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

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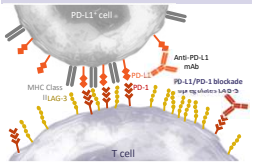
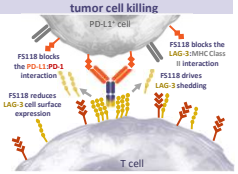
Background

- Many cancer patients are refractory to PD-(L)1 treatment (primary resistance) or relapse during treatment (acquired resistance), with emerging data suggesting resistance may be associated with upregulation of other immune checkpoint receptors.
- FS118 is a tetravalent bispecific antibody (mAb^2) targeting LAG-3 and PD-L1 that can overcome immune suppression with greater preclinical activity than a combination of mAbs [1].
- FS118 is a potent antagonist of both PD-L1 and LAG-3 with a novel mechanism of action which leads to the shedding of LAG-3 from the surface of T cells releasing the brakes on the immune system (see Poster #715).
- Here, we present data from a First-in-Human study of FS118 in patients resistant to PD-(L)1 therapy **(data cut off Sept, 18 2020)**

Immunosuppressive tumor microenvironment



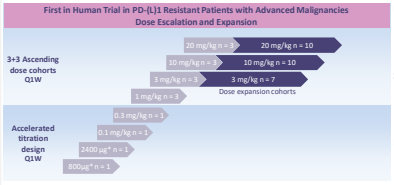
FS118 mAb^2 drives T cell activation and tumor cell killing



See Poster #715

FS118, a tetravalent bispecific antibody targeting LAG-3 and PD-L1, induces LAG-3 shedding resulting in receptor downregulation by T cells via a novel mechanism of action

Study Design and Objectives



MTD = maximum tolerated dose; *Flat dose; Q1W = every 1 week; 3+3 Dose escalation initiated after corresponding dose levels cleared in primary Dose Escalation; monotherapy expansion cohorts are ongoing; ClinicalTrials.gov identifier: NCT03440437;

Primary Objectives
- Safety
- MTD
- Pharmacokinetics

Secondary Objectives
- Disease Response as assessed by RECIST 1.1 and iRECIST
- Immunogenicity

Exploratory Objective
- Characterize the pharmacodynamic profile and correlate primary pharmacology with exposure

Enrolment Criteria

Key Inclusion Criteria
- Patients who have histologically confirmed, locally advanced, unresectable or metastatic solid tumors or hematological malignancies
- All patients **must have confirmed progressive disease after anti-PD-1 or PD-L1 therapy** following a minimum treatment duration of 12 weeks (or 2 response evaluations)

Key Exclusion Criteria
- Prior treatment with a LAG-3 inhibitor
- Patients with active or documented history of autoimmune disease
- Prior history of or active interstitial lung disease or pneumonitis, encephalitis, seizures, severe immune related adverse events with prior PD-(L)1 containing treatments

Results

Baseline Demographics

Characteristic	
Age	Years, median (range)
	59 (30–85)
Gender	n (%)
Female	17 (39.5)
Male	26 (60.5)
ECOG PS	n (%)
0	9 (20.9)
1	33 (76.7)
2	1 (2.3)
Number of Prior Regimens for Locally Advanced/ Metastatic disease	All Regimens / ICB regimens
	n (%) / *n* (%)
0	1 (2) / 0 (0)
1	3 (7) / 33 (77)
2	9 (21) / 7 (16)
3	14 (33) / 3 (7)
4+	16 (37) / -
Median (range)	3 (0-11) / 1 (1-3)

Cancer Type	Abbreviations	n (%)
Non-small-cell lung cancer	NSCLC	9 (20.9)
Head & neck squamous cell	HNSCC	6 (14.0)
Ovarian	OVRY	4 (9.3)
Melanoma*	MEL	4 (9.3)
Sarcoma	SARC	4 (9.3)
Colorectal	CRC	4 (9.3)
Bladder	BLA	2 (4.7)
Prostate	PRST	2 (4.7)
Other	OTH	8 (18.6)

*includes 1 case of uveal melanoma

43 subjects were recruited across 8 cohorts from a total of 58 subjects screened.

FS118 Treatment

- A median number of 3 treatment cycles was received (range: 0 to 26 cycles).
- Up to the highest dose of 20 mg/kg, no dose-limiting toxicities were reported and a MTD was not reached.
- 3 patients were eligible for intra-patient dose escalation according to the protocol: One patient from 0.3 mg/kg to 1mg/kg and two patients from 1 mg/kg to 3 mg/kg.
- 2 patients are receiving ongoing treatment: Anaplastic Thyroid Carcinoma; 20 mg/kg, 26 cycles and Leiomyosarcoma; 20 mg/kg, 19 cycles
- 41 patients have discontinued treatment. The reasons for discontinuation of FS118 were disease progression (20/41), investigator decision (10/41), withdrawal of informed consent (7/41) and adverse events (4/41).

Safety Summary

Adverse Event Summary

FS118 was well tolerated for up to 26 cycles (79 weeks) without DLT at dose levels up to and including 20mg/kg QW

- No treatment related SAEs; No dose- or treatment-limiting toxicity observed and MTD was not reached

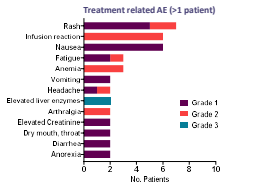
	Number of Events	Number of patients	Reported in % of patients
Overall AE	469	42	98%
AE leading to drug withdrawn	5	5	11%
TRAEs	96	25	58%
Grade 1	55	22	51%
Grade 2	36	14	33%
Grade 3	5	2	5%
Grade 4	0	0	0
Grade 5	0	0	0
TRAEs leading to drug withdrawal*	1	1	2%
SAE reported as related to FS118	0	0	0

AE = Adverse Event; TRAE = Treatment Related Adverse Event; SAE = Serious Adverse Events

*One patient had FS118 treatment withdrawn as a result of adverse events related to study drug (grade 3 alkaline phosphatase elevation)

Adverse Events were graded according to CTCAEv5.0 classification

Treatment Related Adverse Events

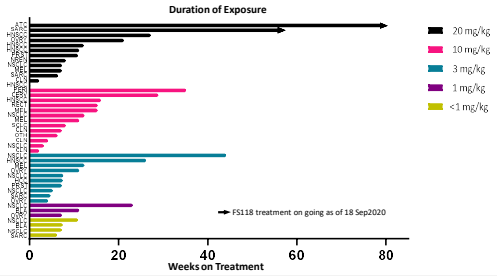


Grade 3 TRAE were observed in 2 patients:
- Elevated ALT, elevated AST, bilirubin increase
- Elevated ALP

No Grade 4 or 5 TRAEs were observed.

Immune Related Treatment Related Adverse Events	
irTEAEs	%
Skin type reactions	26
GI	23
Laboratory changes	15
Infusion related reactions	11
Anemia	7
Fatigue	7

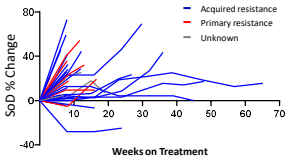
FS118 Clinical Efficacy



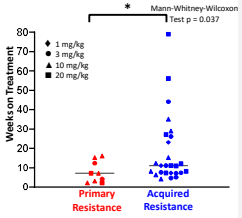
Long-term Disease Control in Acquired Resistance Patients

Defining prior resistance based on retrospective analysis of FS118 data, based on outcome of any prior PD-(L)1 treatment	
Primary Resistance	PD or SD for 3 months or less by RECIST
Acquired Resistance	CR/PR or SD for more than 3 months by RECIST
Unknown Resistance	RECIST data not available for prior PD-(L)1 therapy

Percentage Change From Baseline in Sum of Diameter (SoD) of Target Lesions



FS118 Duration of Treatment by Checkpoint Resistance Status



Disease Control Rates	All patients	Cohorts 5-8 ≥1 mg/kg	Resistance Category		
			Primary	Acquired	Unknown
# Patients	43	39	9	27	3
DCR	47% (20/43)	49% (19/39)	22% (2/9)	59% (16/27)	33% (1/3)

FS118 Pharmacokinetic and Pharmacodynamics

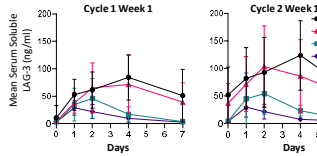
- **Pharmacokinetics:** FS118 exhibited dose-linear pharmacokinetics across the 1 to 20 mg/kg dose range.
- **Immunogenicity:** Low titers of anti-drug antibodies (ADA) were observed in 42% of patients. At higher dose levels, ADAs were transient in nature and no effect on exposure was observed.
- **Pharmacodynamics:** Pharmacodynamic exposure was maintained across the dosing interval, as measured by soluble LAG-3 capture.

A. FS118 Exposure

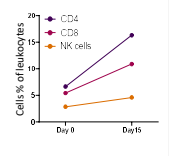
Dose	C_{max} (ug/ml) Mean (SD)	AUC_{inf} (d.ug/ml) Mean (SD)	T ½ (days)
1 mg/kg	22.15 (±7.49)	18.34 (±7.7)	0.65
3 mg/kg	67.68 (±15.95)	81.99 (±39.5)	0.89
10 mg/kg	233.36 (±35.91)	323.56(±79.10)	1.12
20 mg/kg	523.69 (±147.08)	628.18 (±234.02)	1.15

A. FS118 exposure summarised by dose.
B. Dose-dependent shedding of soluble LAG-3 observed in the serum of FS118-treated patients.
C. Changes in circulating lymphocytes (measured as percentage from total leukocytes) post dose as observed in Anaplastic Thyroid Carcinoma patient.

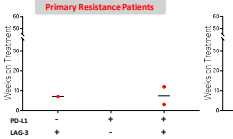
B. Blood Soluble LAG-3



C. Circulating Lymphocytes



Co-expression of PD-L1 and LAG-3 in acquired resistance patient tumor is associated with better outcome



- Baseline PD-L1 and LAG-3 positive tumor biopsies

17 suitable biopsies available for analysis. No "double negatives" were identified from the evaluable biopsies. Ovarian patient (▲) had no available RECIST data for prior PD-(L)1 therapy but was on prior treatment >1 year so classed as Acquired for expression analysis. One patient left trial after one dose and hence not shown. Data included from 1 mg/kg and above.

Conclusions

- FS118 is well-tolerated with no DLT at all dose levels up to 20 mg/kg for up 79 weeks treatment
- Pharmacokinetics confirm exposure broadly consistent with preclinical data with low immunogenicity
- Pharmacodynamic activity was prolonged demonstrated by sustained increased levels of soluble LAG-3 throughout the dosing period and an increase in immune cell numbers
- Early signs of clinical efficacy in a highly pre-treated patient population characterized by long-lasting disease control (over 1 year), particularly in patients with Acquired Resistance to PD-1 pathway blockade
- Clinical benefit was observed in patients with tumors co-expressing LAG-3 and PD-L1
- A RP2D of 10 mg/kg QW was selected based on safety, PK/PD, ADA and efficacy data.
- A Proof-of-Concept single arm PhII study is planned in patients with Acquired Resistance and efficacy will be evaluated in patients with LAG-3+ and PD-L1+ (IHC) tumors

Acknowledgments:
We would like to thank the patients who participated in this clinical study, their families and caregivers. Our thanks also go to the investigators, site personnel and all staff involved in operations of this trial. Thank you to colleagues at F-star for scientific, clinical and operational input.

[1] Kraman et al, Clinical Cancer Research, (2020) DOI:10.1158/1078-0432.CCR-19-3548