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, increasing the presence of activated dendritic cells (DCs) 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 altering the suppressive feature of the TME by decreasing the presence of activated T cells. Preclinically, VISTA monoclonal antibody treatment increased the number of tumor-specific T cells in the periphery, and enhanced the infiltration, clonal antibody treatment increased the number of tumor-specific T cells in the periphery, and enhanced the infiltration, memory. Antitumor activity extends beyond the treated lesions and inhibited growth of non-injected distant tumors.

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


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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) G1x 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 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.
Background CTLA-4 pathway blockade with ipilimumab (IPI) + nivolumab (NIVO) or ipilimumab + nivolumab (NIVOL) has been effective for several cancers. A nonfucosylated version of IPI, BMS-986218, was developed to increase the effects of CTLA-4 blockade and enhance intratumoral regulatory T-cell depletion via its increased affinity for Fcγ receptors (FcγR, CD16) on natural killer T cells and macrophages, resulting in enhanced antibody-dependent cellular cytotoxicity. Preclinical data supported the mechanism of action of BMS-986218 and demonstrated greater antitumor activity in an MC38 tumor model vs IPI.1 Here, we present initial results from the first-in-human phase 1/2a trial of BMS-986218 + NIVO in previously treated patients with advanced cancer (NCT03110107).

Methods Patients with ≥1 prior therapy received BMS-986218 2–70 mg intravenously Q4W. Safety, tolerability, pharmacokinetics, and pharmacodynamics were evaluated. Results As of December 12, 2019, 65 patients (median age, 61 years [range, 24–85 years]) received BMS-986218 monotherapy. TRAEs occurred in 52% of patients; most were grade 1–2. The most common (≥10%) TRAEs (any grade; grade 3) were pruritus (12%; 0%) and diarrhea (11%; 3%). Eight patients (12%) had grade 3 TRAEs; most resolved with protocol-defined management. No grade 4 TRAEs were reported; 1 grade 5 TRAE (pneumonitis; 2 mg) occurred. Seven patients (11%) discontinued treatment due to TRAEs; 4 dose-limiting toxicities occurred. The maximum tolerated dose has not been reached. BMS-986218 exposure increased dose proportionally, and the half-life was ~2 weeks. Increased levels of serum chemokine ligands 9 and 10 and interferon-γ indicate that pharmacodynamic changes occurred at the lowest dose tested (2 mg [=0.03 mg/kg]), similar to previous findings with IPI 3 mg/kg, and at higher doses (40–70 mg [=0.06–1 mg/kg]), consistent with findings with IPI 10 mg/kg. In a subset of patients with paired biopsies, BMS-986218 was associated with an increased gene signature linked to CD8+ T-cell infiltration and inflammation. In a highly heterogeneous population, as part of dose escalation, BMS-986218 monotherapy treatment was associated with clinical activity in some patients. Updated data based on a September 2020 data cutoff will be presented.