411 NOVEL INTRATUMORAL AGENT, INT230–6 INDUCES CANCER CELL DEATH, INCREASES TUMOR INFILTRATES AND RESULTS IN DURABLE BENEFIT ALONE OR IN COMBINATION WITH PEMBROLIZUMAB IN REFRACTORY PATIENTS

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Background INT230-6 is a novel formulation of cisplatin and vinblastine with an amphiphilic cell penetration enhancer that has been shown to enhance dispersion of the drug throughout tumors and allow diffusion into cells when given intratumorally. In preclinical models, INT230-6 has resulted in cell death, dendritic cell influx, antigen presentation and T-cell engagement with strong synergy when combined with checkpoint inhibitors

Methods This phase 1/2 study evaluated Q2week injections of INT230-6 x 5 dosed by tumor volume alone or with 200 mg pembrolizumab IV Q3 weeks. Eligble patients had any advanced malignancy refractory to standard therapy with an injectable tumor.

Results Sixty subjects (median 3 prior therapies (range 0–10)) were enrolled (53 monotherapy, 7 combo). Median age was 60 (42–85). 19 different cancer types were accrued with breast cancer and sarcoma being the most frequent. Over 200 deep tumor injections were administered at doses of up to 172 ml of INT230-6 (86 mg of CIS, 17 mg of Vin). PK analysis revealed <5% of the drugs were measured in systemic circulation, indicative of minimal systemic exposure. There was no dose limiting toxicity. The most frequent monotherapy drug related AE's reported were: injection-site pain 58%, nausea 37%, fatigue 33%, and vomiting 27% with only 18% of subjects experiencing a grade 3 AE (no grade 4 or 5). Rates were comparable for the single agent INT230-6 and the combination with pembrolizumab. In the overall monotherapy cohort, patients completing all 5 doses of INT230-6 over 56 days (n=16), the median overall survival has not yet been reached. after a median followup of 408 days. In the 5 evaluable patients who received the pembrolizumab combination, the median TTP has not been reached with a median follow up of 6 mo. Paired biopsies (pre, 1 month) were available in 10 monotherapy patients and revealed a median of 63% reduction in viable cancer cells on H&E (30% had no viable cancer) that was also associated with qualitative decreases in Ki67, increases of CD4 and CD8 T-cells and reduction in FoxP3 Tregs. Despite receiving only 2 month of monotherapy, short half lives of the active agents, and no subsequent therapies, 8 injected tumors continued to regress past 1 year.

Conclusions INT230-6 is well tolerated when administered intratumorally alone or in combination with pembrolizumab. Pharmacodynamic assessments provides proof of concept that this drug can reduce viable cancer cells and increases CD4/CD8 T-cell infiltrates leading to durable clinical benefit off treatment.

Trial Registration NCT 03058289

Ethics Approval The study was approved by USC, Princess Margaret Cancer Center, Fox Chase, UMass, Columbia, and Johns Hopkins Institution's Ethics Board

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal

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412 FIRST-IN-HUMAN PHASE I/IIA TRIAL TO EVALUATE THE SAFETY AND INITIAL CLINICAL ACTIVITY OF DUOBODY®-PD-L1×4–1BB (GEN1046) IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Agonistic 4-1BB monoclonal antibodies were preclinically validated as promising cancer immunotherapies, both as monotherapy and as potentiators of the activity of PD-(L)1–blocking agents. However, toxicity and a narrow therapeutic window have hampered their clinical development. DuoBody-PD-L1×4-1BB, a first-in-class, bispecific, next-generation checkpoint immunotherapy, was designed to overcome these limitations by activating T cells through conditional 4-1BB costimulation, while simultaneously blocking the PD-L1 axis. We present preliminary data from the ongoing, first-in-human, open-label, phase I/IIa trial of DuoBody-PD-L1×4-1BB in advanced solid tumors (NCT03917381).

Methods During dose escalation, patients with metastatic or unresectable solid tumors not eligible for standard therapy received flat-dose DuoBody-PD-L1×4-1BB (25–1200 mg) intravenously every 3 weeks until disease progression or unacceptable toxicity. Primary endpoints were dose-limiting toxicities (DLTs) and adverse events (AEs). Secondary endpoints included pharmacokinetic parameters and antitumor activity (RECIST 1.1). Pharmacodynamic biomarkers and antitumor activity (iRECIST) were assessed as exploratory endpoints.

Results As of June 22, 2020, 61 patients were enrolled (median age: 59 years). The most common cancer types were colorectal (19.7%), ovarian (14.8%), pancreatic (9.8%), and NSCLC (9.8%). Patients had previously received a median (range) of 3 (1–11) treatments; 44.2% had prior anti-PD-(L)1 immunotherapy. Patients received a median (range) of 4 (1–15) treatment cycles; Cmax was observed shortly after the end of infusion (mean T½: 2.3–10.3 days). Maximum tolerated dose was not reached; 6 patients experienced DLTs. The most common (=10%) treatment-related AEs (all grades; grades 3–4) were transaminase elevation (24.6%; 9.8%), hypothyroidism (16.4%; 1.6%), and fatigue (13.1%; 1.6%). Treatment-related grade-3 transaminase elevations decreased upon corticosteroid administration; no treatment-related bilirubin increases or grade-4 transaminase elevations occurred. Disease control, including stable disease at first assessment and partial responses in triple-negative breast cancer, ovarian cancer, and immune checkpoint inhibitor (ICI)–pretreated NSCLC, occurred in 40/61 patients (65.6%). Pharmacologic activity, as measured by modulation of adaptive immunity mediators, was observed across a broad range of dose levels. Peripheral proliferating (Ki67+) CD8+ effector memory T cells and serum interferon-gamma levels showed maximum induction relative to baseline (p=0.01) 8 days following treatment.

Conclusions DuoBody-PD-L1×4-1BB demonstrated biologic activity and a manageable safety profile. Encouraging early clinical activity across different dose levels was observed in a heavily pretreated population with advanced solid tumors, including those resistant to prior immunotherapy or typically less sensitive to ICIs. Expansion cohorts of patients for whom DuoBody-PD-L1×4-1BB treatment could be relevant and biologically sound have started enrollment. Updated data will be presented.

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Trial Registration ClinicalTrials. gov; trial number: NCT03917381

Ethics Approval This trial is undertaken following full approval of the final protocol, amendments, informed consent form, applicable recruiting materials, and subject compensation programs by the Independent Ethics Committee/Institutional Review Board.

Consent Written informed consent, in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines including ICH-GCP E6(R2), applicable regulatory requirements, and sponsor policy, was provided by the patients.

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413 GEN-009, A PERSONALIZED NEOANTIGEN VACCINE, ELICITS ROBUST IMMUNE RESPONSES IN INDIVIDUALS WITH ADVANCED OR METASTATIC SOLID TUMORS

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Background ATLAS^{TM} is a cell-based bioassay that utilizes a cancer patient's own monocyte-derived dendritic cells and $CD4^+$ and $CD8^+$ T cells to screen their mutanome and identify neoantigens that elicit robust anti-tumor T cell responses, as well as, deleterious InhibigensTM.[1] GEN-009, a personalized vaccine comprised of 4–20 ATLAS-identified neoantigens combined with Hiltonol®, harnesses the power of neoantigen-specific T cells to treat individuals with solid tumors. The safety and efficacy of GEN-009 is being assessed in a phase 1/2a clinical trial (NCT03633110).

Methods A cohort of 15 adults with solid tumors were enrolled in the study. During the screening period, patients received standard of care PD-1-based immunotherapies appropriate for their tumor type. Subsequently, patients were immunized with GEN-009 with additional doses administered at 3, 6, 12, and 24 weeks. Peripheral blood mononuclear cells (PBMCs) were collected at baseline, pre-vaccination (D1), as well as 29, 50, 92, and 176 days post first dose. Vaccine-induced immunogenicity and persistence were assessed by quantifying neoantigen-specific T cell responses in ex vivo and in vitro stimulation dual-analyte fluorospot assays. Polyfunctionality of neoantigen-specific T cells was evaluated by intracellular cytokine staining. Additionally, potential correlations between the ATLAS-identified profile and vaccine-induced immunogenicity were assessed.

Results GEN-009 augmented T cell responses in 100% of evaluated patients, attributable to vaccine and not checkpoint blockade. Furthermore, neoantigen-induced secretion of IFNγ and/or TNFα by PBMCs, $CD4^+$, and $CD8^+$ T cells was observed in all patients. Responses were primarily from polyfunctional T_{EM} cells and detectable in both $CD4^+$ and $CD8^+$ T cell subsets. Some patients had evidence of epitope spreading. Unique response patterns were observed for each patient with no apparent relationship between tumor types and time to emergence, magnitude or persistence of response. Ex vivo vaccine-induced immune responses were observed as early as 1 month, and in some cases, persisted for 176 days. Clinical efficacy possibly attributable to GEN-009 was observed in several patients, but no correlation has yet been identified with neoantigen number or magnitude of immune response.

Conclusions ATLAS empirically identifies stimulatory neoantigens using the patient's own immune cells. GEN-009, which is comprised of personalized, ATLAS-identified neoantigens, elicits early, long-lasting and polyfunctional neoantigen-specific $CD4^+$ and $CD8^+$ T cell responses in individuals with advanced cancer. Several patients achieved clinical responses that were possibly attributable to vaccine; efforts are underway to explore T cell correlates of protection. These data support that GEN-009, in combination with checkpoint blockade, represents a unique approach to treat solid tumors.

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Trial Registration NCT03633110

Ethics Approval This study was approved by Western Institutional Review Board, approval number 1-1078861-1. All subjects contributing samples provided signed individual informed consent.

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414 ENHANCING T CELL THERAPY FOR PATIENTS WITH RELAPSED/REFRACTORY WILMS TUMOR

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Background Patients with relapsed or refractory Wilms tumor (WT) have poor prognoses with limited treatment options.[1–3] Immunotherapy offers a promising alternative for targeted therapy but has been limited by immune evasion tactics.[4–6] Adoptive cell therapy with patient-derived tumor-associated antigen-specific T cells (TAA-T) targeting 3 antigens (WT1, PRAME, and survivin) has the potential to overcome antigen loss. The objective of this phase I clinical trial is to determine the safety of administering TAA-T to patients with high-risk, relapsed/refractory solid tumors. Secondary objectives include determination of clinical efficacy and immunobiology following infusion.