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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. Eligible 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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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 pre-clinically 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; C_{max} was observed shortly after the end of infusion (mean T_{1/2}: 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.