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Lay Summary:

Enfortumab vedotin is an important new drug for the treatment of patients with advanced bladder cancer, which was approved by the FDA in 2019. In this study, we looked at the effectiveness of this drug as it has been used at multiple centers since approval, focusing on important patient populations previously excluded from clinical trials. This included patients with decreased kidney function, diabetes, and important mutations. We found that enfortumab vedotin is effective for treating these patients and were able to replicate clinical trial data in a real-world setting, supporting the use of this drug in broader populations of patients.

Precis:

Based on the initial data from UNITE study, enfortumab vedotin has activity in diverse populations of patients with urothelial cancer, including patients with variant histologies, *FGFR3* alterations, and patients with significant comorbidities previously excluded from clinical trials. Additionally, in this large multi-institutional retrospective cohort of patients with urothelial

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cancer, responses to enfortumab vedotin in patients treated outside of a clinical trial were consistent with and complementary to prior clinical trial data.

Abstract:

Background: Enfortumab vedotin (EV) is a novel antibody-drug conjugate (ADC) approved for advanced urothelial cancer (aUC) refractory to prior therapy. In the UNITE study, we looked at the experience with EV in patient subsets of interest where activity has not been well defined in clinical trials.

Methods: UNITE is 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 review by investigators at each site. Observed response rate (ORR) was investigator-assessed for patients with at least one post-baseline scan or clear evidence of clinical progression. ORR was compared across subsets of interest for patients treated with EV monotherapy.

Results: Initial UNITE analysis included 304 patients from 16 institutions, of whom 260 were treated with EV monotherapy and included in analyses. In the monotherapy cohort, ORR was 52% and >40% in all reported subsets of interest, including patients with comorbidities previously excluded from clinical trials (baseline renal impairment, diabetes, neuropathy) and with *FGFR3* alterations. PFS and OS were 6.8 months and 14.4 months respectively. Patients with pure urothelial histology had higher ORR relative to patients with variant histology component (58% vs 42%, p=0.06).

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 those with variant histology, *FGFR3* alterations, and patients previously excluded from clinical trials with eGFR<30 mL/min and significant comorbidities.

Key Words: urothelial cancer; bladder cancer; enfortumab vedotin; Nectin-4; urinary bladder; antibody-drug conjugate

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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 systemic therapies for disease control.[1-8] Enfortumab vedotin (EV) received accelerated FDA approval in December 2019 for patients with aUC progressing on platinum-based chemotherapy and ICI. EV is an antibody-drug conjugate (ADC) consisting of a monoclonal antibody targeting Nectin-4, which is conjugated to a microtubule-disrupting agent, monomethyl auristatin E (MMAE).[9-11] Initial FDA approval of

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EV was based on the results of EV-201 trial, and the benefit of EV for treatment-refractory aUC was subsequently confirmed in the randomized EV-301 phase III trial, leading to full approval in July 2021.[12,13] EV is also being investigated in earlier treatment settings as frontline regimen for cisplatin-ineligible aUC.[14]

Recent pre-clinical 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 UC may be more likely to respond to EV.[15] Additionally, patient populations with certain comorbidities common among aUC patients were excluded from EV clinical trials. This included patients with significant neuropathy (≥G2), uncontrolled pre-existing diabetes, and renal insufficiency (eGFR < 30). Consequently, certain patient populations with aUC may be more or less likely to benefit from EV treatment based on their specific pathologic or clinical characteristics, and EV efficacy in specific patient populations of interest (non-urothelial histology variants, patients with certain comorbidities, *FGFR3*-altered patients, etc.) remains to be further defined.

As clinical experience with EV grows, multi-institutional retrospective analyses can help shed further light on these important questions and complement important information derived from clinical trials. Here we present the initial results from the 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 among the more narrowly selected patients in clinical trials.

Patients and Methods:

The Urothelial Cancer Network to Investigate Therapeutic Experiences (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 aUC patients treated with EV. The study met the principles set forth by the declaration of Helsinki and was approved by the institutional review board (IRB) at each participating institution. Patient eligibility criteria included: histologically confirmed carcinoma of urothelial origin (variant histologic component of any % allowed), presence of locally

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advanced/unresectable or metastatic disease, at least one dose of EV administered, and available clinicopathologic and imaging data in the electronic medical record (EMR). To be considered eligible for response assessment, a patient needed to have at least one scan following initiation of EV treatment or clear evidence of clinical progression as assessed by the treating physician. Both patients treated on a clinical trial (as long as trial results previously reported) and as 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 (PHI) specifically excluded. Data were collected and managed using secure REDCap electronic data capture tools hosted at the University of Michigan.[16]

Assessment of observed response rate (ORR), defined as a complete response (CR) or partial response (PR); or alternatively of stable disease (SD) or progressive disease (PD) was determined based on the judgment of the investigator assessing EMR using the available information from imaging reports or clinical notes. In making these assessments, investigators were encouraged to adhere to RECIST criteria,[17] however specific tumor measurements were not collected and central assessment of imaging responses was not done. 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 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 ORR. OS and PFS curves were constructed using the Kaplan-Meier method. Primary analysis was assessment of ORR, PFS and OS in patients treated with EV monotherapy and comparison of these outcomes with data previously reported in clinical trials of EV. Secondary analysis focused on comparison of ORR and OS among specific subsets of interest; specifically for patients with pure urothelial vs mixed/variant histology, primary tumor origin in bladder vs upper tract, presence vs absence of liver metastases, and also based on number of prior treatment lines, TMB status, PD-L1 status and other characteristics. For patients with an evaluable response, ORR comparisons were made using chi-square tests for equality of proportions and confidence intervals constructed by the Wilson method.

Results:

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The overall cohort included 304 patients from 16 academic institutions in the United States (Supplementary 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 of the EV monotherapy cohort, including the tumor molecular characteristics. Notably, FoundationOne CDx was the most common NGS panel used (44% of patients with NGS) and about 20% of patients had *FGFR3* alterations.

Among 260 patients treated with EV monotherapy, median follow-up from initial UC diagnosis to time of last follow-up was 35.9 months, while median time from initial diagnosis to date of advanced disease was 10.9 months. The median time from advanced disease diagnosis to EV treatment start was 12.0 months. Most patients were treated with EV after ≥2 prior lines of therapy for advanced UC (67%) and most received EV outside of 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 EV start was 7.2 months (IQR: 3.7 - 11.6 months), and median treatment duration was 4.1 months (IQR: 1.6 - 6.9 months). Most patients (82%, n=212) were evaluable for response and among these patients, 24% (50/212) were still on EV treatment at the time of analysis (71/260, 27% in the overall monotherapy group). Among 162 evaluable patients who discontinued EV treatment, the most common reasons were disease progression (64%), treatment intolerance (24%) or other (12%).

ORR for the primary analysis among evaluable patients is shown in Table 2. Investigator assessed ORR was 52%, which was similar to the ORR observed in the overall 304 patient cohort (54%). Notably only 22% of patients had progressive disease as best response to EV monotherapy. Among responders, median time to 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 with unknown status). Median PFS and OS were 6.8 months and 14.4 months, respectively from the start of EV treatment (Figure 1).

For the secondary analysis comparing patient subsets of interest, ORRs for evaluable patients are shown in Table 3, and were robust in most patient categories (ORR > 40%). ORR was lower in patients whose tumors had a component of variant histology (42%, N=66) relative to pure urothelial histology (58%, N=142) (p=0.056). For 77 patients treated with EV monotherapy whose tumors had a variant histology component, the histology breakdown and

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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, 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 response rates to EV treatment. Among 28 patients whose tumors harbored *FGFR3* alterations, ORR was 57%. Responses to EV were also seen independent of TMB and PD-L1 status or prior treatment regimens (Supplementary Table 2). For the most part no OS differences were observed in comparing relevant subsets of patients (Figure 2). However, patients with liver metastases had higher ORR (64% vs 47%, p=0.04), but shorter OS (8.3 months vs 15.7 months, p=0.005) relative to 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 in prospective clinical trials. Moreover, EV has robust activity in clinically relevant subsets of patients with aUC previously excluded from clinical trials, including patients with poor performance status, low eGFR, and patients with relevant medical comorbidities, such as peripheral neuropathy and diabetes mellitus. Altogether, these results offer important insights for understanding the efficacy of EV outside of the clinical trial setting, and the clinical context in which this novel drug can be best utilized to help patients.

In EV-201 (Cohort 1) and EV-301, ORR in patients treated with EV monotherapy following prior treatment with platinum-based chemotherapy and ICIs were 44% and 41% respectively, and 12% and 5% of patients achieved a CR. In Cohort 2 of EV-201 which included cisplatin-ineligible patients previously treated with ICI but not platinum-based chemotherapy, ORR was 52%.[18] The UNITE study analysis presented here, including both platinum pretreated and platinum-naïve patients, demonstrates an ORR of 52% with 7% CR, consistent with previously reported clinical trial data. The median PFS and OS in this analysis of 6.8 and 14.4 months respectively is also comparable to 5.5 months 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 impacted by investigators not being blinded to the outcomes of

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their patients and non-adherence to RECIST criteria in determining responses. PFS can also be impacted by not having strictly defined imaging schedule as part of this assessment. Median time to response in the UNITE analysis of 1.9 months is also almost identical to the previously reported data in EV-201 and EV-301. The data on median duration of response is not yet mature in the UNITE analysis. Looking ahead, it will be important to define how long these patients can remain on EV therapy in the context of both toxicity and efficacy considerations, given the availability of other treatment options like 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 in patients with pure urothelial histology (ORR 58%). Prior studies have shown lower Nectin-4 expression in rare histological variants compared to pure UC,[21,22] while pre-clinical data has suggested that Nectin-4 expression is both necessary and sufficient for 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 dataset who had pure variant or variant predominant tumor histology, only one partial response was observed (ORR 13%). Patients with upper urinary tract primary tumors were noted to have numerically higher responses relative to 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 luminal molecular subtype which has a 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 ORR at 57%. Responses were also observed in a subset of these patients previously treated with the *FGFR3* inhibitor erdafitinib (PR in 2 of 5 patients) suggesting 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 can help answer these important questions as treatment paradigms in aUC continue to evolve.

Finally, UNITE study shows the efficacy of EV in patient subsets typically associated with a poor prognosis, including patients with liver metastases, high disease burden, and multiple lines of prior treatment. It should be noted that although patients with liver metastases had higher

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ORR, they still had inferior OS relative to patients without liver metastases, suggesting 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. This included patients with poor performance status (ECOG 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 impact the duration of treatment with EV as well as treatment-related adverse events, which will be further explored in future UNITE analyses.

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 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 done in future analyses of the UNITE study. Furthermore, there was no central radiology or pathology review, which may impact efficacy results interpretation and association with histology variants. There may have been practice-related variability in disease monitoring and follow up periods, which could affect ascertainment of response and progression. Molecular diagnostics, such as NGS, PD-L1, TMB, MSI-status, were obtained from various heterogeneous platforms/assays and relied upon 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 upon published clinical trial data.

In conclusion, this initial large retrospective analysis from the UNITE study, which included patients with aUC treated with EV, showed treatment efficacy of EV to be consistent with what was previously reported in 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 (e.g. patients with significantly diminished renal function, uncontrolled diabetes mellitus, and peripheral neuropathy). EV is also effective for patients with mixed/variant histologies, although ORR is lower relative to patients with pure urothelial histology.

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Figure Legends:

Figure 1: A) Progression-free survival and B) Overall survival in patients treated with enfortumab vedotin monotherapy

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PFS and OS measured from enfortumab vedotin treatment initiation and illustrated using Kaplan-Meier curves.

Figure 2: Comparison of overall survival in subsets of patients treated with enfortumab vedotin monotherapy

Comparison of OS from enfortumab vedotin treatment start using the Kaplan-Meier method in 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 OS relative to patients without liver metastases (Figure 2C).
TMB: tumor mutational burden; PD-L1: programmed death-ligand 1; CPS: combined positive score

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Table 1: Patient characteristics in the UNITE study

Characteristics	All patients receiving enfortumab vedotin N = 304	Patients receiving enfortumab vedotin monotherapy N = 260
Median Age (at enrollment)	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: 8 (3%) 18 - 25: 119 (39%) 25 - 30: 97 (32%) ≥ 30: 71 (23%) Unknown: 9 (3%)	< 18: 8 (3%) 18 - 25: 102 (39%) 25 - 30: 87 (34%) ≥ 30: 57 (22%) Unknown: 6 (2%)
Location of Primary	Bladder: 215 (71%)	Bladder: 189 (73%)

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Tumor	Upper Tract: 81 (27%) Urethra: 1 (0.3%) Unknown: 7 (2%)	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%) Chemo/RT: 3 (2%) No Treatment: 136 (78%)	Chemotherapy only: 31 (22%) Radiation only: 2 (1%) Chemo/RT: 2 (1%) No Treatment: 109 (76%)
Number of Therapy	None: 44 (15%)	None: 13 (5%)

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Lines For Metastatic Disease Prior to EV:	1 line: 79 (26%) 2 lines: 113 (37%) 3 lines: 47 (16%) >3 lines: 18 (6%) Unknown: 3 (1%)	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: Liver Metastases: Non-Liver Visceral Metastases:	 61 (20%) 95 (31%) 148 (49%)	 52 (20%) 84 (32%) 124 (48%)
Patient Molecular Characteristics		
Available NGS Results PD-L1 Status Available MSI Status Available TMB Available	184 (61%) 119 (39%) 157 (52%) 127 (42%)	160 (62%) 101 (39%) 139 (53%) 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*	36/184 (20%)	33/160 (21%)
Tumor Mutational Burden (TMB)	Median = 6.19 Range = 0 - 48 ≥ 10 Mut/mb: 32/ 127 (25%)	Median = 6.08 Range = 0 - 48 ≥ 10 Mut/mb: 24 / 113 (21%)

BMI: body mass index; ECOG PS: eastern cooperative oncology group performance status; CIS: carcinoma in situ; SOC: standard of care; LN: lymph nodes

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NGS: next generation sequencing; PD-L1: programmed death-ligand 1; MSI: microsatellite instability; FGFR3: fibroblast growth factor receptor 3; TMB: Tumor Mutational Burden

*FGFR3 alterations include all mutations or fusions considered pathogenic

Percentages in some categories add up to >100% due to rounding

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Table 2: Best response to enfortumab vedotin monotherapy among evaluable patients

Best Response	EV monotherapy, ORR [95% CI] N=212
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%]

CR: complete response; PR: partial response; SD: stable disease; PD progressive disease;

ORR: observed response rate is composite of CR and PR

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Table 3: Comparison of ORR among relevant subgroups in patients treated with enfortumab vedotin monotherapy and evaluable for response

Subgroups	Patients (N)	ORR (%, 95% CI)	p-value
Pure urothelial histology	142	58% (49%, 66%)	0.06
Variant histology (any component)	66	42% (31%, 55%)	
Bladder Primary Tumor	151	50% (42%, 58%)	0.21
Upper Tract Primary Tumor	56	61% (47%, 73%)	
Age ≥ 75	69	51% (39%, 63%)	0.85
Age < 75	139	53% (45%, 62%)	
BMI ≥ 30	48	56% (41%, 70%)	0.63
BMI < 30	161	51% (43%, 59%)	
Prior Definitive Surgery or Chemotherapy/RT*	126	53% (44%, 62%)	0.93
No Prior Definitive Treatment	70	51% (39%, 63%)	
Treatment Lines Before EV**			
0-2 Lines Prior Treatment	158	49% (41%, 57%)	0.18
> 2 Lines Prior Treatment	54	61% (47%, 74%)	
Liver Metastases	66	64% (51%, 75%)	0.04
No Liver Metastases	146	47% (39%, 56%)	
Bone Metastases	75	51% (39%, 62%)	0.83
No Bone Metastases	137	53% (45%, 62%)	
ECOG PS 0/1	173	56% (48%, 63%)	0.18
ECOG PS 2/3	34	41%(25%, 59%)	
Baseline Neuropathy	71	62% (50%, 73%)	0.08
No Neuropathy	139	48% (40%, 57%)	
Baseline Diabetes Mellitus	29	59% (39%, 76%)	0.60
No Diabetes Mellitus	183	51% (44%, 59%)	
eGFR < 30	25	40% (22%, 61%)	0.27

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eGFR ≥ 30	187	54% (47%, 61%)	
FGFR3 Altered	28	57% (37%, 75%)	0.93
FGFR3 Wild Type	102	54% (44%, 64%)	
PD-L1 Positive***	42	50% (36%, 65%)	0.23
PD-L1 Negative	38	66% (49%, 80%)	
TMB ≥ 10	21	62% (39%, 81%)	0.51
TMB < 10	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	115	55% (45%, 64%)	0.53
No Prior Platinum-Based Therapy	97	50% (39%, 60%)	

ORR: observed response rate; BMI: body mass index; ECOG PS: eastern cooperative oncology group performance status; eGFR: estimated glomerular filtration rate (mL/min); PD-L1: programmed death-ligand 1; TMB: tumor mutational burden (Mutations/megabase); platinum-based therapy includes at least one prior cisplatin or carboplatin-based regimen

*Prior definitive surgery or chemotherapy/RT includes prior treatment with a curative intent

**Treatment lines before EV include treatment in the advanced or metastatic setting

***For PD-L1 status, Combined positive score (CPS) ≥ 10 considered positive

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Table 4: Variant histology subtypes and observed response rates based on histology

Variant Histology	Number Total	Number Evaluable	CR	PR	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*	4	3	0	1	33%
Other/Unknown	9	8	0	4	50%
Total	77	66	3	25	42%

ORR: observed response rate is composite of CR (complete response) and PR (partial response)
Among evaluable patients, 8 had majority non-urothelial histology with either variant predominant (6) or pure variant (2) histology. Among these patients, 1 PR and no CRs were observed.

*Among 4 patients with mixed histology, the histology breakdown and responses were as follows:

Patient 1: Micropapillary, squamous – partial response

Patient 2: Sarcomatoid, glandular, neuroendocrine – stable disease

Patient 3: Plasmacytoid, squamous – progressive disease

Patient 4: Plasmacytoid, glandular, micropapillary - not evaluable

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Figure 1: A) Progression-free survival and B) Overall survival in patients treated with enfortumab vedotin monotherapy

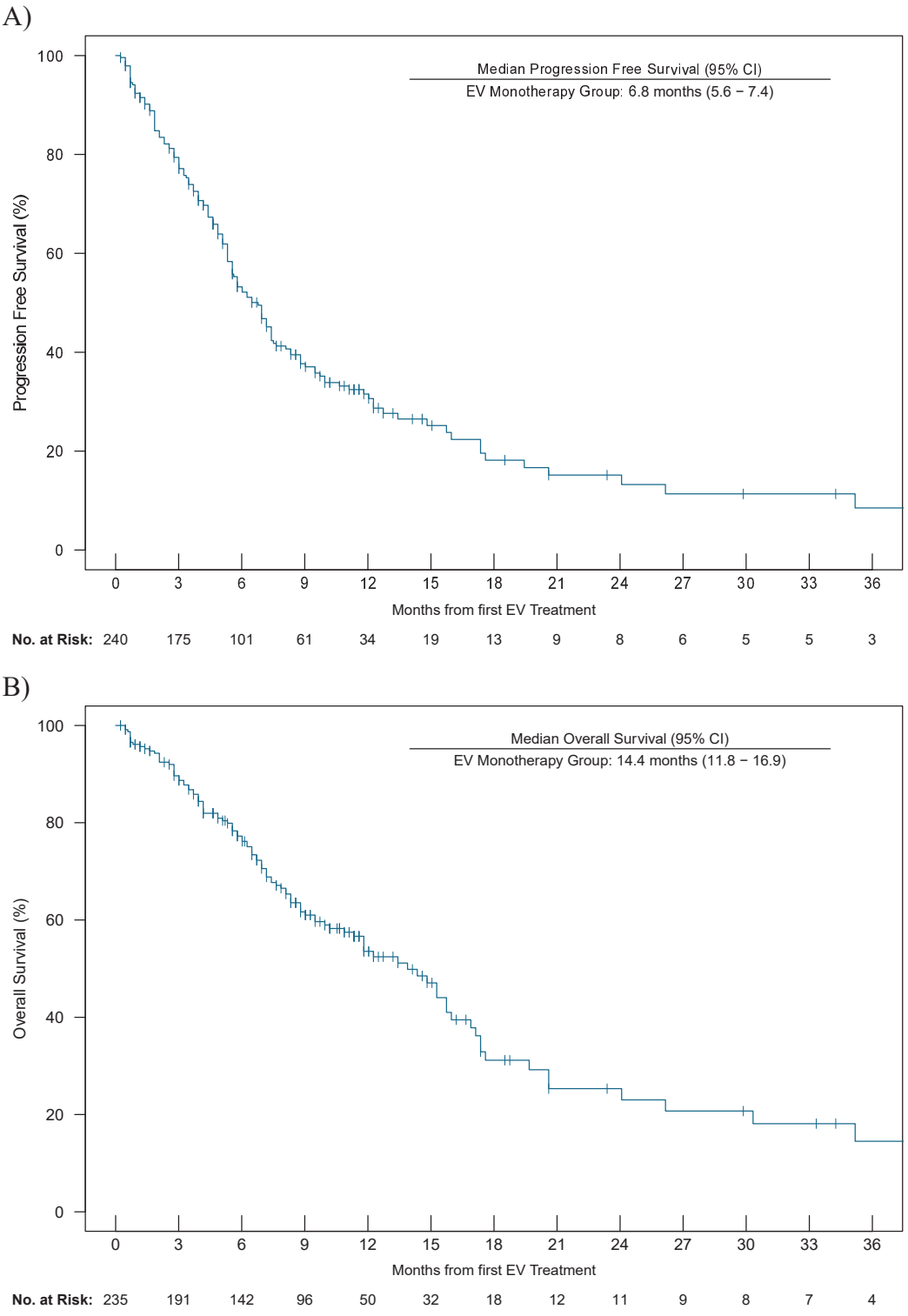

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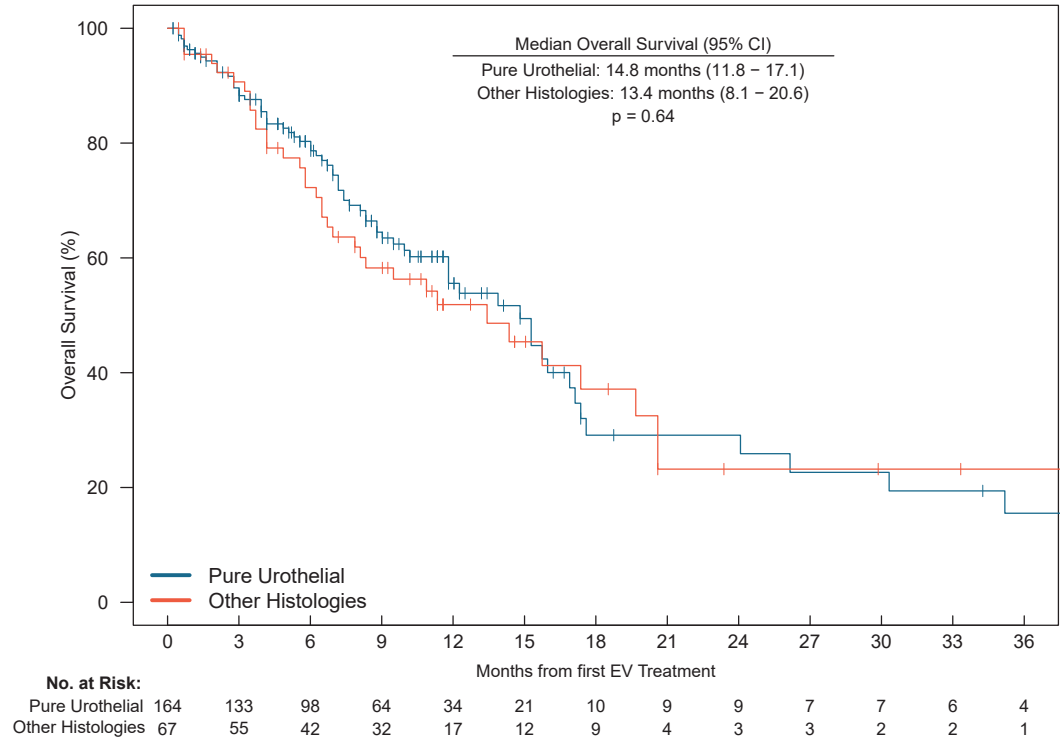
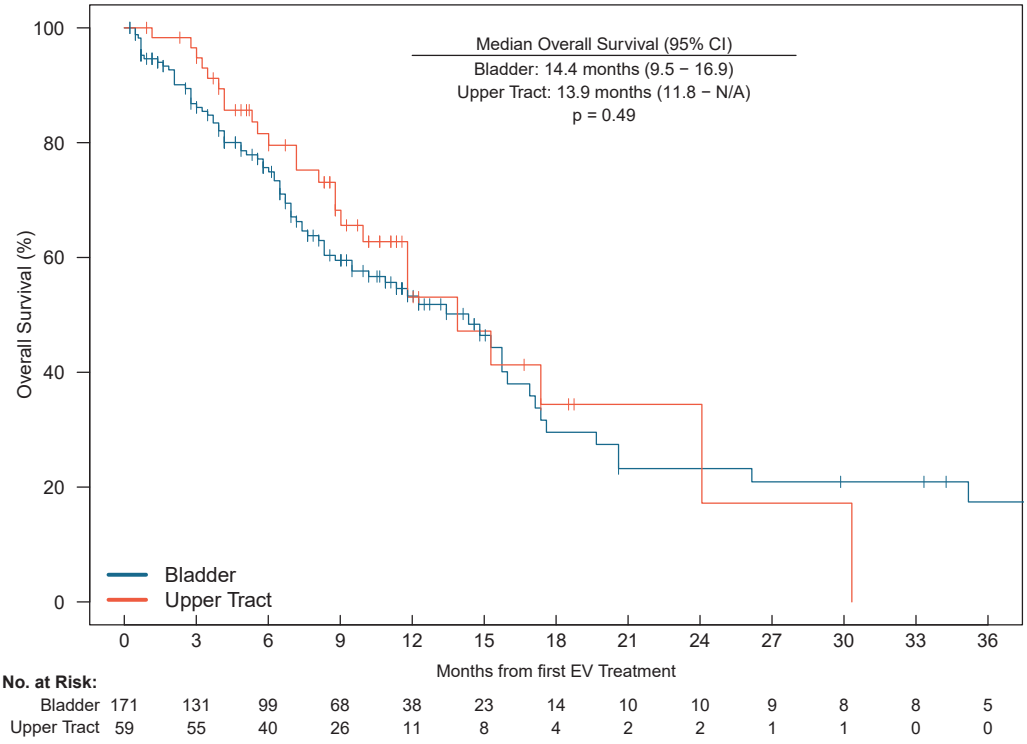
Figure 2: Comparison of overall survival in subsets of patients treated with enfortumab vedotin monotherapy

A) Pure Urothelial Histology vs Mixed/Variant Histology



No. at Risk:													
Pure Urothelial	164	133	98	64	34	21	10	9	9	7	7	6	4
Other Histologies	67	55	42	32	17	12	9	4	3	3	2	2	1

B) Primary Bladder Tumors vs Primary Upper Tract Tumors



No. at Risk:													
Bladder	171	131	99	68	38	23	14	10	10	9	8	8	5
Upper Tract	59	55	40	26	11	8	4	2	2	1	1	0	0

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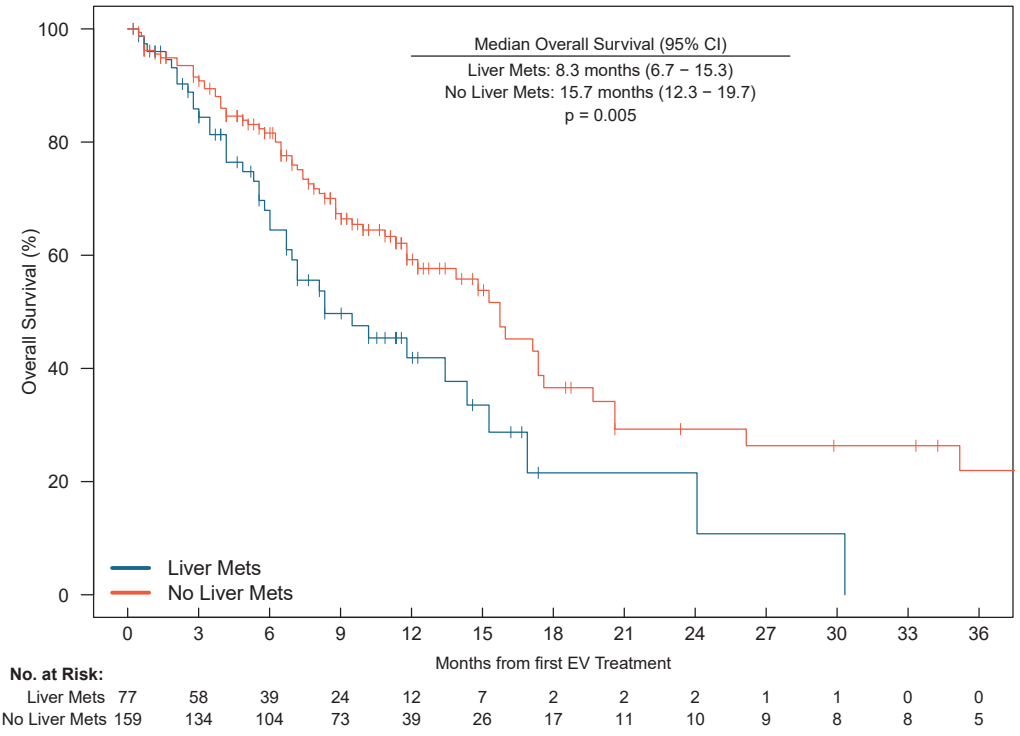
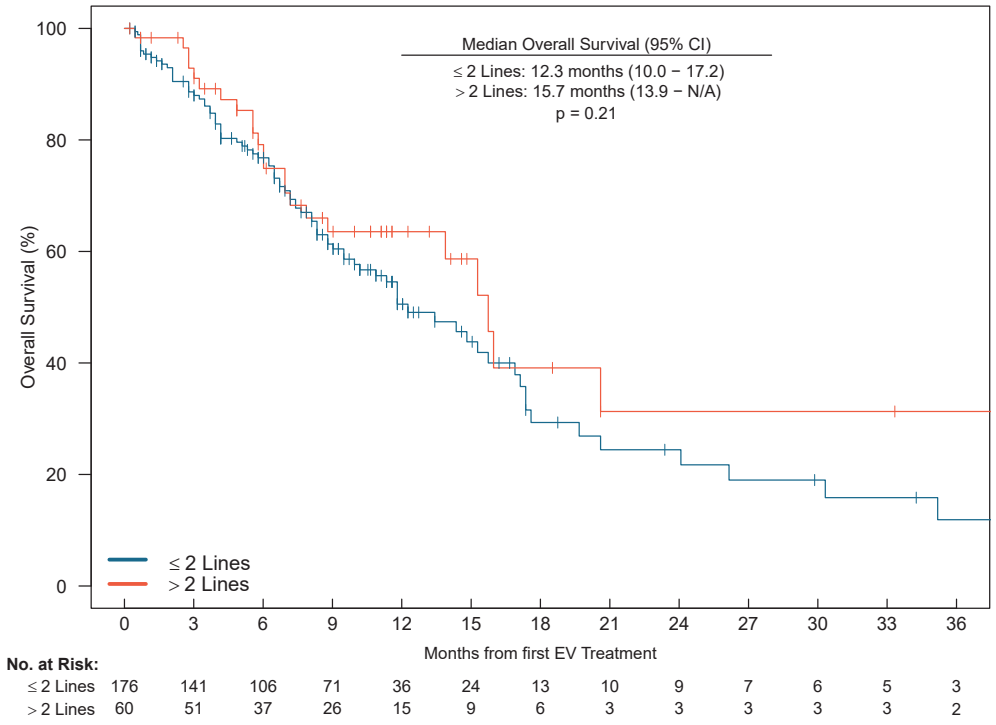
C) Patients with Liver Metastases vs Patients Without Liver Metastases



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



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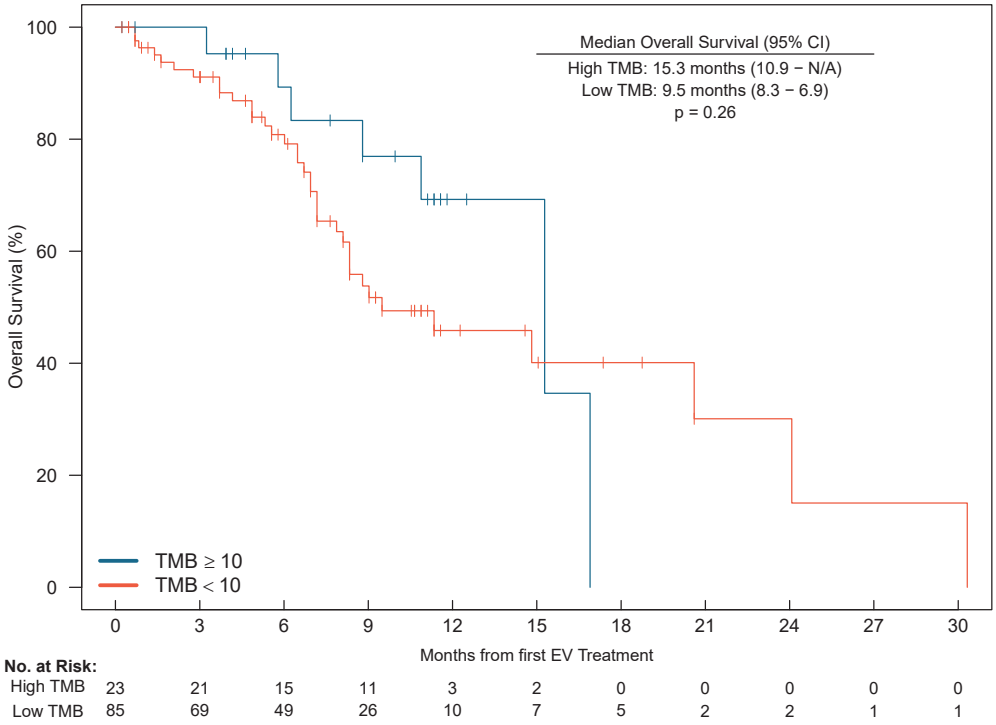
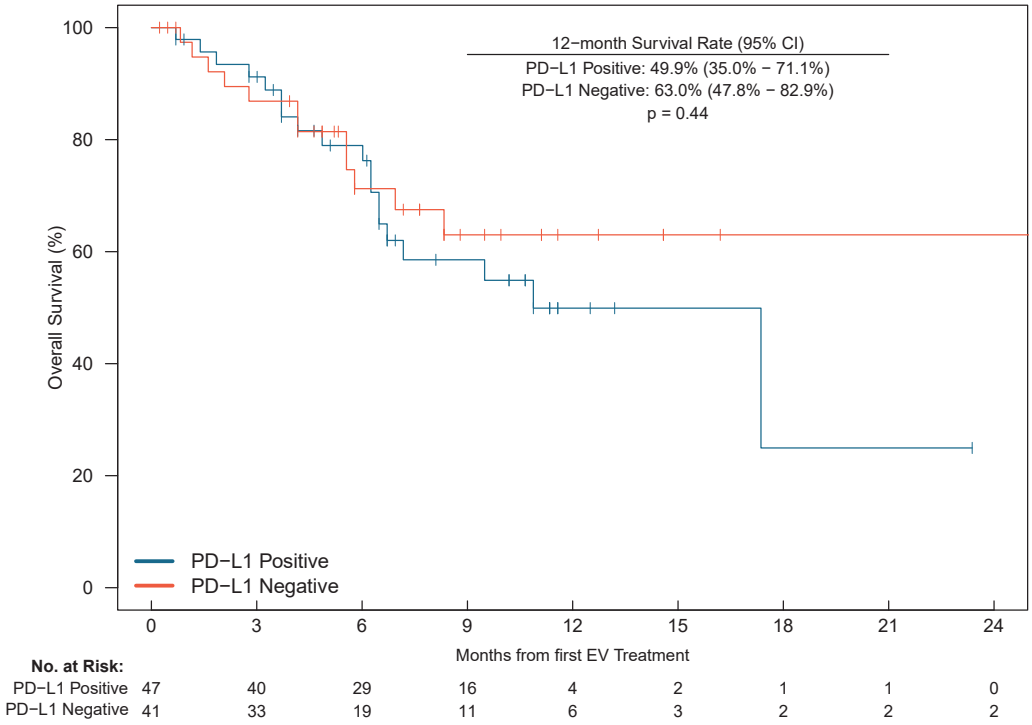
E) TMB Low (<10 Mut/mb) vs TMB High (≥10 Mut/mb) Tumors



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



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