

Real-World Effectiveness and Safety of Enfortumab Vedotin Plus Pembrolizumab in Metastatic Urothelial Carcinoma

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Background: Enfortumab vedotin plus pembrolizumab (EV+P) is the current preferred first-line treatment for locally advanced or metastatic urothelial carcinoma following the phase III EV-302/KEYNOTE-A39 trial. This systematic review evaluated real-world evidence to determine whether the effectiveness and safety observed in clinical trials are maintained in routine clinical practice.

Methods: A systematic review was conducted according to PRISMA guidelines. PubMed, Embase, Scopus, and Web of Science were searched through January 2026. Studies reporting real-world outcomes in patients treated with EV+P were included. Primary outcomes were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TRAEs).

Results: Twelve studies involving approximately 2,400 patients met inclusion criteria. In the pivotal EV-302 trial, EV+P achieved an ORR of 67.7%, median PFS of 12.5 months, and median OS of 31.5 months. Across real-world cohorts, treatment effectiveness was consistent with trial findings despite broader patient inclusion and greater clinical heterogeneity. A network meta-analysis demonstrated improved OS (HR 0.47) and PFS (HR 0.45) compared with alternative regimens. Clinical benefit was maintained in patients aged ≥ 75 years (median PFS 12.3 months; median OS 24.4 months). Grade ≥ 3 TRAEs occurred in 55.9% of patients, leading to treatment discontinuation in 35.0%. Real-world discontinuation rates among frail and elderly patients were comparable to trial reports.

Conclusions: Real-world evidence supports the effectiveness and manageable safety profile of EV+P in metastatic urothelial carcinoma. Outcomes in routine practice

closely mirror EV-302 trial results, supporting EV+P as a standard first-line treatment across diverse patient populations.

Keywords: metastatic urothelial carcinoma; enfortumab vedotin; pembrolizumab; real-world evidence; immunotherapy