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

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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-L1 blockade. 1 We report initial data from a first-in-human study evaluating FS118 in patients with advanced cancer and resistance to PD-L1 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. 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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