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Real-World Comparative Effectiveness of First-Line Enfortumab Vedotin Plus Pembrolizumab Versus Gemcitabine Plus Platinum in Metastatic Urothelial Carcinoma: A Propensity-Matched TriNetX Analysis

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Abstract

Background

Enfortumab vedotin plus pembrolizumab (EV + Pem) has become a preferred first-line regimen for locally advanced or metastatic urothelial carcinoma after EV-302/KEYNOTE-A39 demonstrated superior survival versus platinum-based chemotherapy. However, real-world comparative data evaluating survival, treatment durability, health-care utilization, and tolerability remain limited.

Methods

We conducted a retrospective cohort study using the TriNetX Research Network. Adults aged ≥ 18 years with metastatic urothelial carcinoma who initiated first-line EV + Pem or gemcitabine plus platinum (GEM + Plat; cisplatin or carboplatin) between January 1, 2019, and June 30, 2025, were identified. After inclusion/exclusion criteria and laboratory data requirements, 344 EV + Pem and 702 GEM + Plat patients were included. One-to-one propensity-score matching yielded 325 patients per arm. Outcomes included overall survival (OS), emergency department/inpatient utilization, adverse-event proxies, time to next treatment, and laboratory parameters within 0–12 weeks.

Results

After matching, cohorts were well balanced. OS favored EV + Pem at 12 months (72.48% vs 62.82%; HR 0.697, 95% CI 0.517–0.939; p = 0.017) and 24 months (57.13% vs 48.24%; HR 0.701, 95% CI 0.534–0.920; p = 0.010). Median OS was not reached with EV + Pem and was 679 days with GEM + Plat. EV + Pem was associated with lower ED/inpatient utilization at 6 and 12 months, higher neuropathic/dermatologic adverse-event proxies, and fewer hemoglobin values < 10 g/dL.

Conclusions

In this propensity-matched real-world analysis, first-line EV + Pem was associated with improved survival, reduced acute-care utilization, longer treatment durability, and less anemia compared with GEM + Plat.

Introduction

Metastatic urothelial carcinoma remains an aggressive malignancy historically associated with poor long-term outcomes. For decades, first-line systemic therapy was dominated by platinum-based chemotherapy, particularly cisplatin plus gemcitabine among cisplatin-eligible patients and carboplatin plus gemcitabine among patients considered cisplatin-ineligible or less fit for cisplatin-based treatment [1–5]. Although platinum chemotherapy can produce meaningful responses, many patients experience

limited durability, treatment-related cytopenias, renal toxicity, infections, and frequent acute-care utilization [4–7].

The therapeutic landscape has changed substantially with the introduction of immune checkpoint inhibitors, maintenance immunotherapy, antibody-drug conjugates, and targeted therapy for selected molecular subgroups [8–16]. Pembrolizumab improved survival compared with chemotherapy after platinum progression in KEYNOTE-045, and avelumab maintenance improved survival after disease control with first-line platinum chemotherapy in JAVELIN Bladder 100 [8, 12]. Enfortumab vedotin, an antibody-drug conjugate directed against Nectin-4, initially demonstrated activity after platinum and immune checkpoint inhibitor exposure and subsequently improved survival compared with chemotherapy in the post-platinum/post-immunotherapy setting [13–15].

More recently, the combination of enfortumab vedotin plus pembrolizumab transformed first-line therapy for locally advanced or metastatic urothelial carcinoma. In EV-302/KEYNOTE-A39, first-line EV + Pem significantly improved overall survival and progression-free survival compared with platinum-based chemotherapy. The FDA approved enfortumab vedotin with pembrolizumab for locally advanced or metastatic urothelial carcinoma on December 15, 2023, based on EV-302/KN-A39. In that randomized trial of 886 patients, the comparator chemotherapy arm consisted of gemcitabine with cisplatin or carboplatin, and median OS was 31.5 months with EV + Pem versus 16.1 months with chemotherapy; median PFS was 12.5 versus 6.3 months.

Despite these landmark trial data, real-world validation remains important. Patients encountered in routine oncology practice may be older, more comorbid, less trial-eligible, and more heterogeneous with respect to platinum eligibility and metastatic disease burden. Real-world studies are also well positioned to examine outcomes not always emphasized in pivotal trials, including emergency department/inpatient utilization, treatment switching, and laboratory tolerability. Therefore, we conducted a propensity-matched real-world comparative analysis of first-line EV + Pem versus GEM + Plat in metastatic urothelial carcinoma using the TriNetX Research Network.

We hypothesized that EV + Pem would be associated with improved real-world survival and treatment durability compared with GEM + Plat, with lower acute-care utilization and less chemotherapy-associated anemia, but higher neuropathic and dermatologic adverse-event proxies.

Methods

Data Source

This retrospective cohort study used the TriNetX Research Network, a federated electronic health record network containing de-identified patient-level data from participating health care organizations. The study report was generated using the TriNetX Compare Outcomes platform. The uploaded TriNetX report describes the Research Network as including 111 health care organizations and containing electronic

medical record data including diagnoses, procedures, medications, laboratory values, and related clinical information.

Study Population

Adults aged ≥ 18 years with metastatic urothelial carcinoma treated between January 1, 2019, and June 30, 2025, were eligible. Metastatic urothelial carcinoma was identified using diagnosis and oncology staging terms for malignant neoplasm of the bladder or urethra with metastatic disease or stage IV disease. Non-urothelial histologies, including small-cell, neuroendocrine, squamous, and adenocarcinoma variants, were excluded based on the query definitions.

The EV + Pem cohort required evidence of enfortumab vedotin and pembrolizumab within the prespecified regimen window. The GEM + Plat cohort required gemcitabine with either cisplatin or carboplatin. The TriNetX setup file defines the GEM + Plat regimen as gemcitabine plus cisplatin or carboplatin using medication and HCPCS terms.

After applying all inclusion/exclusion criteria and requiring the specified baseline laboratory data, the analytic cohort included 344 patients treated with EV + Pem and 702 treated with GEM + Plat. After 1:1 propensity-score matching, 325 patients remained in each cohort.

Exposure Definition

The primary exposure was first-line systemic regimen that included EV + Pem (enfortumab vedotin plus pembrolizumab) vs GEM + Plat (gemcitabine plus cisplatin or gemcitabine plus carboplatin)

The index date was defined by the first qualifying treatment event within each cohort's regimen definition.

Propensity-Score Matching

One-to-one propensity-score matching was performed to reduce baseline imbalance between treatment groups. Variables used for matching included age at index, sex, race, ethnicity, metastatic sites, selected comorbidities, smoking history, and cancer-history variables. Specifically, the TriNetX report states that matching included male sex, age at index, Not Hispanic or Latino ethnicity, Black or African American race, secondary malignant neoplasm of bone and bone marrow, secondary malignant neoplasm of liver and intrahepatic bile duct, heart failure, atherosclerosis, chronic kidney disease, diseases of liver, nicotine dependence, tobacco use, secondary malignant neoplasm of bladder and other/unspecified urinary organs, malignant neoplasms of respiratory and intrathoracic organs, malignant neoplasms of urinary tract, and malignant neoplasms of ill-defined/other secondary/unspecified sites.

Outcomes

The primary outcome was overall survival at 12 and 24 months after index treatment initiation. Secondary outcomes included ED or inpatient visits at 6 and 12 months, time to next treatment, adverse-event proxies, and laboratory values within 0–12 weeks after treatment initiation

Adverse-event proxies were based on diagnosis codes for drug-induced polyneuropathy, unspecified polyneuropathy, allergic contact dermatitis, irritant contact dermatitis, dermatitis due to substances taken internally, and pruritus.

Laboratory outcomes included eGFR, creatinine, albumin, hemoglobin, AST, ALT, hemoglobin < 10 g/dL, and albumin < 3 g/dL.

Statistical Analysis

TriNetX-generated Kaplan–Meier analyses and risk analyses were used. Time windows were defined from index treatment initiation to the prespecified follow-up period: 180 days for 6-month outcomes, 360 days for 12-month outcomes, and 720 days for 24-month outcomes. Kaplan–Meier estimates were prioritized for time-to-event outcomes because they account for censoring due to incomplete follow-up.

Hazard ratios with 95% confidence intervals were extracted from TriNetX outputs when available. Risk differences, risk ratios, and odds ratios were also available for selected binary risk analyses. Laboratory comparisons used TriNetX-generated group means, standard deviations, and t-tests.

Given the more recent approval and adoption of EV + Pem, follow-up time differed between cohorts and was considered in interpretation. After matching, mean follow-up was 320.97 days in the EV + Pem cohort and 450.44 days in the GEM + Plat cohort.

Results

Cohort Construction and Baseline Characteristics

After eligibility filtering and laboratory restrictions, 344 patients were included in the EV + Pem cohort and 702 in the GEM + Plat cohort. Propensity-score matching yielded 325 patients per arm.

Baseline characteristics were well balanced after matching (Table 1). Mean age was 71.0 ± 9.8 years in the EV + Pem cohort and 70.7 ± 9.1 years in the GEM + Plat cohort. Male sex predominated in both groups. Bone metastases were present in approximately one-third of patients, liver metastases in approximately 15%, and chronic kidney disease in approximately one-quarter of patients.

Table 1
Baseline Characteristics After Propensity-Score Matching

Characteristic	EV + Pem (n = 325)	GEM + Plat (n = 325)
Age at index, mean ± SD, years	71.0 ± 9.8	70.7 ± 9.1
Male sex, n (%)	241 (74.2)	245 (75.4)
Female sex, n (%)	77 (23.7)	74 (22.8)
White race, n (%)	270 (83.1)	266 (81.8)
Black/African American race, n (%)	16 (4.9)	16 (4.9)
Not Hispanic/Latino, n (%)	282 (86.8)	288 (88.6)
Bone metastasis, n (%)	114 (35.1)	112 (34.5)
Liver metastasis, n (%)	46 (14.2)	50 (15.4)
Chronic kidney disease, n (%)	79 (24.3)	81 (24.9)
Diseases of liver, n (%)	49 (15.1)	47 (14.5)
Heart failure, n (%)	22 (6.8)	20 (6.2)
Atherosclerosis, n (%)	13 (4.0)	10 (3.1)
Nicotine dependence, n (%)	46 (14.2)	46 (14.2)
Personal history of nicotine dependence, n (%)	106 (32.6)	111 (34.2)
Secondary malignant neoplasm of bladder/other urinary organs, n (%)	105 (32.3)	98 (30.2)
Malignant neoplasms of respiratory/intrathoracic organs, n (%)	19 (5.8)	22 (6.8)
Malignant neoplasms of urinary tract, n (%)	321 (98.8)	321 (98.8)
Malignant neoplasms of ill-defined/other secondary/unspecified sites, n (%)	288 (88.6)	288 (88.6)

Overall Survival

Overall survival favored EV + Pem at both 12 and 24 months (Table 2). At 12 months, Kaplan–Meier survival probability was 72.48% with EV + Pem versus 62.82% with GEM + Plat (HR 0.697, 95% CI 0.517–0.939; log-rank p = 0.017).

Table 2
Key Clinical Outcomes After Propensity-Score Matching

Outcome	EV + Pem	GEM + Plat	Effect Estimate
12-month OS	72.48%	62.82%	HR 0.697 (95% CI 0.517–0.939), p = 0.017
24-month OS	57.13%	48.24%	HR 0.701 (95% CI 0.534–0.920), p = 0.010
Median OS	Not reached	679 days	—
ED/inpatient visits by 6 months	58.20%	71.10%	HR 0.757 (95% CI 0.625–0.918), p = 0.004
ED/inpatient visits by 12 months	65.80%	78.20%	HR 0.781 (95% CI 0.651–0.937), p = 0.008
AE proxies	45.10%	27.80%	HR 2.707 (95% CI 2.012–3.643), p < 0.001
Hemoglobin < 10 g/dL	46.50%	80.00%	HR 0.468 (95% CI 0.382–0.573), p < 0.001
Albumin < 3 g/dL	19.20%	24.50%	HR 0.752 (95% CI 0.505–1.120), p = 0.159
Mean eGFR, 0–12 weeks	63.85	65.06	p = 0.591
Mean hemoglobin, 0–12 weeks	11.35	9.49	p < 0.001
Mean AST, 0–12 weeks	31.21	26.08	p = 0.002
Mean ALT, 0–12 weeks	27.38	22.69	p = 0.030

At 24 months, survival probability was 57.13% with EV + Pem versus 48.24% with GEM + Plat (HR 0.701, 95% CI 0.534–0.920; log-rank p = 0.010). Median OS was not reached in the EV + Pem cohort and was 679 days in the GEM + Plat cohort.

ED or Inpatient Utilization

EV + Pem was associated with lower acute-care utilization. At 6 months, ED or inpatient visits occurred in 58.2% of EV + Pem patients versus 71.1% of GEM + Plat patients. Kaplan–Meier analysis showed a lower hazard of ED/inpatient utilization with EV + Pem (HR 0.757, 95% CI 0.625–0.918; p = 0.004).

At 12 months, ED or inpatient visits occurred in 65.8% of EV + Pem patients versus 78.2% of GEM + Plat patients, again favoring EV + Pem (HR 0.781, 95% CI 0.651–0.937; p = 0.008).

Treatment Durability / Time to Next Treatment

In exploratory treatment-switching analyses, treatment durability favored EV + Pem. In the EV + Pem time-to-next-treatment analysis, 64 of 325 EV + Pem patients initiated subsequent treatment within the 720-day window, and median time to next treatment was not reached. In comparison, 278 of 325 GEM + Plat patients met the outcome in that analysis, with a median time of 25 days.

A separate GEM + Plat switching analysis showed median time to new treatment of 186 days in the GEM + Plat group. Because the exported TriNetX output contains treatment-specific switching definitions, the manuscript should present this endpoint as exploratory unless a single unified “any next systemic therapy” analysis is confirmed.

Adverse-Event Proxies

Adverse-event proxies were more frequent with EV + Pem. In the risk analysis excluding patients with prior events, adverse-event proxies occurred in 45.1% of EV + Pem patients versus 27.8% of GEM + Plat patients. Kaplan–Meier analysis showed higher risk with EV + Pem (HR 2.707, 95% CI 2.012–3.643; $p < 0.001$). These proxies primarily represented neuropathy and dermatologic/pruritic events.

Laboratory Outcomes

No significant differences were observed in mean eGFR, creatinine, or albumin within 0–12 weeks. Mean eGFR was 63.85 versus 65.06, mean creatinine was 86.79 versus 66.80, and mean albumin was 3.57 versus 3.53 in the EV + Pem and GEM + Plat cohorts, respectively.

Hemoglobin outcomes favored EV + Pem. Mean hemoglobin was 11.35 g/dL in the EV + Pem cohort versus 9.49 g/dL in the GEM + Plat cohort. Hemoglobin < 10 g/dL occurred in 46.5% of EV + Pem patients versus 80.0% of GEM + Plat patients, with a lower hazard in the EV + Pem cohort (HR 0.468, 95% CI 0.382–0.573; $p < 0.001$).

AST and ALT were statistically higher in the EV + Pem cohort, although mean values remained modest: AST 31.21 versus 26.08 U/L and ALT 27.38 versus 22.69 U/L.

Discussion

In this propensity-matched real-world TriNetX analysis of patients with metastatic urothelial carcinoma, first-line EV + Pem was associated with improved overall survival compared with GEM + Plat. The survival advantage was observed at both 12 and 24 months, with median OS not reached in the EV + Pem group and 679 days in the GEM + Plat group. These findings are directionally consistent with EV-302/KEYNOTE-A39, which established EV + Pem as a superior first-line regimen compared with platinum-based chemotherapy [17]. The FDA approval summary similarly reported major improvements in OS and PFS for EV + Pem compared with gemcitabine plus cisplatin or carboplatin in EV-302/KN-A39.

The novelty of this analysis is not simply that EV + Pem was associated with improved survival. Rather, the study provides a broader real-world effectiveness profile, showing concordant benefits across survival, acute-care utilization, treatment durability, and anemia. This broader framing is clinically

important because treatment selection in metastatic urothelial carcinoma is influenced not only by efficacy but also by frailty, comorbidities, renal function, cytopenias, and the likelihood of treatment-related hospital encounters.

EV + Pem was associated with lower ED/inpatient utilization at both 6 and 12 months. This finding may reflect improved disease control, less chemotherapy-associated toxicity, or both. Although this observational analysis cannot determine the cause of reduced acute-care utilization, the direction of effect is clinically meaningful. Patients receiving GEM + Plat often require supportive care for cytopenias, renal function concerns, hydration, infection, nausea, and treatment-related complications. In contrast, EV + Pem toxicities may often be managed in the outpatient setting when recognized early.

Adverse-event proxies were more frequent with EV + Pem, consistent with the known toxicity profile of enfortumab vedotin and pembrolizumab. The FDA approval summary lists common adverse reactions and laboratory abnormalities with EV + Pem, including rash, peripheral neuropathy, pruritus, increased AST and ALT, fatigue, diarrhea, decreased hemoglobin, and other laboratory abnormalities. In our study, adverse-event proxies were primarily neuropathic and dermatologic/pruritic diagnoses, which aligns with biologic expectations for enfortumab vedotin and immune checkpoint inhibition.

A key finding was the lower frequency of anemia with EV + Pem. Mean hemoglobin was higher with EV + Pem, and hemoglobin < 10 g/dL was substantially less frequent than with GEM + Plat. This finding likely reflects avoidance of gemcitabine/platinum-associated myelosuppression and may partially explain reduced acute-care utilization. Importantly, eGFR, creatinine, and albumin did not significantly differ between groups in the early post-index laboratory window, suggesting no major early renal or nutritional laboratory disadvantage with EV + Pem in this matched cohort.

Treatment durability also favored EV + Pem, although this endpoint should be interpreted cautiously until a unified TTNT definition is confirmed. In the EV + Pem switching analysis, median time to next treatment was not reached, and only 64 of 325 patients switched treatment. In contrast, the GEM + Plat group demonstrated substantially earlier switching in the available outputs. This likely reflects both improved disease control with EV + Pem and inherent differences in treatment strategy: platinum chemotherapy is often given for a finite number of cycles, whereas EV + Pem may be continued until progression, unacceptable toxicity, or completion of pembrolizumab duration. Therefore, TTNT should be interpreted as a pragmatic durability endpoint rather than a direct surrogate for progression-free survival.

This study has several limitations. First, it is retrospective and observational; residual confounding remains possible despite propensity-score matching. Important variables such as ECOG performance status, cisplatin eligibility, tumor burden, visceral disease details, PD-L1 expression, dose reductions, and treatment discontinuation reasons were not fully available. Second, the comparator arm included both cisplatin and carboplatin. This improves generalizability because it reflects real-world platinum practice, but it also introduces heterogeneity because cisplatin-eligible and carboplatin-treated patients differ clinically. Third, follow-up was shorter in the EV + Pem cohort, reflecting recent approval and adoption of this regimen. Fourth, adverse events were captured using diagnosis-code proxies rather than CTCAE-

graded toxicity, which may underestimate or misclassify events. Fifth, the study required specified laboratory data, which may select for patients with more complete monitoring. Finally, the TTNT endpoint requires final confirmation using a single, prespecified “any next systemic therapy” definition.

Despite these limitations, this study provides early real-world evidence that first-line EV + Pem is performing favorably in routine clinical practice. The combined pattern of improved survival, reduced acute-care utilization, less anemia, and higher but expected neuropathic/dermatologic adverse-event proxies provides a clinically balanced view of the regimen’s real-world impact.

Conclusion

In a propensity-matched real-world cohort of patients with metastatic urothelial carcinoma, first-line enfortumab vedotin plus pembrolizumab was associated with improved 12- and 24-month overall survival, lower ED/inpatient utilization, longer treatment durability, and less anemia compared with gemcitabine plus platinum. These benefits occurred alongside higher neuropathic and dermatologic adverse-event proxies. These findings support the real-world effectiveness of EV + Pem and provide a pragmatic complement to EV-302/KEYNOTE-A39.

Declarations

Competing interests

The authors declare no competing interests.—or customize if anyone has disclosures.

Ethics approval

This study used de-identified aggregate data from the TriNetX Research Network. Institutional determination/IRB exemption should be stated here once confirmed.

Consent to participate

Not applicable due to use of de-identified data.

Consent for publication

Not applicable.

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Author Contribution

B.J. contributed to study concept, data interpretation, manuscript drafting, and revision. J.C. contributed to data extraction and statistical analysis. A.K. supervised the project. All authors reviewed and approved the final manuscript.

Data availability

The data supporting this study are available through the TriNetX Research Network but are not publicly available due to data-use restrictions.

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