A First-in-Human Phase 1 Study of FS120, an OX40/CD137 tetravalent bispecific antibody, in patients with advanced malignancies

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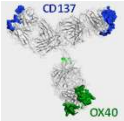
Background

In early clinical studies, agonistic antibodies targeting the T cell costimulatory receptors OX40 and CD137 have shown immune-stimulatory effects. Dose-limiting hepatotoxicity significantly hindered further development of CD137 monotherapies. FS120 is a novel tetravalent bispecific antibody incorporating OX40 binding into the Fc-region (termed an Fcab) and CD137 Fabs in a natural human IgG1 antibody and with silenced FcγR activity for reduced toxicity, as shown in preclinical safety studies. FS120 crosslinks and clusters the receptors eliciting a robust immune stimulation and activity in mouse tumor models, independent of FcγR crosslinking[1]. FS120 has the potential to deliver tumor-agnostic clinical efficacy with good tolerability.

1. FS120; Improving Anti-tumor Immune Response by "Triple Activation" Mechanism



1. *Activation of effector cells (CD8⁺ T cells and NK cells)*
2. *Stimulation of helper activity (CD4⁺ T cells)*
3. *Potentially decreases Treg activity, making them unstable and fragile*

Key Properties:
- CD137 agonist with K_D = 0.2 nM
- OX40 agonist with K_D = 0.2 nM
- Dual conditional agonist activity dependent on coexpression of OX40 and CD137 in the tumor
- Natural IgG format for ease of manufacture and Fc gamma binding null for safety

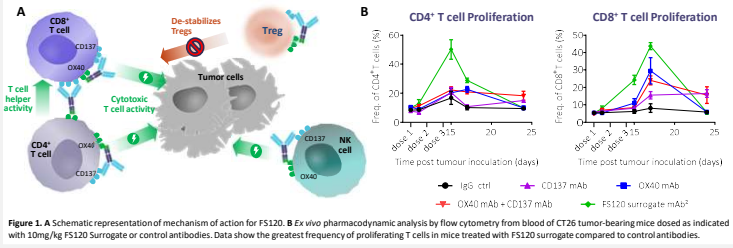


Figure 1. A Schematic representation of mechanism of action for FS120. **B** *Ex vivo* pharmacodynamic analysis by flow cytometry from blood of CT26 tumor-bearing mice dosed as indicated with 10mg/kg FS120 Surrogate or control antibodies. Data show the greatest frequency of proliferating T cells in mice treated with FS120 surrogate compared to control antibodies.

2. Preclinical Data Indicates Wide Therapeutic Window and Supports Clinical Study Design

- GLP toxicity study was performed in NHPs with FS120 or vehicle control administered on Day 1 and 8
- Histopathology showed recoverable minimal-moderate changes consistent with expected pathology in some tissues
- No acute cytokine release or changes in clinical haematology
- Clinical chemistry measurements relating to liver function showed limited and minimal changes outside of control values (Table 1)
- FS120 was well tolerated. HNSTD set at 30mg/kg/dose
- T cell and NK cell proliferation (Fig 2) and sCD137 capture (data not shown) are indicative of FS120 pharmacology and support the clinical biomarker strategy used in the Phase 1

	Study Day 15		End of Treatment Free Period (Day 43)	
	Control	FS120	Control	FS120
ALP (U/L)	344 - 1416	297 - 1047	327 - 1494	404 - 908
ALT (U/L)	26 - 87	18 - 91	22 - 52	35 - 60
AST (U/L)	26 - 54	24 - 70	30 - 56	30 - 48
TBIL (mg/dL)	0.07 - 0.43	0.07 - 0.37	0.08 - 0.33	0.11 - 0.18
TRIG (mg/dL)	31 - 50	18 - 344	30 - 62	39 - 62

Table 1. Selected clinical chemistry parameters at indicated timepoints

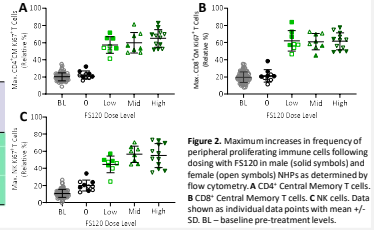
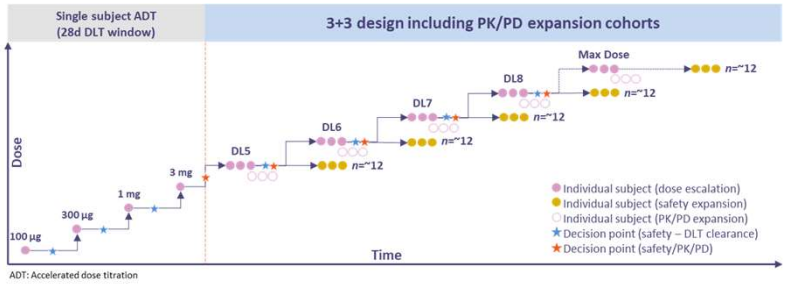


Figure 2. Maximum increases in frequency of peripheral proliferating immune cells following dosing with FS120 in male (solid symbols) and female (open symbols) NHPs as determined by flow cytometry. **A** CD4⁺ Central Memory T cells. **B** CD8⁺ Central Memory T cells. **C** NK cells. Data shown as individual data points with mean +/- SD. BL – baseline pre-treatment levels.

3. Clinical Trial Design



ADT: Accelerated dose titration

- FS120 monotherapy is administered Q4W by IV at flat doses in 28-day treatment cycles until progression, unacceptable toxicity, withdrawal, or death.
- In cohorts 1 and 2 FS120 administered over 3 and 5 minutes respectively
- In cohorts 3-6 FS120 administered over 30 minutes by continuous infusion pump
- In cohorts 7+ administered over 60 minutes by continuous infusion pump

4. Eligibility Criteria

Selected Inclusion Criteria
- Histologically confirmed, locally advanced, unresectable, or metastatic solid tumors. Specific tumor types include: NSCLC, head and neck cancer, bladder cancer and gastric cancer.
- Max. 3 prior systemic therapies for metastatic disease
- Max. 1 prior line of a prior CPI containing regimen
- Measurable disease by RECIST v1.1
- ECOG ≤1
- Pre-treatment and on-treatment biopsies

Selected Exclusion Criteria
- Received systemic anticancer chemotherapy within 28 days or five half-lives, whichever is shorter
- Prior treatment with >1 CPI, or prior treatment with any OX40 agonist, CD137 agonist, CD40 agonist, GITR, or CD27 targeting
- Autoimmune disorders
- Haematological malignancies
- History of uncontrolled hypertension, diabetes or cardiac abnormalities
- Prior allogenic or autologous transplantation
- Active infections
- Uncontrolled CNS metastases

5. Dose Limiting Toxicity Criteria

28 day DLT assessment period ● Toxicity evaluated according to NCI CTCAE v5.0 ● TEAE at least possibly related to FS120

The following events are considered DLTs
- Any grade 3 or 4 laboratory finding, regardless of duration, that is identified as clinically significant by the investigator (with exceptions)
- Any grade ≥3 non-haematological TEAE (with exceptions)
- Grade ≥3 elevation of serum total bilirubin in the absence of cholestasis
- ALT or AST >3 × ULN AND total bilirubin >2 × ULN (Hy's Law)
- Any Grade ≥3 elevation in AST, ALT, or ALP with no elevation in serum total bilirubin (with exceptions)
- Any Grade 2 non-haematological CNS TEAE (with exceptions)
- Grade 3 and 4 haematological AEs e.g. Grade ≥4 anaemia, Grade 4 neutropenia lasting >7 days
- SIRS lasting >3 days and Grade ≥2 CRS

5. Endpoints

Primary Endpoint
- Incidence, severity, and duration of adverse events

Secondary Endpoints
- Response as assessed by RECIST 1.1. Determine disease control rate (DCR), ORR, duration of response (DoR), duration of disease control (DoC), progression free survival (PFS) and overall survival (OS)
- Evaluation of soluble CD137 in serum with correlation to PK exposure and antitumor activity
- PK parameters including but not limited to C_{max}, T_{max}, C_{trough}, terminal elimination half-life ($t_{1/2}$), Area Under the Concentration-time-Curve (AUC), systemic clearance (CL) and volume of distribution (V_d) and accumulation ratio from Cycle 1 to Cycle 2
- Incidence of FS120 immunogenicity

Exploratory Endpoints
- Response as assessed by iRECIST to include DCR, ORR, DoR, DoC, PFS, and OS
- Assessment of serum biomarkers such as soluble OX40 and serum cytokines and chemokines
- Gene expression profile of tumor biospecimens
- Whole blood flow cytometry evaluation of T cell and NK cell proliferation and activation
- Assessment of CD137 and OX40 expression and TIL infiltration in tumor biospecimens

6. Clinical Sites in the USA

START San Antonio, Texas
Dr. Kyriakos Papadopoulos

Houston, Texas
Dr. Sarina Piha-Paul

Salt Lake City, Utah
Dr. Siwen Hu-Lieskovan

New Haven, Connecticut
Dr. Patricia LoRusso

7. Future Plans

This monotherapy dose escalation aims to identify a safe, tolerated and pharmacologically active dose of FS120 for exploration in future clinical studies as monotherapy, and in combination with other agents.

Following determination of a safe, tolerated and pharmacologically dose, a combination arm will be added to the clinical protocol. FS120 will be evaluated in combination with KEYTRUDA, with the potential for early demonstration of clinical activity in specific tumor subtypes. F-star expects to provide a progress update on the FS120 monotherapy accelerated dose titration cohorts later this year and plans to initiate the KEYTRUDA combination cohorts in the second half of 2022, following completion of the FS120 monotherapy dose escalation.

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Presenting Author Disclosure:
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[1] *Gaspar et al, Cancer Immunology Research doi: 10.1158/2326-6066*