A PHASE 1, FIRST-IN-HUMAN, DOSE-ESCALATION AND EXPANSION STUDY OF FX-909 IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES, INCLUDING ADVANCED UROTHELIAL CARCINOMA

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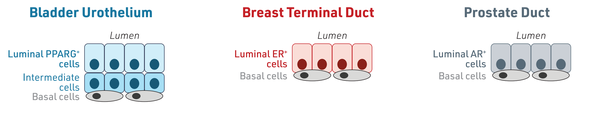
TPS709

INTRODUCTION AND STUDY RATIONALE

- Urothelial carcinoma (UC) remains a disease with high unmet need, in which the 5-year survival for patients with locally advanced muscle-invasive disease is < 40% in the USA and falls to 8% in patients with distant metastases.[1-3]
- Novel agents are needed to improve outcomes in UC treated with standard of care (eg, platinum-doublet chemotherapy, PD-(L)1 checkpoint inhibition, and antibody-drug conjugates (enfortumab vedotin and sacituzumab govitecan).
- Peroxisome proliferator-activated receptor gamma (PPARG) plays an essential lineage-determining role in normal urothelium[4,5] and is crucial for urothelial homeostasis and regeneration. Activation of PPARG-dependent transcription, either owing to mutations in its binding partner RXRA or amplification of the *PPARG* gene, occurs in 30% of luminal tumors.[6-9] Mutations in FGFR3 are more frequently observed in cancers with high expression of PPARG that are classified as luminal.
- FX-909 is a new, orally available molecular entity that irreversibly, specifically, and potently inhibits basal- and ligand-activated transcription by PPARG. FX-909 is being investigated in the clinical trial FX-909-CLINPRO-1 (NCT05929235).

DISEASE BACKGROUND

PPARG maintains luminal identity in UC

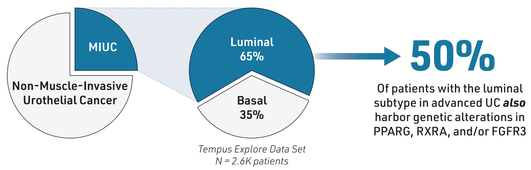


Urothelial Cancer Cell of Origin
- 50-60% luminal
- PPARG maintains luminal identity
- PPARG-RXRA mutations occur in 30% of cases with advanced MIUC

Breast Cancer Cell of Origin
- 60-70% luminal
- ER maintains luminal identity
- ER inhibitors are backbone therapies in luminal breast cancer

Prostate Cancer Cell of Origin
- 100% luminal
- AR maintains luminal identity
- AR inhibitors are backbone therapies in prostate cancer

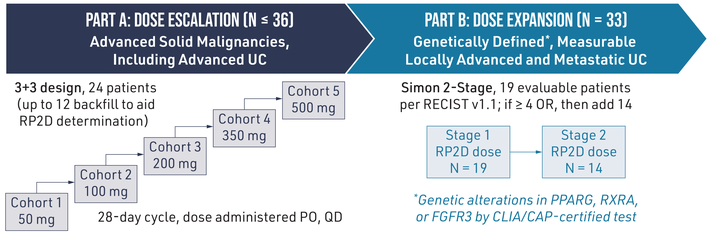
PPARG Genetic Status Defines the Luminal Lineage in a Large Molecular Real-World Cohort of Advanced UC[1,8-10]



FX-909-CLINPRO-1 PHASE 1 STUDY

Study Design

Evaluation of the safety and tolerability, PK, PD, and preliminary clinical activity of FX-909 given orally in patients with advanced solid malignancies.



Objectives and Endpoints

	Objectives	Endpoints
Primary (Pt. A)	To assess safety and tolerability	Incidence of DLTs, SAE/AEs
Primary (Pt. B)	To evaluate antitumor activity in locally advanced (unresectable) and metastatic UC	OR
Secondary	To determine RP2D, assess PK and anti-tumor activity	Plasma and urine PK, ORR, DOR, DCR, PFS, and OS per RECIST version 1.1 criteria
Exploratory	To evaluate PD, exposure-response, exposure-safety, patient selection biomarkers, immunomodulatory effect	Skin & periphery PD (PPARG target genes), ctDNA, PPARG IHC, WES, RNAseq, PD-L1 IHC, CD8 IHC, CD8 topology, and scRNAseq on PBMC

Patient Screening Criteria

Inclusion Criteria
Age ≥ 18 years
ECOG Score 0-2
Screening Laboratory Values Meet the criteria outlined per protocol, including: » HbA1c < 7.0% » Fasting glucose ≤ 140 mg/dL » Fasting triglycerides ≤ 200 mg/dL » CrCl > 60 mL/min
Part A (Dose Escalation) » Any advanced solid cancer » Measurable disease **NOT** required
Part B (Dose Expansion) » Advanced UC » Measurable Disease per RECIST v1.1 » Mutation/Amplification/Fusion in PPARG, RXRA, or FGFR3

Exclusion Criteria
T1DM or inadequately controlled T2DM **(Patients on insulin are excluded)**
QTcF > 470 msec in screening
Active diagnosis of lipodystrophy/lipoatrophy
Uncontrolled or symptomatic CNS metastases
Chronic or recurrent pancreatitis at any time, or diagnosis of acute pancreatitis < 6 mos of Screening

Exploratory Biomarkers and Collection Timepoints

Assessment	Biospecimen	Screening	C1D1	C1D15	C2D1	C3D1	C4D1	EOT
PK	Plasma	●	●	●	●	●	●	●
	Urine	●	●	●				
PD	Skin biopsy	●		●				
	Plasma	●	●	●	●	●	●	●
Patient Selection Biomarker Analysis	FFPE (IHC, H&E)	●						
	FFPE (WES, RNAseq)*	●				○ *optional*		○ *optional*
	ctDNA	●			●	●	●	●
Immunoprofiling	PBMC (scRNAseq)	●			●	●	●	●

*supported by ctDNA analysis

Phase 1 US Sites

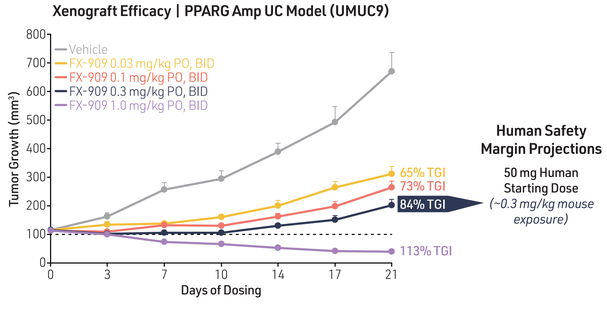
PRECLINICAL EVALUATION OF FX-909

Key Properties

FX-909 is an irreversible covalent inverse agonist that specifically and potently inhibits PPARG.

Property	FX-909
Potency	Target gene suppression in cells IC_{50} = 1-2 nM
Selectivity	> 2,000-fold vs PPARA and PPARD
Absorption	Projected to be 70%
Metabolism	Hepatic; no unique human metabolites expected
Drug-Drug Interactions	No significant liability anticipated
Dosing	Projected clearance supports QD or BID dosing
Phase 1 Formulation	Tablets

FX-909 Drives Durable Tumor Regression in Preclinical Models at Very Low Oral Doses



Abbreviations: AE = adverse event; BID = twice daily; CNS = central nervous system; CrCl = creatinine clearance; ctDNA = circulating tumor DNA; CxDy = cycle x day y; DCR = disease control rate; DLT = dose-limiting toxicity; EOT = end of treatment; HbA1c = hemoglobin A1c; IC_{50} = half maximal inhibitory concentration; ORR = objective response rate; DOR = durability of response; OR = objective response; OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; PO = administered orally; QD = once daily; QTcF = corrected QT interval (via Fridericia formula); RP2D = recommended Phase 2 dose; SAE = significant adverse event; TGI = tumor growth inhibition; T1DM/T2DM = Type 1/2 diabetes mellitus.

References: 1) Surveillance, Epidemiology, and End Results Program. NCI. 2022. **2)** Powles T, et al. *N Engl J Med* 2020. **3)** Friedlander TW et al. 2021 ASCO Annual Meeting Abstract:4528. **4)** Varley CL et al. *J Cell Sci* 2004. **5)** Liu C et al. *Nat Commun* 2019. **6)** Biton A et al. *Cell Reports* 2014. **7)** Damrauer JS et al. *Proc Natl Acad Sci* 2014. **8)** Robertson AG et al. *Cell* 2017. **9)** Hedegaard J et al. *Cancer Cell* 2016. **10)** Motley W et al. 2022 EORTC-NCI-AACR, Abstract 333.

SUMMARY

- Activating alterations in PPARG/RXRA and FGFR3 are observed in 50% of patients with advanced luminal UC. Targeting of PPARG is a novel therapeutic target in advanced UC and offers hope for improving clinical outcomes in patients with a luminal subtype.
- FX-909-CLINPRO-1 (NCT05929235) is a first-in-human, multicenter, open-label Phase 1 study to evaluate the safety and tolerability, PK, PD, and preliminary clinical activity of the PPARG inverse agonist FX-909 given orally in patients with advanced solid malignancies.
- Exploratory objectives include the evaluation of patient selection biomarkers from tissue and blood samples and association with clinical outcomes.
- In the US, approximately 11 sites are planned for Phase 1A and 12-15 sites for Phase 1B.

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