388 PRELIMINARY RESULTS FROM KEYNOTE-A36, A STUDY OF GB1275, A FIRST-IN-CLASS ORAL CD11B MODULATOR, ALONE AND WITH PEMBROLIZUMAB OR CHEMOTHERAPY IN SPECIFIED ADVANCED SOLID TUMORS

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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 immuno-oncology therapies.[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 castrate-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 4 (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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389 COMBINING TRANSCRIPTOMIC- AND TISSUE-BASED IMMUNE BIOMARKERS TO EVALUATE GB1275, A CD11B MODULATOR, AS A SINGLE AGENT OR WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background GB1275 is a first-in-class CD11b modulator in development as monotherapy and in combination with pembrolizumab or chemotherapy for the treatment of advanced solid tumors. Nonclinical data show that GB1275 reduced influx of tumor-associated myeloid-derived suppressor cells (MDSCs) and macrophages (TAMs), and repolarized M2 immuno-suppressive TAMs towards an M1 phenotype. We hypothesize that GB1275 administration can alleviate myeloid cell-mediated immunosuppressive effects and improve cancer treatment outcomes. A phase 1 trial evaluating GB1275 as monotherapy and in combination with pembrolizumab in specified advanced tumors in ongoing (NCT04060342).

Methods Blood gene expression variations as well as core tissue biopsies pre- and post-treatment were assessed following GB1275 monotherapy and combination with pembrolizumab. After obtaining informed consent, peripheral blood for MDSCs was collected from 21 patients pre- and two weeks post-treatment; core tissue biopsies were collected from 13 patients pre- and post-treatment. The frequency of MDSCs in whole blood was measured using the Serametrix MDSC FACS Assay. Gene expression transcriptome profiles were generated using NovaSeq platform. CD8 staining was performed at Neogenomics, and tumor infiltrating lymphocyte (TIL) quantification was performed by an independent pathologist.

Results Preliminary statistical analysis of MDSC immunophenotyping pre- and post- treatment is consistent with the proposed mechanism of GB1275, showing modulation of peripheral blood MDSCs in some patients. Preliminary gene expression analysis in the blood showed dose-dependent clusters following treatment with GB1275 alone. Moreover, the transcriptomic analysis revealed two unique expression patterns for patients treated with GB1275 monotherapy or in combination with pembrolizumab. Gene Set Enrichment Analysis showed that the CD11b pathway is downregulated in patients

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 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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390 EMERGING SAFETY AND ACTIVITY DATA FROM GEN-009–101: A PHASE 1/2A TRIAL OF GEN-009, A NEOANTIGEN VACCINE IN COMBINATION WITH PD-1 CHECK-POINT INHIBITORS (CPI) IN ADVANCED SOLID TUMORS

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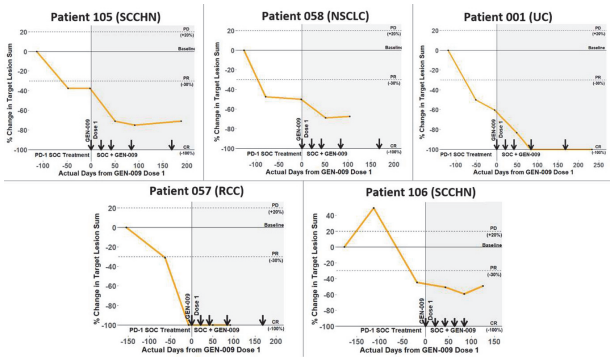
Background GEN-009 is an adjuvanted personalized cancer vaccine containing up to 20 neoantigens selected by ATLAS™, an *ex vivo* bioassay screening autologous T cells to identify both neoantigens as well as Inhibigens™ empirically and without *in silico* predictions. Inhibigen-specific T cells suppress immunity and have been shown to accelerate tumor progression in mice. Inhibigens are avoided in GEN-009. Previous data from patients treated with GEN-009 monotherapy showed 99% of selected peptides generated immune responses including *ex vivo* $CD4^+$ and $CD8^+$ fluorospot responses specific for 51% and 41% of immunized peptides respectively.

Methods GEN-009 is being evaluated in patients (pts) with advanced cancer who received standard-of-care (SOC) PD-1 inhibitor as monotherapy or in combination therapy during vaccine manufacturing; they subsequently received 5 vaccine doses over 24 weeks in combination with the PD-1 inhibitor. Patients who progressed prior to vaccination could receive alternate therapy followed by GEN-009 combined with an appropriate salvage regimen. Peripheral T cell responses were evaluated pre-and post-vaccination by dual-analyte fluorospot assays measured both directly *ex vivo* and after *in vitro* stimulation.

Results As of August 18, 2020, 15 pts received GEN-009 in combination with a PD-1 inhibitor. Their median TMB was



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) Inhibigens. 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 IFNγ 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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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.[1] SAR441000 is a novel saline-formulated mixture of four mRNAs encoding interleukin-12 single chain,