A Phase 1 Study of FPT155, a First-In-Class CD80 Extracellular Domain-Fc Fusion Protein, in Patients with Advanced Solid Tumors

Lisa Horvath[1], Jermaine Coward[2], Hui Gan[3], James Kuo[4], Michael Millward[5], Gary Richardson[6], Wei Deng[7], Siddhartha Mitra[7], Maike Schmidt[7], Hong Xiang[7], Amy Prawira[8]

[1]Chris O'Brien Lifehouse, Camperdown, NSW, Australia [2]ICON, Auchenflower, QLD, Australia [3]Olivia Newton-John Cancer Center, Heidelberg, VIC, Australia [4]Scientia Clinical Research, Randwick, NSW, Australia [5]Linear Clinical Research, Nedlands, WA, Australia [6]Cabrini Hospital, Malvern, VIC, Australia [7]Five Prime Therapeutics, Inc., South San Francisco, CA, USA [8]St. Vincent's Hospital Sydney, Darlinghurst, NSW, Australia

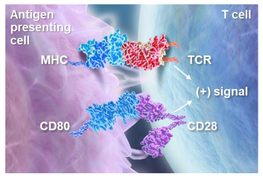
P442

Background

FPT155 is a First-In-Class CD80-Fc Fusion Protein

CD80:

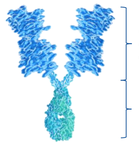
- CD80 is a co-stimulatory molecule expressed on activated antigen presenting cells that binds to CD28 on T cells



- Concurrent T-cell receptor and CD80-CD28 engagement are required for efficient T-cell activation
- Following activation, T cells upregulate the inhibitory molecule CTLA-4 which binds to CD80 with higher affinity than CD28
  - CTLA-4 shifts the balance away from ongoing immune activation by shunting CD80 away from CD28

FPT155: Direct immune agonism and checkpoint inhibition

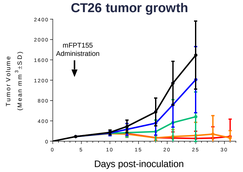
- FPT155 is a recombinant protein composed of the extracellular domain of CD80 fused to human IgG1 Fc
- FPT155 directly activates naïve and memory T cells by binding to CD28
- FPT155 de-represses T-cell activation by binding to CTLA-4, enabling the interaction of endogenous CD80 with CD28 at the immune synapse



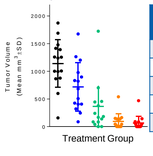
FPT155

The Murine Surrogate mFPT155 Can Induce Complete Tumor Regression After a Single Dose‡

CT26 tumor growth



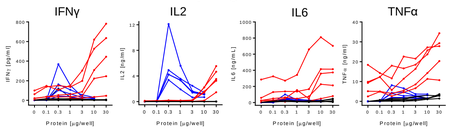
Day 21 tumor volume



Treatment Group (mg/kg)	Complete regressions
mIgG2a control	0/15
mFPT155 0.1	0/15
mFPT155 0.2	2/15
mFPT155 0.6	10/15
mFPT155 0.9	13/15

- mFPT155 has monotherapy anti-tumor activity in multiple tumor models (including some that are resistant to PD(L)-1 blockade: CT26, MC38, EMT6, A20, and WEHI164)
- Mice that reject tumors in response to mFPT155 are protected from subsequent rechallenge through the generation of lasting immunity

FPT155 is NOT a CD28 superagonist‡



- TGN1412, a superagonist CD28 antibody induced cytokine release *in vitro*[1] and led to severe clinical cytokine release syndrome (CRS)[2]
- Unlike TGN1412, effective T cell stimulation by FPT155 requires separate TCR engagement

‡Results presented at AACR 2019

[1]Stebbings, J Immunol 2007; DOI: 10.4049/jimmunol.179.5.3325
[2]Suntharalingam, NEJM 2006; DOI: 10.1056/NEJMoa063484

Methods

FPT155-001 (NCT04074759)

- Phase 1a Dose Escalation and Dose Exploration (ongoing; presented here)
- Phase 1b Cohort Expansions (to follow Phase 1a)

Phase 1a Objectives

Primary: Assess safety, tolerability; identify recommended dose

Secondary: Evaluate pharmacokinetic (PK) parameters, immunogenicity, clinical activity

Exploratory: Evaluate pharmacodynamic (PD) parameters in tumor and peripheral blood

Primary Endpoint: Incidence of dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), laboratory abnormalities and ECG abnormalities

Key Inclusion Criteria

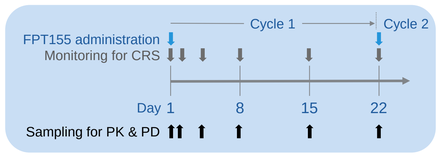
- Adults with incurable solid tumor without other standard treatment options
- ECOG 0-1
- At least 1 measurable lesion (RECIST v1.1)

Key Exclusion Criteria

- Primary CNS tumor
- Autoimmune disease
- Prior treatment with anti-CTLA4
- Prior treatment with other IO agents cannot have been stopped due to toxicity or administered within 90 days of study treatment

FPT155 Administration and Safety Monitoring

- Flat dose of FPT155 IV administered over 1 hour every 3 weeks
- Intensive laboratory monitoring for CRS



Response Assessment

- Tumor assessment with CT or MRI per RECIST v1.1
- Assessment every 6 weeks for 24 weeks then every 12 weeks thereafter until either disease progression or initiation of subsequent anti-cancer therapy

Dose Escalation

Enrollment	Dose Level	FPT155 (flat dosing)
Accelerated Titration (single patient)	1	0.07 mg*
	2	0.21 mg
	3	0.7 mg
	4	2.1 mg
3+3	5	7 mg
	6	21 mg
	7	42 mg
	8	70 mg
Planned additional dose levels	9	140 mg
	10	280 mg
	11	560 mg
	12	700 mg

If any DLTs† or ≥ 2 Grade 2 TEAEs attributed to FPT155 occur, design converts to 3+3

Currently enrolling (Oct 2019)

*Minimum anticipated biologically effective level (MABEL) starting dose based on *in vitro* binding to CTLA-4 and CD28

Dose Exploration

Up to 30 additional patients at dose levels that have cleared in escalation

All patients will have on-treatment biopsies at Cycle 3

Enrolled Patients

	0.07 mg	0.21 mg	0.7 mg	2.1 mg	7 mg	21 mg	42 mg
Number of patients	1	1	2*	1	4^	3	3
Median age (range)	53	61	66 (58,73)	42	66 (47-76)	63 (60-70)	68 (65-74)
Number of prior cancer regimens (range)	4	2	6 (4,7)	6	5 (2-8)	5 (3-5)	2 (2-3)
Type(s) of cancer	Colorectal	Mesothelioma	Cervical Breast	Colorectal	Cholangio Colorectal Lung Pancreas	Colorectal Lung	Gallbladder Mesothelioma Thyroid
Median duration of exposure in days (range)	41	190	63,64	63	57 (42-84)	42 (42-42)	21 (21-42)#
DLTs†	0	0	0	0	0	0	0

*Two patients identified for participation simultaneously (not due to adverse events)

^1 patient in dose exploration; #3 patients continuing on treatment as of September 30, 2019

†DLT criteria: Events attributed to FPT155 occurring in the first 21 days: ≥ Grade 3 neutropenia for longer than 5 days or febrile neutropenia; thrombocytopenia Grade 3 with significant bleeding or any Grade 4; AST/ALT > 3xULN with total bilirubin > 2xULN not related to liver involvement of malignancy; Grade 2 treatment emergent neurological toxicity; > Grade 2 non-hematologic toxicity *except for*: Grade 3 fatigue or nausea improved with supportive care; Grade 3-4 vomiting or Grade 3-4 diarrhea lasting <72 hours; Grade 3 endocrinopathy adequately treated by hormone replacement; lab value that may be corrected by replacement within 48 hours

Results

Serious and ≥ Grade 3 Treatment Emergent AEs

	Patients with ≥ Grade 3 AE	SAE	Preferred Term(s)
0.07 mg (N=1)	1	1	Bile Duct Obstruction
0.21 mg (N=1)	0	0	
0.7 mg (N=2)	1	1	CNS Lesion
2.1 mg (N=1)	0	0	
7 mg (N=4)	1	1	Haemoptysis, Pleural Effusion
21 mg (N=3)	1	1	Deep Vein Thrombosis
42 mg (N=3)	0	1	Herpes Zoster

Irrespective of attribution; as of Sept 30, 2019

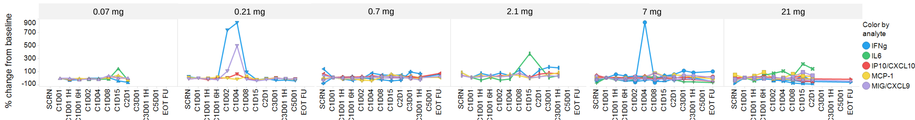
- **No ≥ Grade 4 AEs**
- **No ≥ Grade 3 AEs or SAEs attributed to FPT155**

Treatment Emergent AEs in more than 1 Patient (Any Grade)

	0.07 mg (N=1)	0.21 mg (N=1)	0.7 mg (N=2)	2.1 mg (N=1)	7 mg (N=4)	21 mg (N=3)	42 mg (N=3)
Any TEAE	1	0	2	1	3	2	2
Fatigue	0	0	1	1	1	1	0
Decreased appetite	0	0	1	0	1	0	0
Deep vein thrombosis	0	0	0	0	1	1	0
Dyspnoea	0	0	0	1	1	0	0
Peripheral Oedema	0	0	1	0	0	1	0

Irrespective of attribution; as of Sept 30, 2019

Preliminary Peripheral Blood Biomarker Results



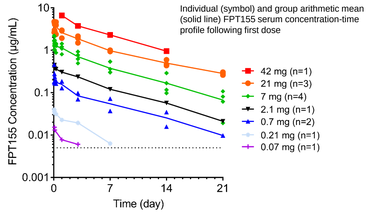
- No consistent treatment emergent elevation in cytokines
- No dose-response between FPT155 and cytokine elevation to date
- No significant treatment-related changes in peripheral T cell compartment (data not shown)
- No clinical responses to therapy through FPT155 21mg Q3W

≥ Grade 3 Treatment Emergent Lab Abnormalities

	0.07 mg (N=1)	0.21 mg (N=1)	0.7 mg (N=2)	2.1 mg (N=1)	7 mg (N=4)	21 mg (N=3)	42 mg (N=3)
Hemoglobin decreased	0	0	0	0	0	0	1
Alkaline Phosphatase increased	1	0	0	1	2	1	0
Urate increased	1	0	0	0	1	0	1
Glucose increased	0	0	0	0	0	0	2
Potassium decreased	0	0	0	0	0	1	0
Sodium decreased	0	0	0	0	0	0	1

Irrespective of attribution; as of Sept 30, 2019

Preliminary Pharmacokinetic Profile of FPT155 from Phase 1 Dose Escalation



- Linear clearance (based on 7-21mg, n≥3)
- Elimination half-life ($t_{1/2}$) approximately 1 week
- Minimal accumulation following repeat Q3W dosing
- FPT155 induced anti-drug antibodies in 2/13 patients

Conclusions

Dose escalation with FPT155 is ongoing

- No DLTs, well-tolerated in dose escalation through October 2019; FPT155 70mg Q3W cohort currently enrolling
- No acute immunologic toxicities to date and no evidence of clinical or laboratory CRS

Preliminary PK evaluation shows:

- Dose-proportional increase in exposure
- $t_{1/2}$ of ~ 1 week, minimal accumulation with Q3W dosing

FivePrime