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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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) Inhibigen. 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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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

1Oliver Bechter*, 1Jochen Utikal, 1Jean-Francois Baurain, 4Christophe Massard, 1Ugur Sahin, 2Evelyna Derhovanessian, 1Marie-Laure Ozoux, 2Rahul Marpadga, 1Esteban-Rodrigo Imedio, 2Nicolas Azquelleda, 1Carmen Loquial, 4University Hospitals Leuven, Leuven, Belgium; 4Université Catholique de Louvain, Bruxelles, Belgium; 5BioNTech, Mainz, Germany; 6Sarah Cannon Research Institute, Nashville, TN, USA; 6Dana-Farber Cancer Institute, Boston, MA, USA

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

REFERENCE

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0391

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 enhances the suppressive feature of the TME by decreasing the presence of monocytes myeloid-derived suppressor cells and increasing the presence of activated dendritic cells (DCs) within the TME leading to enhanced T cell mediated immunocompetence. 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) G1k monoclonal antibody (mAb) against the VISTA ligand. Prior human clinical evaluation of CI-8993 demonstrated targeted vaccination efficacy 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.

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

REFERENCE

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