A First-in-Human Phase I study of FS118, an anti-LAG-3/PD-L1 bispecific antibody, in patients with solid tumors that have progressed on prior PD-1/PD-L1 therapy

Timothy A. Yap¹, Patricia LoRusso², Deborah J.L. Wong³, Siwen Hu-Lieskovan3-5, Josefín-Beate Holz², Lyon Gleich², and Kyriakos P. Papadopoulos²

¹The University of Texas MD Anderson Cancer Center, Houston, TX; ²Yale University School of Medicine—Yale Cancer Center, New Haven, CT; ³Department of Medicine, University of California, Los Angeles, Los Angeles, CA; ⁴Huntsman Cancer Institute – University of Utah Health, Salt Lake City, Utah; ⁵star, Cambridge, United Kingdom; ⁶Medpace Inc, Cincinnati, Ohio; ⁷START, San Antonio, TX

Background

PD-L1/PD-L2 checkpoint inhibitors have demonstrated remarkable anti-tumor activity, but only a minority of patients achieve full clinical benefit with deep and durable responses. Translational studies suggest resistance to cancer immunotherapy can be mediated by additional immune checkpoints e.g. lymphocyte activation gene 3 (LAG-3). The combination of anti-LAG-3 and anti-PD-1 antibodies synergistically improved anti-tumor response in murine models and early clinical trials. In a small published cohort study, LAG-3 expression in tumor infiltrating lymphocytes (TILs) correlated with response in the combination to PD-L1 blockade/refractory patients. FS118 is a novel bispecific antibody incorporating a LAG-3 binding Fv region to PD-L1-specific IgG1 antibody to potentially deliver superior anti-tumor efficacy while limiting immunotherapy-related adverse effects by dual targeting.

Method

The FIH study (NCT03444437) is being conducted in adult patients with solid tumors who failed prior PD-1/PD-L1 treatment. Primary objectives of the study are to determine safety, PK, and the maximum tolerated dose/recommended Phase 2 dose of FS118. Secondary objectives include preliminary evidence of efficacy, immunogenicity, PD profile and exposure/response correlation. SSUs from subjects in the USA are enrolled into 2 dose escalation studies initiated with anticipated titration of 5 single subject cohorts followed by 3+3 design and expansion cohorts. FS118 is administered weekly IV in 21-day treatment cycles until progression, unacceptable toxicity, withdrawal or death. Patients are followed for safety, overall survival and initiation of subsequent therapy. DLT clearances, dose escalation and cohort expansion (to further characterize PK/PD of clinical efficacy) are supervised by a safety review committee (SRC). Translational studies assess PD-L1/LAG-3 receptor occupancy, soluble PD-L1/LAG-3 levels and the correlation of FS118 exposure with selected PD markers of target engagement and response. Translational endpoints include TIL analysis, transcriptomic profiles and target expression analyses on tumor tissues. Cohorts 1 through 6 have been completed, enrolment in cohort 7 began December 2018.

1. FS118 has the potential to overcome PD-L1-mediated compensatory upregulation of LAG-3 induced by single-agent checkpoint blockade

2. FS118 translational hypotheses and mechanism of action

- FS118 target engagement and mediated T cell activation resulted in reduced surface expression of LAG-3 on exhausted T cells in the tumor and promote the release of soluble LAG-3 (LAG-3s)
- FS118 target engagement blocks available PD-L1 binding site and induces the release of soluble PD-L1 (PD-L1)

3. Clinical trial design and endpoints

- Single patient cohorts (21 days (DT window))
- 3/PD-L1 expansion (21 days (DT window))

4. SRC (Safety review committee)

- SRC members are study investigators, medical monitors and invited clinical experts in case of TEAEs that require special attention (e.g. cardiologists, immunologists, neurologists)
- During dose escalation and expansion, weekly SRC meetings are conducted
- Cycle 1 data are reviewed from actively enrolling cohorts with study subjects status based on each investigator’s report (available data include monitored and unmonitored data) AND subsequent cycle information from all treated subjects in all cohorts are reviewed to assess safety findings in later cycles
- Upon review of safety data (S2, severe/significant toxicities) SRC may recommend switches to 3+3 design, expansion of cohorts, completion/closing of cohorts and completion/stop of study
- Upon review of PK/PD data the SRC may recommend modifications to the subsequent dosing and scheduling regimen and/or expansion of the cohorts to further characterize the PK and pharmacodynamic profiles
- At the MTD or in case an early sign of clinical efficacy is seen in any of the cohorts, the SRC may recommend a cohort expansion to further characterize the safety, the PK and pharmacodynamic profiles and efficacy of FS118

5. Eligibility criteria

Selected inclusion criteria
- Patients with histologically confirmed, locally advanced, incurable or metastatic solid tumors that progressed while on or after anti-PD-1 or PD-L1 therapy for whom no effective standard therapy is available or standard therapy has failed
- Minimum treatment duration of prior PD-1 or PD-L1-containing regimen is 12 weeks (or equivalent of 2 response evaluations)
- The patient agrees to undergo a pre-treatment and on-treatment biopsy of the tumor and the biopsy procedure is not judged to be high-risk by the Investigator

Key exclusion criteria
- Received systemic anti-cancer chemotherapy within 28 days or five half-lives, whichever is shorter, of the first dose of study drug, prior treatment with more than one checkpoint inhibitor [except as a combination in approved indications] that was not standard of care, or prior treatment with an LAG-3 inhibitor or multi-specific checkpoint inhibitor molecules
- Significant cardiac abnormalities
- History of uncontrolled hypertension or diabetes
- Prior history of or active interstitial lung disease or pneumonitis, encephalitis, seizures, severe immune-related adverse events with prior PD-1/PD-L1 containing treatments, history or life-threatening skin adverse reaction prior to treatment with other immune stimulatory anticancer agents

6. Study start-up and cohort recruitment timelines

We are grateful for the valuable contribution of:
- our patients who participate in this clinical trial and their supporting families
- our investigators and their invaluable site staff
- the FS118-17101 joint F-star and MEDPACE study team
- all our vendors and partners

ASC0 Annual Meeting 2019 | 31 May - 04 June | Chicago | Poster Number: TPS2652

Strictly for personal use - DO NOT POST ONLINE - may not be reproduced without permission from ASCO and the author