A First-in-Human Phase 1 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. Yap[1],Patricia LoRusso[2], Deborah J.L. Wong[3], Siwen Hu-Lieskovan[3,4], Josefin-Beate Holz[5], Lyon Gleich[6], and Kyriakos P. Papadopoulos[7]

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

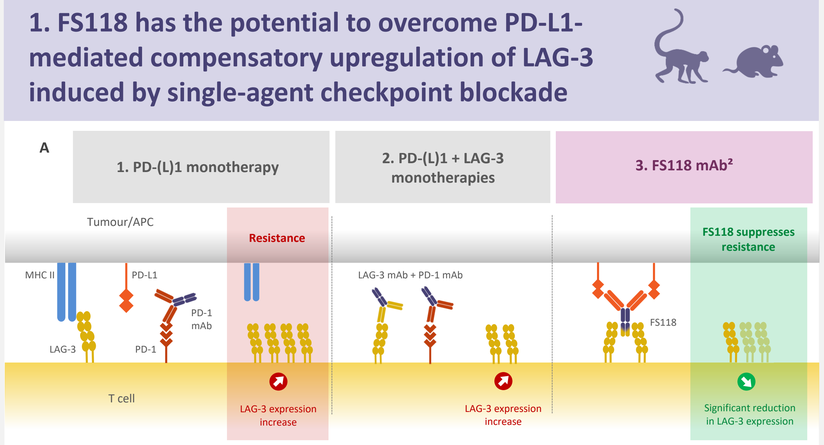
Background

PD-1/PD-L1 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 (TIL) correlated with responsiveness to the combination in PD-(L)1 relapsed/refractory patients. FS118 is a novel bispecific antibody incorporating a LAG-3 binding Fc-region into a PD-L1-specific IgG1 antibody to potentially deliver superior anti-tumor efficacy while limiting immunotherapy-related adverse effects by dual targeting.

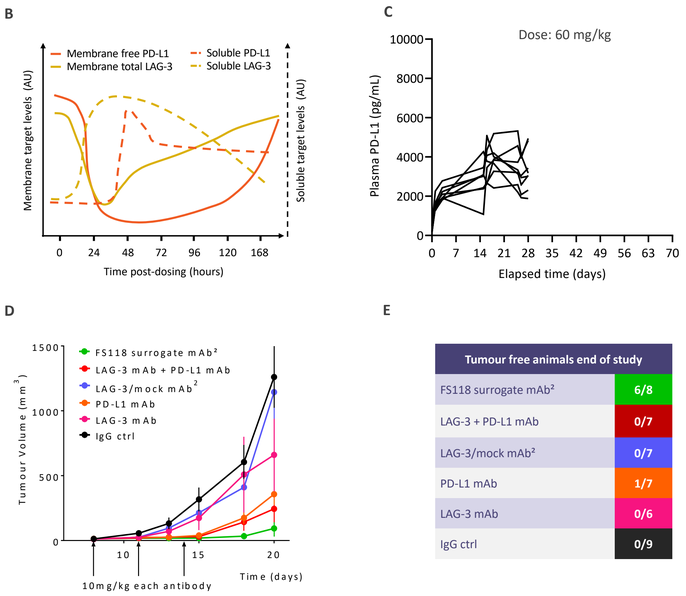
Method

The FiH study (NCT03440437) 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/recommended Phase 2 dose of FS118. Secondary objectives include preliminary evidence of efficacy, immunogenicity, PD profile and exposure/response correlation. 50 subjects from four sites in the USA are planned to enroll in dose escalation study initiated with accelerated titration (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 clearance, dose escalation and cohort expansion (to further characterize safety, PK/PD or 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



Koyama et al - Nat Commun. 2016 Feb 17;7:10501
Huang RY et al. Oncoimmunology. 2016 Oct 28;6(1):e1249561



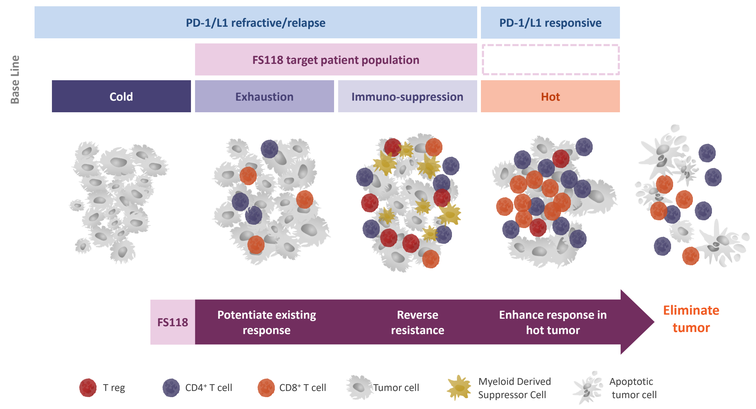
E

Tumour free animals end of study	
FS118 surrogate mAb²	6/8
LAG-3 + PD-L1 mAb	0/7
LAG-3/mock mAb²	0/7
PD-L1 mAb	1/7
LAG-3 mAb	0/6
IgG ctrl	0/9

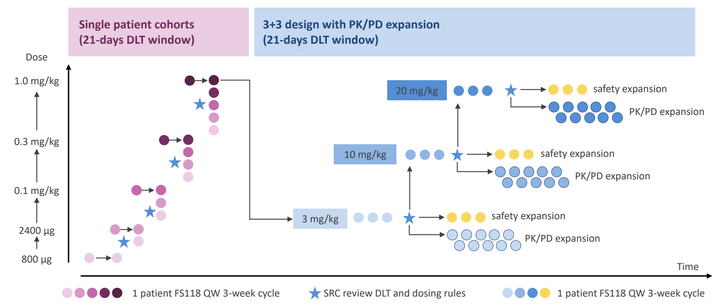
Figure 1. A – Schematic representation of a possible molecular mechanism of action for FS118. **B –** Relative changes in LAG-3 and PD-L1 expression (membrane and soluble) over time after treatment with FS118 surrogate mAb² as described by Faroudi et al. (March 2019) - Poster at the annual AACR meeting. Data describe a correlation between the reduction of membrane LAG-3 level and the increase of soluble LAG-3 level. Similar results are observed with PD-L1. **C -** Pharmacodynamic changes in total soluble PD-L1 in cynomolgus monkeys who received intravenous injection of the FS118 mAb² dosed twice-weekly at 60 mg/kg in a 4-week GLP toxicity study. The capture of soluble PD-L1 is indicative of target engagement. **D -** MC38 tumor cells were injected subcutaneously into C57/Bl6 mice and grown until a palpable tumor formed. Three doses were administered at day 8, day 11, and day 14. In all cohorts a total of 20mg/kg (10mg/kg FS118 or 10mg/kg antibody A + 10mg/kg antibody B or IgG control) of total antibody was administered. **E –** Overall survival of MC38 tumor-bearing mice showing that surviving animals are more numerous at the end of the study in the group treated with FS118 than those treated with other controls.

2. FS118 translational hypotheses and mechanism of action

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



3. Clinical trial design and endpoints



Acceleration titration phase (up to 1 mg/kg):
- Single-patient cohorts 800 µg → 1mg/kg
- SRC review weekly safety + D21 escalation decision
- Safety expansion if DLT or significant toxicity > Grade and switch to 3+3
- Intra-patient dose escalation permitted after DLT clearance of next dose level

3+3 phase (start from 3 mg/kg)
- SRC review of D21 window and ongoing safety
- Safety expansion if DLT
- PK/PD expansion if dose level tolerated
- Efficacy at RP2D or if clinical efficacy signal start indication expansion

Primary Endpoints

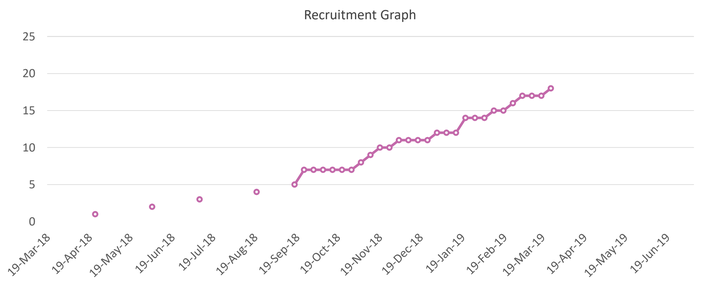
- Incidence, severity, and duration of adverse events;
- PK parameters, including C_{max}, T_{max}, C_{trough}, terminal elimination half-life ($t_{1/2}$), Area Under the Concentration-time-curve (AUC), systemic clearance (CL), volume of distribution at steady-state (V_{ss}), and accumulation ratio from first dose to steady-state.

Secondary Endpoints

- Response as assessed by RECIST 1.1 and iRECIST. Determine the disease control rate (DCR), ORR, duration of response (DoR), progression-free survival (PFS)/iPFS and overall survival (OS)
- Incidence of FS118 immunogenicity, ADA characterization

Exploratory Endpoints

- Percentage PD-L1 and LAG-3 receptor occupancy in T cell populations by flow cytometry of whole blood
- Change in peripheral blood immune cell profiles from baseline
- PD-L1 and LAG-3 expression by immunohistochemical analysis on tumor biospecimens and
- Soluble PD-L1 and LAG-3 receptor levels
- Evaluation of gene expression profile of tumor biospecimen
- Evaluation of TIL T cell receptor frequency
- Systemic cytokine/chemokine profile
- Tumor mutational burden and MSI/MMR status in tumor biospecimens



4. SRC (Safety review committee)

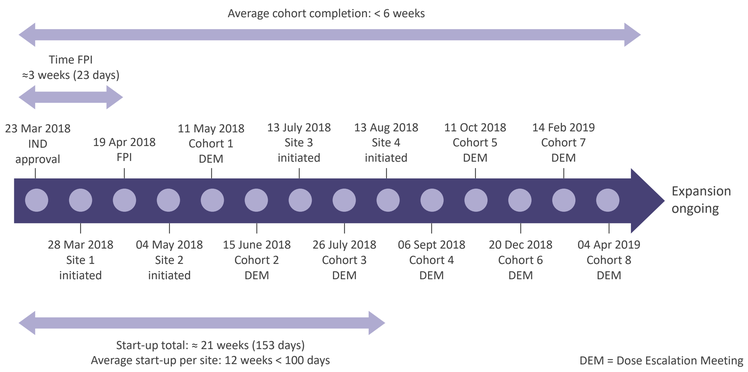
- SRC members are study investigators, medical monitors and invited clinical experts in case of TEAEs that require special attention (e.g. cardiologists, immunologists, neurologists)
- During dose escalation and expansion, weekly SRC meetings are conducted
- Cycle 1 data are reviewed from actively enrolling 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 (DLT, severe/significant toxicities) SRC may recommend switch 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, unresectable 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 a 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 on prior 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

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