FLARE THERAPEUTICS

# FX-909 PHASE 1 PART A DATA IN ADVANCED SOLID MALIGNANCIES INCLUDING ADVANCED UROTHELIAL CARCINOMA

October 24, 2025

*Data cut: 17-SEPT-25*

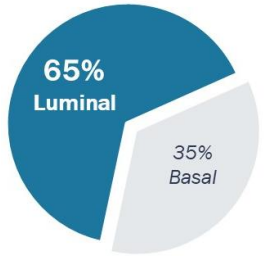
# Changing the Paradigm in Drugging Transcription Factors

## Elusive Targets for Drug Development

**<1% TFs have been drugged**

Critical role in cell and tissue identity driving disease

## FX-909, a First-in-Class PPARG Inhibitor




Targeting the master regulator of luminal lineage in advanced urothelial cancer

## Abysmal 5-year Survival Rates

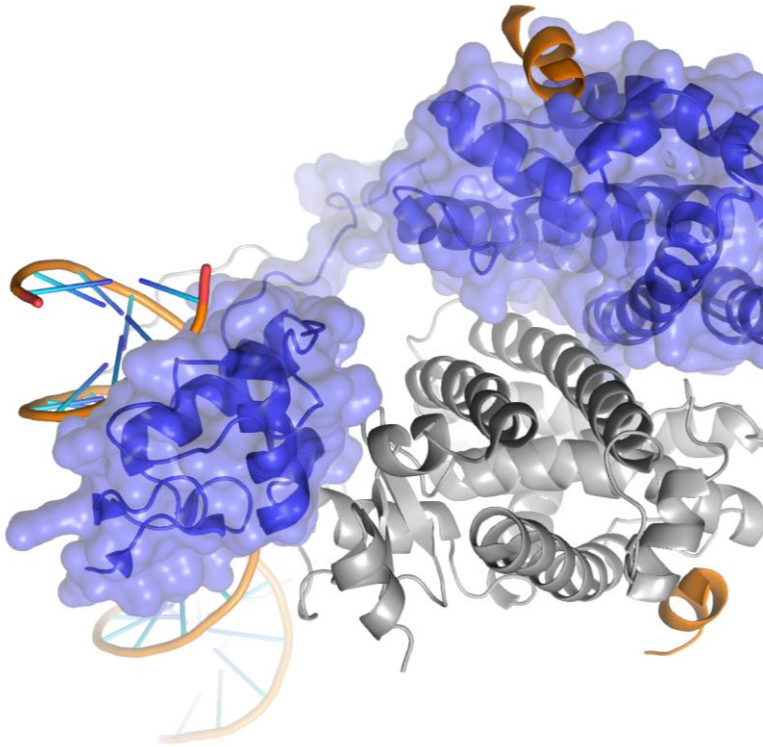
**8% in metastatic urothelial cancer**

Highest lifetime treatment costs of all cancers

**Flare Therapeutics Pipeline is Focused on Regaining Transcriptional Control That is Highjacked by Disease**

# Targeting PPARG in Urothelial Cancer

- 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



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)

# 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

- 36 ***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
- 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
- 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

***Abbreviations:*** *UC, urothelial carcinoma; QD, once daily; HgA1c, Hemoglobin A1c; QD, OR, Objective Response; IHC, immunohistochemistry; TPS, tumor proportional score*

# Demographic and Baseline Characteristics of Patients

## 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/m$^2$)** | |
| Overweight ≥25<30 | 15 (33.3) |
| Obese ≥30 | 9 (20) |

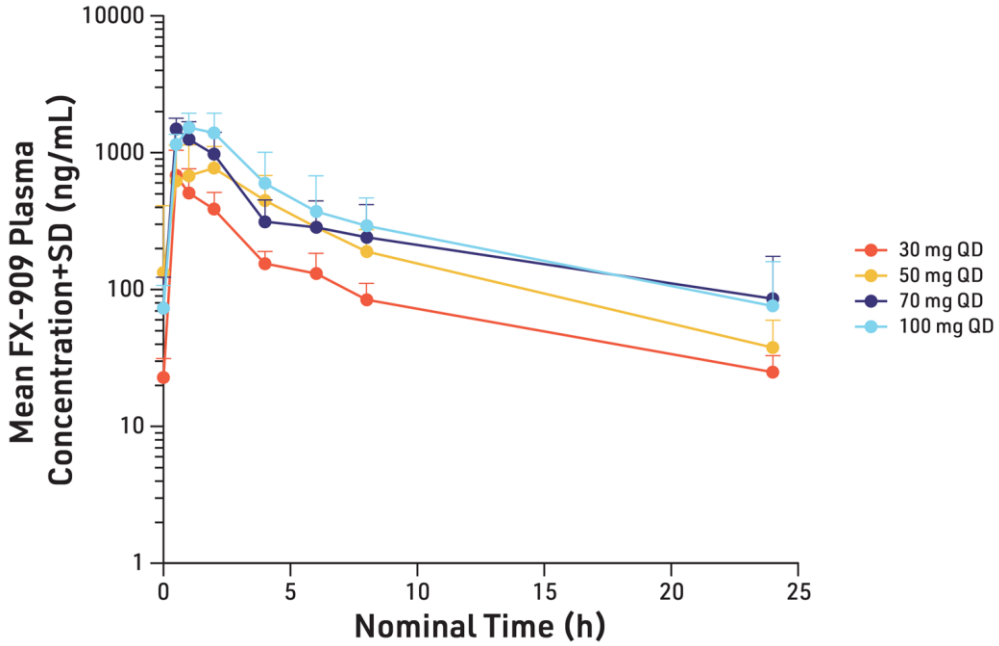
EV – Enfortumab Vedotin; P – Pembrolizumab

## 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) |

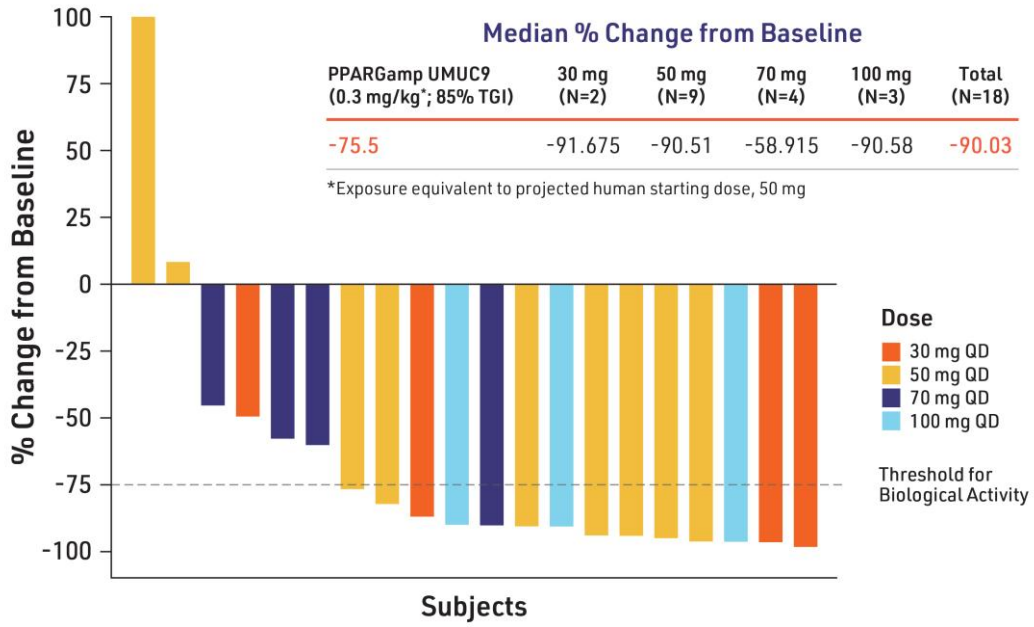
# Plasma PK and Skin PD Support FX-909 is a Pharmacologically Active Drug

## 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.

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

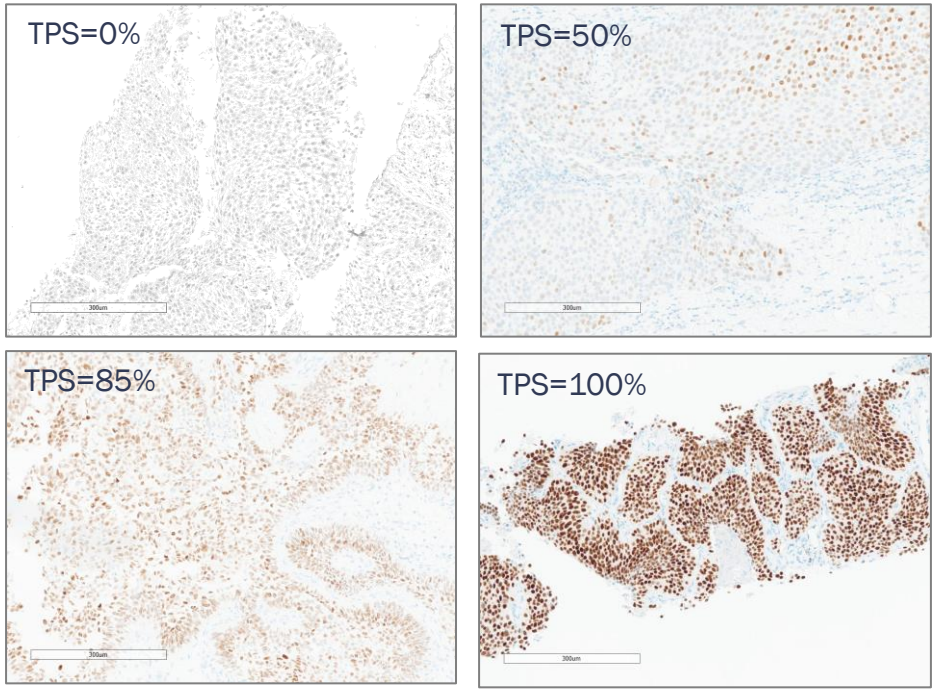



- Pharmacodynamic effect exceeded pre-clinical threshold for biological activity of ≥75% PPARG target gene suppression observed in PPARG amplified xenograft model

# PPARG Immunohistochemistry Assay in Development to Identify FX-909 Responders

## PPARG Protein Expression

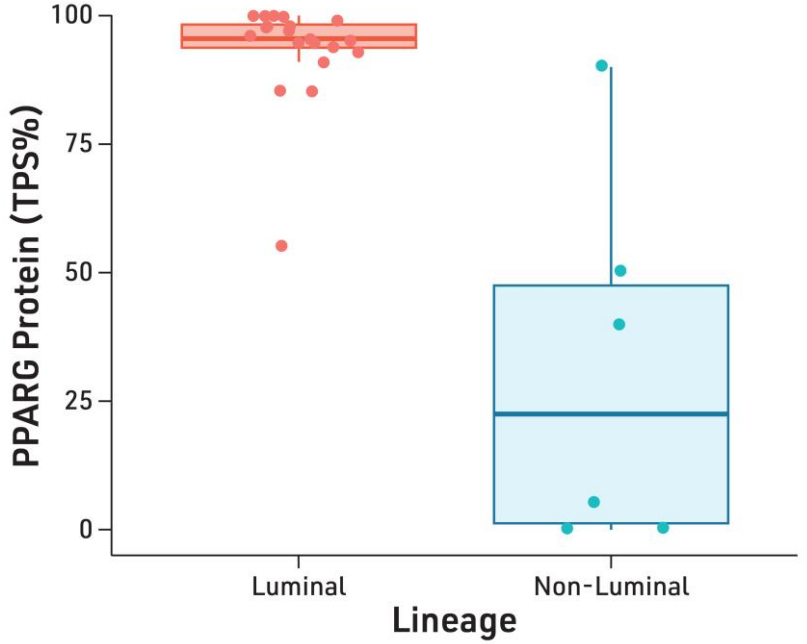
Strong nuclear staining of tumor cells tissues collected from adv UC patients at baseline enrolled in Part A




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

## Lineage Stratification

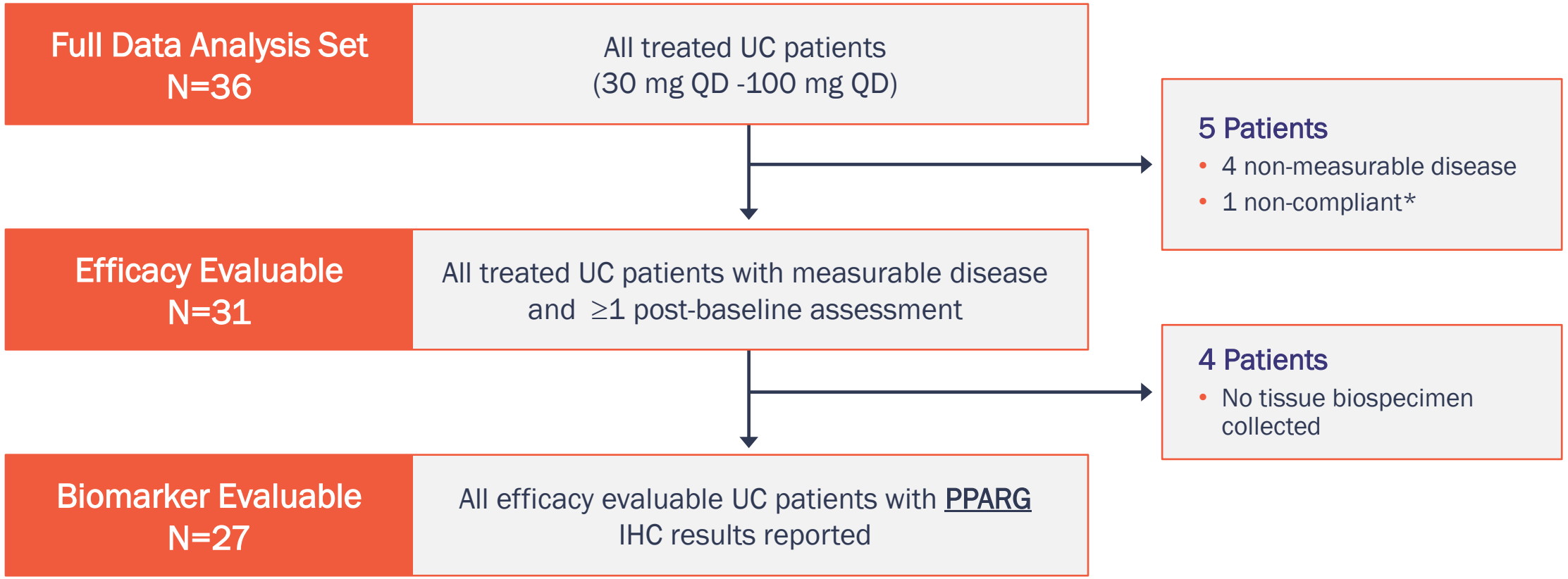
High expression of PPARG accurately predicts for luminal lineage[1,2]




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

**1.** Gjini et al. *JCO* 43, 856-856(2025); **2.** Robertson et al. *Cell* (2017); **TPS** – Tumor Proportional Score; **MRWD** – Molecular Real-World Data; Datacut:06-AUG-25

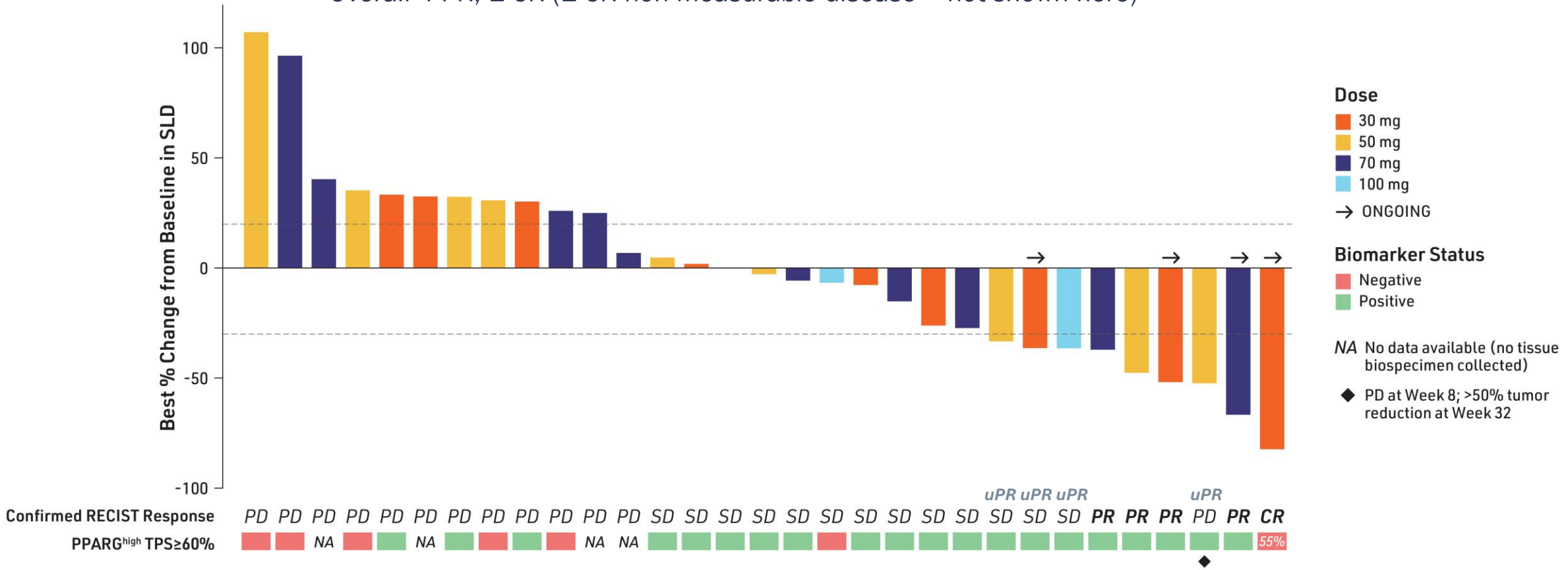
# FX-909 Phase 1 Part A: Efficacy Evaluable Advanced UC Cohort



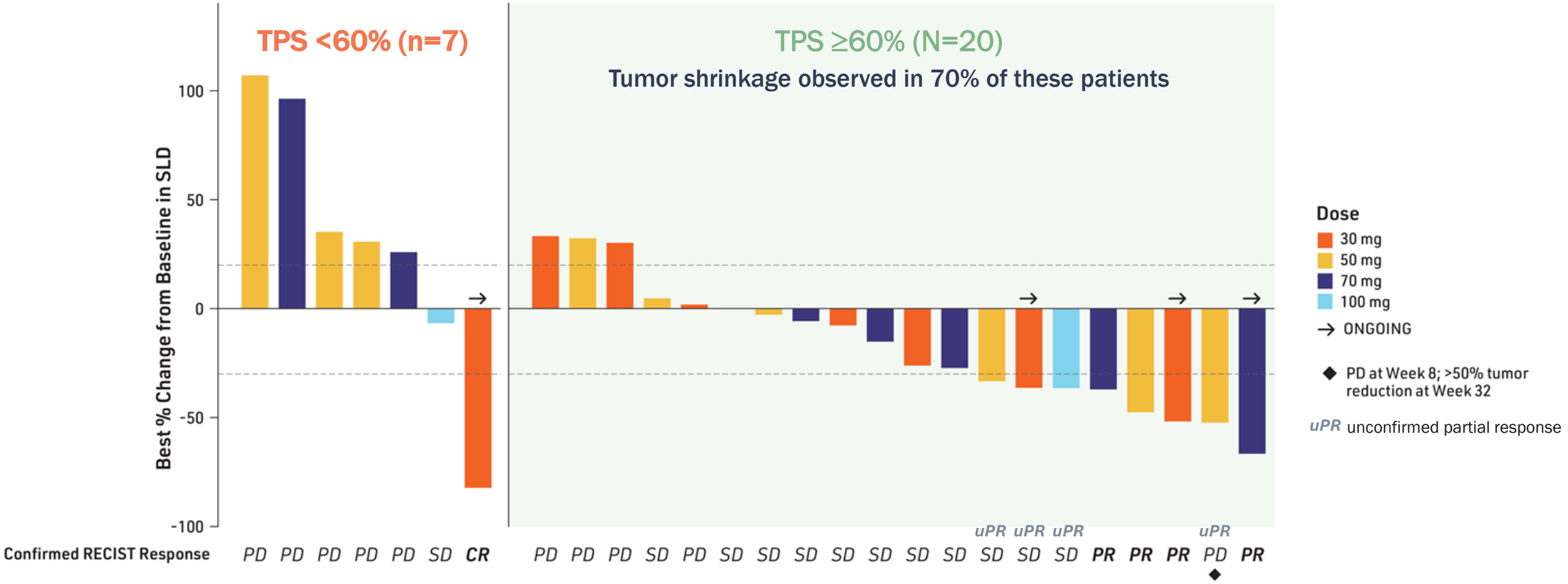

*1 patient is excluded from the analysis due to significant protocol deviation; Datacut:17-SEPT-25

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

- Overall 4 PR, 1 CR (1 CR non-measurable disease – not shown here)

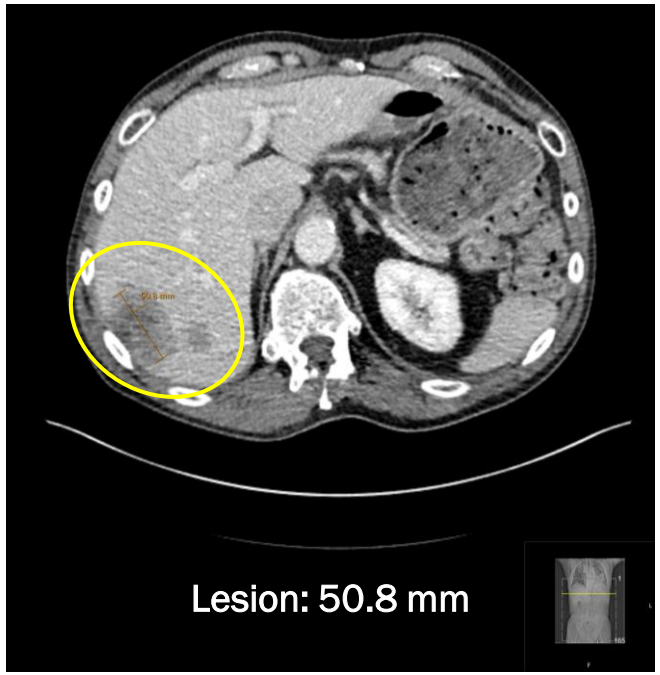


# Emerging Clinical Activity in Biomarker-Positive Sub-Group - PPARGhigh (N=20)

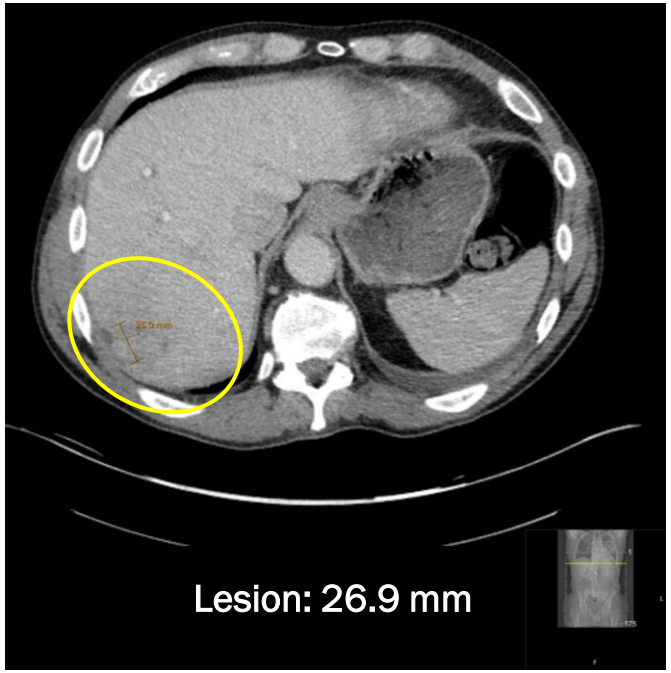


# Heavily-Treated FGFR3mt Patient with Responding Liver Lesion

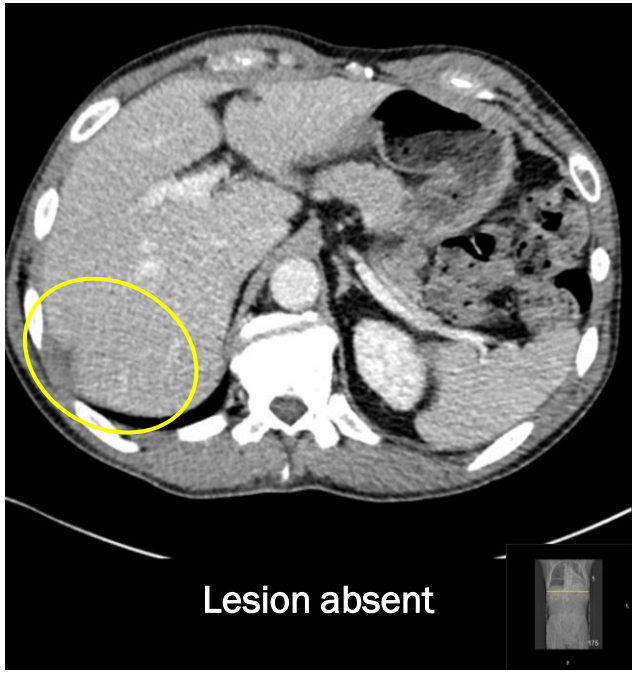
## Baseline




## Post-Baseline (17 weeks)




## Post-Baseline (24 weeks)

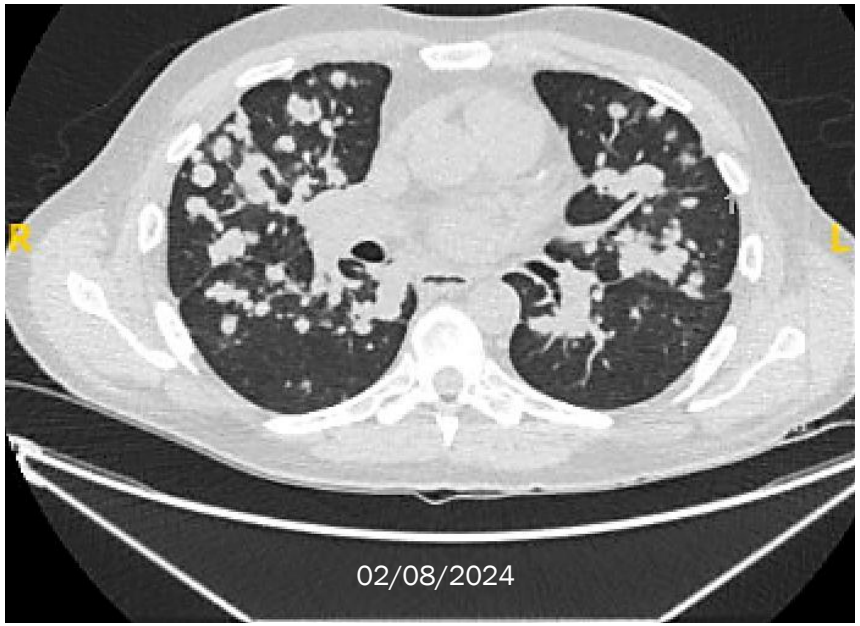



- PPARG$^{high}$ patient with significant tumor burden (SLD: 210 mm) and 8 lines of therapy prior to receiving 50 mg FX-909

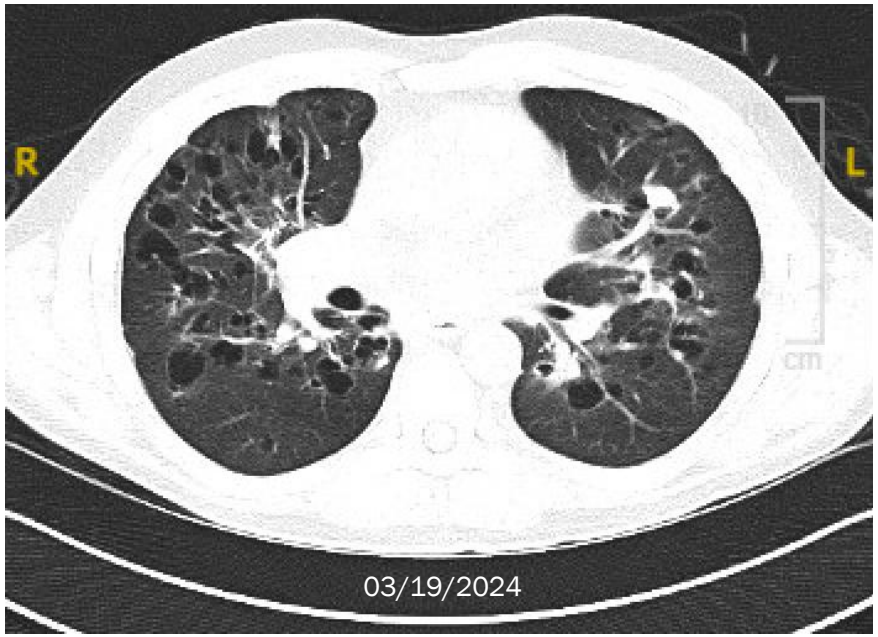
♦ PD at Week 8; >50% tumor reduction at Week 32

# Heavily-Treated FGFR3mt Patient with Responding Lung Lesions

## Baseline



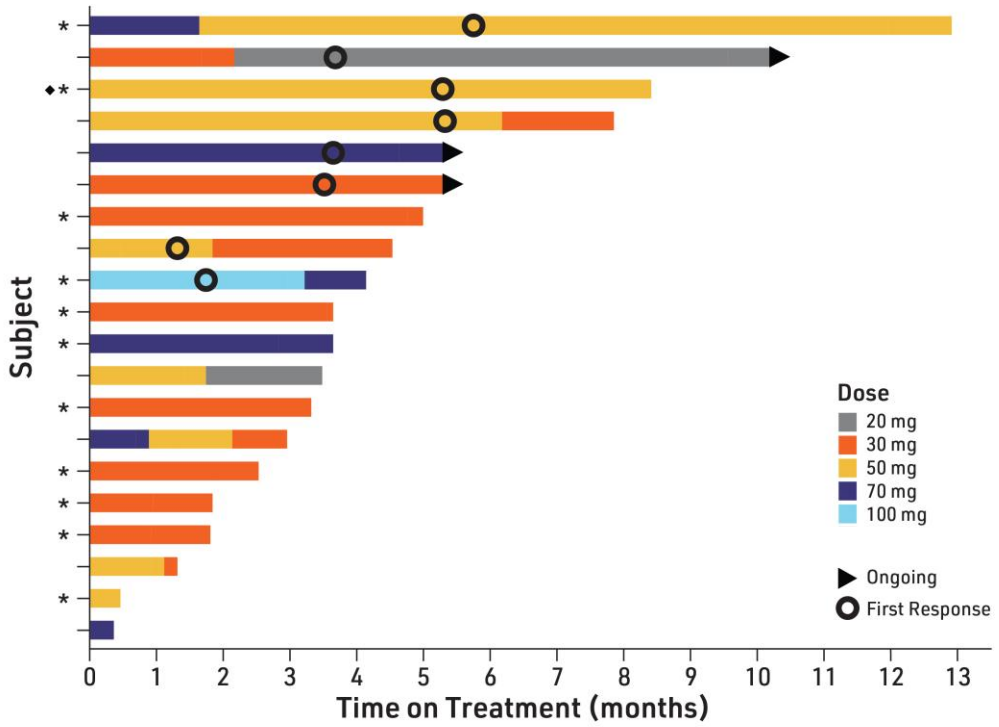

## Post-Baseline (8 weeks)



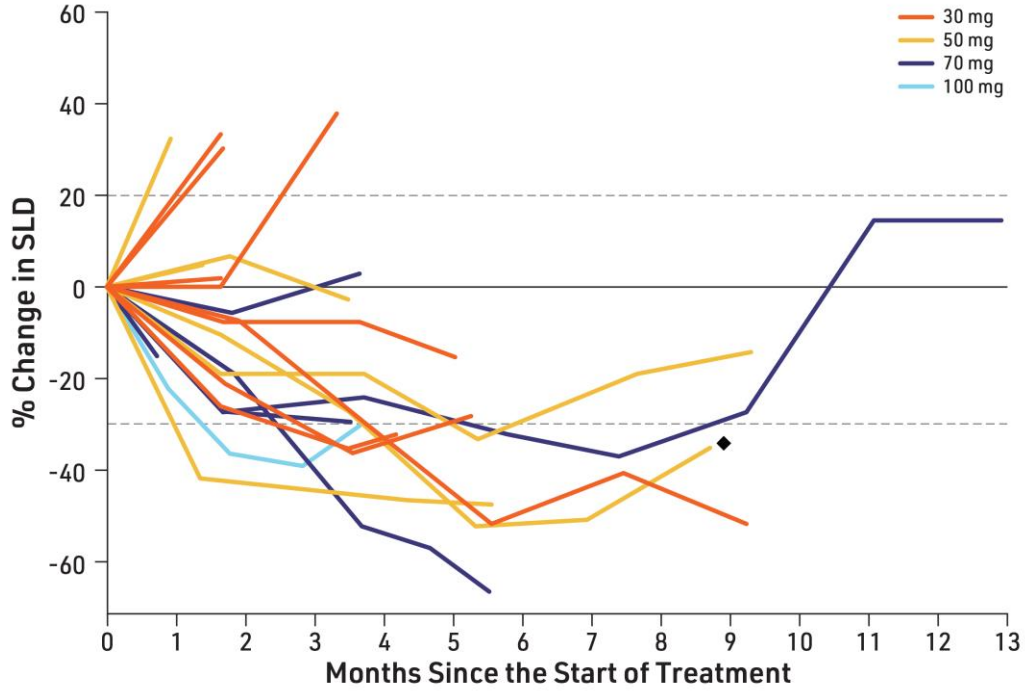

- PPARG$^{high}$ patient with significant tumor burden (SLD: 142 mm) and 6 lines of therapy prior to receiving 100 mg FX-909

# Emerging Duration and Depth of Treatment Response in Biomarker-Positive Subgroup – PPARG$^{high}$ (N=20)

## Preliminary Tolerability and Durability




## Percent Change in Sum of Target Lesion Diameters Over Time




- 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

Datacut:17-SEPT-25 ◆ PD at week 8; >50% tumor reduction at week 32 * EOT due to disease progression

# FX-909 Phase 1 Part A Safety Profile

| Preferred Term | 30 mg (N=12) | 50 mg (N=15) | 70 mg (N=13) | 100 mg (N=6) | Total (N=46) |
|---|---|---|---|---|---|
| | | | n (%) | | |
| 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

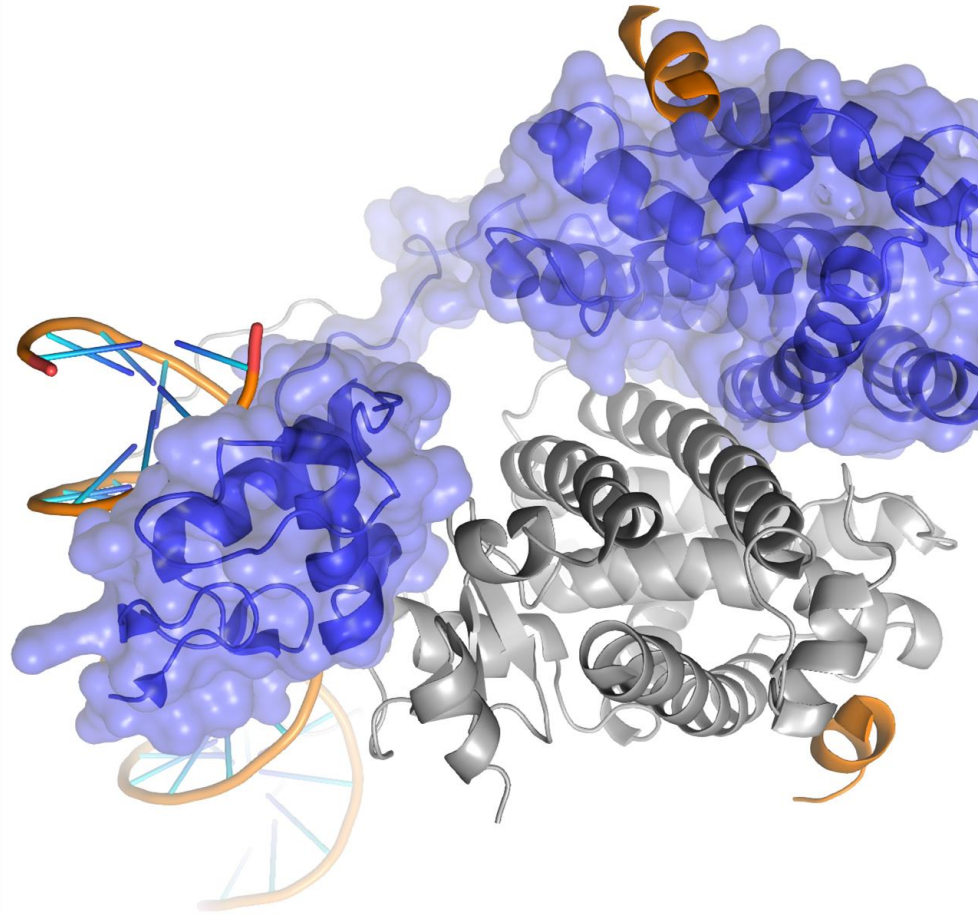
- Most common TEAEs were thrombocytopenia, fatigue, diarrhoea, anaemia, and hyperglycemia

- Most common Gr3 TRAEs were anemia, thrombocytopenia, and fatigue
- 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.

- Overall, number of permanent discontinuations due to AE's or lack of tolerability was low
- Patients receiving 30 mg QD dose
  - Experienced lower incidence of Gr3 TEAE/TRAEs
  - Required fewer dose interruptions and reductions
  - Received higher % of planned dose intensity associated with greater tolerability

# Key Takeaways

- 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 will be 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



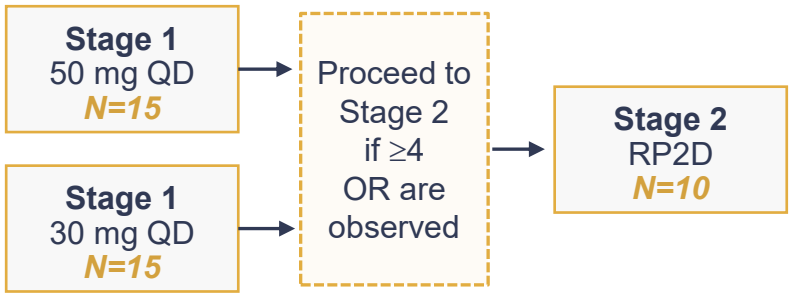
# FX-909 Phase 1 Part B Expansion Study

## PART B: Dose Expansion

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




### 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 Eligibility Criteria for Part B

- Measurable disease per RECIST v1.1
- ≤4 prior lines of therapy
- ≥60% TPS PPARG*

### Key Objectives for Part A & Part B

- Safety, tolerability
- Determine RP2D
- Pharmacokinetics
- Preliminary efficacy per RECIST v1.1
- Exploratory biomarkers for patient selection

- The Phase 1 Part B expansion study is actively recruiting **PPARG$^{high}$** LA/mUC patients to Stage 1 of the randomized 2-Stage design [NCT05929235]

*Prospective IHC-based test to select for PPARG$^{high}$ patients (pre-screening eligibility requirement based on TPS cutoff); **UC** – Urothelial carcinoma; **QD** – Once daily; **HgA1c** – Hemoglobin A1c; **OR** – Objective Response; **IHC** – Immunohistochemistry; **TPS** – Tumor proportional score

# FX-909 Clinical Development Strategy

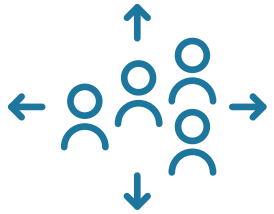
## Current Clinical Development Path

2L+ *monotherapy* in PPARG$^{high}$ patients with luminal lineage

## Line of Sight to Frontline

1L FX-909/Anti-PD1i LA/mUC patients *and earlier stages of UC**

## Indication Expansion with Immunogenic MOA



FX-909 +/- IO via tumor extrinsic MOA applicable to all solid tumors^, where IO is SOC

INCREASING MARKET POTENTIAL

FX-909 CLINICAL DEVELOPMENT OPPORTUNITIES

** Earlier stages of disease (Adjuvant high-risk MIUC, BCG-refractory high-risk MIUC, intermediate-to-high risk NMIUC)*

*^ Additional indications, where IO is SOC (e.g. NSCLC,* HCC, CRC, gastric, melanoma*)*

# Acknowledgements


- **We would like to thank:**
  - All the patients, their families and caregivers who have participated and continue to participate and support this clinical trial
  - All the investigators and research staff
  - And the Flare Tx team


**11 Study Sites**

https://clinicaltrials.gov/study/NCT05929235

Clinical trial is sponsored by Flare Therapeutics