but duration of response remains a challenge.[1,2] AFNT-211 represents a novel strategy to address the immunosuppressive tumor microenvironment and improve response rate as well as duration of response in solid tumors. **Methods:** This ongoing Phase 1, first-in-human, multicenter, open-label study of AFNT-211evaluates safety/tolerability, as well as its clinical (antitumor) activity with the goal to identify an optimal biological dose (OBD) and recommended Phase 2 dose (RP2D) in patients with HLA 11:01 who suffer from cancers driven by the KRAS G12V mutation. The initial dose escalation part of the study follows Bayesian optimal interval Phase 1/2 (BOIN12), which quantifies the desirability of a dose in terms of toxicity-efficacy tradeoff and adaptively allocates patients to the dose with the highest estimated desirability. After determination of OBD and RP2D based on the totality of the risk/benefit assessment and the BOIN12, the study is planned to proceed to the dose expansion phase which will consist of cohorts enrolling patients with tumors with high KRAS G12V prevalence (pancreatic cancer, colorectal cancer, non small cell lung cancer) as well as a tumor agnostic arm (any other solid tumor with KRAS G12V). This study has started enrolling patients $\geq$ 18 years old positive for HLA-A*11:01-positivewithadvanced/metastatic solid tumors harboring a KRAS G12V mutation who have proven intolerant of or refractory to at least one prior standard of care systemic therapy. Patients undergo leukapheresis to collect T cells for the manufacturing of AFNT-211, and receive lymphodepleting chemotherapy prior infusion of their autologous AFNT-211 product. Following this, patients proceed into a 28-day dose-limiting toxicity observation period (during dose escalation) followed by a post-treatment follow-up period for 24 months/until disease progression. The study is open for recruitment in the United States (NCT06105021). References: 1. Cook J, Melloni G, Gulhan D, *et al.* The origins and genetic interactions of KRAS mutations are allele- and tissue-specific. *Nat Commun* 2021;12:1808. 2. Hofmann MH, Gerlach D, Misale S, *et al.* Expanding the reach of precision oncology by drugging all KRAS mutants. *Cancer Discov.* 2022;12:924–937. Clinical trial information: NCT06105021. Research Sponsor: Affini-T Therapeutics, Inc.

TPS2679 **Poster Session**

Safety and efficacy of HLA-G–targeted CAR T cells (IVS-3001) in patients with advanced HLA-G–positive solid tumors: Clinical trial in progress.

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Background: Immunotherapies have transformed cancer treatment, yet only a small proportion of patients experiences durable responses. IVS-3001 is an innovative autologous chimeric antigen receptor (CAR) T-cell therapy specifically targeting Human Leukocyte Antigen (HLA-G). HLA-G is an immune-modulatory checkpoint molecule expressed on various solid tumors, positioning it as an ideal a tumor-specific targeted antigen. Our third-generation CAR construct features enhanced T cell activation and persistence against HLA-G. By harnessing IVS-3001 to target HLA-G and revitalize immune cells, we aim to overcome the suppressive tumor microenvironment and improve antitumor activity, potentially leading to better outcomes for patients with advanced solid tumors who otherwise have no standard options known to confer clinical benefit. **Methods:** Study NCT05672459 is a First-in-Human, phase 1/2a, safety and efficacy study of IVS-3001 in subjects with previously treated advanced HLA-G-positive solid tumors. Phase 1 ($n \leq 24$ patients) is a Bayesian Optimal Interval Design (BOIN) with primary objective to determine the safety, tolerability and the recommended phase 2 dose. The primary objective for phase 2 ($n \leq 90$ patients) is to evaluate the anti-tumor activity of IVS-3001. The secondary objectives of the study are to evaluate i) pharmacokinetic profile of IVS-3001 (persistence, expansion); ii) the clinical activity of IVS-3001 in selected HLA-G+ solid tumor types; iii) assess the long-term safety of IVS-3001. Exploratory endpoints include functionality of CAR-T cells, immune biomarker changes, and relationships with clinical response. Key inclusion criteria: adults with advanced solid tumors expressing HLA-G; ECOG < 2; adequate organ function. Key exclusion criteria: uncontrolled brain metastasis; prior exposure to HLA-G targeted therapy. Subjects undergo lymphodepletion with fludarabine and cyclophosphamide on days -5 to -3, followed by CAR-T cell infusion on day 0 and a 28-day monitoring period for dose limiting toxicity. Response assessment per RECIST criteria. Study is currently accruing at Dose level 3. Active recruitment and enrollment are ongoing at The University of Texas MD Anderson Cancer Center, Houston, Texas. Clinical trial information: NCT05672459. Research Sponsor: Invectys; National Cancer Institute.

TPS2680 Poster Session

QUILT 3.076 phase 1 study of memory-like cytokine-enriched natural killer (M-CENK) cells plus N-803 in locally advanced or metastatic solid tumors.

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Background: Lymphopenia and low levels of natural killer (NK) cells may contribute to poor prognosis and response to therapy in cancer patients, conditions that may be addressed by infusion of memory-like cytokine-enriched NK (M-CENK) cells stimulated ex vivo by IL-12, IL-18, and the IL-15 agonist N-803 (ANKTIVA). M-CENK cells express elevated IFN-γ and granzyme B compared to healthy donor NK cells, and display toxicity against multiple tumor cell lines including SCLC lines [Fousek 2023 JITC 11 ab358]. The phase 1 study QUILT-3.076 (NCT04898543) assesses the safety and preliminary efficacy of M-CENK cells plus N-803 in participants with locally advanced or metastatic solid tumors. **Methods:** In this first-in-human study, cohort 1 (up to n = 40) includes participants with newly diagnosed solid tumors who have not received prior 1st line treatment; cohort 2 (up to n = 21) includes participants with relapsed/refractory solid tumors who progressed after $\geq$ 2 prior therapies. Both cohorts undergo apheresis (part A), but only cohort 2 undergoes treatment with M-CENK cells and N-803 (part B). During M-CENK cell generation, cohort 2B participants receive oncologist-recommended therapy. Cohort 1 participants may subsequently enroll in cohort 2B if they have progressive disease (PD) after $\geq$ 2 prior therapies or within 12 months of receiving neoadjuvant/adjuvant chemotherapy. In part B, M-CENK cells are administered weekly up to 10 times and N-803 SC for up to 5 doses every 2 weeks prior to every other dose of M-CENK cells. Key inclusion criteria are age $\geq$ 18 years, ECOG performance status of 0 to 2, and histologically confirmed locally advanced or metastatic solid tumor, with at least 1 measurable lesion and/or non-measurable disease in accordance with RECIST v1.1. There are no exclusion criteria for part A (apheresis). Key exclusion criteria for part B are life expectancy $<$ 16 weeks, involuntary weight loss of $>$ 10%, serious uncontrolled concomitant disease, systemic autoimmune disease requiring medical treatment, and/or currently receiving or received antibiotics since enrollment. The primary objective is safety as assessed and recorded by TEAEs, SAEs, and clinically significant changes in laboratory tests and vital signs. Toxicities are graded using CTCAE v5.0 or a specified grading system for CRS. Secondary measures evaluate the quantity and quality of the investigational M-CENK cells (number of MNCs for manufacturing M-CENK cells, number of cryopreserved M-CENK aliquots, % NK cells, and number, phenotype, and function of M-CENK cells). Preliminary efficacy objectives in cohort 2B are objective response rate (RECIST v1.1 and iRECIST criteria) and progression-free and overall survival evaluated using Kaplan-Meier methods. As of January 27, 2025, 15 participants have been enrolled in cohort 1, 21 participants in cohort 2 have undergone apheresis, and 10 participants have been treated with study therapies. Clinical trial information: NCT04898543. Research Sponsor: ImmunityBio, Inc.

TPS2681 Poster Session

A phase I, multicenter, open-label study of UB-VV111 in combination with rapamycin in relapsed/refractory CD19+ B-cell malignancies.

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Background: Autologous, ex vivo-manufactured chimeric antigen receptor (CAR) T cells directed against CD19 have demonstrated clinical activity. These products have gained approvals in the relapsed/ refractory (R/R) setting in multiple B-cell malignancies (BCMs), including large B-cell lymphoma (LBCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). However, challenges in product availability due to limited manufacturing capacity, the need for apheresis and lymphodepletion, failure to prior ex vivo CAR T therapy, and the level of patient fitness needed to wait for and receive ex vivo autologous CAR T therapy all pose significant challenges to the field, presenting significant unmet clinical need. UB-VV111 is a third-generation, self-inactivating, replication-incompetent lentiviral vector (LVV) investigational drug product comprising an envelope with cocal virus fusion glycoprotein (cocal) and surface engineered with a membrane-bound multidomain fusion (MDF) protein. The MDF protein contains CD58, CD80, and anti-CD3 single-chain variable fragment (scFv) components that provide both T-cell tropism and activation signals thought to be critical for effective CAR T-cell generation. UB-VV111 addresses the limitations of currently available autologous CD19-directed CAR T therapies to deliver a product that would generate CD19-directed cells in the patient. UB-VV111 is to be administered by either intranodal (IN) or intravenous (IV) route of administration (ROA). Administration of UB-VV111 by either the IN or IV ROA is expected to transduce T cells to generate CAR T cells designed to bind to CD19 antigen to mediate cell killing and express the rapamycin-activated cytokine receptor (RACR) system which, in the presence of rapamycin, is designed to enhance specific enrichment and expansion of transduced cells. **Methods:** Study UB-VV111-01 (INVICTA, [NCT06528031CO]) is a first-in-human, global, multicenter, dose-finding study of UB-VV111 administered IN or IV +/- rapamycin in CAR-naïve and CAR-exposed subjects with R/R LBCL and CLL/SLL. Dose escalation will proceed independently for each ROA using a Bayesian optimal interval (BOIN) design. Confirmation of CD19 expression will be required for all subjects with prior CD19-directed therapy. Major eligibility criteria include adults with R/R LBCL/CLL/SLL following at least 2 lines of prior therapy who have standard organ function, measurable disease according to Lugano 2014 (LBCL) or iwCLL 2018 (CLL/SLL), ECOG 0 or 1, and no prior allogeneic transplant. Primary objectives include determining the safety profile, maximum tolerated/administered dose, and recommended Phase 2 dose of UB-VV111 +/- rapamycin. Secondary/exploratory objectives include measuring preliminary antitumor activity (magnitude and durability), as well as translational correlates of safety/efficacy. Clinical trial information: NCT06528301. Research Sponsor: Umoja Biopharma.

TPS2682 Poster Session

Phase 1 clinical trial of autologous T-cells genetically engineered with a chimeric receptor to target the follicle-stimulating hormone receptor (FSHR) in recurrent ovarian cancer (OVCA).

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Background: FSHR is a tissue specific antigen expressed in $>$ 55% of high-grade epithelial OVCAs with negligible FSHR expression in non-ovarian tissues. OVCA xenografts treated with FSHCER T (FSH-Chimeric Endocrine Receptor + T-Cell (CER T)) cells demonstrated cytotoxic activity against patient-derived FSHR+ ovarian carcinomas. We hypothesize targeting FSHR in women with FSHR+ OVCA will result in improved response rates due to engraftment, expansion, and survival of these adoptively transferred FSHCER T-cells and will have acceptable toxicity. **Methods:** The primary objective of this phase 1 dose-escalation study (NCT05316129) in high-grade epithelial OVCA using T-cells genetically modified to express CER targeting FSHR is to assess the safety of the intraperitoneal (IP) and intravenous (IV) infusions of FSHCER T-cells. Secondary objectives include antitumor efficacy, persistence of transferred FSHR T cells, expansion of endogenous tumor-targeted cells, and comparison of IP and IV administration routes. Patients unable to be treated in the IP arm may be treated in the IV arm in the lowest unfilled cohort for that arm. Cohorts of 3 to 6 patients will be infused with escalating doses of FSHCER T-cells to establish the maximum tolerated dose (MTD) with 6 planned dose levels from 1 x10^5 to 1 x 10^7 cells/kg with the 5^{th} level receiving lymphodepleting chemotherapy. Following MTD determination, an expansion phase will be initiated. Nine patients have been enrolled in the first three dose-level cohorts. Eight have cleared the DLT period and one patient is currently being treated. One patient received a second dose of 3 x 10^5 cells/kg after 20 months apparent stable disease. Cohorts 1 and 2 correlates are being processed. NCT05316129. Moffitt Scientific Review #21113. Advarra Institutional Review Board #00000971. Clinical trial information: 05316129. Research Sponsor: Anixa BioSciences Inc., San Jose CA, USA.

TPS2683 **Poster Session**

INVOKE: A phase 1 study of OKN4395, a first-in-class EP2/EP4/DP1 triple prostanoid receptor antagonist, in patients with advanced solid tumors.

Neal Shiv Chawla, Luke Kuttschreuter, Kamlesh Kumar Sankhala, Sarah Benafif, Louise Carter, Nicholas Coupe, T.R. Jeffry Evans, Timothy Guy Humphries, Steven Chuan-Hao Kao, Harriet S. Walter, Andy Karabajakian, Alexandre Grimaldi, Caroline Hoffmann, Gill Low, Andrew Pierce, Stephane Champiat; Sarcoma Oncology Center, Santa Monica, CA; Owkin, London, United Kingdom; Precision NextGen Oncology and Research Center, Beverly Hills, CA; NIHR University College London Hospitals Clinical Research Facility, London, United Kingdom; The Division of Cancer Sciences, The University of Manchester and Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; Oxford University Hospital, Oxford, United Kingdom; Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, United Kingdom; Linear Clinical Research Ltd, Perth, Western Australia, Australia; Department of Medical Oncology, Chris O'Brien Lifehouse, Sydney, NSW, Australia; University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; Owkin France, Paris, France; Precision for Medicine, Norton, MA; Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immunotherapy is an established cancer therapy, although mechanisms of non-response & resistance are emerging, leaving few options post-relapse. The immunosuppressive pathway of prostaglandin E_2 (PGE_2), part of the cyclooxygenase (COX) pathway, is upregulated in certain cancers and has been implicated in tumor evasion of CD8 T, NK, and dendritic immune cells, allowing tumor growth and metastasis (Jin et al., 2023). COX2 inhibitors, aspirin and nonsteroidal anti-inflammatories (NSAIDS) have shown some survival benefit in patients with colon, lung, prostate, and endometrial cancer (Cao et al., 2016; Lim et al., 2012; Huang et al., 2014; Takiuchi et al., 2018), however results are inconsistent, likely due to toxicity limiting complete blockade of the pathway, highlighting the need for more potent but selective COX pathway inhibitors. OKN4395 is a first-in-class, highly selective, equipotent inhibitor of EP2, EP4 and DP1, downstream receptors for COX-derived PGE_2, and PGD_2, respectively. DP1 has described roles in immunosuppression and inhibition of apoptosis, supporting the therapeutic rationale (Luo et al., 2024; Peinhaupt et al., 2017). OKN4395 is hypothesized to modulate the tumor microenvironment to allow an effective immune response as monotherapy, and to potentiate the effect of immunotherapies such as checkpoint inhibitors, both of which are evaluated in INVOKE. **Methods:** INVOKE (OKN-4395-121; NCT06789172) is a Ph1a/1b, first-in-human study of OKN4395 (oral, BID) as monotherapy (mono) or in combination with pembrolizumab 200mg IV 3-weekly (combo), in patients with advanced solid tumors that have evidence of COX-associated immunosuppression. Ph1a is a Bayesian dose escalation in mono, followed by combo dose confirmation, primarily assessing safety, establishing the optimal dose for Ph1b. Using multimodal artificial intelligence (AI) drug-matching algorithms, Ph1b tumor types were selected, and response will be assessed (cohorts of n = 20 each): select sarcomas (mono), pancreatic carcinoma (mono), non-small cell lung cancer (combo), colorectal carcinoma (combo), head and neck squamous cell carcinoma (combo). Key inclusion criteria include COX-active (Ph1a) or above-listed (Ph1b) tumors, performance status 0-1, biopsy-amenable lesions, and adequate organ function. Active CNS metastases, upper GI bleed risk factors, untreated H. pylori infection, and concomitant NSAIDs/COX inhibitors/prostaglandins are exclusionary. Ph1b mono cohorts will include exploratory analyses including evaluation of the effect of food & gastric pH on OKN4395 pharmacokinetics. Trial data, paired pre- and on-treatment biopsies, and exploratory biomarkers will be used to enhance development using advanced agentic AI systems, including a synthetic digital twin control arm. Ph1a of the study is currently recruiting in the US, UK, and Australia. Clinical trial information: 06789172. Research Sponsor: Epkin.

TPS2684 Poster Session

An open-label, phase Ib dose-expansion study to assess the efficacy of CD137/FAP agonist BI 765179 plus pembrolizumab as a first-line treatment in metastatic or incurable, recurrent programmed cell death ligand-1 (PD-L1)-positive head and neck squamous cell carcinoma (HNSCC).

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Background: HNSCC is the seventh most common cancer globally and is often associated with poor quality of life and a dismal prognosis. Median overall survival for advanced HNSCC with first-line standard-of-care pembrolizumab ± chemotherapy is approximately 13 months, highlighting the need for new therapies. Fibroblast activation protein (FAP)-positive fibroblasts are frequently present in the tumor stroma of HNSCC tumors, representing a potential therapeutic target. BI 765179 is a bispecific antibody that simultaneously binds to FAP and CD137 expressed on T-cells, leading to local activation of tumor-specific CD137-positive T-cells. The Phase Ia part of the present study (NCT04958239) determined safety and doses for dose escalated BI 765179, both as monotherapy and in combination with an anti-programmed cell death protein 1 (PD-1) antibody in patients with advanced solid tumors. Here we present the design of the Phase Ib dose-expansion part, which aims to assess the preliminary efficacy of two doses of BI 765179 in combination with pembrolizumab in patients with metastatic or incurable, recurrent HNSCC whose tumors express PD-L1. **Methods:** In the Phase Ib dose-expansion part, approximately 60 patients with a histologically or cytologically confirmed diagnosis of metastatic or incurable, recurrent HNSCC will be enrolled. Key inclusion criteria are: no prior systemic therapy administered in the metastatic or incurable recurrent setting; primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx; at least one measurable lesion outside of the central nervous system (modified RECIST v1.1); a PD-L1-positive tumor (combined positive score ≥1, local assessment); and Eastern Cooperative Oncology Group performance status 0–1. Patients who have previously received CD137-targeted or anti-PD-1/PD-L1 agents are not eligible. Patients will be randomized 1:1 to receive either Dose 1 or Dose 2 of BI 765179 intravenously in combination with pembrolizumab. The primary endpoint is objective response (OR), defined as best overall response of confirmed complete or partial response (RECIST v1.1). Secondary endpoints include occurrence of adverse events (AEs) and serious AEs, OR (immune-related RECIST v1.1), duration of response, progression-free survival, and overall survival. Clinical trial information: NCT04958239. Research Sponsor: Boehringer Ingelheim.

TPS2685 **Poster Session**

A phase 1, first-in-human study of CTIM-76, a claudin-6 (CLDN6)-directed bispecific antibody, in patients with recurrent ovarian cancer and other advanced solid tumors.

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Background: CLDN6 is an oncofetal protein expressed at high levels in many solid tumors while expressed at very low levels in adult normal tissues. The high target antigen density and slow rate of internalization makes it an attractive target in cancer therapeutics. CTIM-76, a CLDN6 x CD3 T cell engager bispecific antibody is engineered to bind with high selectivity to CLDN6 and redirect the immune system's T cells to recognize and kill CLDN6-expressing cancer cells. CTIM-76 effectively inhibited tumor growth, inducing complete responses in ovarian cancer xenograft models. The first in human study of CTIM-76 in patients with advanced ovarian, endometrial, and testicular cancers (NCT06515613) is described here. **Methods:** Part 1 dose escalation exploring 9 ascending dose levels with a 3+3 design. The first two dose levels are single patient cohorts (22.5 μg starting dose), CTIM-76 delivered as weekly iv infusions, with step dosing and steroid premedication to minimize cytokine release syndrome. Approximately 40 patients with platinum resistant ovarian cancer, or endometrial or testicular cancers relapsed after standard of care will be enrolled. Tumors from patients with ovarian or endometrial cancer require prospective CLDN6 + confirmation by IHC (10% $\geq$ 1+), testicular cancer patients will not require prospective screening due to the known uniformly high prevalence of CLDN6. The primary objective is to evaluate safety and tolerability (incidence and severity of adverse events per NCI CTCAE v5.0) and establish the recommended dose for expansion. Secondary objectives include assessment of antitumor activity (RECIST v1.1, iRECIST), pharmacokinetics, and pharmacodynamic correlates of immune activation. Part 2 will evaluate two doses in approximately 30 patients with one tumor type, with efficacy and further safety as primary objectives. This multicenter study has currently five sites open for enrollment. The first patient was dosed in January 2025. Clinical trial information: NCT06515613. Research Sponsor: None.

TPS2686 **Poster Session**

A phase 1a/1b study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of IMGS-001 in patients with relapsed or refractory advanced solid tumors.

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Background: IMGS-001 is a fully human, dual specific immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds both PD-L1 and PD-L2, silencing the entire PD-1 inhibitory circuit, with an engineered fragment crystallizable (Fc) region designed to induce robust antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP). IMGS-001 mediated killing of PD-L1+ and PD-L2+ tumor and stromal cells can reduce the level of multi-modal immune suppression throughout the tumor microenvironment while catalyzing cross presentation of tumor antigens to the adaptive immune system. IMGS-001 also blocks binding of the T cell co-inhibitory receptor PD-1 with its ligands, restoring activation and function to tumor-specific T cells. In addition, IMGS-001 blocks binding of PD-L1 to B7-1, increasing costimulation of tumor-specific T cells. A phase 1a/1b study has been opened to investigate IMGS-001 safety, anti-tumor activity, and pharmacokinetics (PK) in solid tumor patients (Protocol IMGS-001-011; NCT06014502). **Methods:** This multi-center, first-in-human study is enrolling subjects with advanced solid tumors refractory to standard of care therapy. Phase 1a uses a Bayesian optimal interval (BOIN) dose-escalation design to investigate doses from 0.3-15 mg/kg (Q2W). Phase 1b is a two-part design in subjects with PD-L1+ expression $\geq$ 5% across 5 tumor types: triple negative breast, bladder, gastric/esophageal, colorectal, ovarian. Part 1 will enroll up to 10 subjects per cohort. Cohorts meeting prespecified efficacy criteria will proceed to Part 2 dose optimization randomly assigning 40 subjects (1:1) between two doses. The primary objective of Phase 1a is to assess IMGS-001 safety, and of Phase 1b is to define the pharmacologically optimal dose (POD). Both study phases will assess tolerability, PK, immunogenicity, and anti-tumor activity including objective response rate and progression free survival, as well as exploratory tissue and serum biomarker analyses. The study will enroll approximately 25 patients in Phase 1a and up to 250 in Phase 1b. The first two cohorts (0.3 and 1 mg/kg) have completed without any dose limiting toxicities (DLTs), and cohort 3 (3 mg/kg) is enrolling as of the submission date. Clinical trial information: NCT06014502. Research Sponsor: ImmunoGenesis; Cancer Prevention and Research Institute of Texas (CPRIT); Cancer Focus Fund.

TPS2687 Poster Session

Phase 2 dose expansion of START-001: A phase 1/2 study of invikafusp alfa (STAR0602), a first-in-class, selective T cell receptor (TCR)-targeting, bifunctional antibody-fusion molecule, as monotherapy in patients with antigen-rich tumors resistant to anti-PD(L)-1.

Claire Frances Friedman, Ryan J. Sullivan, Nicholas Tschernia, Guru P. Sonpavde, Mercedes Herrera, Kai He, Marijo Bilusic, Elena Garralda, Alberto Hernando Hernando-Calvo, Ann W. Silk, Matthieu Roulleaux-Dugage, Antoine Italiano, Manuel Pedregal, M Wasif Saif, Kevin Chin, Zhen Su, Ke Liu, Lillian L. Siu, James L. Gulley, Aurelien Marabelle; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; Center for Immuno-Oncology, CCR, NCI, NIH, Bethesda, MD; AdventHealth Cancer Institute and University of Central Florida, Orlando, FL; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada; James Cancer Hospital and Solove Research Institute, Columbus, OH; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Gustave Roussy Cancer Institute, Villejuif, France; Early Phase Trials Unit, Institut Bergonié, Bordeaux, France; Hospital Universitario Fundación Jimenez Diaz, Madrid, Madrid, Spain; Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI; Marengo Therapeutics, Inc., Cambridge, MA; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; Gustave roussy, Villejuif, France

Background: Many patients do not respond to anti-PD(L)-1-based therapies and most responders eventually develop resistance. Thus, the development of effective therapies for anti-PD(L)-1 resistance is a significant unmet medical need. Invikafusp, a selective, dual T cell agonist targeting Vβ6/Vβ10 T cells, is being evaluated in START-001: a multicenter Phase 1/2 monotherapy trial in patients with anti-PD(L)1-resistant, antigen-rich (TMB-H, MSI-H/dMMR, or virally associated) solid tumors. The completed Phase 1 dose escalation of intravenous invikafusp, Q2W, per 3+3 design, identified a recommended Phase 2 dose (RP2D) of 0.08 mg/kg, and demonstrated clinically meaningful single-agent anti-tumor activity in patients with anti-PD(L)-1 resistant tumors, including confirmed partial responses in TMB-H, microsatellite stable, colorectal cancer (CRC) patients with one durable response lasting ~12 months. It promoted potent and selective expansion of mainly CD8+ Vβ6/ Vβ10 T cells with a novel central memory T cell phenotype, and led to ctDNA decrease and expansion of antigen-specific T cells. Based on these results, the US FDA granted Fast Track Designation for invikafusp in TMB-H CRC. **Methods:** Study design: Using an optimal Simon's 2 stage design, Phase 2 of START-001 is a dose expansion at the RP2D, to further investigate the safety and anti-tumor activity of invikafusp in 9 cohorts of patients who have the following solid tumors: 1) tissue-agnostic, TMB-H; 2) tissue-agnostic, dMMR/MSI-H; 3) CRC (both Ras wild-type and mutant) TMB-H and/or MSI-H/dMMR); 4) virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or EBV-related solid tumors; 5) metastatic triple-negative breast cancer; 6) platinum-resistant epithelial ovarian cancer; 7) metastatic castration-resistant prostate cancer; 8) primary stage IV or recurrent non-small cell lung cancer; and 9) immunogenic tumors (e.g., cSCC, melanoma and RCC). Major Eligibility criteria: ≤ 3 lines of prior cancer therapies [anti-PD(L)-1s allowed] for advanced or metastatic disease; intolerance to standard therapies including anti-PD(L)-1s allowed; no liver metastases or adequately treated liver metastases either locally (e.g., by surgery, radiofrequency ablation, or chemoembolization) or systemically and stable for 3 months. Primary objective: to further evaluate anti-tumor activity of invikafusp as monotherapy in each of the above-described 9 cohorts of patients with anti-PD(L)-1-resistant, unresectable, locally advanced, or metastatic solid tumors. Primary endpoint: overall response rate (ORR) per iRECIST. The enrollment to the first three cohorts has begun. Clinical trial information: NCT05592626. Research Sponsor: Marengo Therapeutics, Inc.

TPS2688 **Poster Session**

A phase 1 first-in-human study of the novel anti-LLT1 antibody (ZM008) alone and in combination with anti-PD1 antibody in patients with advanced solid tumors.

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Background: ZM008 is a first-in-class, fully human, IgG1 monoclonal antibody targeting the LLT1 antigen. It disrupts the interaction of LLT1-CD161, an NK-mediated innate immunity checkpoint. LLT1 expression on tumor cells has been associated with poor overall survival in multiple solid tumors. *Ex vivo* experiments with lung and bladder cancer biopsies showed significant tumor reduction and immune cell infiltration were observed with ZM008 monotherapy. Synergistic anti tumor effects were observed with ZM008 in combination with pembrolizumab. An open-label, phase 1, first-in-human study evaluating the safety, tolerability, pharmacokinetics (PKs), preliminary anti-tumor activity and the Recommended Phase 2 Dose (RP2D) of ZM008 alone and in combination with pembrolizumab in advanced solid tumors is now ongoing at 3 US sites (NCT06451497). **Methods:** The study includes a dose-escalation Part 1 and a dose-expansion Part 2. In dose escalation (part 1), ZM008 monotherapy follows 3+3 standard design starting with 0.15 mg/Kg and up to 18 mg/Kg IV Q3W. A staggered parallel arm will explore ZM008 in combination with pembrolizumab (200mg Q3W) from dose level 6. Histologically confirmed advanced or metastatic non-small cell lung, head & neck, pancreatic, biliary, prostate, colorectal, triple negative breast, urothelial, ovarian and diffuse large B cell malignancies with no standard alternative are included. Measurable disease by RECIST v1.1, adequate haematological, hepatic and renal functions are required. In Part 2, two or more doses of ZM008 will be used to select RP2D and indications of interest. Major exclusion criteria include, patients with history of uncontrolled brain metastasis, autoimmune disease, pneumonitis, active infections, and significant cardiovascular diseases. The primary objective is to determine the maximum tolerated dose (MTD) and RP2D of ZM008. Secondary objectives include PKs, incidence and severity of treatment-emergent AEs as per common terminology criteria for adverse events (CTCAE) v.5.0, immunogenicity, pharmacodynamic changes, and preliminary anti-tumor activity. Exploratory biomarkers will evaluate pharmacodynamics changes, receptor occupancy, immune and cytokine profiling, ctDNA, and transcriptomics. Paired pre- and on-treatment biopsies will be analysed using immunohistochemistry and the spatial distribution of immune and tumor cells in the tumor microenvironment. At the time of submission, enrollment of 9 subjects were completed in three dose cohorts with no reported DLTs. The study is ongoing and open for enrolment at NEXT Oncology (San Antonio and Austin sites) and Dana-Farber Cancer Institute, Boston. Clinical trial information: NCT06451497. Research Sponsor: Zumutor Biologics Inc.

TPS2689 Poster Session

ELEPHAS-01, ELEPHAS-02 and ELEPHAS-04: Multi-institutional observational prospective clinical trials to assess the accuracy of an ex vivo live tumor fragment platform for predicting immunotherapy response.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, existing FDA approved companion diagnostic biomarkers like PD-L1, dMMR/MSI-H and TMB have low accuracy in predicting response. Ex vivo cytokine profiling of live tumor samples has shown promise as an improved means of predicting response to PD-1 blockade (Voabil, et al. *Nat Med.* 2021), but this approach has been limited to tumor resections given the need for large amounts of tissue. Here we present three clinical trials that leverage a novel approach using limited tissue from a single core needle biopsy (CNB) (20 gauge or larger). A sequential ex vivo treatment strategy is used, eliminating the need for a separate control arm and addressing challenges with tumor heterogeneity, particularly in CNBs where tissue is limiting. Using a specialized instrument, CNBs are cut into live tumor fragments (LTFs) which are viable in culture and retain the native tumor microenvironment, enabling cytokine profiling in response to ICI treatment ex vivo. **Methods:** ELEPHAS-01 (NCT05478538), ELEPHAS-02 (NCT05520099) and ELEPHAS-04 (NCT06349642) are observational prospective clinical trials initiated to characterize the accuracy of this approach for predicting ICI response. Over 750 patients that are being considered for standard of care (SOC) ICI therapy in the metastatic/relapse or neoadjuvant setting will be enrolled (Table). Fresh live CNBs are collected prior to treatment start and processed within 24 hrs enabling prediction of results within 72 hrs of receipt. LTFs are treated using a strategy where control (IgG) and SOC ICI treatments are performed sequentially on the same tissue in a single well. Changes in the cytokine secretion rates are then compared between ICI and control to characterize immunotherapy response. Additionally, tissue viability and tumor content measurements are used to assess tissue quality. Clinical response is measured using pathologic response in patients receiving neoadjuvant ICI therapy, while RECIST v1.1 is used in all other patients. The primary objective of these trials is to determine the platform's ex vivo accuracy (e.g., sensitivity, specificity) for predicting clinical response to ICIs and comparing it to the accuracy of PD-L1, dMMR/MSI-H and TMB. Clinical trial information: NCT06349642, NCT05478538, NCT05520099. Research Sponsor: None.

	ELEPHAS-01 (Lung)	ELEPHAS-02 (Hoosier)	ELEPHAS-04 (Mayo)
Setting	Metastatic & recurrent	Metastatic & recurrent	Metastatic, recurrent & neoadjuvant
Tumor type	Lung	Bladder, kidney, colorectal, head and neck, lung, melanoma, endometrial	Metastatic/recurrent: lung, skin, esophageal, cervical, endometrial, colon, liver, kidney, bladder Neoadjuvant: breast—TNBC, lung
Enrollment as of 1/27/2025	26	44	20
Est. total enrollment	216	216	324
Clinical endpoints	RECIST v1.1	RECIST v1.1	RECIST v1.1 & Pathologic response at surgery

TPS2690 **Poster Session**

Phase II basket study to evaluate the tissue-agnostic efficacy of anti-PD1 in patients with advanced rare tumors: The ANTARES trial.

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Background: Rare tumors account for 25-30% of all malignancies; however, patients (pts) with these cancers are underrepresented in clinical trials. The limited evidence on sequential oncologic treatment strategies in this population leads to a poorer prognosis compared to pts with more common malignancies. The predictive role of the tissue-agnostic biomarker PD-L1 and the combined positive score (CPS) in determining the efficacy of anti-PD1 therapy remains poorly understood in this population. **Methods:** ANTARES TRIAL (NCT06638931) is a basket phase 2 single-arm multicentric study to evaluate the efficacy of anti-PD 1 in rare tumors. Key inclusion criteria are invasive neoplasia with incidence lower than 6/100.000 people-year, expressing PD-L1 with a combined positive score (CPS) ≥10, ECOG 0-1, measurable disease by RECIST v1.1, progression or intolerance to all available treatments for metastatic disease. Patients will receive nivolumab 480 mg intravenously every 4 weeks until disease progression or for a maximum duration of 12 months. The primary endpoint was the disease control rate (DCR) assessed by RECIST v1.1. Based on Simon's two-stage design (DCR under alternative hypothesis > 25%; DCR under null hypothesis ≤5%), nine patients were accrued in the first stage. If ≥1 responses are observed, the trial will accrue an additional 16 pts. The study will be considered positive if 4 or more pts achieve DCR among 25 pts in the second stage. Considering a drop-out rate of 10%, a sample size of 28 patients will be needed to attain 90% power and alpha 0.05. Secondary endpoints include progression-free survival, overall survival, response duration, and response time. Blood samples for circulating tumor DNA, microvessels, and seric immune checkpoint biomarkers will be collected at screening, at 8, 20, 32, 44 weeks, and at the final visit. Enrollment started in Brazil on June/24 at Instituto do Câncer do Estado de São Paulo (ICESP) and Instituto D'Or de Pesquisa e Ensino (IDOR); 8 sites are planned to open later in 2025. Clinical trial information: NCT06638931. Research Sponsor: FINEP - Financiadora de Estudos e Projetos, Brazil; Reference 1676/22 protocol FADDE222-E1AE-45D9-A318-0C8477BEA1D9.

TPS2691 Poster Session

Phase 2 trial of TU2218, TGFβ-RI, and VEGF-R2 dual inhibitor in combination with pembrolizumab in patients with biliary tract cancer and head and neck cancer.

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Background: TU2218 is a low molecular weight dual kinase inhibitor highly specific to TGFβR1 and VEGFR2 and has a potential to be an efficacious therapy against cancer growth. In vitro and in vivo nonclinical studies have shown that TU2218 reduced the growth and migration/invasion of tumor cells and increased antitumor effects in combination with anti-PD-1/anti PD-L1 antibodies. To investigate safety and tolerability of TU2218 Phase 1a trial was conducted with 6 dose level escalation (30mg/day → 60mg/day → 105mg/day → 150mg/day → 195mg/day → 270mg/day) of TU2218 alone, and it was confirmed that TU2218 was safe and tolerated in all dose levels. And to explore the synergistic effect of TU2218 in combination with Pembrolizumab and to decide RP2D Phase 1b trial was conducted with 3 dose level escalation (105mg/day → 150mg/day → 195mg/day) of TU2218 in combination with Pembrolizumab in patients with advanced solid tumors. The RP2D of TU2218 was established as 195mg/day in combination with Pembrolizumab, the total 19 patients received the treatment and most frequently observed TRAE was pruritus and proteinuria, and three Grade 3 TRAEs (Pruritus, Rash Maculo-Popular, Malaise) were observed. The MTD was not identified during dose escalation period. The ORR of overall dose levels demonstrated 19%, and DCR was about 63%. In particular, 80% DCR was observed in TU2218 195mg/day in combination with Pembrolizumab. The trial was expanded to the specific cancer types, Biliary Tract Cancer and Head and Neck Cancer using the established RP2D for Phase 2 trial. **Methods:** Locally advanced unresectable or metastatic biliary tract cancer (BTC) patient whose tumor has progressed on/after first line standard anticancer therapy and anti-PD-(L)1 agent-naïve metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) patient whose tumor express PD - L1 (CPS ≥1) as determined by an FDA-approved test or recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy are eligible for this non-randomized, open-label multicenter trial. All patients are administered with TU2218 195mg/day (97.5mg BID) on a 2 weeks-on/1 week-off in combination with Pembrolizumab 200mg IV Q3 weeks and will be evaluated by investigator-assessed objective response rate (ORR) defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) according to RECIST version 1.1. If 2 or less patients out of 22 evaluable BTC patients are observed with CR/PR and 3 or less patients out of 22 evaluable HNSCC patients are observed with CR/PR, this suggests futility and the cohort may be stopped. Up to 40 BTC patients and up to 36 HNSCC patients are planned to be enrolled and a dropout rate of up to 10% is expected. As of this abstract submission date, 14 BTC patients and 8 HNSCC patients have been enrolled. Clinical trial information: NCT05784688. Research Sponsor: TiumBio., Co., Ltd.; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

TPS2692 Poster Session

A multi-center, single-arm, phase II study of pemigatinib combined with immune checkpoint inhibitor in FGFR1/2/3 alteration advanced solid tumor.

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Background: FGFR mutations are a significant genetic factor contributing to the onset and progression of various cancers. FGFRs are aberrantly activated, including single-nucleotide variants, gene fusions, and copy number amplifications in human cancer. FGFR mutation alterations are most commonly observed in urothelial carcinoma, breast cancer, endometrial cancer, squamous cell carcinoma of the lung, etc. The preliminary efficacy of FGFR inhibitors in solid tumors has been established ORR ranged from 20% to 30% [1,2,3]. However, the efficacy of FGFR inhibitors as monotherapy in treating FGFR mutations of solid tumors has not yet met the clinical needs. Evidence from preclinical research suggested that a combination of FGFR inhibition and PD-1 suppression expanded the T-cell clones and caused immunological changes in the tumor microenvironment to enhance anti-tumor immunity and survival [4]. Based on the synergistic interplay between the FGFR signaling pathway and immune mechanisms, this study aims to evaluate the safety and efficacy of combining the FGFR inhibitor pemigatinib plus PD-1 inhibitor to treat solid tumors harboring FGFR mutations. **Methods:** 1. This study is a single-arm, multicenter, prospective Phase II clinical trial. Gene testing confirms FGFR1/2/3 variants, including but not limited to mutations, fusions/rearrangements in solid tumors. 2. Patients have not previously used specific small molecule multi-target inhibitors of the FGFR pathway, as assessed by investigators, and have been treated with immune checkpoint inhibitors. 3. Patients receive pemigatinib (13.5 mg QD, orally, 2 weeks on 1 week off, 21 days per-cycle), with immune checkpoint inhibitor therapy (strictly follow instructions). Treatment should continue until disease progression or unacceptable toxicity occurs of intolerable toxicities. 4. At least one measurable lesion per RECIST v1.1 criteria. 5. The safety of the study will be assessed using the NCI-CTCAE v5.0 criteria. The primary outcome measures: objective response rate (ORR). Secondary outcome measures: disease control rate (DCR), progression-free survival (PFS); overall survival (OS); safety and quality of life. Clinical trial information: NCT06551896. Research Sponsor: None.

TPS2693 Poster Session

IMMUNORARE[5]: A national platform of 5 academic phase II trials coordinated by Lyon University Hospital to assess the safety and the efficacy of the immunotherapy with domvanalimab + zimberelimab combination in patients with advanced rare cancers—The Anaplastic Thyroid Carcinomas Cohort.

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Background: In patients with rare cancers, there is an unmet medical need for investigating innovative therapeutics beyond standard first-line treatment. Indeed, these diseases are rarely assessed in clinical trials. Anaplastic thyroid carcinomas (ATC) represent 2-3 % of thyroid carcinomas, but are responsible for 15-40% of thyroid cancer mortality. Most cases (> 90%) are diagnosed with advanced unresectable disease. In such patients carrying the BRAFV600 mutation (20-30%), the standard 1st-line treatment relies on dabrafenib & trametinib. In patients without BRAF mutation, the 1st line treatment is chemoradiation. There is no validated 2nd line treatment, but immunotherapy combinations seem promising. In DUTHY trial (Durvalumab + tremelimumab), the 6month-OS was 65.6% in ATC. Moreover, TIGIT expression increased during ICI treatment, suggesting potential synergistic effects by simultaneous blockade of TIGIT and PD-1. **Methods:** IMMUNORARE[5] (NCT06790706) is a platform of 5 single arm phase II trials testing the efficacy and safety of DOMVANALIMAB (anti-TIGIT) and ZIMBERELIMAB (anti PD-1) in 5 independent cohorts of rare cancers. The trial, sponsored by Lyon University Hospital, is conducted in 15 French centers, led in partnership with the corresponding French national reference centers. The ATC cohort, led in collaboration with the French network ENDOCAN-TUTHYREF (https://www.tuthyref.com/fr), will enroll 24 patients with either non-mutated BRAF tumours with persistent disease at the first evaluation after chemoradiation or disease progression/relapse after the end of chemoradiation, or with mutated B-RAF tumors in progression after a standard B-RAF inhibitor. Patients will receive intra-venous DOMVANALIMAB and ZIMBERELIMAB, every three weeks, until disease progression. The primary endpoint is the survival rate at 6 months. The secondary objectives are overall response rate and duration of the response, progression-free survival and tolerability. The trial is designed with a two-stage Simon design, with early termination for futility (5% one-sided alpha level, 80% power. The treatment would be considered interesting if the survival rate at 6 months is statistically higher than 25%; 50% is expected. Translational research projects will be developed aiming at deciphering cellular and molecular mechanisms involved in response to treatment. Moreover, data from the prospective database of the ENDOCAN-TUTHYREF network will be investigated to build a synthetic historical arm representative of the efficacy of the standard treatments in a similar population of patients. Clinical trial information: NCT06790706. Research Sponsor: None.

TPS2694 **Poster Session**

Trial in progress: A first-in-human (FIH) phase I study of PTX-912 in patients with locally advanced or metastatic solid tumors.

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Background: High-dose IL-2 (HD IL-2) received FDA approval for metastatic melanoma (mM) and metastatic renal cell carcinoma (mRCC), but its use is limited by severe systemic toxicities. While PD-1 blockade has improved overall survival in 20–30% of cancer patients, resistance remains a significant challenge. Notably, HD IL-2 has shown durable anti-tumor effects in mM and mRCC patients who have progressed on anti-PD-1 therapy. Moreover, combining IL-2 with pembrolizumab in mRCC demonstrated a durable response rate of 70%, compared to objective response rates (ORR) of 20% and 33% with IL-2 and pembrolizumab monotherapy, respectively (*Chatzkel et al., Clin Genitourin Cancer(2022)*). These findings suggest that combining IL-2 receptor (IL-2R) activation with PD-1 blockade may be a promising strategy to overcome PD-1 resistance and enhance clinical outcomes. PTX-912 is a novel, first-in-class bifunctional PD-1-proIL-2v fusion protein designed to synergize PD-1 blockade with PD-1-cis-directed IL-2R agonism specifically within the tumor microenvironment (TME), reducing systemic toxicities typically associated with high dose IL-2 therapy. **Methods:** This first-in-human (FIH), multicenter Phase I study (NCT06190886) evaluates the safety, tolerability, and preliminary efficacy of PTX-912 in patients with locally advanced or metastatic solid tumors who have had disease progression on all available standard of care and/or refused available standard of care therapies that would confer clinical benefit. Eligible patients must have measurable disease per RECIST v1.1 and may have received any number of prior therapies. Key exclusions include immunodeficiency, unresolved toxicities > Grade 1 per NCI CTCAE from prior therapy, active autoimmune disease, primary CNS or leptomeningeal involvement, history of transplant, recent major surgery, and significant cardiac or pulmonary dysfunction. The study includes dose escalation (Part 1a) and dose expansion (Part 1b) cohorts. In Part 1a, seven dose levels (DL1–7) will be tested, with DL1–3 following an accelerated titration design and DL4–7 using a standard 3+3 design. The primary objectives are to determine the maximum tolerated dose (MTD), optimal biological dose (OBD), and/or the recommended Phase II dose (RP2D) of PTX-912, assessed via dose-limiting toxicities (DLTs). Patients with melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), or other populations identified based on Part 1a data will be enrolled in Part 1b. In Part 1a, patients will receive intravenous infusions of PTX-912 every two weeks (Q2W), followed by subsequent cycles with a 28-day DLT observation period. Study enrollment began in June 2024 in the United States at 3 centers. Cohorts 1 to 4 (6 patients) have been completed without DLT. Enrollment to cohort 5 is currently ongoing. Clinical trial information: NCT06190886. Research Sponsor: Proviva Therapeutics.

TPS2695 Poster Session

Phase 1/2 study of tiragolumab and atezolizumab in patients with relapsed or refractory SMARCB1- or SMARCA4-deficient tumors: PEPN2121.

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Background: The SMARCB1/A4 gene products are core subunits of the SWItch/Sucrose Non Fermentable (SWI/SNF) chromatin remodeling complex. Tumors with defects in SWI/SNF are histologically distinct aggressive cancers occurring in children and young adults. SMARCB1/A4 deficient tumors, particularly malignant rhabdoid tumor (MRT), atypical teratoid rhabdoid tumor (ATRT), poorly differentiated chordoma (PDC), epithelioid sarcoma (ES), and renal medullary carcinoma (RMC), have immune cell infiltrates and programmed death ligand 1 (PD-L1) expression. Responses to immune checkpoint inhibition (CI) have been observed in SMARCB1/A4 deficient tumors; however, responses are not durable. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel inhibitory receptor expressed on multiple immune cells. TIGIT inhibits T and NK cells by binding to its ligand poliovirus receptor (PVR) and Nectin2 on both tumor and antigen-presenting cells. Utilizing RNAseq data, SMARCB1/A4 deficient tumors demonstrate high expression of PVR and Nectin2. Tiragolumab is an antibody to the TIGIT receptor. The combination of tiragolumab and atezolizumab has shown promising activity in early phase studies, and phase 3 studies are ongoing in multiple adult indications. Thus, there is rationale that the addition of tiragolumab to CI may also enhance response rates in patients with SMARCB1/A4 deficient tumors. **Methods:** This is a phase 1/2 trial of tiragolumab monotherapy (300 mg if $\leq$ 15 kg; 420 mg if $>$ 15 kg to $\leq$ 40 kg; 600 mg if $>$ 40 kg or $\geq$ 18 years) and in combination with atezolizumab (15 mg/kg [max 1200 mg]) if $<$ 18 yrs or 1200 mg if $\geq$ 18 years) administered IV on Day 1 of 21-day cycles in patients $>$ 12 months of age with SMARCB1/A4 deficient tumors. Part A evaluating the safety of tiragolumab monotherapy in patients $<$ 18 years based on cycle 1 dose limiting toxicities is complete. Part B estimates the antitumor activity of tiragolumab in combination with atezolizumab in 6 histology-specific cohorts (RMC, MRT, ATRT, PDC, ES, and other SMARCB1/A4 deficient tumors) and is now open to all eligible age groups. Each cohort is conducted using a 6+4 Simon's two stage design. Enrollment for each cohort is as follows: Part A 6/6, Part B RMC 1/6, MRT 1/6, ATRT 4/6, PDC 2/6, ES 3/6, other 6/6. Radiographic imaging central response assessment for the first stage of the "other" cohort is ongoing. Cycle 1 toxicities of the combination therapy are monitored in Part B patients $<$ 12 yrs using a Bayesian Optimal INterval (BOIN) design with a target toxicity of 17%. Secondary objectives are to characterize the pharmacokinetics/anti-drug antibody development and to estimate progression free survival, overall survival, and duration of response. Enrollment is open at all Pediatric Early Phase Clinical Trial Network sites. Data cutoff: Jan 10, 2025. Clinical trial information: NCT05286801.
Research Sponsor: National Cancer Institute; UM1CA22882; Cookie for Kids Foundation; Genentech, A Member of the Roche Group,; NIH, NCI Intramural research program.

TPS2696 **Poster Session**

A phase 1b study of combined treatment with dupilumab (anti-IL-4Ra) and cemiplimab (anti-PD-1) in patients with early-stage, resectable NSCLC.

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Background: For resectable stage II/III non-small cell lung cancer (NSCLC), neoadjuvant chemoimmunotherapy has become standard of care. Patients with Stage I disease (as per AJCC 8) were excluded from chemoimmunotherapy studies given prior data demonstrating no survival benefit from perioperative chemotherapy. However, even patients with Stage 1A (< 2cm) tumors have a 30% chance of recurrence (Altorki *et al*, *NEJM* 2023). Recent research has revealed that tumor-infiltrating myeloid cells express an IL-4 responsive transcriptional signature, and IL-4 signaling within monocyte-derived macrophages plays an essential role in NSCLC progression and tumor microenvironment remodeling. Dupilumab, a monoclonal antibody targeting IL-4 receptor alpha (IL-4Rα), is currently approved for treating asthma and allergic rhinitis, and preclinical studies have demonstrated that blocking IL-4 signaling can significantly reduce lung tumor burden by activating dendritic cells and effector T cells to generate a robust immune response against tumor antigens. These findings are supported by early clinical evidence from a phase 1/2 trial showing that dupilumab can work synergistically with PD-(L)1 inhibition to induce sustained tumor responses in some patients with metastatic NSCLC who had previously progressed on immunotherapy. Whether similar synergy would be seen in the pre-operative setting in patients with Stage 1 tumors, or patients not suitable for chemoimmunotherapy, is not known, though an immunotherapy-alone approach may enable much more brief pre-operative treatment given that T cell changes peak at one week in the metastatic setting, and prior studies show PD-1 blockade alone can cause robust responses in some patients within only a few weeks. **Methods:** This Phase 1b/2a single-arm trial will enroll patients with early-stage (> T1b), resectable NSCLC. Patients will receive one dose each of dupilumab (600mg SC) and cemiplimab (350mg IV) on day 1, followed by surgical resection within 15-21 days, with delays beyond 8 weeks considered a delay of surgery. The trial consists of a 3+3 safety run-in (Phase 1b, up to 6 patients) followed by a Simon's two-stage expansion (Phase 2a, up to 24 total patients). The primary endpoints are safety/feasibility (Phase 1b) and major pathological response rate, defined as ≤10% viable tumor at resection (Phase 2a). Secondary endpoints include time to surgery, pathological complete response rate, event-free survival, and overall survival. Comprehensive correlative studies will characterize the immune response through serial blood sampling (days 1, 4, 8, 15, surgery, and 30 days post-op), matched proteomic and transcriptomic tumor tissue analysis (pre-treatment and operative samples), and stool microbiome profiling to identify potential biomarkers of response. Clinical trial information: NCT06088771. Research Sponsor: Cancer Research Institute.

TPS2697 Poster Session

A phase 1 trial of APX-343A, NOX inhibitor targeting CAF-mediated immunosuppression, as monotherapy or in combination with pembrolizumab in patients with advanced solid tumors.

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Background: Cancer-associated fibroblasts (CAFs), a key component of tumor stroma, promote tumor growth and resistance to anticancer therapy. They contribute to immune suppression within the tumor microenvironment (TME), with evidence linking CAFs to immune checkpoint inhibitor (ICI) resistance and T-cell exclusion. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), which is clinically upregulated by CAF in many human cancers, has been reported to be a critical effector of myofibroblast transformation during fibrosis. Inhibiting NADPH oxidases, NOX2 and NOX4, restored cluster of differentiation 8 + T-cell proliferation by reducing reactive oxygen species (ROS) generation in CAF-induced myeloidderived suppressor cells (MDSCs). A pivotal role of CAFs in regulating monocyte recruitment and differentiation demonstrated that CC-chemokine receptor 2 inhibition and ROS scavenging abrogate the CAF-MDSC axis, illuminating a potential therapeutic path to reversing the CAF-mediated immunosuppressive microenvironment. APX-343A, a selective NOX1, NOX2, and NOX4 inhibitor, has been shown to ameliorate the fibrotic and immunosuppressive properties of CAFs. In CAF-rich tumor mouse models that do not respond to ICIs, APX-343A demonstrated significant anticancer efficacy by modulating both fibrosis and immunosuppression via NOX inhibition. **Methods:** This is a Phase 1, open-label, dose-escalation study designed to assess the safety, tolerability, PK, and preliminary efficacy of APX-343A as monotherapy (Part A) and in combination with pembrolizumab (Part B) in patients with advanced solid tumors. The trial aims to determine the MTD and/or RP2D. Part A is a dose-escalation study of APX-343A monotherapy, starting at a dose of 100 mg BID (Cohort 1) and escalating up to 600 mg BID (Cohort 6) until dose-limiting toxicity (DLT) is identified. APX-343A will be administered on a continuous daily dosing schedule in 21-day cycles. Part B is a dose-escalation study of APX-343A in combination with pembrolizumab (200mg IV, Q3W). Using the BOIN design, the dose level of APX-343A will escalate from 200 up to 600 mg BID without exceeding the MTD. The BOIN design will guide dose escalation based on safety, with decisions made by the Safety Review Committee (SRC). Dose finding will be conducted independently for Parts A and B. APX-343A selective NOX inhibitor has the potential to become an effective treatment option in combination with ICIs for patients with CAF-rich solid tumors that are unresponsive to current immunotherapies. By inhibiting CAF activity in the TME and resensitizing tumors to cancer immunotherapy, APX-343A offers a promising therapeutic approach. Phase 1 results are anticipated in Q1 2026. Research Sponsor: Aptabio Therapeutics Inc.

TPS2698 Poster Session

A phase Ib study of a pooled synthetic long peptide mutant KRAS vaccine combined with balstilimab/botensilimab in metastatic pancreatic cancer and metastatic MMR-proficient colorectal cancer in the maintenance setting.

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Background: Expressed in > 90% of all patients with pancreatic ductal adenocarcinoma (PDAC) and ~40% in mismatch repair-proficient colorectal cancer (MMRp CRC), the mutated oncoprotein KRAS (mKRAS), is an attractive neoantigen vaccine target. Efforts to sensitize these immunologically 'cold' tumors to immune checkpoint inhibitors have just started to yield encouraging clinical data with novel agents. In an ongoing pilot study in patients with resected PDAC and metastatic MMRp CRC (NCT04117087), we demonstrated that a pooled synthetic long peptide (SLP) mKRAS vaccine in combination with ipilimumab and nivolumab was safe and well tolerated. This combination induced robust de novo mKRAS-specific T cells in peripheral blood associated with improved disease-free survival (Haldar *et al.*, 2023). Recently, the Fc-enhanced anti-CLTA-4 antibody, botensilimab (bot), in combination with balstilimab (bal; anti-PD-1) has been shown to demonstrate clinical activity in metastatic relapsed/refractory MMRp CRC (Bullock *et al.*, 2024). Based on these encouraging data, our study combines mKRAS vaccine with dual checkpoint blockade to assess safety and early clinical efficacy in patients with metastatic PDAC and metastatic MMRp CRC in the maintenance setting. **Methods:** This is a first-in-human, single-arm, open-label phase Ib trial evaluating mKRAS vaccine with bal/bot in patients with metastatic PDAC (Cohort A, n = 21) and metastatic MMRp CRC (Cohort B, n = 21). The vaccine consists of SLPs corresponding to six common mKRAS alleles: G12D, G12V, G12R, G12C, G12A, G13D admixed with poly-ICLC adjuvant. In the priming phase (Cycle 1) the mKRAS vaccine is given on days 1, 8, 15 and 22 along with bal/bot on day 1 and bal on day 15. In the boost phase, (Cycle 2 and beyond), patients receive bal every 2 weeks and boost vaccines starting on Cycle 4 and every other cycle for a maximum of 2 years. Eligible patients must have metastatic PDAC or MMRp CRC and measurable disease per RECIST 1.1 amenable to biopsies at baseline and week 9. Patients must have one of the six KRAS mutations contained in the vaccine. Patients must have received 4-6 months of 1st line standard chemotherapy without disease progression. The primary endpoints are safety and tolerability, 4-month progression free survival (Cohort A), and objective response rate (Cohort B). Secondary endpoints include disease control rate, objective response rate (Cohort A), and progression free survival (Cohort B). Correlative studies will examine T cell receptor (TCR) clonal expansion in peripheral blood and paired tumor specimens pre- and post-vaccination by next generation TCR sequencing. Patient accrual began in October 2024 with the safety run in completed. Enrollment is currently ongoing. Study drug support provided by Agenus. Trial information: NCT06411691. Clinical trial information: NCT06411691. Research Sponsor: U.S. Department of Defense; U.S. National Institutes of Health.

TPS2699 Poster Session

A phase I study of a pooled synthetic long peptide mutant KRAS vaccine in patients with pancreatic cystic neoplasms at risk for developing pancreatic cancer.

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Background: Mutant KRAS (mKRAS) is an oncogenic driver expressed in > 90% of patients with pancreatic ductal adenocarcinoma (PDAC) and the majority of pancreatic precursors, including > 90% of intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasia (PanIN) (Kanda *et al.*, 2012). If left untreated, approximately 40-60% of high-risk IPMNs will have malignant transformation (Fonseca *et al.*, 2018). mKRAS vaccines have recently demonstrated encouraging results in generating mKRAS-specific T cell responses that correlate with clinical benefit in patients with resected PDAC. We previously reported that a mKRAS-targeted *Listeria*-based vaccine given with Treg-depleting agents results in slowing of PanIN progression to PDAC in a murine model (Keenan *et al.*, 2014). Based on these data, we have initiated a clinical trial testing this vaccine in individuals at high-risk of developing pancreatic cancer. In our first Cohort [A], we have tested this vaccine in individuals at high-risk due to a known germline mutation or familial predisposition (n = 20). Our current study [Cohort B] aims to determine the safety and immunogenicity of a pooled synthetic long peptide (SLP) mKRAS vaccine with poly-ICLC adjuvant in patients with pancreatic cystic neoplasm at risk for developing PDAC and who are scheduled to undergo surgical resection. **Methods:** This is a single-arm, open-label phase I trial evaluating mKRAS vaccine in patients with pancreatic cystic neoplasms at risk for developing PDAC and scheduled to undergo surgical resection (n = 10). The vaccine consists of SLPs corresponding to six common mKRAS mutations: G12D, G12V, G12R, G12C, G12A, G13D admixed with poly-ICLC adjuvant. A two-dose series of the mKRAS vaccine is administered at weeks 1 and 2 followed by pancreatic surgery at week 4. Peripheral blood will be collected pre-vaccination (week 1) and post-vaccination (weeks 4 and 8). Following completion of the treatment phase, patients have the option to continue annual follow-up visits until study closure. Eligible patients must have clinical, radiographic, or histologic evidence of a pancreatic cystic neoplasm with features warranting surgical resection per the discretion of the treating hepatobiliary surgeon. Co-primary endpoints include the safety profile per NCI CTCAE v5.0 and maximal percent change of mutant-KRAS-specific T cells measured by IFNg ELISPOT at weeks 4 and 8 post-vaccination compared to pre-vaccination baseline. Correlative studies of resected specimens will include characterization of the premalignant microenvironment and mKRAS-specific T cell trafficking post-vaccination. Methods of analyses include bulk RNA and T cell receptor (TCR) sequencing, spatial transcriptomics, and imaging mass cytometry. Patient accrual began in December 2024 and is currently ongoing. Clinical trial information: NCT05013216. Research Sponsor: Lustgarten Foundation for Pancreatic Cancer.

TPS2700 **Poster Session**

A phase 2 basket trial of tarlatamab in patients with advanced DLL3-expressing tumors: University of California Lung Cancer Consortium UCCC-01/UCLA L-10.

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Background: Delta-like ligand 3 (DLL3) is an inhibitory Notch ligand that is aberrantly expressed on the surface of tumor cells, in particular on those with neuroendocrine differentiation. Tarlatamab is a bispecific T cell engager that binds to DLL3 and CD3 to promote T cell killing of DLL3-expressing cells. Prior studies of tarlatamab have demonstrated encouraging antitumor activity and manageable toxicity in patients with small cell lung cancer (SCLC; DeLLphi-301) and neuroendocrine prostate cancer (NEPC; DeLLpro-300). Meanwhile, DLL3 has been reported to be highly expressed in multiple tumor types, including in many neuroendocrine neoplasms (NENs) other than SCLC and NEPC. The role of anti-DLL3 therapies in these cancers has not been established. **Methods:** This is a phase 2, multicenter, open-label, basket study designed to evaluate the efficacy of tarlatamab in patients with DLL3-expressing cancers. Key inclusion criteria include presence of advanced stage disease with progression following ≥1 prior line of therapy and positive tumor DLL3 expression by immunohistochemistry (Ventana SP347 assay). Patients with de novo SCLC or NEPC are excluded, but all other tumor types and NENs are eligible, including large cell neuroendocrine carcinoma and SCLC transformed from previously treated NSCLC. Tarlatamab will be administered at an initial step-up dose (1 mg on D1 and 10 mg on D8 and D15 of cycle 1) followed by 10 mg every 2 weeks. Treatment will continue until unacceptable toxicity, progressive disease, or withdrawal of consent. The study will follow a Simon's two-stage design: in Stage 1, 10 patients with tumor DLL3 expression ≥25% will be enrolled, and the study will be stopped if ≤1 patient achieves an objective response; otherwise, an additional 19 patients with tumor DLL3 expression ≥1% will be enrolled for Stage 2. The primary endpoint is the objective response rate. Secondary endpoints include safety, progression free survival, duration of response, and overall survival. Exploratory studies will evaluate correlation of antitumor activity with tissue and blood-based biomarkers, such as DLL3 expression on tumor and liquid biopsies. This study is currently enrolling patients through the University of California Lung Cancer Consortium (UCLCC). Clinical trial information: NCT06788938. Research Sponsor: None.

TPS2701 **Poster Session**

EXPAND-1, a phase I/II study with ANV600, a novel PD-1 targeted IL-2R-βγ agonist, in monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors.

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Background: ANV600 is a novel PD-1 targeted, interleukin-2 receptor beta/gamma (IL-2Rβ/γ) selective agonist. This bispecific agent comprises two functionally distinct arms: a PD-1 targeting arm consisting of an anti-PD-1 antibody binding to an epitope that does not overlap with pembrolizumab or other PD-1 checkpoint inhibitors and an IL-2 receptor (IL-2R) agonistic arm, composed of an interleukin-2 (IL-2)/anti-IL-2 antibody fusion protein which selectively signals through IL-2Rβ/γ. ANV600 is expected to promote anti-tumor activity by preferentially stimulating and expanding antigen-experienced PD-1$^+$ CD8$^+$ T cells and be combinable with existing anti-PD-1 clinical therapies. ANV600 will be studied as single agent and in combination with pembrolizumab for the treatment of advanced solid tumors. **Methods:** Study ANV600-001 (EXPAND-1) is a global, multicenter, open-label, first-in-human Phase I/II study to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity and antitumor activity of ANV600 administered as a single agent or in combination with pembrolizumab in patients with advanced solid tumors. The Phase I will determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of ANV600 administered intravenously every 2 weeks (Q2W) either as single agent or in combination with pembrolizumab in previously treated advanced solid tumors. A Bayesian Optimal Interval (BOIN) design will guide the dose escalation to determine the MTD and/or RP2D. Once the RP2D has been determined, ANV600 will be further evaluated as monotherapy and in combination with pembrolizumab in the Phase II part of the study for efficacy and safety in PD-1 experienced patients with advanced melanoma, NSCLC and HNSCC. Additional cohorts may be selected based on emerging data. Tumor response will be assessed using RECIST v1.1. Enrolment began in June 2024, with 10 patients enrolled in the monotherapy arm and 4 in the combination arm. Up to 240 participants will be enrolled in 7 countries: Belgium, France, Germany, the Netherlands, Spain, Switzerland and the USA. Research Sponsor: ANAVEON AG. Clinical trial information: NCT06470763. Research Sponsor: None.

TPS2702 **Poster Session**

Fecal microbiota transplantation combined with sintilimab and SOX as first-line treatment for advanced gastric cancer (FMT-JSNO-01): A prospective, multicenter, double-blind, randomized placebo-controlled phase II trial.

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Background: Chemotherapy in combination with immunotherapy has emerged as the first-line(1L) standard of care for gastric cancer (GC) patients(pts); nonetheless, the overall prognosis remains suboptimal. Fecal microbiota transplantation (FMT) holds promise in modulating the patient's gut microbiota and immune milieu, thereby augmenting the efficacy of tumor immunotherapy and enhancing long-term survival outcomes. We propose to integrate FMT into the regimen of chemotherapy plus immunotherapy, aiming to assess its efficacy and safety in pts with advanced GC (NCT06405113). **Methods:** FMT-JSNO-01 is a prospective, multicenter, randomized, double-blind, placebo-controlled phase II trial designed to enroll pts with previously untreated, unresectable advanced gastric or gastroesophageal junction adenocarcinoma (GAC/GEJAC) that is human epidermal growth factor receptor 2 (HER2) negative. The physical status score of Eastern Tumor Collaboration Group (ECOG) was 0-1.The study will be conducted in more than 15 multidisciplinary treatment centers for GC in China.The eligible pts were randomly assigned to arm A and arm B. Using a network random system, subjects are randomly assigned in a 1:1 ratio to the experimental group and control group, and competitive random enrollment is conducted at each center.Pts in arm A received fecal microbiota capsule transplantation combined with sintilimab immunotherapy plus S-1 and oxaliplatin (SOX) chemotherapy, while pts in arm B received placebo combined with sintilimab plus SOX . If there is no progression of the disease after 4-6 cycles of 1L treatment, both arms of pts will enter the 1L maintenance treatment stage: S-1 plus sintilimab, until disease progression, intolerance, or death occurs.The primary endpoint of the study is the 2-year overall survival rate (2-year OS rate), with secondary endpoints including median progression-free survival (mPFS), objective response rate (ORR), incidence of adverse events (AEs), diversity of fecal microbiota, and quality of life (QoL). Additionally, exploratory endpoints will encompass efficacy prediction markers in the gut microbiota and proteomics. This study began recruiting pts in June 2024 and is currently ongoing. Clinical trial information: NCT06405113. Research Sponsor: the 2022 Clinical Research project of Changzhou Medical Center, Nanjing Medical University; CMCC202201; 2022 Changzhou 8th Batch of Science and Technology Project (Applied Basic Research); CJ20220086; 2023 Clinical Research Project of Changzhou Medical Center,Nanjing Medical University; CMCC202307; 2023 Changzhou Health Commission Science and Technology Project; QN202320.

TPS2703 **Poster Session**

A first-in-human phase 1 clinical trial of INI-4001, a novel TLR7/8 agonist, in patients with advanced solid tumors.

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Background: Inimmune has developed INI-4001, a novel TLR7/8 agonist as an immunotherapy treatment for cancer. Pre-clinically, the lead formulation of INI-4001 was able to eliminate Lewis Lung Carcinoma (LLC) flank tumors in mice after just two treatments. Moreover, INI-4001 slowed the growth of MC38 and B16F10 tumors and synergized when combined with anti-PD-1 therapy, leading to an increased cure rate in both MC38 and B16F10 flank tumors in mice when both drugs were used compared to either treatment alone. In July of 2024, we dosed our first patient in a Phase 1 clinical trial in patients with advanced solid tumors. **Methods:** INI-4001 will be evaluated in a Phase Ia/Ib, open-label, dose-escalation, and dose expansion study. This study will be conducted in two parts: Phase Ia (dose escalation) and Phase Ib (dose expansion). Phase Ia will initially seek to establish the MTD or OBD of INI-4001 administered as monotherapy. Using a BOIN design, we have planned six ascending 1-3-subject cohorts with weekly dosing on continuous 21-day cycles. Imaging shall occur after each 3 cycles, and combination therapy with a checkpoint inhibitor is allowable under certain conditions after 3 cycles of monotherapy. Combination with checkpoint inhibitor is allowed if the subject has progressed or achieved stable disease according to iRECIST criteria and has a tumor type for which a checkpoint inhibitor is approved. Following identification of the MTD or OBD, Phase 1b allows any dose level at or below the MTD to be expanded with up to 20 additional subjects to further explore the safety, PK, PD, and preliminary efficacy of INI-4001 alone or as combination therapy. Currently in Phase Ia, Cohorts 1, 2, and 3 have been completed without DLT. Enrollment to Cohort 4 will begin in February 2025. INI-4001 may continue as monotherapy or combination as long as the subject receives benefit. Following cessation of INI-4001, patients will be requested to participate in long-term follow-up to assess overall survival. Clinical trial information: NCT06302426. Research Sponsor: None.