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/sha/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/or 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

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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(L1) THERAPY

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.1 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 RECISTv1.1 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 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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