# PHASE 1 CLINICAL DATA SHOW FX-909, A FIRST-IN-CLASS ORAL PPARG INHIBITOR, DRIVES IMMUNE MODULATION AND PRO-INFLAMMATORY CYTOKINE INDUCTION IN IO-EXPERIENCED PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA

Abstract #1318

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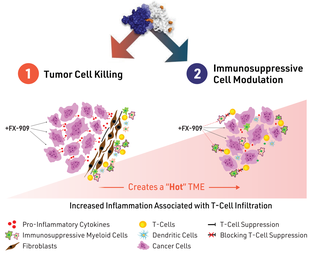
## INTRODUCTION

- In urothelial carcinoma (UC), PPARG (peroxisome proliferator-activated receptor gamma) is a master regulator of luminal lineage, driving tumorigenesis and disease progression. About two-thirds of advanced UC are luminal tumors with elevated PPARG expression.[1]
- PPARG activation promotes an immunosuppressive tumor microenvironment (TME), marked by reduced T-cell infiltration, T-cell dysfunction, and enrichment of MDSCs.[2,3] In muscle-invasive UC, PPARG overexpression correlates with low PD-L1, a cold immune phenotype, and therapy resistance.[2-4]
- Beyond tumor intrinsic biology, PPARG regulates immune cell function, including monocytes and macrophages, driving anti-inflammatory, immunosuppressive phenotypes.[2,5]
- FX-909 is a potent, selective, irreversible PPARG inhibitor with favorable PK and toxicity profiles, currently in Phase 1 clinical trials for advanced UC (NCT05929235).[6,7]
- We hypothesize that FX-909 mediates its therapeutic effects through 2 complementary mechanisms: **1.** direct effect on luminal UC cells; and **2.** induction of a pro-inflammatory cytokine cascade promoting T-cell infiltration and disruption of immune evasion within the TME (**Figure 1**).
- Data from the Phase 1a study presented here demonstrate that FX-909 exerts immune-modulatory activity as a single agent, supporting the rationale for combination with an anti-PD-1 inhibitor in advanced UC. In combination, FX-909 may enhance T-cell trafficking, alleviate immunosuppression, and sustain T-cell activation to promote a robust and durable antitumor response.

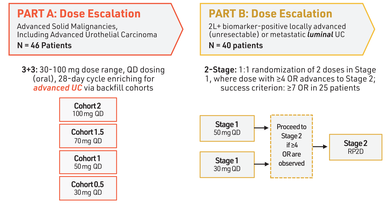
### FIGURE 1. FX-909 Mechanism of Action




## METHODOLOGY

- The Phase 1A open-label dose escalation study utilized a 3+3 design (30-100 mg QD, in 28-day cycles) with backfilling of up to 30 patients. As of August 26, 2025, 36 advanced UC patients had been treated across four dose levels (**Figure 2**)[7]. Results shown here are from a subset of patients in the Phase 1A dose-escalation study.
- Proteomic profiling from longitudinal plasma samples collected from 20 UC patients were analyzed by Olink® Explore HT at Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) (**Figure 3**).
- Peripheral blood mononuclear cells (PBMCs) from a subset of these patients (n =11) were analyzed by single cell RNAseq at screening and on-treatment (**Figure 3**). On-treatment samples were collected 28-56 days after treatment initiation. Data for >1 on-treatment samples from the same patient were averaged. Data processing and analysis followed established methods[5]. Aitchison distances were used to assess immune cell composition shifts pre- to on-treatment between responders and non-responders (one-sided Wilcoxon test).
- Pre-treatment archival tumor tissues or fresh tumor biopsies from a subset of patients were analyzed by PPARγ IHC ( n=27), RNAseq (n=26) and whole exome sequencing (WES; n=26). Gene signature scores were defined as the mean $\log_2$(TPM+1) mRNA expression of genes comprising each published signature[8-11].
- Preliminary efficacy was assessed per RECIST v1.1.

### FIGURE 2. FX-909 Phase 1 Study

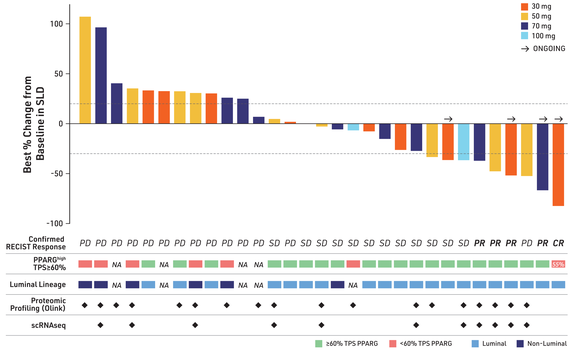



- PK and PD support FX-909 is a pharmacologically active drug at all doses evaluated.
- Preliminary anti-tumor activity was observed at all doses evaluated in advanced UC patients with PPARG high expression.
- Based on Part A review, 30 mg and 50 mg QD doses were selected for further optimization in the Phase 1 Part B dose expansion study.

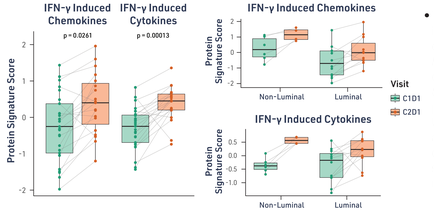
PK – Pharmacokinetics; PD – Pharmacodynamics; OR – Overall Response; TPS – Tumor Positivity Score; RP2D – Recommended Phase 2 Dose; ECOG PS – Eastern Cooperative Oncology Group Performance Status; RECIST – Response Evaluation Criteria in Solid Tumors; HbA1c – Hemoglobin A1c.

## RESULTS

### FIGURE 3. Emerging Clinical Activity in Efficacy Evaluable Advanced UC Patients (N=31)

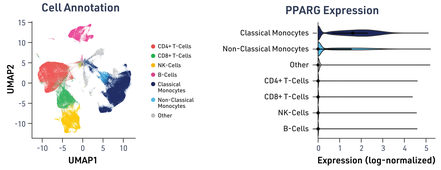



### FIGURE 5. Proteomic Profiling of Plasma Indicates FX-909 Activates IFNγ-Induced Inflammatory Pathways in Advanced UC patients (N=20)



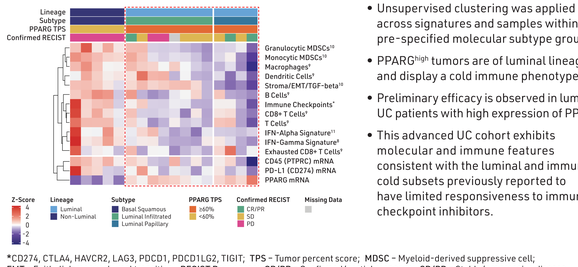

- Treatment with FX-909 induces IFNγ-associated cytokines (*IL12, TNFA, IL-1RA, IL-18*) and chemokines (*CXCL9, CXCL10*) in plasma from patients with advanced UC, indicating immune activation independent of tumor lineage (two-sided paired Wilcoxon rank-sum test ).

### FIGURE 6. PPARG Expression in PBMCs of Advanced UC Patients Treated with FX-909




- PPARG expression is predominantly in classical monocytes.

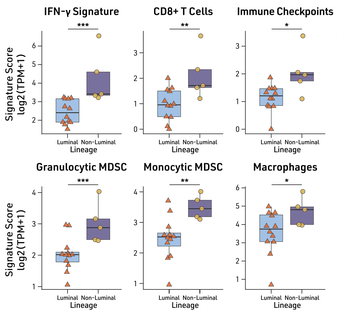
### FIGURE 4A. Molecular Profiling of Pre-Treatment Biopsies from FX-909–Treated Advanced UC Patients Indicates that the Luminal Subtype Exhibits an Immune-Cold Tumor Microenvironment Signature (N=17)




- Unsupervised clustering was applied across signatures and samples within pre-specified molecular subtype groups.
- PPARG high tumors are of luminal lineage[13] and display a cold immune phenotype.
- Preliminary efficacy is observed in luminal UC patients with high expression of PPARG.
- This advanced UC cohort exhibits molecular and immune features consistent with the luminal and immune-cold subsets previously reported to have limited responsiveness to immune checkpoint inhibitors.

*CD274, CTLA4, HAVCR2, LAG3, PDCD1, PDCD1LG2, TIGIT; TPS – Tumor percent score; MDSC – Myeloid-derived suppressive cell; EMT – Epithelial-mesenchymal transition; RECIST Responses: CR/PR – Confirmed/partial response; SD/PD – Stable/progressive disease.

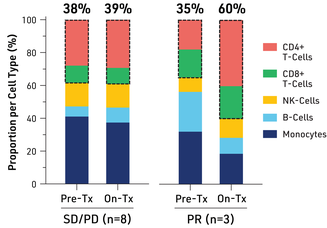
### FIGURE 4B. Luminal PPARG high Tumors Show Reduced Immune Activity vs Non-Luminal PPARG low Tumors (N=17)




- Pre-treatment tumors of luminal lineage with PPARG high exhibit a "colder" immuno-phenotype compared to tumors of non-luminal lineage with PPARG low expression (two-sided Wilcoxon rank-sum test).

PPARG TPS
≥60%
<60%

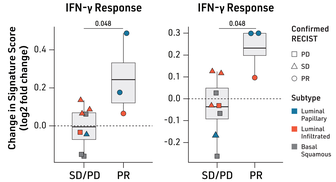
### FIGURE 7A. FX-909 Induces Activated T-Cell Expansion in PBMCs of PPARG high Responding Patients (N=11)




- FX-909 drives CD4+ and CD8+ T-cell expansion in PPARG high responders (TPS ≥60% ), whereas patients with SD/PD show no such expansion.

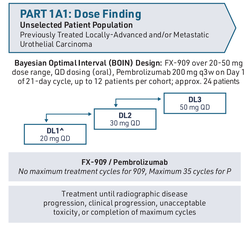
Median number of annotated cells per sample: 5958 (IQR: 4879–6826).

### FIGURE 7B. FX-909 Induces Activated Circulating T-Cell Expansion in PPARG high Responding Patients (N=11)




- Activation of CD4+ and CD8+ T cells is observed in PRs following FX-909 treatment, but not in non-responders or patients with stable disease (two-sided Wilcoxon rank-sum test).

### FIGURE 8. Phase 1 Part 1A1 Dose Escalation of FX-909 and Pembrolizumab Conducted as an Integrated Component of the Phase 1 Study




- Findings from the FX-909 monotherapy study suggest that PPARG modulation may contribute to immune activation, supporting exploration of FX-909 in combination with pembrolizumab.
- FX-909 dosing will begin at 20 mg QD; a lower dose than being currently tested in the Phase 1 Part B dose expansion monotherapy study and allows for DL-1 per protocol allows or lowest potential dose of 10 mg QD to be tested.
- Correlative exploratory biomarkers will include:
  - **a.** Tissue-based biomarkers: PD-L1 IHC, CD8 IHC, PPARG IHC, TMB, luminal syntyping (RNAseq).
  - **b.** Peripheral blood-based biomarkers: scRNAseq.

## CONCLUSION

- The clinical activity observed with FX-909 monotherapy, along with Phase 1A correlative data showing induction of pro-inflammatory cytokines and chemokines and promotion of T-cell expansion in circulation, supports PPARG inhibition as a potential strategy to overcome immune resistance in advanced UC.
- To further test this hypothesis, Flare Therapeutics, in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, will initiate a Phase 1 of FX-909 in combination with pembrolizumab in the first quarter of 2026 to evaluate the safety, tolerability, immunologic activity, and preliminary efficacy of escalating doses of FX-909 in combination with standard-dose pembrolizumab in patients with advanced UC (**Figure 8**).

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References 1. Tate et al, 2021 *Nat Commun* Oct 25;12(1):6160; 2. Galsky et al, 2018 *Bladder Cancer* Apr 26;4(2):227-238; 3. Xiong et al, 2023 *Gut* Sep;72(9):1758-1773; 4. Gjini et al, *2023 Society for Immunotherapy of Cancer (SITC) 38th Annual Meeting*; 5. Nguyen et al, *2024 AACR Annual Meeting*; 6. Iyer et al, Trials in Progress, *2024 ASCO Genitourinary Cancers Symposium*; 7. Gao et al, *2025 AACR-NCI-EORTC International Conference*; 8. Ayers et al, 2017 *J Clin Invest* Aug 1;127(8):2930; 9. Danaher et al, 2017 *J Immunother Cancer* Feb 21;5(18); 10. Cristescu et al, 2021 *Clin Cancer Res* Dec 27;28(8):1680; 11. Liberzon et al, 2015 *Cell Syst* Dec 23;1(6):417; 12. Cristescu et al, 2022 *J Immunother Cancer* Jan 31;10(1):e003091; 13. Robertson et al, 2017 *Cell Oct* 19;171(3):540-556.e25.