UROLOGICAL CANCER

New targeted agents for urothelial carcinoma

Despite the development of immune-checkpoint inhibitors (ICIs), the majority of patients with advanced-stage and/or metastatic urothelial carcinoma continue to lack effective alternatives to chemotherapy, which typically confers a median overall survival (OS) duration of 7–9 months. Now, data from two phase II trials reveal the potential of two targeted therapies, the FGFR1–4 inhibitor erdafitinib and the antibody–drug conjugate (ADC) enfortumab vedotin, in this setting.

"While conducting trials of ICIs in patients with metastatic urothelial carcinomas, I was noticing a lack of response in patients with *FGFR3*-altered tumours", explains Arlene Siefker–Radtke, lead investigator on the erdafitinib trial, adding "this might reflect an unmet need in such patients". In order to test this hypothesis, 99 patients with locally advanced and unresectable, or metastatic urothelial carcinomas with at least one *FGFR3* alteration or *FGFR2/3*-containing fusion were assigned (following a protocol amendment) to receive daily erdafitinib (8 mg) with the potential for dose adjustment based on ongoing pharmacokinetic assessments, with a primary end point of objective response rate (ORR).

After a median follow-up duration of 11.2 months, 40% of patients had an objective response to erdafitinib (34% according to independent radiological review, including 3 complete responses). Patients had a median progression-free survival (PFS) duration of 5.5 months and median OS duration of 13.8 months. Notably, a higher ORR (59%) was observed among patients who had previously received ICIs.

Approximately half of all patients receiving erdafitinib (46%) had at least one grade ≥3 treatment-related adverse event (TRAE), including hyponatraemia (11%), stomatitis (10%) and asthenia (7%). A total of 13 patients discontinued treatment owing to adverse events.

In the other phase II study, patients with locally advanced or metastatic urothelial carcinomas with disease progression on anti-PD-1 or anti-PD-L1 antibodies received enfortumab vedotin. "Enfortumab vedotin is an ADC targeting nectin-4, a cell adhesion molecule that is overexpressed in urothelial carcinomas compared with both other cancers and nonmalignant tissues", explains lead author Jonathan Rosenberg. Summarizing previous research, Rosenberg adds "enfortumab vedotin was tested in a phase I study and found to have a tolerable safety profile, and an expansion cohort suggested a high degree of antitumour activity in urothelial carcinoma."

In the phase II study, 125 patients received three 1.25 mg/kg doses of enfortumab vedotin per 28-day cycle until disease progression or withdrawal from treatment. The primary end point was ORR.

After a median follow-up duration of 10.2 months, 44% of patients had an objective response (including 12 complete responses). The estimated median PFS duration at the time of analysis cut-off was 5.8 months, with an estimated median OS duration of 11.7 months. ORRs were generally similar across the various subgroups, including those who had received ≥3 prior lines of therapy. Grade ≥3 TRAEs were observed in 54% of patients, and resulted in treatment discontinuation in 12% (15 patients).

Taken together, these data provide evidence for the efficacy of novel targeted therapies in patients with advanced-stage urothelial carcinoma who have already failed to respond to or who are unlikely to respond to ICIs.

"The patients in this trial had received multiple prior treatment regimens, >70% had visceral metastases and >50% of patients had an estimated glomerular filtration rate <60 ml/min/1.73 m^2", highlights Siefker–Radtke, and emphasizes "these prognostic factors are typically associated with poor clinical outcomes". Rosenberg adds "44% of patients had objective responses to enfortumab vedotin, including 12% of patients with complete responses", clarifying "this is quite a high level of activity for a highly treatment-refractory patient population, especially compared with the historical ORR of 10% to taxane monotherapy".

When asked about further directions, both authors comment that later phase trials involving both agents, as monotherapies and in combinations with ICIs, are underway. Such trials are expected to provide further support for the use of erdafitinib or enfortumab vedotin in patients with advanced-stage urothelial carcinoma.

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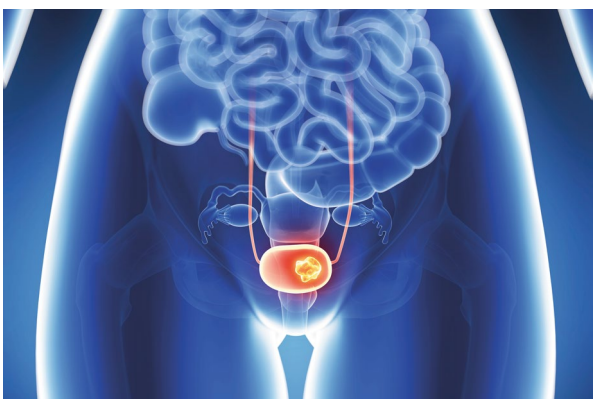

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ORIGINAL ARTICLES Loriot, Y. et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N. Engl. J. Med.* **381**, 338–348 (2019) | Rosenberg, J. E. et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.19.01140 (2019)