

**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 ( $\geq 5\%$  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.

**Acknowledgements** The authors acknowledge Dr Charles Drake while at Columbia University Medical Center, New York, NY, USA, for his contributions to the study.

**Trial Registration** NCT034400332

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

## REFERENCES

- David JM, Dominguez C, Hamilton DH, *et al.* The IL-8/IL-8R axis: a double agent in tumor immune resistance. *Vaccines (Basel)* 2016;4:22.
- Schalper KA, Carleton M, Zhou M, *et al.* Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune-checkpoint inhibitors. *Nat Med.* 2020;26:688–692.
- Bilusic M, Heery CR, Collin JM, *et al.* Phase I trial of HuMax-IL-8 (BMS-986253), an anti-IL-8 monoclonal antibody, in patients with metastatic or unresectable solid tumors. *J Immunother Cancer* 2019;7:240.
- Yuen KC, Liu L-F, Gupta V, *et al.* High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. *Nat Med* 2020;26:683–698.
- Sanmamed MF, Perez-Gracia JL, Schalper KA, *et al.* Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. *Ann Oncol* 2017;28:1988–1995.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0394>

395

## 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

<sup>1</sup>Timothy Yap\*, <sup>2</sup>Deborah Wong, <sup>3</sup>Siwen Hu-Lieskovan, <sup>4</sup>Kyriakos Papadopoulos, <sup>5</sup>Michelle Morrow, <sup>5</sup>Urszula Grabowska, <sup>5</sup>Daniel Gliddon, <sup>5</sup>Josefin-Beate Holz, <sup>6</sup>Patricia LoRusso. <sup>1</sup>MD Anderson Cancer Center, Houston, TX, USA; <sup>2</sup>UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; <sup>3</sup>Huntsman Cancer Institute and Hospital, Salt Lake City, UT, USA; <sup>4</sup>START, San Antonio, Texas, USA; <sup>5</sup>F-star Therapeutics Ltd, Cambridge, UK; <sup>6</sup>Yale Cancer Center, New Haven, CT, USA

**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.<sup>1</sup> 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 CTCAEv4.03 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  $\geq 3$  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](http://www.clinicaltrials.gov), NCT03440437

## REFERENCE

- Kraman M, Faroudi M, Allen N, Kmiecik K, Gliddon D, Seal C, Koers A, Wydro M, Winnewisser J, Young L, Tuna M, Doody J, Morrow M, Brewis N. FS118, a bispecific antibody targeting LAG-3 and PD-L1, Enhances T-Cell activation resulting in potent antitumor activity. *Clin Cancer Res* 2020; 26:3333–3344.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0395>