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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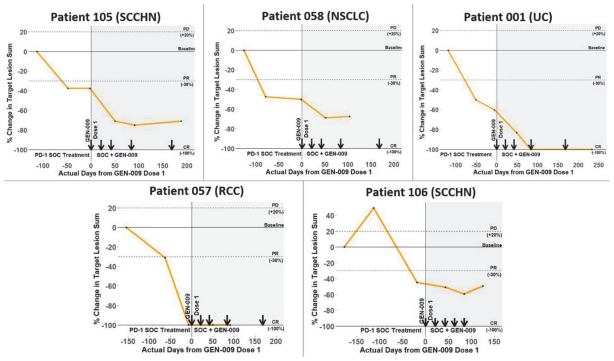
Background GEN-009 is an adjuvanted personalized cancer vaccine containing up to 20 neoantigens selected by ATLAS™, an *ex vivo* bioassay screening autologous T cells to identify both neoantigens as well as Inhibigens™ empirically and without *in silico* predictions. Inhibigen-specific T cells suppress 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,

Abstract 391 Table 1 Frequency of patients with a TEAE related to SAR44100* by dose group and grade

	Escalation Monotherapy															
	DL1		DL2		DL3		DL4		DL5		DL6		DL7		Al	
	(N=1)		(N=1)		(N=3)		(N=3)		(N=3)		(N=3)		(N=3)		(N=	
Preferred Term n (%)	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	
Number of Patients with a TEAE	1 (100)	0	1 (100)	1 (100)	3 (100)	1 (33.3)	3 (100)	1 (33.3)	3 (100)	2 (66.7)	3 (100)	1 (33.3)	2 (66.7)	1 (33.3)	16 (94.1)	
Number of Patient with a TEAE related to study treatment	1 (100)	0	1 (100)	0	2 (66.7)	0	2 (66.7)	0	2 (66.7)	0	2 (66.7)	0	2 (66.7)	0	11(70.1)	
Fatigue	1 (100)	0	1 (100)	0	0	0	0	0	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0	5 (29.4)	
Chills	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (33.3)	0	0	0	2 (11.7)	
Vomiting	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (33.3)	0	2 (11.7)	
Arthralgia	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	1 (5.9)	
Axillary pain	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	1 (5.9)	
Injection site reaction	0	0	0	0	2 (66.7)	0	0	0	0	0	0	0	0	0	2 (11.7)	
Myalgia	0	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (5.9)	
Nausea	0	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	1 (5.9)	
Pruritis	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	1 (5.9)	
Pyrexia	1 (100)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (5.9)	
Rash	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	0	0	1 (5.9)	
Tumor pain	0	0	0	0	0	0	0	0	0	0	1 (33.3)	0	0	0	1 (5.9)	

TEAE: Treatment emergent adverse event, PT: Preferred term; MedDRA 23.0; * Adverse events related to study treatment were those TEAE which were considered related by both the Investigator and Sponsor.

n (%) = number and percentage of patients with at least one TEAE;

Abstract 391 Table 2 Frequency of patients with a TEAE related to study treatment (SAR441000+cemiplimab) * by dose group and grade

Escalation Combination Therapy						
	DL4		DL5		All	
	(N=3)		(N=3)		(N=6)	
Preferred Term n (%)	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Number of Patients with a TEAE	3 (100)	0	3 (100)	2 (66.7)	6 (100)	2 (33.3)
Number of Patients with a TEAE related to Study Treatment	2 (66.7)	0	3 (100)	0	5 (83.3)	0
Fatigue	2 (66.7)	0	3 (100)	0	5 (83.3)	0
Diarrhea	0	0	2 (66.7)	0	2 (33.3)	0
Nausea	0	0	2 (66.7)	0	2 (33.3)	0
Vomiting	0	0	2 (66.7)	0	2 (33.3)	0
Dermatitis acneiform	1 (33.3)	0	0	0	1 (16.7)	0
Decreased appetite	1 (33.3)	0	0	0	1 (16.7)	0

TEAE: Treatment emergent adverse event, PT: Preferred term; MedDRA 23.0

n (%) = number and percentage of patients with at least one TEAE

* Adverse events related to study treatment were those TEAE which were considered related by both the Investigator and the Sponsor.

interferon alpha-2b, granulocyte-macrophage colony-stimulating factor, and interleukin-15 sushi that we have identified as mediators of tumor regression across different murine tumor models. Local intratumoral administration of SAR441000 in immunocompetent mice, mediates successful antitumor immunity leading to tumor eradication. Effective antitumor activity of these cytokines involved multiple immune cell populations and was accompanied by intratumoral interferon gamma induction, systemic antigen-specific T-cell expansion, increased granzyme B+ T-cell infiltration, and formation of immune memory. Antitumor activity extended beyond the treated lesions and inhibited growth of non-injected distant tumors. Combining the mRNAs with checkpoint inhibitors enhanced antitumor responses in both injected and non-injected tumors, improving survival and tumor regression in mice. Based on these preclinical observations a clinical study was initiated.

Methods In a phase 1 dose escalation study, patients with advanced solid tumors were treated with weekly intratumoral administration of SAR441000 monotherapy and in combination with fixed dose of cemiplimab 350 mg. Plasma samples for cytokine analysis and tumor biopsies were collected at baseline and throughout the study to characterize the PK/PD profile of SAR441000, immune cell tumor infiltration by immunohistochemistry and the presence of corresponding tumor proinflammatory signatures by RNA sequencing.

Results As of July 2020, 17 patients received SAR441000 monotherapy (melanoma 7, breast 4, sarcoma 2, Cutaneous Squamous Cell 2, Basal Cell 1, and Merkel Cell 1) at dose levels 1 through 7. Six patients received SAR441000 in combination therapy (melanoma 3, breast 3) at dose levels 4 and 5. No patient experienced a Dose Limiting Toxicity. No grade 3, 4 or 5 adverse events related to study treatment were reported. Adverse events related to study treatment in two or more subjects in both treatment groups combined were nonserious grade 1 or 2 fatigue (43%;10/23), vomiting (17%; 4/23), nausea (13%;3/23); local injection site reaction (11.7%, 2/23); and chills, diarrhea, and rash were reported as 9% (2/23), respectively (table 1 and 2). In some patients, increases in plasma IP10 and IFN gamma and CD8+ T cell infiltration in tumor biopsies were observed.

Conclusions SAR441000 administered as monotherapy and in combination with cemiplimab was generally well tolerated. An immunomodulatory effect is suggested by downstream effector cytokines and T cell infiltration. These data support further clinical evaluation of SAR441000.

Ethics Approval The study was approved by each participating Institution's Ethics or Institutional Review Board(s).

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392 PHASE 1 STUDY OF CI-8993 ANTI-VISTA ANTIBODY IN PATIENTS WITH ADVANCED SOLID TUMOR MALIGNANCIES

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Background VISTA (V-domain Ig suppressor of T cell activation) is a key negative immune checkpoint regulator, locking T cells in a quiescent state, unlike PD1 and CTLA4, which are expressed on activated T cells. Preclinically, VISTA monoclonal antibody treatment increased the number of tumor-specific T cells in the periphery, and enhanced the infiltration, proliferation and effector function of tumor-reactive T cells within the tumor microenvironment (TME). VISTA blockade alters the suppressive feature of the TME by decreasing the presence of monocytic myeloid-derived suppressor cells and increasing the presence of activated dendritic cells (DCs) within the TME leading to enhanced T cell mediated immunity. VISTA monoclonal antibody administration as a monotherapy has been shown to suppress the growth of both transplantable and inducible melanoma in preclinical models. CI-8993 is a first-in-class, fully human immunoglobulin (Ig) G1κ monoclonal antibody (mAb) against the VISTA ligand. Prior human clinical evaluation of CI-8993 demonstrated target-related clinical findings and pharmacodynamic activity at 0.15 mg/kg.

Methods This phase 1 study is being conducted in the USA (NCT04475523) and is designed as a 3+3 dose escalation study beginning at 0.15 mg/kg. Patients with solid tumor malignancy (non-lymphoma) that is metastatic or unresectable and considered relapsed and/or refractory to prior therapy will be included, excluding prior CAR-T therapy or allogenic transplant. Patients will be treated with an initial step-dose of CI-8993 by IV infusion, followed by every 2 weeks of a full dose, until disease progression or toxicity. Efficacy, pharmacokinetics, pharmacodynamic and safety endpoints will be monitored and reported.