**Results**

N/A

**Conclusions**

N/A

**Ethics Approval**

The study was approved by Dartmouth-Hitchcock, Norris Cotton Cancer Center Ethics Board, approval number IRB00012031. The study was approved by Sarah Cannon Cancer Research Institute, approval number IORG0000689.

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**Background**

CTLA-4 pathway blockade with ipilimumab (IPI) ± nivolumab (NIVO; anti–PD-1) is an effective strategy for several cancers. A nonfucosylated version of IPI, BMS-986218, was developed to increase the effective dose 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 enhancement of 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.

**Conclusions**

BMS-986218 monotherapy demonstrated an acceptable safety profile and signs of clinical benefit in this heterogeneous patient population with select advanced cancers. Preliminary pharmacodynamic activity was consistent with enhanced effects of CTLA-4 blockade. Data from continuing dose escalation of BMS-986218 ± NIVO along with preclinical results provide support for ongoing monotherapy expansions and for BMS-986218 + NIVO expansions in patients with advanced cancer.

**Acknowledgements**

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**Trial Registration**

NCT03110107

**Ethics Approval**

This study was approved by the WCG Independent Review Board, approval number 20170464.

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**Background**

Interleukin 8 (IL-8) is a C-X-C chemokine that exerts protumorigenic effects in the tumor microenvironment, including recruiting immunosuppressive PMN-MDSCs and promoting angiogenesis.1–3 Elevated serum IL-8 (sIL-8) is a negative prognostic indicator in patients with solid tumors and may have predictive value in patients treated with immunotherapies.2 4 5 BMS-986253, a fully human-sequence IgG1 anti–IL-8 monoclonal antibody, binds IL-8 and prevents signaling through CXCR1/CXCR2 and has been shown to be safe in patients with advanced cancers.3 We present initial results of BMS-986253 + NIVO from a phase 1/2a trial in patients with advanced cancers who had detectable sIL-8 levels, the majority of whom had progressed on/after prior anti–PD-(L)1 (NCT03400332).

**Methods**

During safety evaluation/dose exploration, patients with advanced metastatic solid tumors (melanoma, NSCLC, SCCHN, RCC, or UCC) and detectable sIL-8 (>10 pg/mL at screening) received BMS-986253 600 mg (n=16), 1200 (n=15), or 2400 mg (n=18) Q4W, or 1200 (n=12) or 2400 mg (n=59) Q2W, + NIVO 480 mg intravenously Q4W. Safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity were evaluated (investigator-assessed, RECIST v1.1).
Results As of March 20, 2020, 120 patients (median age, 63 years [range, 35–87 years]) received BMS-986253 + NIVO; 97% of patients received prior anti-PD-(L)1 therapy, and 25% received prior anti-CTLA-4 therapy. BMS-986253 + NIVO was well tolerated with no dose-limiting toxicities observed. Most TRAEs were grade 1–2. The most common (≥5% of patients) TRAEs (any grade; grade 3–4) were fatigue (9%; 1%), nausea (7%; 0%), rash/rash maculopapular (6%; 0%), pruritus (5%; 0%), and decreased appetite (5%; 0%). Grade 3–4 serious TRAEs were reported in 2 patients (infusion-related reaction, BMS-986253 2400 mg Q2W + NIVO; AST/ALT increased, BMS-986253 1200 mg Q4W +NIVO). BMS-986253 exposure increased dose proportionally and was not altered with NIVO. BMS-986253 resulted in dose-dependent reductions in free sIL-8 levels, with tumor IL-8 suppression detected in most patients evaluated; additional pharmacodynamic endpoints will be presented. Partial responses were observed in multiple tumor types, including 5 of 28 patients with melanoma who had progressed on/after prior anti-PD-(L)1; 4 of the 5 patients were also previously treated with anti-CTLA-4.

Conclusions BMS-986253 + NIVO demonstrated a tolerable safety profile with dose-proportional pharmacokinetics and robust sIL-8 suppression. Preliminary antitumor activity was observed across a range of doses/regimens in this biomarker-enriched, anti-PD-(L)1–experienced, heterogeneous patient population with advanced cancers. These findings support further evaluation of BMS-986253 in select advanced tumors.

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Trial Registration NCT03440332

Ethics Approval This study was approved by the WCG Independent Review Board, approval number 20172711.

REFERENCES


Background Upregulation of immune checkpoints, such as LAG-3, plays an important role in promoting resistance to anti-PD-(L)1 therapy. Targeting PD-L1 and LAG-3 using a bispecific antibody may overcome resistance to PD-(L)1 blockade. We report initial data from a first-in-human study evaluating FS118 in patients with advanced cancer and resistance to PD-(L)1 therapy.

Methods The ongoing Phase I FIH study (NCT03440437) is being conducted to evaluate safety, tolerability, immunogenicity, PK/PD and clinical activity of FS118 administered IV weekly to heavily pre-treated patients who had previously received anti-PD-(L)1 therapy for a minimum of 12 weeks. Adverse events were assessed using CTCAE v4.03 and tumor responses assessed using RECIST v1.1 and iRECIST. Single subject dose escalation cohorts were followed by a 3+3 ascending dose design. Three cohorts (3, 10, 20 mg/kg) were expanded to evaluate PK, PD and clinical activity. Pharmacodynamic studies examined soluble LAG-3 production and peripheral T-cell expansion.

Results Forty-three patients (median 6 lines of prior therapy, including ICB) with solid tumors received FS118 at doses from 0.8 mg up to 20 mg/kg across 8 dose levels. Weekly administration of FS118 was well tolerated and did not result in dose- or treatment-limiting toxicities. An MTD was not reached. No safety signals unexpected for the drug class of immune-checkpoint inhibitors were identified in the early study population. The majority (95%) of treatment-emergent adverse events (TEAE) considered by the Safety Review Committee (SRC) to be treatment-related were Grade 1 and 2. Grade 3/4 TEAEs toxicities (elevated liver enzymes) were observed in 2 patients (5%). No SAEs or deaths were attributed to FS118 treatment. Anti-drug antibodies, observed in half of patients, were typically transient in nature. The pharmacokinetic profile confirmed preclinical predictions and PD parameters included a dose-dependent increase in serum soluble LAG-3 and expansion of peripheral T cells. Long-lasting disease stabilisation (≥6 months) was observed in a subset of patients with acquired resistance (defined as a CR, PR or SD ≥3 months on previous PD-(L)1 treatment), but not in patients with primary resistance. Two patients remain on FS118 treatment as of 2 Jul 2020 (duration 10 and 16 months). Retrospective IHC analysis of PD-L1 and LAG-3 co-expression in the tumor was assessed as a potential biomarker associated with clinical outcome.

Conclusions Weekly treatment with FS118 was well tolerated up to 20 mg/kg and was associated with pharmacodynamic markers of FS118 activity. Encouraging signs of clinical activity were observed in highly pre-treated patients who had acquired resistance to prior PD-(L)1 therapy.

Trial Registration Registered at www.clinicaltrials.gov, NCT03440437

REFERENCE


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A FIRST-IN-HUMAN STUDY OF FS118, A TETRAVALENT BISPECIFIC ANTIBODY TARGETING LAG-3 AND PD-L1, IN PATIENTS WITH ADVANCED CANCER AND RESISTANCE TO PD-(L)1 THERAPY

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