SAFETY AND CLINICAL ACTIVITY OF FX-909, A FIRST-IN-CLASS ORAL SMALL MOLECULE INHIBITOR OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARG), A MASTER REGULATOR OF LUMINAL LINEAGE, IN PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA

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Abstract #LB-B007

BACKGROUND

The transcription factor PPARG is the master regulator of the luminal lineage in advanced urothelial cancer.[1,2] High PPARG expression is the defining feature of the luminal lineage, representing approximately **65%** of all advanced UC patients.[3,4] FX-909 is a novel **first-in-class**, orally bioavailable potent and selective inhibitor of PPARG that stably enforces a conformationally 'repressive' state that elicits durable tumor regressions in xenograft models.[5] The Phase 1 dose escalation and expansion study of FX-909 [*NCT05929235*] in locally-advanced (unresectable) and metastatic urothelial carcinoma is ongoing. We present the Phase 1 Part A results, including efficacy in a **PPARG^{high}** population.

MATERIALS AND METHODS

A Phase 1A open-label dose-escalation study to determine safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary clinical activity of FX-909 administered orally once daily (QD) enrolled pts with advanced solid malignancies, including adv UC (NCT05929235). Phase 1A utilized a 3+3 design exploring a dose range from 30-100 mg QD in 28-day cycles and included backfilling of up to 30 patients. Thirtysix *advanced UC* patients have been treated across the four dose levels of FX-909; 30 mg (12), 50 mg (11), 70 mg (11) and 100 mg (2) QD.

FIGURE 1. FX-909 Phase 1 Part A Study

PART A: Dose Escalation
Advanced Solid Malignancies, Including Advanced Urothelial Carcinoma
N = 46 Patients

3+3: 30-100 mg dose range, QD dosing (oral), 28-day cycle enriching for *advanced UC* via backfill cohorts

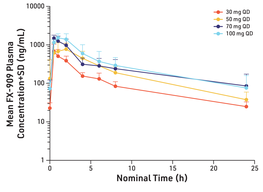
Cohort 2 100 mg QD	N=6
Cohort 1.5 70 mg QD	N=13
Cohort 1 50 mg QD	N=15
Cohort 0.5 30 mg QD	N=12

KEY ELIGIBILITY
- ECOG PS 0-2
- Measurable or non-measurable disease per RECIST v1.1
- Archival tumor tissue or fresh tumor biopsy
- HbA1c ≤7.0%

KEY OBJECTIVES FOR PART A
- Safety, Tolerability
- Determine RP2D
- Pharmacokinetics
- Preliminary efficacy per RECIST v1.1
- Exploratory biomarkers for patient selection

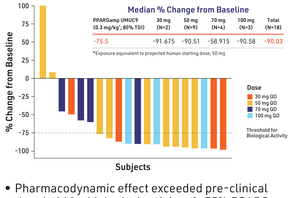
RESULTS

FIGURE 2. Plasma Concentration of FX-909 vs. Time Following Single Oral Administrations of FX-909 on C1D15



- Exposure increases in a roughly dose-proportional manner from 30 to 100 mg QD. The mean steady-state terminal half-lives range from 6.5-7.6 hr.

FIGURE 3. FABP4 Expression Measured as % Change from Baseline in Paired Skin Punch Biopsies, Collected at Screening and C1D15



- Pharmacodynamic effect exceeded pre-clinical threshold for biological activity of ≥75% PPARG target gene suppression observed in PPARG amplified xenograft model.

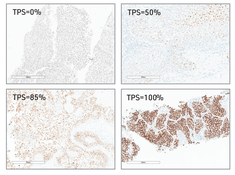
TABLE 1. Total Population – All (N = 46 patients)

Characteristic	No. of Patients (%)
Age (years), median	70.2
≥65	33 (71.7)
Sex	
Female/Male	10 (21.7) / 36 (78.3)
Race	
Asian	3 (6.5)
Black or African American	3 (6.5)
White	40 (87)
ECOG PS	
0	14 (30.4)
1	32 (69.6)
HbA1c (%)	
5.7-6.4	17 (37)
≥6.5	1 (2.2)
BMI (kg/m²)	
Overweight ≥25<30	15 (33.3)
Obese ≥30	9 (20)

TABLE 2. Target Population – Advanced UC (N = 36 patients)

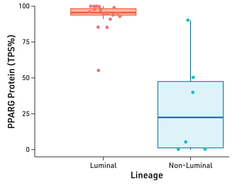
Characteristic	No. of Patients (%)
Age (years), median	70.6
≥65	28 (77.8)
Sex	
Female/Male	6 (16.7) / 30 (83.3)
Race	
Asian	3 (8.3)
Black or African American	1 (2.8)
White	32 (88.9)
ECOG PS	
0	8 (22.2)
1	28 (77.8)
Smoker	17 (47.2)
Urothelial Cancer	
Bladder	24 (52.2)
Other	9 (19.6)
Upper urinary tract	3 (6.5)
Liver Metastasis	8 (22.2)
Hemoglobin (<10g/dL)	9 (25)
≥3 prior Systemic Therapies	19 (52.8)
Prior EV or Anti-PD1/Anti-PDL1	36 (100)
Prior EV and Anti-PD1/Anti-PDL1	21 (58.3)

FIGURE 4. PPARG Protein Expression – Strong nuclear staining of tumor cells tissues collected from adv UC patients at baseline enrolled in Part A



TPS = No. of PPARG positive tumor cells (+1,+2,+3) x 100 / Total No. of viable tumor cells

FIGURE 5. Lineage Stratification – High expression of PPARG accurately predicts for luminal lineage[3,6]



- Provisional *TPS cutoff of ≥60%* determined from integrative biostatistical modeling leveraging Tempus MRWD (data not shown) defines **PPARG^{high}**

FIGURE 6. Emerging Clinical Activity in Efficacy Evaluable Advanced UC Patients (N=31)

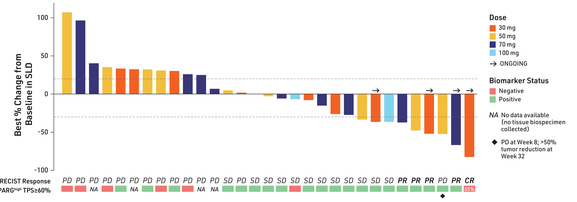


FIGURE 7. Emerging Clinical Activity in Biomarker-Positive Sub-Group – PPARGhigh (N=20)

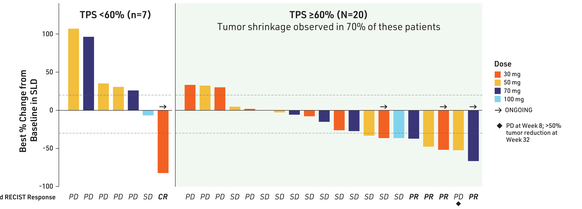
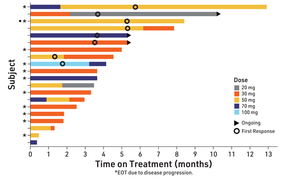


FIGURE 8. Preliminary Tolerability and Durability



- The median duration of response is immature at present, but trend suggests meaningful clinical benefit in heavily-treated, metastatic cohort of patients enrolled in Part A study.

FIGURE 9. Percent Change in Sum of Target Lesion Diameters Over Time

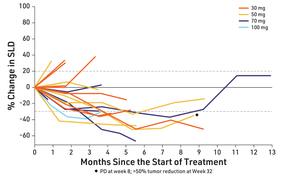


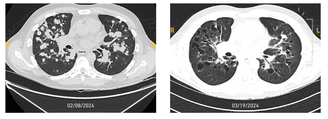
FIGURE 10. Heavily-Treated FGFR3mt Patient with Responding Liver Lesion



- PPARG^{high} patient with significant tumor burden – 5 TLs (SLD: 210 mm) and 4 NTLs and 8 lines of therapy prior to receiving 50 mg FX-909.

PD at Week 8; >50% tumor reduction at Week 32

FIGURE 11. Heavily-Treated FGFR3mt Patient with Responding Lung Lesions



- PPARG^{high} patient with significant tumor burden – 3 TLs (SLD: 142 mm) and 2 NTLs and 6 lines of therapy prior to receiving 100 mg FX-909.

TABLE 3. FX-909 Phase 1 Part A Safety Profile

Preferred Term	30 mg (N=12)	50 mg (N=15)	n (%) 70 mg (N=13)	100 mg (N=6)	Total (N=46)
At Least One TEAE	11 (91.7)	15 (100)	13 (100)	6 (100)	45 (97.8)
Platelet Count Decreased*	5 (41.7)	6 (40.0)	8 (61.5)	3 (50.0)	25 (54.3)
Fatigue	5 (41.7)	8 (53.3)	8 (61.5)	4 (66.7)	25 (54.3)
Diarrhoea	3 (25.0)	6 (40.0)	10 (76.9)	4 (66.7)	23 (50.0)
Anaemia	3 (25.0)	4 (26.7)	8 (61.5)	4 (66.7)	19 (41.3)
Hyperglycaemia	1 (8.3)	6 (40.0)	6 (46.2)	2 (33.3)	15 (32.6)
Hypophosphataemia	4 (33.3)	3 (20.0)	3 (23.1)	3 (50.0)	13 (28.3)
Decreased Appetite	2 (16.7)	4 (26.7)	5 (38.5)	2 (33.3)	13 (28.3)
Nausea	2 (16.7)	4 (26.7)	4 (30.8)	2 (33.3)	12 (26.1)
Vomiting	5 (41.7)	3 (20.0)	2 (15.4)	2 (33.3)	12 (26.1)
ALT Increased	0	1 (6.7)	8 (61.5)	2 (33.3)	11 (23.9)
AST Increased	2 (16.7)	1 (6.7)	6 (46.2)	2 (33.3)	11 (23.9)
Hypertriglyceridaemia	2 (16.7)	4 (26.7)	3 (23.1)	2 (33.3)	11 (23.9)
Hyponatraemia	2 (16.7)	4 (26.7)	5 (38.5)	0	11 (23.9)
Dyspnoea	2 (16.7)	4 (26.7)	4 (30.8)	0	10 (21.7)
Hypomagnesaemia	2 (16.7)	3 (20.0)	4 (30.8)	1 (16.7)	10 (21.7)
Greater than One TRAE with Gr ≥3	4 (33.3)	8 (53.3)	10 (76.9)	5 (83.3)	27 (58.7)
Anaemia	3 (25.0)	2 (13.3)	5 (38.5)	3 (50.0)	13 (28.3)
Platelet Count Decreased*	1 (8.3)	3 (20.0)	5 (38.5)	1 (16.7)	10 (21.7)
Fatigue	0	3 (20.0)	1 (7.7)	1 (16.7)	5 (10.9)
Hyperglycaemia	0	1 (6.7)	1 (7.7)	1 (16.7)	3 (6.5)
Dose Modifications	**30 mg (N=12)**	**50 mg (N=13)^**	**70 mg (N=13)**	**100 mg (N=6)**	**Total (N=44)**
Dose Interruptions ≥7 Days	1 (8.3)	8 (61.5)	7 (53.8)	5 (83.3)	21 (47.7)
Dose Reductions†	1 (8.3)	3 (23.1)	3 (25.0)	1 (25.0)	8 (19.5)

*Grade 4 Platelet Count Decreased (1 70 mg, 1 100 mg); ^Dose interruptions excludes 1 non-evaluable and 1 ineligible patient at 50mg; †Dose reductions (N=41), additionally 3 DLTs (2 100 mg, 1 70 mg) excluded.

- DLT's Gr3 proteinuria and transitory Gr3 hyperglycemia requiring short course of insulin at 100 mg. Gr3 anemia with dyspnea and fatigue, requiring PRBC transfusion at 70 mg.

PART B: Dose Escalation
2L+ biomarker-positive (locally advanced (unresectable) or metastatic *luminal* UC
N = 40 patients

2-Stage: 1:1 randomization of 2 doses in Stage 1, where dose with ≥4 OR advances to Stage 2; success criterion: ≥7 OR in 25 patients

Stage 1 50 mg QD N=15
Stage 1 30 mg QD N=15
→ Proceed to Stage 2 if ≥4 OR are observed
→ Stage 2 RP2D N=10

FIGURE 12. FX-909 Phase 1 Part B Study

KEY ELIGIBILITY CRITERIA FOR PART B
- Measurable disease per RECIST v1.1
- ≤4 prior lines of therapy
- ≥60% TPS PPARG

Prospective IHC-based test to select for PPARGhigh patients (pre-screening eligibility requirement based on TPS cutoff).

CONCLUSION

- FX-909 is a novel first-in-class drug that shows promising efficacy at all doses in heavily pre-treated locally-advanced (unresectable) or metastatic UC patients enrolled in the Phase 1 Part A dose escalation study.
- Preliminary efficacy is observed in luminal UC patients with high expression of PPARG.
- FX-909 has an acceptable safety and tolerability profile.
- Patients are being prospectively identified by validated PPARG immunohistochemistry assay in the Phase 1 Part B dose expansion study, enabling selection of up to 65% of the population.

REFERENCES: **1.** Rochel et al. *Nature Comm* (2019); **2.** Tate et al. *Nature Comm* (2021); **3.** Robertson et al. *Cell* (2017); **4.** Motely et al. *Euro J. Caner* (2022); **5.** Sim er al. Proc. AACR, *Cancer Res* (2023); **6.** Gjini et al. *JCO* 43, 856-856 (2025). **ABBREVIATIONS:** **EV** – Enfortumab-Vedotin; **HgA1c** – Hemoglobin A1c; **IHC** – immunohistochemistry; **MRWD** – Molecular Real-World Data; **OR** – Objective Response; **P** – Pembrolizumab; **QD** – Once daily; **TPS** – Tumor proportional score; **UC** – Urothelial carcinoma.

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https://clinicaltrials.gov/study/NCT05929235