Original Article

Efficacy of enfortumab vedotin in advanced urothelial cancer: Analysis from the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study

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BACKGROUND: Enfortumab vedotin (EV) is a novel antibody-drug conjugate approved for advanced urothelial cancer (aUC) refractory to prior therapy. In the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study, the authors looked at the experience with EV in patient subsets of interest for which activity had not been well defined in clinical trials. **METHODS:** UNITE was a retrospective study of patients with aUC treated with recently approved agents. This initial analysis focused on patients treated with EV. Patient data were abstracted from chart reviews by investigators at each site. The observed response rate (ORR) was investigator-assessed for patients with at least 1 post-baseline scan or clear evidence of clinical progression. ORRs were compared across subsets of interest for patients treated with EV monotherapy. **RESULTS:** The initial UNITE analysis included 304 patients from 16 institutions; 260 of these patients were treated with EV monotherapy and included in the analyses. In the monotherapy cohort, the ORR was 52%, and it was >40% in all reported subsets of interest, including patients with comorbidities previously excluded from clinical trials (baseline renal impairment, diabetes, and neuropathy) and patients with fibroblast growth factor receptor 3 (*FGFR3*) alterations. Progression-free survival and overall survival were 6.8 and 14.4 months, respectively. Patients with a pure urothelial histology had a higher ORR than patients with a variant histology component (58% vs 42%; $P = .06$). **CONCLUSIONS:** In a large retrospective cohort, responses to EV monotherapy were consistent with data previously reported in clinical trials and were also observed in various patient subsets, including patients with variant histology, patients with *FGFR3* alterations, and patients previously excluded from clinical trials with an estimated glomerular filtration rate < 30 mL/min and significant comorbidities. ***Cancer* 2022;128:1194-1205**. © *2021 American Cancer Society*.

LAY SUMMARY:

- Enfortumab vedotin, approved by the Food and Drug Administration in 2019, is an important new drug for the treatment of patients with advanced bladder cancer.
- This study looks at the effectiveness of enfortumab vedotin as it has been used at multiple centers since approval, and focuses on important patient populations previously excluded from clinical trials. These populations include patients with decreased kidney function, diabetes, and important mutations.
- Enfortumab vedotin is effective for treating these patients. Previously reported clinical trial data have been replicated in this real-world setting, and support the use of this drug in broader patient populations.

KEYWORDS: antibody-drug conjugate, bladder cancer, enfortumab vedotin, nectin-4, urinary bladder, urothelial cancer.

INTRODUCTION

Advanced urothelial cancer (aUC) is an aggressive and usually incurable disease. Despite the efficacy of platinum-based chemotherapy and immune checkpoint inhibitors (ICIs), most patients with aUC invariably progress and require other

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systemic therapies for disease control.[1-8] Enfortumab vedotin (EV) received accelerated Food and Drug Administration approval in December 2019 for patients with aUC progressing on platinum-based chemotherapy and ICIs. EV is an antibody-drug conjugate consisting of a monoclonal antibody targeting nectin-4, which is conjugated to the microtubule-disrupting agent monomethyl auristatin E.[9-11] Initial Food and Drug Administration approval of EV was based on the results of the EV-201 trial, and the benefit of EV for treatment-refractory aUC was subsequently confirmed in the randomized phase 3 EV-301 trial, which led to full approval in July 2021.[12,13] EV is also being investigated in earlier treatment settings as a frontline regimen for cisplatin-ineligible aUC.[14]

Recent preclinical data have suggested that nectin-4 expression is both necessary and sufficient for the killing of urothelial cells by EV and that certain molecular subsets of urothelial cancer (UC) may be more likely to respond to EV.[15] Additionally, patient populations with certain comorbidities common among patients with aUC were excluded from EV clinical trials. These populations included patients with significant neuropathy (grade 2 or higher), uncontrolled preexisting diabetes, and renal insufficiency (estimated glomerular filtration rate [eGFR] < 30 mL/min). Consequently, certain patient populations with aUC may be more or less likely to benefit from EV treatment according to their specific pathologic or clinical characteristics, and EV efficacy in specific patient populations of interest (eg, patients with nonurothelial histology variants, patients with certain comorbidities, and fibroblast growth factor receptor 3 [*FGFR3*]–altered patients) remains to be further defined.

As clinical experience with EV grows, multi-institutional, retrospective analyses can help to shed further light on these important questions and complement important information derived from clinical trials. Here we present the initial results from the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study, a large, multi-institutional, retrospective cohort of patients with aUC treated with novel agents recently approved in this disease space. This initial analysis focuses on the efficacy of EV monotherapy, particularly in specific aUC patient subsets of interest. We hypothesized that EV would have robust efficacy across the different subsets of patients with aUC, including those previously excluded from clinical trials. Furthermore, we hypothesized that the efficacy of EV would be consistent in this broader population of aUC patients with what was previously reported for the more narrowly selected patients in clinical trials.

MATERIALS AND METHODS

The UNITE study is a retrospective cohort study with the goal of assessing outcomes in patients with aUC treated with novel agents recently approved for this malignancy. This initial analysis focused on the outcomes of patients with aUC treated with EV. The study met the principles set forth by the Declaration of Helsinki and was approved by the institutional review board at each participating institution. Patient eligibility criteria included the following: histologically confirmed carcinoma of urothelial origin (variant histologic component of any percentage allowed), presence of locally advanced/unresectable or metastatic disease, at least 1 dose of EV administered, and available clinicopathologic and imaging data in the electronic medical record (EMR). To be considered eligible for a response assessment, a patient needed to have at least 1 scan after the initiation of EV treatment or clear evidence of clinical progression as assessed by the treating physician. Both patients treated in a clinical trial (as long as trial results were previously reported) and patients treated according to the standard of care were included, and combination regimens that included EV treatment were also allowed. All patient data were reported in a de-identified manner, with all protected health information specifically excluded. Data were collected and managed with secure REDCap electronic data capture tools hosted at the University of Michigan.[16]

The assessment of the observed response rate (ORR), defined as a complete response or partial response, or, alternatively, of stable disease or progressive disease was determined according to the judgment of the investigator assessing the EMR with the available information from imaging reports or clinical notes. In making these assessments, investigators were encouraged to adhere to the Response Evaluation Criteria in Solid Tumors[17]; however, specific tumor measurements were not collected, and a central assessment of imaging responses was not performed. Progression-free survival (PFS) was defined as the time from EV start to progression or death, and patients alive without disease progression at the time of their last follow-up were censored at the date of last follow-up. Overall survival (OS) was defined as the time from EV start until death of any cause, and patients alive at last follow-up were similarly censored.

Summary statistics were used to describe baseline patient and treatment characteristics as well as ORRs. OS and PFS curves were constructed with the Kaplan-Meier method. The primary analysis was an assessment of ORR, PFS, and OS in patients treated with EV monotherapy and a comparison of these outcomes with

data previously reported in clinical trials of EV. The secondary analysis focused on comparisons of ORR and OS among specific subsets of interest (specifically patients with pure urothelial histology vs mixed/variant histology, patients whose primary tumor origin was in the bladder vs the upper tract, and patients with liver metastases vs no liver metastases) and also on the basis of the number of prior treatment lines, the tumor mutational burden (TMB) status, the programmed death ligand 1 (PD-L1) status, and other characteristics. For patients with an evaluable response, ORR comparisons were performed with χ^2 tests for equality of proportions, and confidence intervals were constructed by the Wilson method.

RESULTS

The overall cohort included 304 patients from 16 academic institutions in the United States (Supporting Table 1). In this cohort, 260 patients were treated with EV monotherapy, and were included in the primary and secondary analyses. Table 1 shows the characteristics of the overall cohort and the EV monotherapy cohort, and it includes the tumor molecular characteristics. Notably, FoundationOne CDx was the most common next-generation sequencing (NGS) panel used (44% of patients with NGS), and approximately 20% of patients had *FGFR3* alterations.

Among the 260 patients treated with EV monotherapy, the median follow-up from the initial UC diagnosis to the time of last follow-up was 35.9 months, whereas the median time from the initial diagnosis to the date of advanced disease was 10.9 months. The median time from the diagnosis of advanced disease to the EV treatment start was 12.0 months. Most patients were treated with EV after 2 or more prior lines of therapy for aUC (67%), and most received EV outside a clinical trial (78%). At the time of EV treatment initiation, 32% had liver metastases, and 80% had visceral metastasis (metastatic disease other than lymph node involvement and/or locoregional or soft tissue recurrence). At the time of analysis, the median follow-up from the start of EV was 7.2 months (interquartile range, 3.7-11.6 months), and the median treatment duration was 4.1 months (interquartile range, 1.6-6.9 months). Most patients (82%; n = 212) were evaluable for a response, and among these patients, 24% (50 of 212) were still on EV treatment at the time of analysis (71 of 260 [27%] in the overall monotherapy group). Among the 162 evaluable patients who discontinued EV treatment, the most common reasons were disease progression (64%), treatment intolerance (24%), and other (12%).

The ORR for the primary analysis among evaluable patients is shown in Table 2. The investigator-assessed ORR was 52%, which was similar to the ORR observed for the overall cohort of 304 patients (54%). Notably, only 22% of the patients had progressive disease as their best response to EV monotherapy. Among responders, the median time to a response was 1.9 months. Among the 260 patients included in the primary analysis, 135 were alive at the time of analysis, and 110 had died (15 had an unknown status). The median PFS and OS were 6.8 and 14.4 months, respectively, from the start of EV treatment (Fig. 1).

For the secondary analysis comparing patient subsets of interest, the ORRs for evaluable patients are shown in Table 3; they were robust in most patient categories (>40%). The ORR was lower for patients whose tumors had a component of variant histology (42%; n = 66) versus pure urothelial histology (58%; n = 142; $P = .056$). For 77 patients treated with EV monotherapy whose tumors had a variant histology component, the histology breakdown and responses among 66 evaluable patients are shown in Table 4. Responses were seen across all variant histologies. Important subsets of patients, including those with upper tract primary tumors, those with liver metastases, heavily pretreated patients (>2 lines of therapy), and patients with comorbidities (including diminished renal function [eGFR < 30 mL/min], peripheral neuropathy, and diabetes mellitus), showed high rates of response to EV treatment. Among 28 patients whose tumors harbored *FGFR3* alterations, the ORR was 57%. Responses to EV were also seen independently of the TMB and PD-L1 status or prior treatment regimens (Supporting Table 2). For the most part, no OS differences were observed in comparisons of relevant subsets of patients (Fig. 2). However, patients with liver metastases had a higher ORR (64% vs 47%; $P = .04$) but shorter OS (8.3 vs 15.7 months; $P = .005$) in comparison with patients without liver metastases.

DISCUSSION

The UNITE study is a multi-institutional, retrospective analysis of patients with aUC receiving novel treatment modalities, including EV. This initial report of EV efficacy in non–clinical trial patients demonstrates notable activity of EV in patients with aUC, which is consistent with data previously reported from prospective clinical trials. Moreover, EV has robust activity in clinically relevant subsets of patients with aUC previously excluded

TABLE 1. Patient Characteristics in the UNITE Study

Characteristic	All Patients Receiving EV (n = 304)	Patients Receiving EV Monotherapy (n = 260)
Median age at enrollment, y	70	71
Gender	Men: 239 (79%) Women: 65 (21%)	Men: 205 (79%) Women: 55 (21%)
Race/ethnicity	White: 262 (86%) Black: 12 (4%) Asian: 9 (3%) Hispanic: 12 (4%) Other: 9 (3%)	White: 224 (86%) Black: 11 (4%) Asian: 8 (3%) Hispanic: 9 (4%) Other: 8 (3%)
Smoking history	Current/former smoker: 198 (65%) Never smoker: 102 (34%) Unknown: 4 (1%)	Current/former smoker: 169 (65%) Never smoker: 87 (34%) Unknown: 4 (2%)
ECOG PS	0: 88 (30%) 1: 148 (50%) 2: 45 (15%) 3: 13 (4%) 4: 1 (0.3%)	0: 74 (29%) 1: 127 (50%) 2: 39 (15%) 3: 13 (5%) 4: 1 (0.4%)
BMI	<18 kg/m^2: 8 (3%) 18-25 kg/m^2: 119 (39%) 25-30 kg/m^2: 97 (32%) >30 kg/m^2: 71 (23%) Unknown: 9 (3%)	<18 kg/m^2: 8 (3%) 18-25 kg/m^2: 102 (39%) 25-30 kg/m^2: 87 (34%) >30 kg/m^2: 57 (22%) Unknown: 6 (2%)
Location of primary tumor	Bladder: 215 (71%) Upper tract: 81 (27%) Urethra: 1 (0.3%) Unknown: 7 (2%)	Bladder: 189 (73%) Upper tract: 65 (25%) Urethra: 1 (0.4%) Unknown: 5 (2%)
Histology	Pure urothelial: 211 (69%) Mixed urothelial predominant: 77 (25%) Mixed variant predominant: 7 (2%) Pure variant: 2 (1%) Unknown: 7 (2%)	Pure urothelial: 177 (68%) Mixed urothelial predominant: 69 (27%) Mixed variant predominant: 6 (2%) Pure variant: 2 (1%) Unknown: 6 (2%)
Prior definitive surgery	174 (57%)	144 (55%)
Pathologic T stage (only for patients who had definitive surgery)	pT0: 5 (3%) pTa/CIS: 10 (6%) pT1: 16 (9%) pT2: 38 (22%) pT3: 79 (45%) pT4: 19 (11%) pTx: 7 (4%)	pT0: 5 (4%) pTa/CIS: 5 (4%) pT1: 15 (10%) pT2: 31 (22%) pT3: 65 (45%) pT4: 17 (12%) pTx: 6 (4%)
Pathologic N stage (only for patients who had definitive surgery)	pN0: 89 (51%) pN1: 24 (14%) pN2-3: 39 (22%) pNx: 22 (13%)	pN0: 71 (49%) pN1: 21 (15%) pN2-3: 35 (24%) pNx: 17 (12%)
Neoadjuvant chemotherapy (for patients who had definitive surgery)	Yes: 81 (47%) No: 93 (53%)	Yes: 69 (48%) No: 75 (52%)
Adjuvant therapy (for patients who had definitive surgery)	Chemotherapy only: 32 (18%) Radiation only: 3 (2%) Chemotherapy/RT: 3 (2%) No treatment: 136 (78%)	Chemotherapy only: 31 (22%) Radiation only: 2 (1%) Chemotherapy/RT: 2 (1%) No treatment: 109 (76%)
No. of therapy lines for metastatic disease before EV	None: 44 (15%) 1 line: 79 (26%) 2 lines: 113 (37%) 3 lines: 47 (16%) >3 lines: 18 (6%) Unknown: 3 (1%)	None: 13 (5%) 1 line: 73 (28%) 2 lines: 110 (42%) 3 lines: 47 (18%) > 3 lines: 17 (7%)
EV treatment as SOC vs clinical trial	SOC: 209 (69%) Trial: 91 (30%) Unknown: 4 (1%)	SOC: 202 (78%) Trial: 57 (22%) Unknown: 1 (0.4%)
Metastatic disease sites		
LN and/or locoregional recurrence only	61 (20%)	52 (20%)
Liver metastases	95 (31%)	84 (32%)
Nonliver visceral metastases	148 (49%)	124 (48%)
Patient molecular characteristics		
Available NGS results	184 (61%)	160 (62%)
PD-L1 status available	119 (39%)	101 (39%)
MSI status available	157 (52%)	139 (53%)
TMB available	127 (42%)	113 (43%)
PD-L1 status (CPS ≥ 10 considered positive)	Positive: 59 (50%) Negative: 60 (50%)	Positive: 54 (53%) Negative: 47 (47%)
MSI-high status	3/157 (2%)	3/139 (2%)
FGFR3 alterations present[a]	36/184 (20%)	33/160 (21%)
TMB	Median = 6.19 Mut/mb Range = 0-48 Mut/mb ≥10 Mut/mb: 32/127 (25%)	Median = 6.08 Mut/mb Range = 0-48 Mut/mb ≥10 Mut/mb: 24/113 (21%)

Abbreviations: BMI, body mass index; CIS, carcinoma in situ; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; *FGFR3*, fibroblast growth factor receptor 3; LN, lymph node; MSI, microsatellite instability; NGS, next-generation sequencing; PD-L1, programmed death ligand 1; PS, performance status; SOC, standard of care; TMB, tumor mutational burden; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

Percentages in some categories add up to more than 100% because of rounding.

[a]*FGFR3* alterations included all mutations or fusions considered pathogenic.

TABLE 2. Best Responses to EV Monotherapy Among Evaluable Patients

Best Response to EV Monotherapy (n = 212)	ORR, % (95% CI)
CR (n = 15)	7 (0-20)
PR (n = 96)	45 (35-55)
SD (n = 54)	26 (14-37)
PD (n = 47)	22 (10-34)
ORR (n = 111)	52 (43-62)

Abbreviations: CI, confidence interval; CR, complete response; EV, enfortumab vedotin; ORR, observed response rate (composite of complete response and partial response); PD, progressive disease; PR, partial response; SD, stable disease.

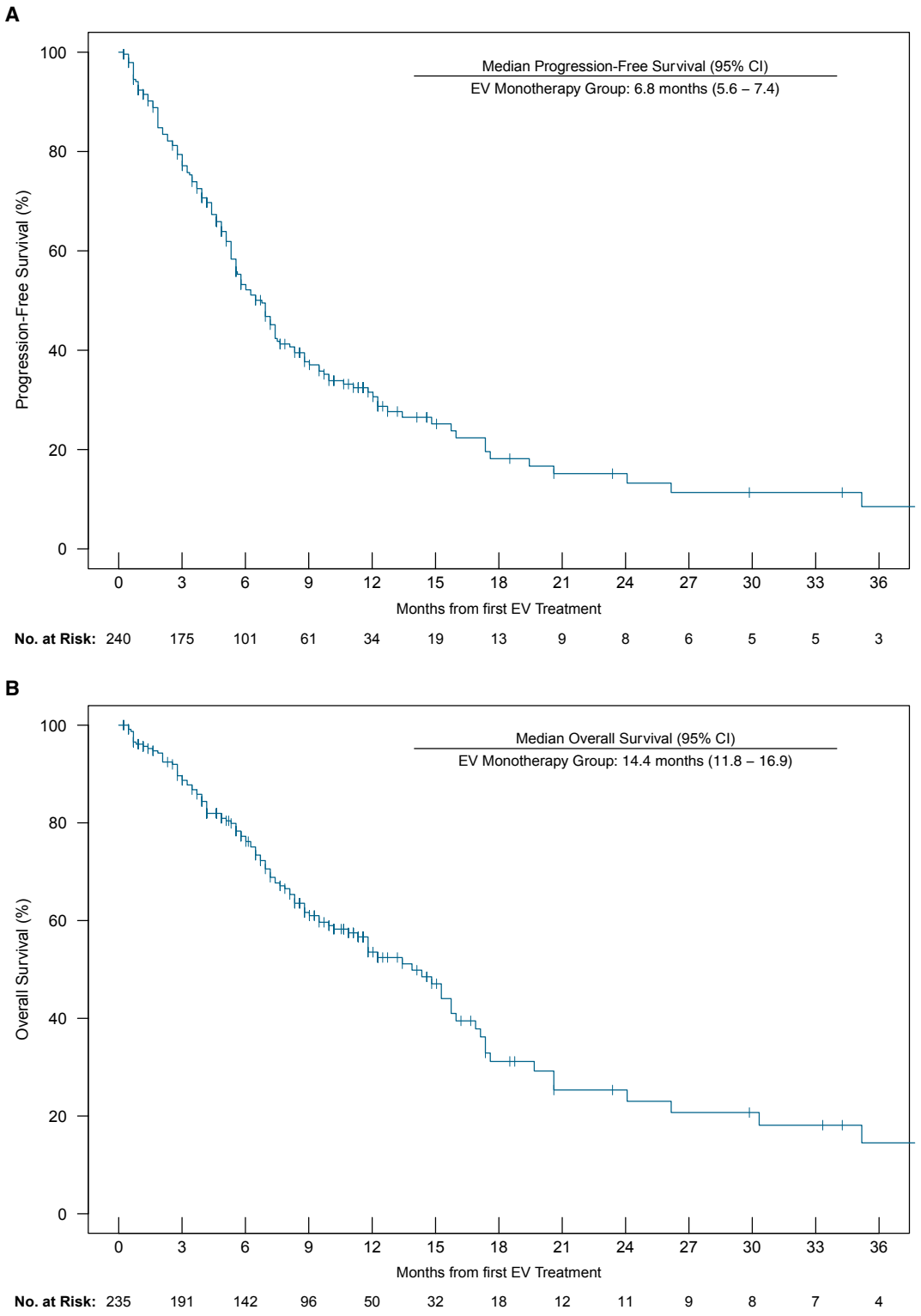


Figure 1. (A) Progression-free survival and (B) overall survival in patients treated with EV monotherapy. Progression-free survival and overall survival were measured from EV treatment initiation and are illustrated with Kaplan-Meier curves. CI indicates confidence interval; EV, enfortumab vedotin.

TABLE 3. Comparison of ORRs Among Relevant Subgroups of Patients Treated With EV Monotherapy and Evaluable for a Response

Subgroup	Patients, No.	ORR, % (95% CI)	*P*
Pure urothelial histology	142	58 (49-66)	.06
Variant histology (any component)	66	42 (31-55)	
Bladder primary tumor	151	50 (42-58)	.21
Upper tract primary tumor	56	61 (47-73)	
Age ≥ 75 y	69	51 (39-63)	.85
Age < 75 y	139	53 (45-62)	
BMI ≥ 30 kg/m^2	48	56 (41-70)	.63
BMI < 30 kg/m^2	161	51 (43-59)	
Prior definitive surgery or chemotherapy/RT[a]	126	53 (44-62)	.93
No prior definitive treatment	70	51 (39-63)	
Treatment lines before EV[b]			.18
0-2 lines of prior treatment	158	49 (41-57)	
>2 lines of prior treatment	54	61 (47-74)	
Liver metastases	66	64 (51-75)	.04
No liver metastases	146	47 (39-56)	
Bone metastases	75	51 (39-62)	.83
No bone metastases	137	53 (45-62)	
ECOG PS of 0/1	173	56 (48-63)	.18
ECOG PS of 2/3	34	41 (25-59)	
Baseline neuropathy	71	62 (50-73)	.08
No neuropathy	139	48 (40-57)	
Baseline diabetes mellitus	29	59 (39-76)	.60
No diabetes mellitus	183	51 (44-59)	
eGFR < 30 mL/min	25	40 (22-61)	.27
eGFR ≥ 30 mL/min	187	54 (47-61)	
FGFR3 altered	28	57 (37-75)	.93
FGFR3 wild type	102	54 (44-64)	
PD-L1 positive[c]	42	50 (36-65)	.23
PD-L1 negative	38	66 (49-80)	
TMB ≥ 10 Mut/mb	21	62 (39-81)	.51
TMB < 10 Mut/mb	75	51 (39-62)	
Neutrophil/lymphocyte ratio < median	101	51 (40-61)	1.0
Neutrophil/lymphocyte ratio ≥ median	101	52 (41-62)	
Prior platinum-based therapy[d]	115	55 (45-64)	.53
No prior platinum-based therapy	97	50 (39-60)	

Abbreviations: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology; eGFR, estimated glomerular filtration rate; EV, enfortumab vedotin; *FGFR3*, fibroblast growth factor receptor 3; ORR, observed response rate; PD-L1, programmed death ligand 1; PS, group performance status; RT, radiation therapy; TMB, tumor mutational burden.

[a]Prior definitive surgery or chemotherapy/RT included prior treatment with a curative intent.

[b]Treatment lines before EV included treatment in the advanced or metastatic setting.

[c]For the PD-L1 status, a combined positive score (CPS) ≥ 10 was considered positive.

[d]Platinum-based therapy included at least 1 prior cisplatin or carboplatin-based regimen.

TABLE 4. Variant Histology Subtypes and ORRs Based on Histology

Variant Histology	Total, No.	Evaluable, No.	CR, No.	PR, No.	ORR, %
Squamous	34	28	1	13	50
Micropapillary	19	17	0	5	29
Sarcomatoid	4	4	0	2	50
Plasmacytoid	4	3	1	0	33
Adenocarcinoma	3	3	1	0	33
Mixed[a]	4	3	0	1	33
Other/unknown	9	8	0	4	50
Total	77	66	3	25	42

Abbreviations: CR, complete response; ORR, observed response rate (composite of complete response and partial response); PR, partial response.

Among evaluable patients, 8 had majority nonurothelial histology with either variant predominant histology (n = 6) or pure variant histology (n = 2). Among these patients, 1 PR and no CRs were observed.

[a]Among 4 patients with mixed histology, the histology breakdown and responses were as follows: patient 1, micropapillary and squamous–partial response; patient 2, sarcomatoid, glandular, and neuroendocrine–stable disease; patient 3, plasmacytoid and squamous–progressive disease; and patient 4, plasmacytoid, glandular, and micropapillary–not evaluable.

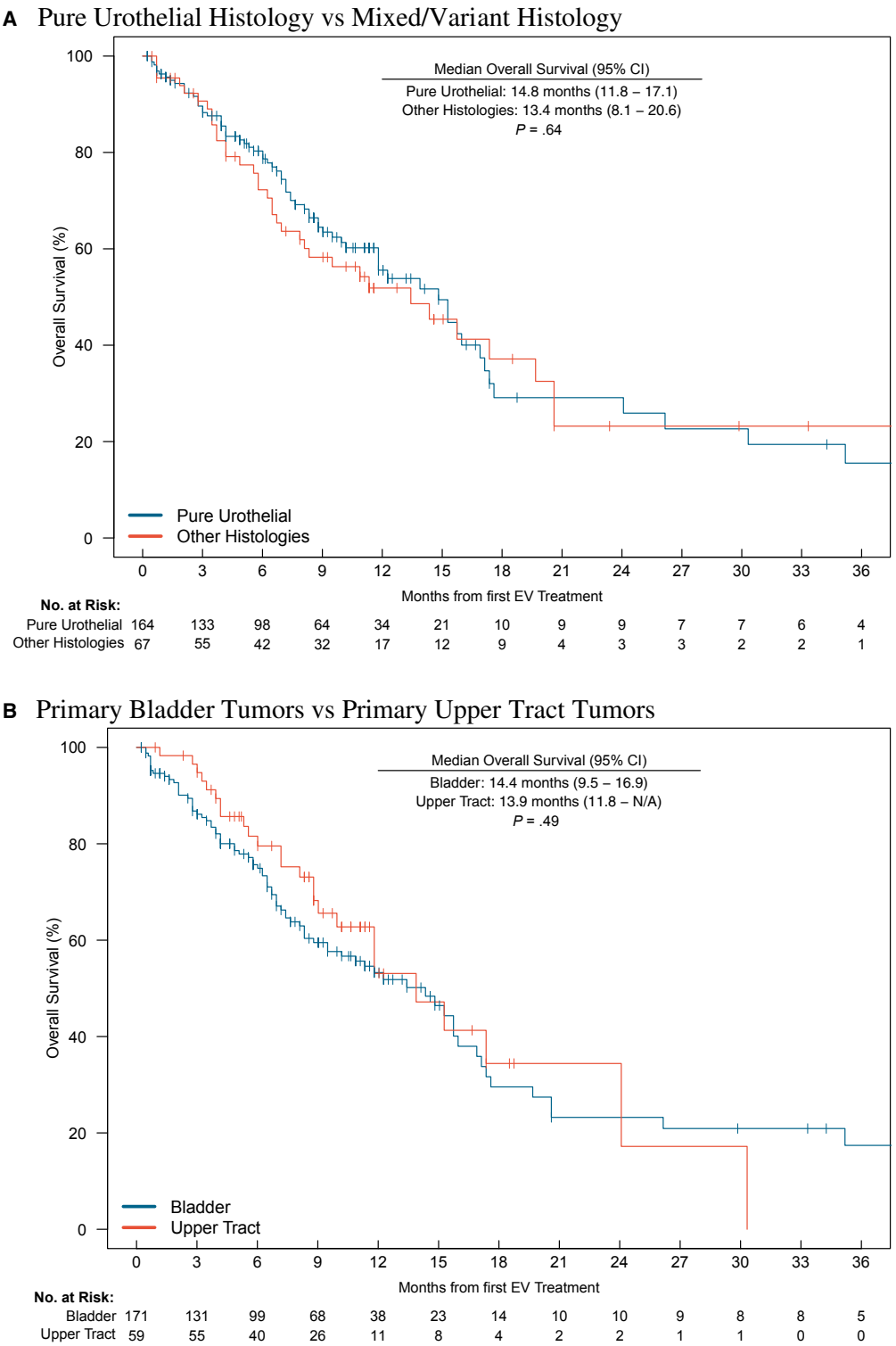
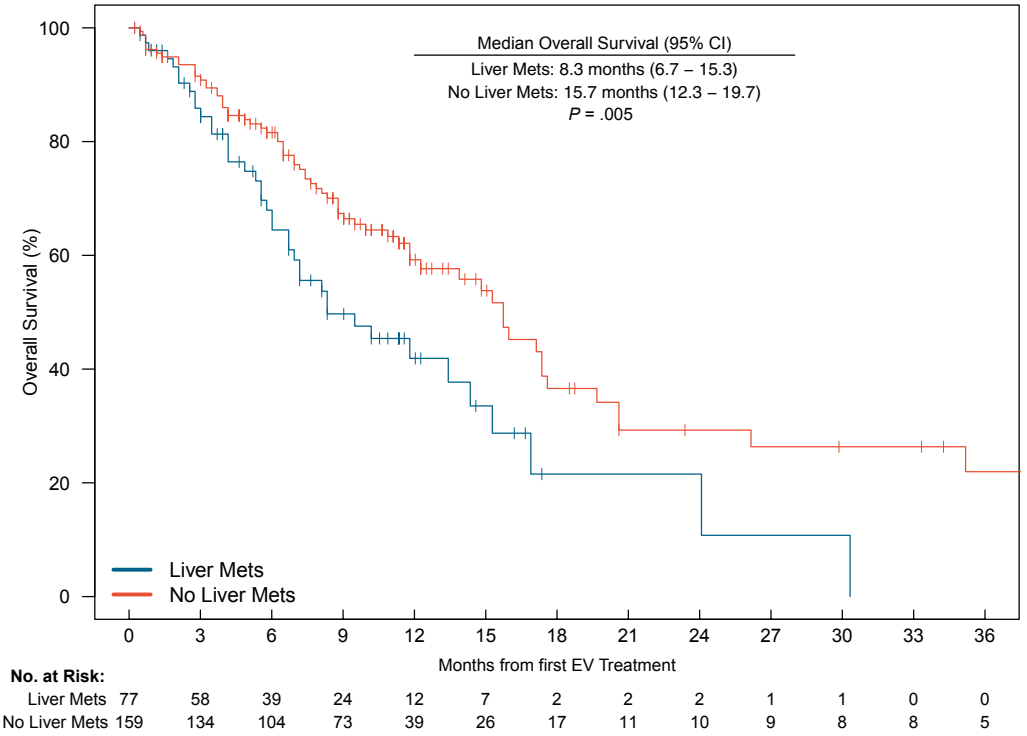


Figure 2. Comparison of overall survival in subsets of patients treated with EV monotherapy. An evaluation of overall survival from the start of EV treatment using the Kaplan-Meier method for patients within various subsets of interest defined by clinical variables or relevant biomarkers did not show significant differences for most comparisons. A notable exception was the group of patients with liver metastases, who were shown to have inferior overall survival in comparison with patients without liver metastases. CI indicates confidence interval; CPS, combined positive score; EV, enfortumab vedotin; N/A, not available; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.

C Patients with Liver Metastases vs Patients Without Liver Metastases



D Prior Treatment: ≤2 Prior Treatment Lines vs >2 Prior Treatment Lines

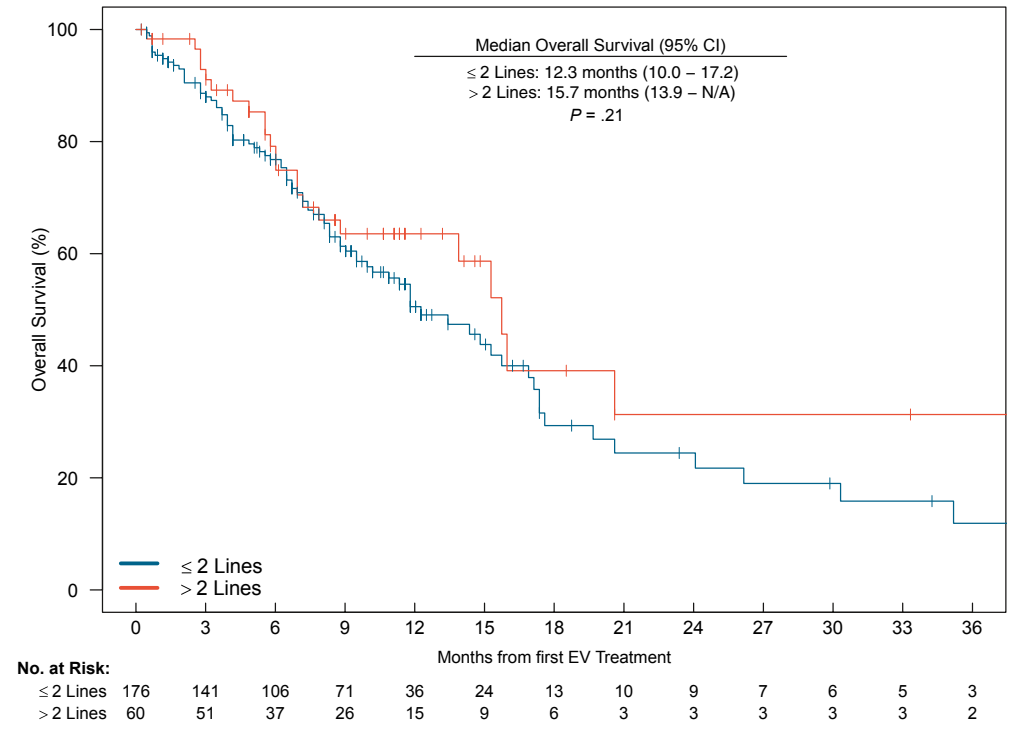
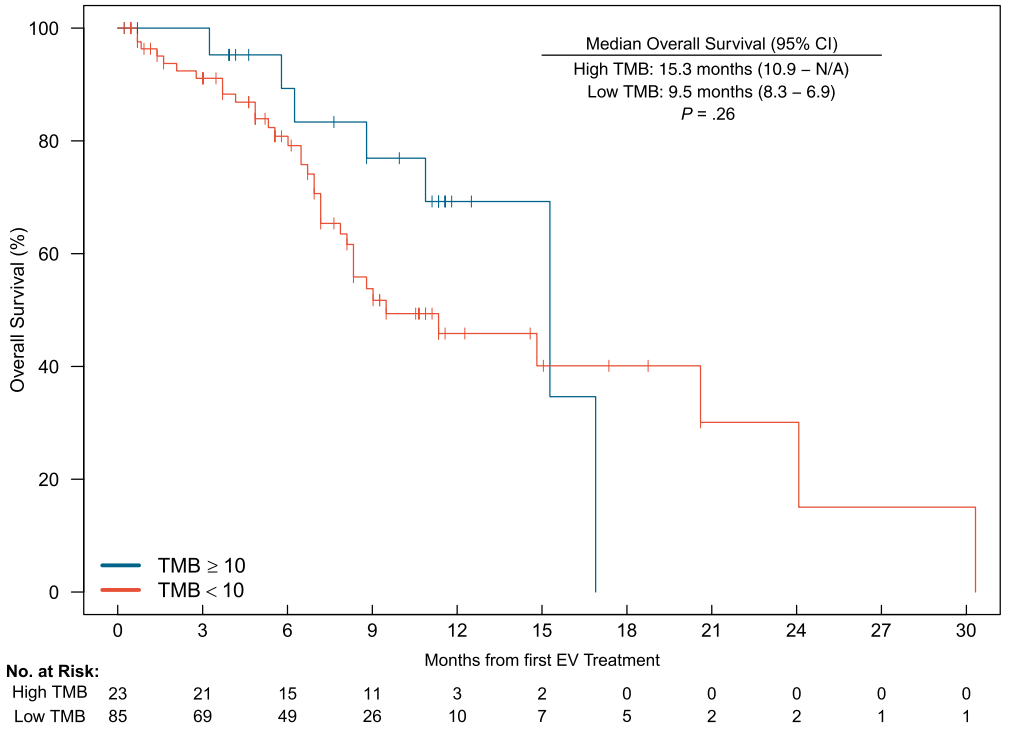


Figure 2. Continued

E TMB Low (<10 Mut/mb) vs TMB High (≥10 Mut/mb) Tumors



F PD-L1 Positive (CPS ≥ 10) vs PD-L1 Negative (CPS < 10) Tumors

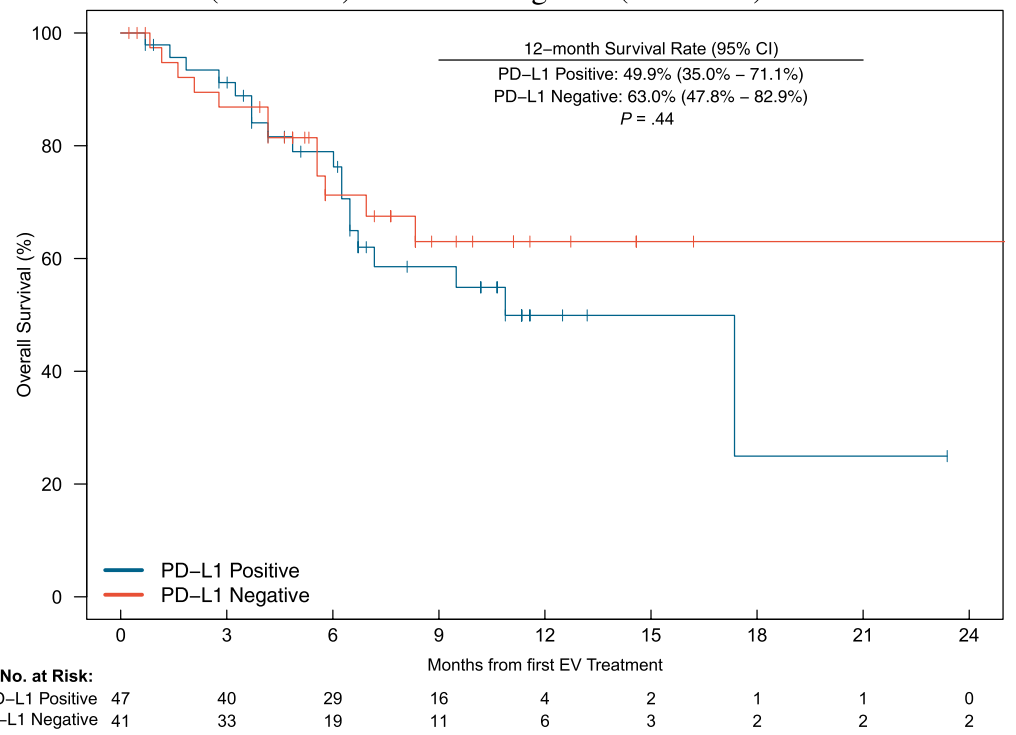


Figure 2. Continued

from clinical trials, including patients with a poor performance status, patients with a low eGFR, and patients with relevant medical comorbidities (eg, peripheral neuropathy and diabetes mellitus). Altogether, these results offer important insights for understanding the efficacy of EV outside the clinical trial setting and the clinical context in which this novel drug can be best used to help patients.

In EV-201 (cohort 1) and EV-301, the ORRs for patients treated with EV monotherapy after prior treatment with platinum-based chemotherapy and ICIs were 44% and 41%, respectively, and 12% and 5% of the patients achieved a complete response. In cohort 2 of EV-201, which included cisplatin-ineligible patients previously treated with ICIs but not platinum-based chemotherapy, the ORR was 52%.[18] The UNITE study analysis presented here, including both platinum-pretreated and platinum-naive patients, demonstrated an ORR of 52% with a 7% complete response rate; this was consistent with previously reported clinical trial data. The median PFS and OS values in this analysis—6.8 and 14.4 months, respectively—are also comparable to the values of 5.5 and 12.9 months reported in the EV-301 trial. The slightly higher values for ORR, PFS, and OS reported in this retrospective analysis are likely reflective of the inclusion of patients treated earlier in their disease course. Furthermore, ORR and PFS may have been affected by investigators not being blinded to the outcomes of their patients and by nonadherence to the Response Evaluation Criteria in Solid Tumors in determining responses. PFS can also be affected by not having a strictly defined imaging schedule as part of this assessment. The median time to a response in the UNITE analysis of 1.9 months was also almost identical to the previously reported data from EV-201 and EV-301. The data on the median duration of response are not yet mature in the UNITE analysis. In the future, it will be important to define how long these patients can remain on EV therapy in the context of both toxicity and efficacy considerations because of the availability of other treatment options such as erdafitinib and sacituzumab govitecan.[19,20]

In the UNITE study, we also examined the efficacy of EV in patient populations of interest, many of which were not included in clinical trials. Patients whose tumors had a component of variant histology had high rates of response to EV (ORR, 42%), but this was lower than the rate in patients with pure urothelial histology (ORR, 58%). Prior studies have shown lower nectin-4 expression in rare histological variants in comparison with pure UC,[21,22] whereas preclinical data have suggested that nectin-4 expression is both necessary and sufficient for a response to EV.[15] Therefore, the observed responses to EV may be potentially driven by the urothelial component in the tumors. In support of this hypothesis, among the 8 patients treated with EV monotherapy in this data set who had a pure variant or variant predominant tumor histology, only 1 partial response was observed (ORR, 13%). Patients with upper urinary tract primary tumors were noted to have numerically higher responses in comparison with patients with tumors originating in the bladder (ORR, 61% vs 50%). A potential explanation is that a higher proportion of upper tract tumors may have the luminal molecular subtype, which has higher nectin-4 expression and thus may be more susceptible to EV.[23] However, these numbers should be confirmed in larger cohorts.

Notably, among 28 evaluable patients with *FGFR3* alterations, EV also had significant activity with an ORR of 57%. Responses were also observed in a subset of these patients previously treated with the *FGFR3* inhibitor erdafitinib (a partial response in 2 of 5 patients), and this suggests that these drugs can successfully be used sequentially for patients with aUC and *FGFR3* alterations. The optimal sequence of EV and other available therapies for treatment-refractory patients remains to be further defined.[24] Additional future data from the UNITE study and future prospective studies could help to answer these important questions as treatment paradigms for aUC continue to evolve.

Finally, the UNITE study shows the efficacy of EV in patient subsets typically associated with a poor prognosis, including patients with liver metastases, a high disease burden, and multiple lines of prior treatment. It should be noted that although patients with liver metastases had a higher ORR, they still had inferior OS in comparison with patients without liver metastases; this suggests a limited durability of benefit with EV in this patient population. Additionally, patient subsets with aUC that were previously excluded from clinical trials were shown to benefit from EV. They included patients with a poor performance status (Eastern Cooperative Oncology Group performance status of 2/3), as well as patients with relevant comorbidities, such as peripheral neuropathy, diabetes mellitus, and impaired renal function (eGFR < 30 mL/min). These comorbidities may affect the duration of treatment with EV as well as treatment-related adverse events, which will be further explored in future UNITE analyses.

The strengths of our study include the use of data from routine oncologic practice across multiple

institutions and the relatively large sample size. This study had a number of important limitations inherent to the retrospective cohort design, including a lack of randomization or matched-control groups, potential missing data, and other selection and confounding biases. We did not report safety or toxicity data, which will be provided in future analyses of the UNITE study. Furthermore, there was no central radiology or pathology review, which may affect the interpretation of efficacy results and the association with histology variants. There may have been practice-related variability in disease monitoring and follow-up periods, which could affect the ascertainment of response and progression. Molecular diagnostics, such as NGS, PD-L1, TMB, and microsatellite instability status, were obtained from various heterogeneous platforms/assays and relied on EMR review. The study was limited to academic sites, which may not reflect the patterns of EV use in community practice settings and may, therefore, make this study's conclusions less generalizable to community oncology practices. Despite these limitations, this analysis provides important preliminary data regarding EV efficacy in aUC and complements and builds on published clinical trial data.

In conclusion, this initial, large, retrospective analysis from the UNITE study, which included patients with aUC treated with EV, has shown the treatment efficacy of EV to be consistent with what was previously reported in the clinical trials that led to the approval of this drug. Importantly, this includes robust activity in clinically relevant patient subsets, such as patients with *FGFR3* alterations and patients previously excluded from clinical trials of EV (eg, patients with significantly diminished renal function, uncontrolled diabetes mellitus, and peripheral neuropathy). EV is also effective for patients with mixed/variant histologies, although the ORR is lower in comparison with patients with pure urothelial histology.

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