Background GB1275 is a first-in-class CD11b modulator that reduced myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs), repolarized M2 immunosuppressive TAMs to an M1 phenotype, and increased tumor infiltration of activated CD8+ T cells in preclinical models. Preclinical anti-tumor activity was observed with single-agent therapy and in combination with chemotherapy or immunotherapy.1 We report results from the dose escalation portion of an ongoing, first-in-human study of GB1275 monotherapy and combined with pembrolizumab in patients with specific advanced solid tumors. (NCT04060342)

Methods This study comprises phase 1 dose escalation followed by phase 2 expansion in specific tumor types. In phase 1, cohorts of 3 to 6 patients with histologically confirmed, locally advanced/metastatic pancreatic, esophageal, gastric, MSS colorectal, metastatic castration-resistant prostate cancer, or triple negative breast cancer are sequentially assigned to one of the ascending dose levels of GB1275 orally twice daily (BID) in 1 of 3 regimens: A (GB1275 monotherapy); B (GB1275 + pembrolizumab) commenced after completion of two cohorts of A; and C (GB1275 + nab-paclitaxel + gemcitabine) will be initiated after A. Patients in Regimens A and B had previously exhausted standard of care treatment options. Dose escalation was based on safety, including dose-limiting toxicity (DLT). Serial blood samples were collected for pharmacokinetic (PK) and biomarker analyses; tumor tissue was also collected for biomarker analysis.

Results As of July 28, 2020, 36 patients were treated, 23 in Regimen A (GB1275 100 mg to 1200 mg BID) and 13 in Regimen B (GB1275 100 mg to 800 mg BID + pembrolizumab). No DLTs or adverse events requiring steroid treatment were reported. GB1275-related adverse events were reported in 19 (52.8%) patients; most were Grade 1 and most frequent events (≥10%) were dysesthesia (13.9%) and photosensitivity reaction (11.1%). Stable disease was reported in 2 (17%) patients in Regimen A and 6 (46%) in Regimen B with a median (range) exposure of 84 days (35–172). A dose-dependent increase in GB1275 exposure was observed. An increase in tumor infiltrating lymphocyte (TIL) counts was noted in both Regimens A and B. Other biomarker analyses in serial blood and tumor tissue are ongoing.

Conclusions Dose escalation of GB1275, up to 1200 mg and 800 mg BID in Regimens A and B, respectively, demonstrated tolerability as monotherapy and combined with pembrolizumab. The maximum tolerated dose has not been reached. Preliminary observation of an increase in TILs after treatment is encouraging.

Ethics Approval This ongoing study is being conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines. The study was approved by the Ethics Boards of the University of Colorado Hospital, Washington University School of Medicine - Siteman Cancer Center, Memorial Sloan Kettering Cancer Center, The Sarah Cannon Research Institute/Tennessee Oncology, South Texas Accelerated Research Therapeutics, and The Royal Marsden NHS Foundation Trust.


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treated with GB1275. Analyses of TIL count revealed an increase in lymphocyte trafficking into the tumor after treatment with GB1275 alone or in combination with pembrolizumab. CD8 expression and transcriptomic analysis are underway and will be presented.

Conclusions GB1275 alone or in combination with pembrolizumab demonstrates biological activity, which may be dose dependent. The observed increase in TILs after treatment is supportive of the mechanism of action of GB1275. Further biomarker analyses in blood and tissues are ongoing and will be correlated with clinical activity in a larger number of patients.

Ethics Approval This ongoing study is being conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines. The study was approved by the Ethics Boards of University of Colorado Hospital, Washington University School of Medicine - Siteman Cancer Center, Memorial Sloan Kettering Cancer Center, The Sarah Cannon Research Institute/Tennessee Oncology, South Texas Accelerated Research Therapeutics, and The Royal Marsden NHS Foundation Trust.

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Abstract 390 Figure 1 Individual patient spider plots. Percent change in target lesion diameter over time

1.37Mut/mb (range 0.31–6.55), with a median of 24 (6–99) neoantigens and 16 (1–86) Inhibigans. The number of neoantigens in each manufactured vaccine ranged from 4–18 (median 13). GEN-009-related adverse events were limited to Grade 1 injection site reactions. Ex vivo T cell responses peaked after the third vaccination for IFNa and some patients showed evidence of epitope spread. The initial 5 patients are evaluable for antitumor activity with at least 3 months follow up after first vaccination. Three patients experienced early tumor responses followed by stabilization on PD-1 inhibitor SOC and demonstrated a further reduction in tumor volume after GEN-009 vaccination (figure 1). One patient experienced a complete response prior to vaccination and the 5th patient had progression on SOC, but had a Partial Response to salvage and remains stable after vaccination.

Conclusions Vaccination with GEN-009 in combination with PD-1 CPI is feasible for patients with advanced solid tumors with little additive toxicity. Preliminary data demonstrate induction of robust, neoantigen-specific immune responses and a potential expansion of stimulatory targets with epitope spreading in the presence of PD-1 inhibitor. Possible additive antitumor activity in combination with PD-1 inhibitors is suggested by tumor shrinkage following GEN-009 dosing. More mature response and immunogenicity data on 10 additional patients is anticipated for November.

Trial Registration ClinicalTrials.gov NCT03633110

Ethics Approval The study was approved by Western Institutional Review Board, approval number 1-1078861-1.

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Abstract 391 A FIRST-IN-HUMAN STUDY OF INTRATUMORAL SAR441000, AN MRNA MIXTURE ENCODING IL-12SC, INTERFERON ALPHA2B, GM-CSF AND IL-15SUSHI AS MONOTHERAPY AND IN COMBINATION WITH CEMIPLIMAB IN ADVANCED SOLID TUMORS

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Background mRNA-based-drugs can be applied for cancer immunotherapy. 1SAR441000 is a novel saline-formulated mixture of four mRNAs encoding interleukin-12 single chain,