New Targeted Therapy Shows Promise for Patients With Advanced Bladder Cancer

FX-909, a first-in-class PPARG inhibitor, showed early signs of clinical benefit in patients with advanced urothelial carcinoma.

October 30, 2025 By American Association for Cancer Research

FX-909, a first-in-class investigational oral small molecule inhibitor of peroxisome proliferator-activated receptor gamma (PPARG), showed early signs of clinical benefit in patients with advanced urothelial carcinoma, according to results from a Phase I clinical trial presented at the AACR-NCI-EORTC International Conference on Molecular Targets, held October 22-26.

Bladder cancer is the sixth most commonly diagnosed cancer in the United States. More than 90% of bladder cancers are urothelial carcinomas, cancers that arise in cells that line the bladder. “Metastatic urothelial cancer is an aggressive disease with limited treatment options and a poor prognosis, with a median survival of 2.5 years, so there is a need for better systemic therapies,” explained Xin Gao, MD, medical oncologist at the Mass General Brigham Cancer Institute and assistant professor of medicine, Harvard Medical School.

PPARG is a transcription factor that is highly expressed in approximately two-thirds of advanced urothelial cancers and, like many transcription factors, has been historically difficult to drug, Gao said. FX-909 is the first PPARG inhibitor to be evaluated clinically in patients with advanced cancer.

In the Phase I dose escalation study, Gao and colleagues evaluated the safety, tolerability, optimal dosing, and preliminary clinical anticancer activity of FX-909 in advanced cancers. Forty-six patients with advanced solid tumors, including 36 with advanced urothelial carcinoma, received FX-909 at doses ranging from 30 mg to 100 mg orally once daily in 28-day cycles. The researchers also conducted biomarker analysis to assess tumor PPARG expression and performed skin biopsies to confirm pharmacodynamic changes in response to treatment.

The maximum tolerated dose was determined to be 70 mg. However, lower doses (30 mg and 50 mg) showed improved tolerability while maintaining similar clinical activity and are being advanced into a randomized expansion study, Gao said.

Among 31 efficacy-evaluable patients with advanced urothelial cancer, 20 had high PPARG

expression (PPARG^{high}) by immunohistochemistry. Of these PPARG^{high} patients, 14 experienced tumor regression with FX-909, including four confirmed partial responses. In addition, one patient with intermediate PPARG expression had a complete response, and another patient with baseline nonmeasurable disease also experienced a complete response.

“This is the first time that a targeted therapy against PPARG has shown clinical antitumor activity in urothelial cancer,” Gao said. “We hope to further characterize the efficacy and safety profiles of FX-909 in the dose expansion study that is currently ongoing.”

The most common grade 3 or higher adverse treatment-related side effects included anemia, low platelet counts, and fatigue. Other commonly reported treatment-emergent side effects included diarrhea and elevated blood sugar levels.

The lower dose of 30 mg was associated with fewer serious side effects, slower onset of side effects, and fewer interruptions or reductions in treatment. “We were encouraged to see that most side effects were manageable and that lower doses of FX-909 were associated with better tolerability and antitumor activity that appeared comparable to higher doses. This helped guide our decision to move forward with the 30 mg and 50 mg doses in the next phase of the study, where we’ll continue to monitor safety while further evaluating the drug’s potential benefits in a biomarker-selected population of advanced urothelial cancer patients with PPARG^{high} tumors as assessed by immunohistochemistry,” said Gao.

Skin samples taken from patients showed that FX-909 was reaching and affecting its intended target. Biomarker analyses showed over 90% suppression of FABP4, a target gene of PPARG, at all dose levels. “One of the key early results of this trial was seeing clear evidence that FX-909 was hitting its intended target in patients across all dose levels, a critical finding for a first-in-mechanism clinical study,” Gao said.

Limitations of this study include its small sample size and shorter duration of follow-up. While early signs of tumor response are encouraging, larger studies and longer follow-up are needed to confirm these results, Gao said.

This study was supported by Flare Therapeutics. Gao serves as a consultant for 858 Therapeutics, Abeona Therapeutics, ADC Therapeutics, Flare Therapeutics, Janssen, Kanaph Therapeutics, and Lilly. He has received research funding to his institution from Acerand Therapeutics, ALX Oncology, Arvinas, Bayer, Lilly, Flare Therapeutics, Halda Therapeutics, Janux Therapeutics, Novartis, Regeneron, and Takeda.

This news release was published by the American Association for Cancer Research on October 22, 2025.
