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 Q2 week injections of INT230-6-x 5 dosed by tumor volume alone or with 200 mg pembrolizumab IV Q3 weeks. Eligible patients had any prior systemic therapy, including prior PD-(L)1/PD-L1 blockade, with 1200 mg pembrolizumab IV Q3 weeks. 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 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 followup of 408 days. 13/16 patients had prior anti-PD-(L)1/PD-L1, and 44.2% had prior anti-PD-(L)1/PD-L1/PD-L2/PD-L3 combination therapy. No new safety signals were reported in the combination arm compared to monotherapy.

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 followup of 16 months. Paired biopsies (pre, 1 month) were available in 6 patients. Disease control was observed in 6 patients (Ki67+ Tregs. Despite receiving only 2 months 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 provide proof of concept that this drug can reduce viable cancer cells and increases CD4/CD8 T-cell infiltration 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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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

Mara Shainheit *, Devin Champagne, Gabriella Santone, Syukri Shukor, Ece Bicak, Samuel Tipps, Li Xue, Thomas Davis, Jessica Flechtn. Genocea Biosciences, Cambridge, MA, USA

Background ATLAS™ 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 Inhibigens™.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. Polyclonality 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 TEM 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.

Acknowledgements We are grateful to the patients and their families who consented to participate in the GEN-009-101 clinical trial.

Trial Registration NCT03633110

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

REFERENCE


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

Amy Hon*, Conrad Cruz, Majda Stanojevic, Robert Urey, Madeline Terpilowski, Emily Reynolds, Fahmida Hoq, Maria Fortiz, Haili Long, Jeffrey Dome, Patrick Hanley, Catherine Ballard, Holly Meany. Children's National Hospital, Washington, DC, USA

Background Patients with relapsed or refractory Wilms tumor (WT) have poor prognoses with limited treatment options.1–5 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.