Genitourinary Masterclass

Conclusions drawn from RWE: Exploring real-world use of EV monotherapy and EV+P

Dr Vadim Koshkin
University of California, San Francisco, US

Dr Dora Niedersüß-Beke
Centre for Oncology and Haematology, Vienna Healthcare Group, Ottakring, Vienna

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EV, in combination with P, is indicated for the 1L treatment of adult patients with unresectable/mUC who are eligible for platinum-containing chemotherapy.
Please note: This indication has received EMA approval; reimbursement in some EU countries is still pending.[1]
EV as monotherapy is indicated for the treatment of adult patients with LA/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor.[1]

1L, first line; EMA, European Medicines Agency; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PD-1/L1, programmed cell death protein 1/ligand 1; RWE, real-world evidence.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Date of preparation: June 2025 | Job code: MAT-NL-PAD-2025-00040

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PADCEV™ ▼
enfortumab vedotin
Injection for IV infusion 20 mg & 30 mg vials

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Speaker disclosures

Dr Vadim Koshkin

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Efficacy and safety outcomes for EV-301 and EV-302 should be referred to in line with the pooled safety data for EV monotherapy and EV+P

EV, enfortumab vedotin; P, pembrolizumab; RWE, real-world evidence.

RWE vs. clinical trials

RWE datasets[1,2]

- Have more open eligibility criteria
- Can have larger sample sizes, as RWE can include any site able to share data
- Evolve over time as the SOC changes
- Are more flexible about treatments allowed
- Can ask a broad range of questions that evolve over time
- However, there is an inherent selection bias in non-randomised groups, as observed in RWE studies

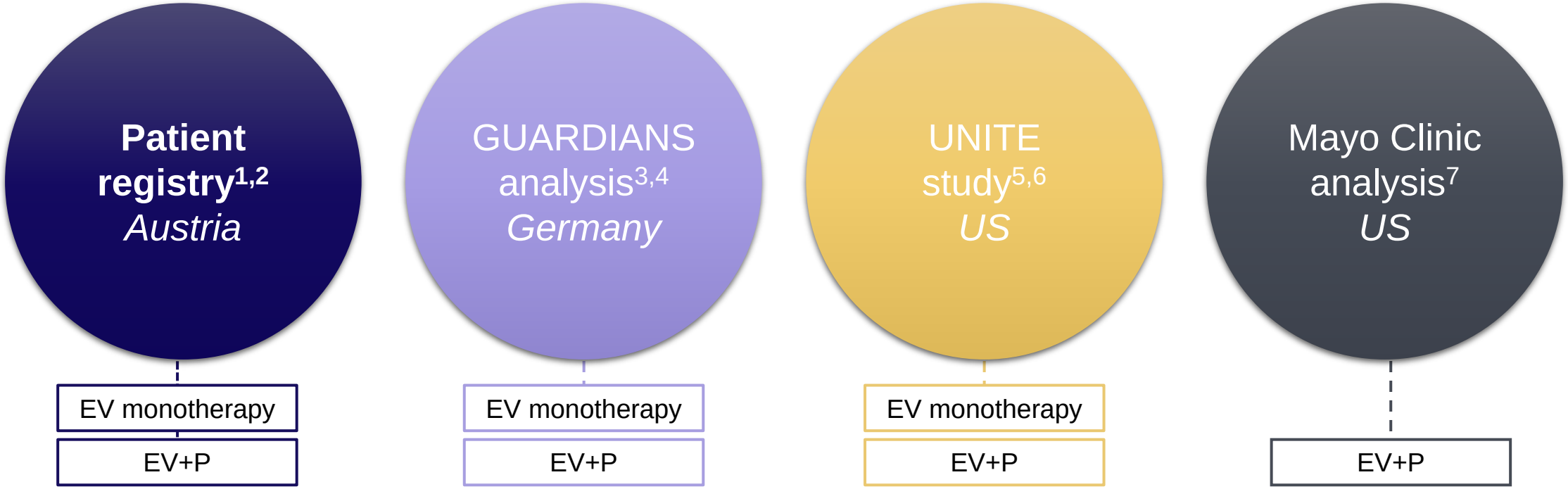
Clinical trials[1,2]

- The data is robust and controlled
- Have strict eligibility
- Only available at certain sites
- Take place over a finite period
- Allow only certain protocol-defined treatments
- Usually have fixed questions and endpoints

RWE, real-world evidence; SOC, standard of care.

1. Azoulay L. *Oncologist* 2022;27:e731–e738; 2. Speaker's own opinion.

Today, we will summarise data from these RWE studies



EV, enfortumab vedotin; RWE, real-world evidence; P, pembrolizumab; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

1. Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278; 2. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 3. Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553;
4. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 5. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 6. Jindal T et al. Presented at ESMO 2024. Abstract 1988P; 7. Jain P et al. Presented at ASCO GU 2025. Abstract 745.

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Genitourinary Masterclass

EV+P in the real-world: Insights from Europe and the US

Did real-world use of EV+P reflect the EV-302 trial results?

EV, in combination with P, is indicated for the 1L treatment of adult patients with unresectable/mUC who are eligible for platinum-containing chemotherapy.[1]

1L, first-line; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

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The Austrian patient registry evaluated real-world outcomes of patients receiving EV+P: Overview

Design

A retrospective, multicentre real-world study conducted across 18 Austrian centres

Cohort

A total of 138 patients who had received 1L EV+P for unresectable or mUC between the observation period of Sept 2023–Dec 2024

Aim

Evaluate **efficacy and safety** outcomes with **EV+P** in patients with unresectable or mUC in a real-world setting

EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab; UC, urothelial carcinoma.
Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry evaluated real-world outcomes of patients receiving EV+P: Baseline characteristics

Demographic and clinical characteristic, n (%)*†	N=138
Sex	
Female	30 (21.7)
Male	108 (78.3)
Age, years	
Median age (range)	71 (26–92)
<75	85 (61.6)
≥75	53 (38.4)
ECOG PS	
0	81 (58.7)
1	44 (31.9)
2	9 (6.5)
3	4 (2.9)
BMI, kg/m²	
Median BMI (range)	25.1 (13.2–37.9)
<30	121 (87.7)
≥30	17 (12.3)
Charlson Comorbidity Index	
Median score	3
Low (score 0–4)	111 (80.4)
High (score ≥5)	27 (19.6)
Diabetes mellitus	
Presence	19 (13.8)
Absence	119 (86.2)
Renal function	
No renal insufficiency to mild CKD (eGFR ≥60 ml/min)	77 (55.8)
Moderate CKD (eGFR 30–59 ml/min)	56 (40.6)
Severe CKD (eGFR <30 ml/min)	5 (3.6)

Demographic and clinical characteristic, n (%)*†	N=138
Location of metastases	
Lymph nodes	51 (37.0)
Lung	45 (32.6)
Liver	23 (16.7)
Bone	27 (19.6)
Brain	2 (1.4)
Other	20 (14.5)
PD-L1 status	
CPS ≥10	42 (30.4)
CPS <10	41 (29.7)
N/A	55 (39.9)
FGFR3 alterations	
Positive	8 (5.8)
Negative	47 (34.1)
NE	83 (60.1)
Previous definitive therapy of primary tumour	
RC/NU	63 (45.7)
Radiochemotherapy	4 (2.9)
None	71 (51.4)
Neoadjuvant therapy	
Yes	36 (26.1)
No	102 (73.9)

*Percentages may not equate to 100 due to rounding; †Unless otherwise indicated.
BMI, body mass index; CKD, chronic kidney disease; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; N/A, not applicable; NE, not evaluable; NU, nephroureterectomy; P, pembrolizumab; PD-L1, programmed cell death ligand 1; RC, radical cystectomy.
Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry: Efficacy outcomes

Efficacy parameter	N=123
Median follow-up, months	5.4
OS Median, months (range)	NR (NR–NR)
PFS Median, months (range)	NR (9.84–NR)
DCR, %	82.1
ORR, %	69.1
Best response, %	
CR	20.3
PR	48.8
SD	13.0
PD	17.9

Findings from real-world settings are in line with the pivotal trial results

Median follow-up: 5.4 months.
CR, complete response; DCR, disease control rate; EV, enfortumab vedotin; NR, not reached; OS, overall survival; P, pembrolizumab; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry: Relevant subgroup analyses

	Overall (N=123)	CCI*		BMI		Renal function, eGFR		Haemoglobin level		Diabetes mellitus	
		Low (n=101)	High (n=22)	<30 kg/m^2 (n=110)	≥30 kg/m^2 (n=13)	<60 ml/min/ 1.73m^2 (n=56)	≥60 ml/min/ 1.73m^2 (n=67)	<10 g/dl (n=23)	≥10 g/dl (n=100)	Absence (n=107)	Presence (n=16)
ORR, %	69.1	71.3	59.1	67.3	84.6	67.9	70.1	47.8	74.0	69.2	68.8
p value		0.26		0.20		0.78		0.01		0.97	

Median follow-up: 5.4 months.

BMI, body mass index; CCI, Charlson comorbidity index; GFR, glomerular filtration rate; ORR, objective response rate.

Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736.

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The Austrian patient registry: Safety outcomes

TRAEs of special interest* (N=138)		
	Any grade, n (%)	**Grade ≥3 n (%)†**
Any event	96 (70.0)	50 (36.2)
Skin disorder	41 (29.7)	6 (4.3)
Gastrointestinal disorder	51 (37.0)	18 (13.0)
Peripheral neuropathy	52 (37.7)	8 (5.8)
Eye disorder	15 (10.9)	1 (0.7)
Endocrine disorder	14 (10.1)	9 (6.5)
Pneumonitis	8 (5.8)	5 (3.6)
Infectious disease	7 (5.1)	5 (3.6)

AEs were reported in 70% of patients, with Grade ≥3 toxicities occurring in 36.2% of patients. Four fatal events occurred†

Therapy with either EV or P was discontinued due to toxicity in 30.4% of patients

Dose reductions due to AEs were reported for 45.6% of patients

No additional safety signals associated with EV+P were identified in the Austrian patient registry analysis

Median follow-up: 5.4 months.
*Although other indicated; †Fatal events: 1) rectal bleeding, 2) enterocolitis, 3) infection with multiorgan failure, 4) pneumocystis pneumonia.
AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab; TRAE, treatment-related adverse event.
Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736.

Job code: MAT-NL-PAD-2025-00040

The GUARDIANS analysis evaluated real-world outcomes of patients receiving EV+P in Germany: Overview

Design

Retrospective, multicentre (19 centres), German real-world study

Cohort

A total of 216 patients with mUC who had received EV+P outside of a clinical trial setting*

Aim

Evaluate **efficacy and safety** outcomes with **EV+P** outside of clinical trials

*Treatment was off-label use and reimbursed by individual patients' insurance before EMA approval of EV+P, or as SOC treatment after EMA approval.
EMA, European Medicines Agency; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab; SOC, standard of care.
Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715.

Job code: MAT-NL-PAD-2025-00040

The GUARDIANS analysis evaluated real-world outcomes of patients receiving EV+P in Germany: Baseline characteristics

Demographic and clinical characteristic	N=272
Sex, n (%)	
Male	189 (69.5)
Female	83 (30.5)
Age, years	
Median (range)	70 (25–89)
≥75, n (%)	91 (33.5)
ECOG PS, n (%)	
0	132 (48.5)
1	85 (31.3)
2	45 (16.5)
≥3	10 (3.7)
Previous (neo)adjuvant therapy, n (%)	43 (15.8)
Cisplatin/gemcitabine, n	29
ICI, n	6
Cisplatin/gemcitabine/ICI, n	4
Other chemotherapy, n	4
Histology, n (%)	
UC	248 (91.2)
UC with divergent differentiation	12 (4.4)
Squamous cell carcinoma	10 (3.7)
Adenocarcinoma	1 (0.4)
Small cell carcinoma	1 (0.4)

Demographic and clinical characteristic	N=272
Primary site of tumour, n (%)	
Bladder	189 (69.5)
Upper tract	69 (25.4)
Urethra	4 (1.5)
>1 location	10 (3.7)
Site of metastases, n (%)	
Lymph nodes	203 (74.6)
Pulmonary	107 (39.3)
Osseous	75 (27.6)
Hepatic	61 (22.4)
Peritoneal	17 (6.3)
Adrenal	10 (3.7)
Brain	5 (1.8)
Other	41 (15.1)
Cisplatin unfit, n (%)	156 (57.4)
Reason	
Renal impairment	105
ECOG	49
Hearing impairment	8
Cardiac impairment	6
Polyneuropathy	4

ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; P, pembrolizumab; UC, urothelial carcinoma.

Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715.

Job code: MAT-NL-PAD-2025-00040

The GUARDIANS analysis: Efficacy outcomes

Efficacy of EV+P (N=272)	
Efficacy parameter	
Median follow-up, months	6
Median PFS, months (95% CI)	13 (5.2–20.8)
Median OS, months	NR
ORR, n (%)	154 (56.6)
DCR, n (%)	188 (69.1)
CR, n (%)	28 (10.3)
PR, n (%)	126 (46.3)
SD, n (%)	34 (12.5)
PD, n (%)	38 (14.0)
Mixed response (as per clinical criteria) , n (%)	14 (5.1)
No post-baseline assessment, patients deceased, n (%)	13 (4.8)
No post-baseline assessment, patients alive, n (%)	18 (6.6)

Findings from real-world settings are in line with the pivotal trial results

Median follow-up: 6 months.
CI, confidence interval; CR, complete response; DCR, disease control rate; EV, enfortumab vedotin; NR, not reached; ORR, overall response rate; OS, overall survival; P, pembrolizumab; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715.

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The GUARDIANS analysis: Safety outcomes

Safety of EV+P: Included are TEAEs that occurred in ≥5% of patients (N=272)

	All grade, n (%)	Grade 3–4, n (%)
TEAEs	214 (78.7)	88 (32.3)
Immune-related adverse events	110 (40.4)	45 (16.5)
Peripheral sensory neuropathy	100 (36.8)	15 (5.5)
Dermatological toxicity Non-bullous exanthema Bullous exanthema Pruritus Alopecia	 75 (27.6) 12 (4.4) 69 (25.4) 31 (11.4)	 8 (2.9) 4 (1.5) 0 1 (0.4)
Fatigue	46 (16.9)	6 (2.2)
Diarrhoea	42 (15.4)	9 (3.3)
Hepatitis/elevated ALAT and/or ASAT	37 (13.5)	17 (6.3)
Anaemia	37 (13.1)	5 (1.8)
Weight loss	37 (13.1)	4 (1.5)
Infection	31 (11.4)	18 (6.6)
Dysgeusia	30 (11.0)	0
Hyperglycaemia	20 (7.4)	9 (3.3)

	All grade, n (%)	Grade 3–4, n (%)
Ocular toxicity	20 (7.4)	1 (0.4)
Pneumonitis	20 (7.4)	9 (3.3)
Arthritis	17 (6.3)	2 (0.7)
Nausea	15 (5.5)	1 (0.4)

	n (%)
Steroid Use, n (%) • Yes • Missing	69 (25.4) 61 (22.4)
EV cycles, median (range)	5 (1–28)
P cycles, median (range)	5 (1–28)
Dose modifications/interruptions: EV, n (%)	102 (37.5)
Dose interruptions: P, n (%)	88 (32.5)
Permanent discontinuation of EV due to toxicity, n (%)	28 (10.3)
Permanent discontinuation of P due to toxicity, n (%)	37 (13.6)

No additional safety signals associated with EV+P were identified in the GUARDIANS analysis

Median follow-up: 6 months.

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; EV, enfortumab vedotin; P, pembrolizumab; TEAE, treatment-emergent adverse event.

Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715.

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Summary of baseline characteristics in European RWE and EV-302

European RWE data

Parameter	Austrian registry[1] (N=138)	GUARDIANS[2] (N=272)
Age, years		
Median age	71	70
ECOG PS, n (%)		
0–1	125 (90.6)	217 (79.8)
2	9 (6.5)	45 (16.5)
3	4 (2.9)	10 (3.7)
Hepatic metastases	23 (16.7)	61 (22.4)

EV-302 pivotal clinical trial data

Parameter	EV-302[3] (N=442)
Age, years	
Median age	69
ECOG PS, n (%)	
0–1	427 (96.7)
2	15 (3.4)
3	–
Hepatic metastases	100 (22.6)

Data shown are for illustrative purposes only; direct comparisons should not be drawn

Median follow-up: Austrian registry: 5.4 months; GUARDIANS: 6 months; EV-302: 29.1 months.

ECOG PS, Eastern Cooperative Oncology Group performance status; RWE, real-world evidence.

1. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 2. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 3. Powles TB et al. Presented at ASCO GU 2025. Abstract #664.

Job code: MAT-NL-PAD-2025-00040

Summary of efficacy outcomes in European RWE and EV-302

European RWE data

Parameter	Austrian registry[1] (N=138)	GUARDIANS[2] (N=272)
Outcome, %		
ORR	69.1	56.6
CR	20.3	10.3
PR	48.8	46.3
DCR	82.1	69.1
mPFS		
Months (95% CI)	NR (9.84–NR)	13 (5.2–20.8)
mOS		
Months (95% CI)	NR (NR–NR)	NR (NR–NR)

EV-302 pivotal clinical trial data

Parameter	EV-302[3] (N=442)
Outcome, %	
ORR	67.5
CR	30.4
PR	37.1
DCR	–
mPFS	
Months (95% CI)	12.5 (10.4–16.6)
mOS	
Months (95% CI)	33.8 (26.1–39.3)

Data shown are for illustrative purposes only; direct comparisons should not be drawn

Median follow-up: Austrian registry: 5.4 months; GUARDIANS: 6 months; EV-302: 29.1 months.

CI, confidence interval; CR, complete response; DCR, disease control rate; mOS, median overall survival; mPFS; median progression-free survival; NR, not reached; ORR, objective response rate; PR, partial response; RWE, real-world evidence.

1. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 2. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 3. Powles TB et al. Presented at ASCO GU 2025. Abstract #664.

Job code: MAT-NL-PAD-2025-00040

Summary of safety outcomes in European RWE and EV-302

European RWE data

Parameter	Austrian registry[1] (N=138)	GUARDIANS[2] (N=272)
Toxicity, %		
All grades	70.0	78.7
Grade ≥3	36.2	32.3
Treatment		
EV dose reduction, n (%)	63 (45.6)	102 (37.5)
Number of cycles		
EV, median (range)	–	5 (1–28)
P, median (range)	6 (1–26)	5 (1–28)

EV-302 pivotal clinical trial data

Parameter	EV-302[3,4] (N=442)
Toxicity, %[3]	
All grade	97.3
Grade ≥3	57.3
Treatment[4]	
EV dose reduction, n (%)	(43.0)
Number of cycles[4]	
EV, median (range)	9 (1–54)
P, median (range)	11 (1–35)

Data shown are for illustrative purposes only; direct comparisons should not be drawn

Median follow-up: Austrian registry: 5.4 months; GUARDIANS: 6 months; EV-302: 29.1 months.

EV, enfortumab vedotin; P, pembrolizumab; RWE, real-world evidence.

1. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 2. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 3. Powles T, presented at ASCO GU 2025. Abstract #664;
4. Gupta S et al. Presented at ASCO 2025. Abstract #4502.

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The outcomes observed in Austrian and German real-world data were consistent with those seen in EV-302

- Real-world data on EV+P from Austria and Germany are consistent with the findings of the pivotal EV-302 trial[1–4]
- Longer follow-up and treatment sequences are needed[5]
- No additional safety signals were identified and the safety profile of EV+P in real-world data is consistent with EV-302[1–3]
- Future analyses will include variant histology, secondary resection/local therapy, and the impact of biomarkers[5]

1L, first line; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; P, pembrolizumab; RWE, real-world evidence; SOC, standard of care.

1. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 2. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 3. Powles T et al. *Ann Oncol* 2024;35:485–490; 4. EAU. Muscle-invasive and metastatic bladder cancer. Available at: https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. Last accessed: June 2025; 5. Speaker's own opinion.

The UNITE study investigated real-world outcomes in patients with LA/mUC treated with targeted therapies including EV monotherapy and later, EV+P: Overview

Design[1]

Retrospective, multicentre, real-world study in the US

Cohorts[1–3]

Included analyses in EV monotherapy cohort and EV+P cohort

Aim[1]

Assess **outcomes**, **AEs**, and **biomarkers** in patients with **LA/mUC treated** with **targeted therapies** (including EV-based regimens)

AE, adverse event; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; P, pembrolizumab; UC, urothelial carcinoma; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. Jindal T et al. Presented at ESMO 2024. Abstract 1988P; 3. Jindal T et al. Presented at ASCO GU 2025. Abstract 867.

The UNITE study investigated real-world outcomes of EV+P in the US: Baseline characteristics*

Demographics and baseline characteristics	N=171
Sex, n (%)	
Male	124 (73)
Female	47 (27)
Age, years	
Median (range)	71 (36–91)
Race, n (%)	
Caucasian	143 (84)
Non-Caucasian	26 (15)
Unknown	2 (1)
Smoking history, n (%)	
Yes	104 (61)
No	65 (38)
Unknown	2 (1)
ECOG PS, n (%)	
0/1	126 (74)
≥2	38 (22)
Unknown	7 (4)

Demographics and baseline characteristics	N=171
Primary tumour location, n (%)	
Lower tract	133 (78)
Upper tract	38 (22)
Unknown	0
Histology, n (%)	
Pure urothelial	107 (62)
Variant histology	56 (33)
Pure variant	8 (5)
Prior therapy lines, n (%)	
<2	150 (88)
≥2	21 (12)
Site of metastases, n (%)	
LN-only disease	52 (30)
Visceral metastases	77 (45)
Liver metastases	27 (15)
Bone metastases	44 (26)

*Cohort included patients who received EV+P treatment outside of clinical trials.
ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; LN, lymph node; P, pembrolizumab; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.
Jindal T et al. Presented at ESMO 2024. Abstract 1988P.

Job code: MAT-NL-PAD-2025-00040

The UNITE study investigated real-world outcomes of EV+P in the US: Initial efficacy outcomes

Treatment and survival outcomes (N=171 at 14 US sites)				
Efficacy parameter	**Population**			
	All (n=171)	**Frontline (n=101)**	**Treatment refractory (n=70)**	**Prior ICI (n=35)**
12-month OS, % (95% CI)	58 (48–71)	67 (54–83)	52 (39–71)	56 (39–81)
12-month PFS, % (95% CI)	31 (21–45)	30 (15–60)	30 (19–49)	32 (17–58)
ORR, % (95% CI)	51 (42–60)	54 (41–65)	47 (34–61)	41 (24–61)
DCR, %	84	88	80	76
mFU, months	5.5	5.3	8.3	11.7

Median follow-up in the overall population: 5.5 months.

CI, confidence interval; DCR, disease control rate; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; mFU, median follow-up; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

Jindal T et al. Presented at ESMO 2024. Abstract 1988P.

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Subsequent UNITE analysis evaluated EV+P in patients with prior ICI: Baseline characteristics

In a retrospective analysis of the UNITE study (N=220 patients who received EV+P), patients treated with ICI prior to receiving EV+P were identified (n=43)[1,2]

Demographics and baseline characteristics of patients previously treated with ICI[1,2]

n (%)	n=43
Sex	
Male	34 (79)
Female	9 (21)
Race	
Caucasian	40 (93)
Non-Caucasian	3 (7)
Primary tumour location	
Lower tract	28 (65)
Upper tract	15 (35)
Histology	
Pure urothelial	27 (63)
Variant histology	12 (28)
Pure variant	4 (9)
Liver metastases	9 (21)

n (%)	n=43
ECOG PS	
0/1	29 (67)
≥2	11 (26)
Unknown	3 (7)
Prior ICI	
Peri-operative	4 (9)
Nivolumab	3
Pembrolizumab	1
Metastatic	39 (91)
Pembrolizumab	19
Avelumab maintenance	8
Nivolumab	6
Pembrolizumab maintenance	2
Atezolizumab	1
Ipilimumab/nivolumab	1
Durvalumab/tremelimumab	1
Nivolumab/NKTR-214	1

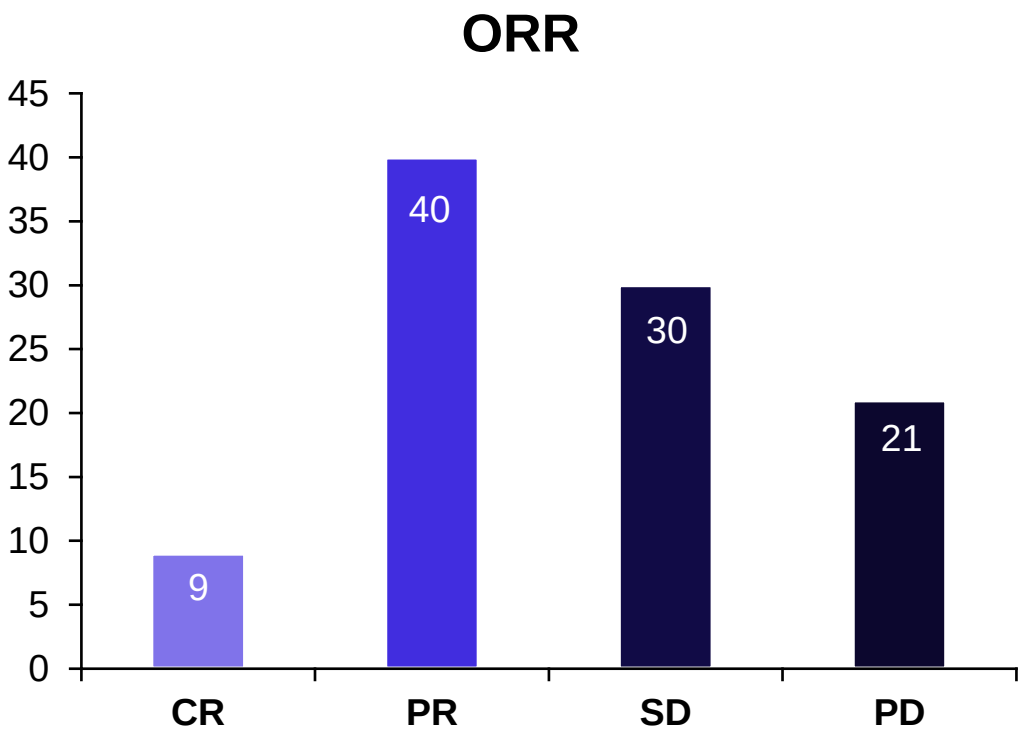
Median follow-up: 14 months.

ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; P, pembrolizumab; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

1. Jindal T et al. Presented at ASCO GU 2025. Abstract 867; 2. UroToday.com. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-bladder-cancer/158264-asco-gu-2025-outcomes-of-enfortumab-vedotin-and-pembrolizumab-for-patients-previously-treated-with-immune-checkpoint-inhibitors-in-the-unite-study.html. Last accessed: June 2025.

Job code: MAT-NL-PAD-2025-00040

Subsequent UNITE analysis evaluated EV+P in patients with prior ICI: Efficacy outcomes



Treatment and survival outcomes	N=43
mFU, months	14
mOS, months (95% CI)	15.4 (8.7–NR)
mPFS, months (95% CI)	6.9 (3.9–12.2)
ORR, % (95% CI)	48 (31–66) [16/33]
DCR (CR/PR/SD), % (95% CI)	79 (65–93) [26/33]

Median follow-up: 14 months.

CI, confidence interval; CR, complete response; DCR, disease control rate; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; mFU, median follow-up; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, observed response rate; P, pembrolizumab; PR, partial response; SD, stable disease; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

Jindal T et al. Presented at ASCO GU 2025. Abstract 867. UroToday.com. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-bladder-cancer/158264-asco-gu-2025-outcomes-of-enfortumab-vedotin-and-pembrolizumab-for-patients-previously-treated-with-immune-checkpoint-inhibitors-in-the-unite-study.html. Last accessed: June 2025.

More to come…

Upcoming analyses of patients in the UNITE study treated with EV+P

- Outcomes of patients with variant histology subtypes treated with EV+P
- Prognostic scores for mUC treated with EV+P treatment
- AEs associated with EV+P treatment
- Biomarkers of subsets of interest

AE, adverse event; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.
Speaker's own opinion.

The Mayo Clinic analysis evaluated real-world outcomes of patients receiving EV+P in the US: Overview[1,2]

Design

Retrospective, real-world study, from a single centre in the US

Cohort

Patients with LA/mUC within the Mayo Clinic who completed ≥1 cycle of EV+P (July 2022–Aug 2024)

Aim

Assess **outcomes** of **EV+P** in patients with LA/mUC in the real-world clinical setting

EV, enfortumab vedotin; LA, locally advanced; mUC, metastatic urothelial carcinoma; P, pembrolizumab.

1. Jain P et al. Presented at ASCO GU 2025. Abstract 745; 2. UroToday.com. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-bladder-cancer/158303-asco-gu-2025-clinical-efficacy-of-enfortumab-vedotin-pembrolizumab-in-locally-advanced-or-metastatic-urothelial-carcinoma-a-real-world-retrospective-study.html. Last accessed: June 2025.

The Mayo Clinic analysis evaluated real-world outcomes of patients receiving EV+P in the US: Baseline characteristics

Variable	mUC (n=98)	LA (n=22)
Age, years		
Median (IQR)	72 (65–77)	
Sex, n (%)		
Female Male	32 (32.6) 66 (67.3)	8 (36.3) 14 (63.6)
Race, n (%)		
White Non-White	90 (91.8) 8 (8.1)	19 (86.3) 3 (13.6)
Ethnicity, n (%)		
Hispanic or Latino Non-Hispanic or Latino	1 (1.0) 97 (98.9)	0 (0.0) 22 (100.0)

Median follow-up: 7.1 months.

EV, enfortumab vedotin; IQR, interquartile range; LA, locally advanced; mUC, metastatic urothelial carcinoma; P, pembrolizumab.

Jain P et al. Presented at ASCO GU 2025. Abstract 745. UroToday.com. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-bladder-cancer/158303-asco-gu-2025-clinical-efficacy-of-enfortumab-vedotin-pembrolizumab-in-locally-advanced-or-metastatic-urothelial-carcinoma-a-real-world-retrospective-study.html. Last accessed: June 2025.

The Mayo Clinic analysis evaluated real-world outcomes of patients receiving EV+P in the US: Efficacy outcomes (1/2)

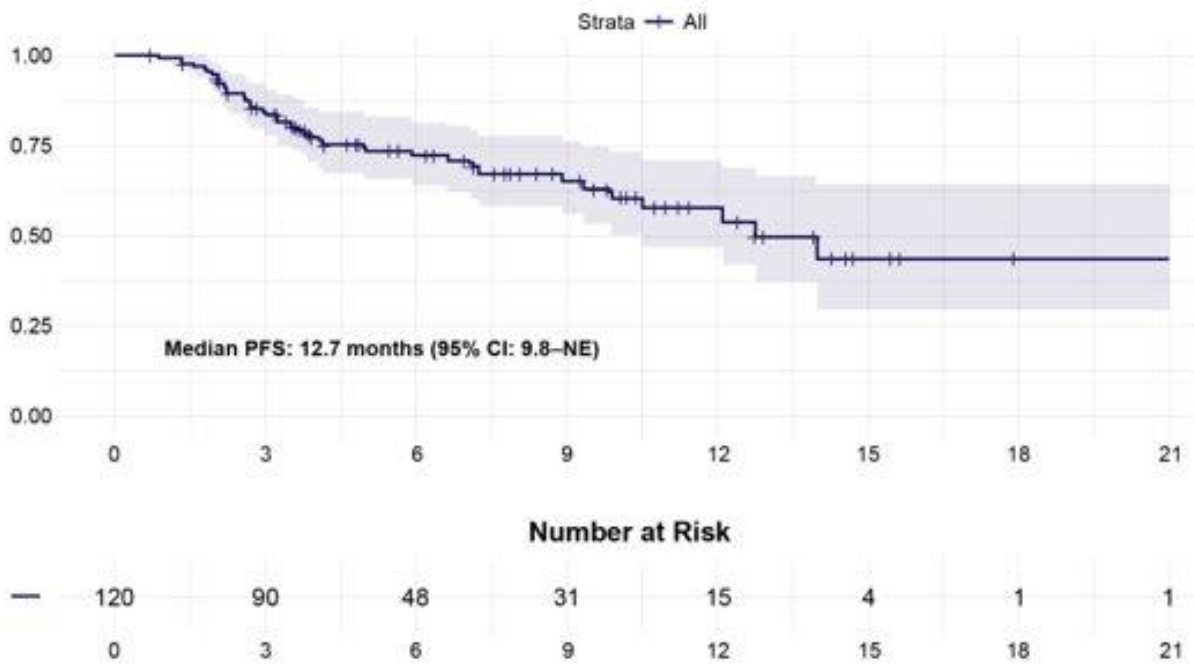
Best overall response across patient subgroups				
	mUC			LA
	Overall mUC (n=98)	LTUC (n=62)	UTUC (n=36)	(n=22)
Best overall response, n (%)				
CR	23 (23.4)	13 (20.9)	10 (28.5)	11 (50.0)
PR	49 (52.6)	31 (50.0)	18 (50.0)	7 (31.8)
SD	6 (6.4)	2 (3.2)	4 (11.4)	2 (9.0)
PD	10 (10.7)	9 (15.5)	1 (2.8)	2 (9.0)
MR	7 (7.5)	5 (8.6)	2 (5.7)	0 (0)

Median number of treatment cycles to first response:
3 (IQR: 2.3–4.0)

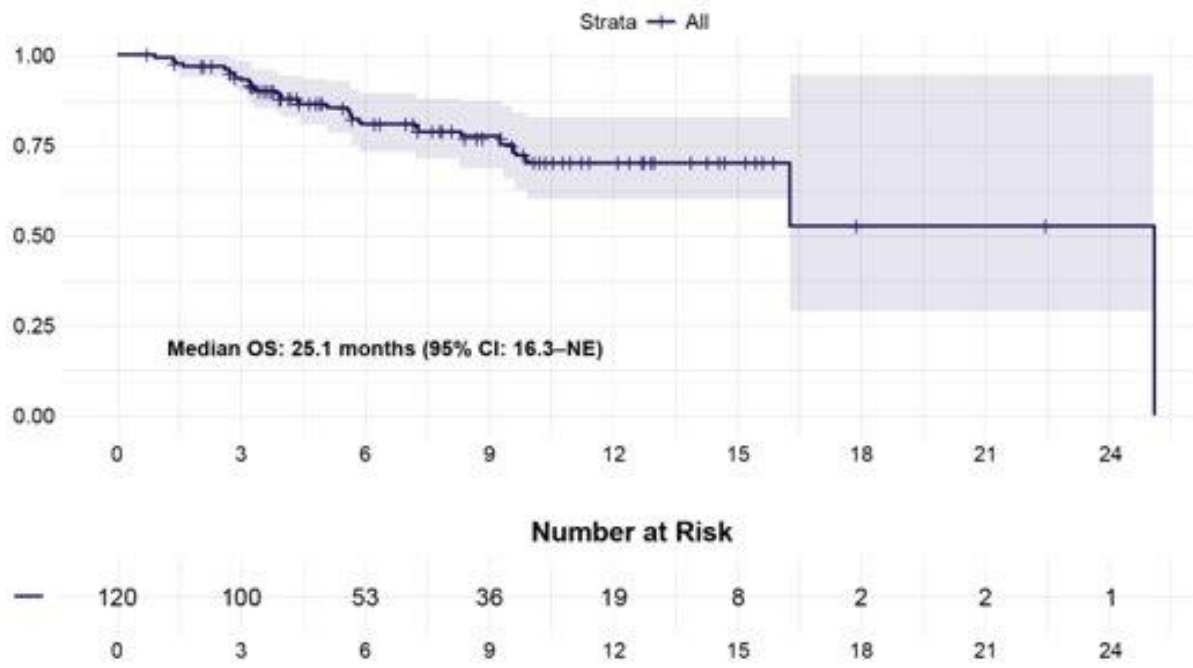
Median follow-up: 7.1 months.
Percentages may not equal 100 due to rounding.
CR, complete response; EV, enfortumab vedotin; IQR, interquartile range; LA, locally advanced; LTUC, lower-tract urothelial carcinoma; MR, mixed response; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease; UTUC, upper-tract urothelial carcinoma.
Jain P et al. Presented at ASCO GU 2025. Abstract 745. UroToday.com. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-bladder-cancer/158303-asco-gu-2025-clinical-efficacy-of-enfortumab-vedotin-pembrolizumab-in-locally-advanced-or-metastatic-urothelial-carcinoma-a-real-world-retrospective-study.html. Last accessed: June 2025.

The Mayo Clinic analysis evaluated real-world outcomes of patients receiving EV+P in the US: Efficacy outcomes (2/2)

Kaplan-Meier curve for OS



Kaplan-Meier curve for PFS



Median follow-up: 7.1 months.

CI, confidence interval; EV, enfortumab vedotin; NE, not evaluable; OS, overall survival; P, pembrolizumab; PFS, progression-free survival.

Jain P et al. Presented at ASCO GU 2025. Abstract 745. UroToday.com. Available at: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-bladder-cancer/158303-asco-gu-2025-clinical-efficacy-of-enfortumab-vedotin-pembrolizumab-in-locally-advanced-or-metastatic-urothelial-carcinoma-a-real-world-retrospective-study.htm. Last accessed: June 2025.

Summary of US RWE efficacy outcomes with EV+P

US RWE data

Parameter	Study	
	UNITE[1] (N=171)	Mayo Clinic[2] (N=120)
ORR, %	51	75
mPFS, months (95% CI)	Immature	12.7
mOS, months (95% CI)	Immature	25.1
mFU, months	5.5	7.1

EV-302 clinical trial data

Parameter	Study
	EV-302[3] (N=442)
ORR, %	67.5
mPFS, months (95% CI)	12.5 (10.4–16.6)
mOS, months (95% CI)	33.8 (26.1–39.3)
mFU, months	29.1

Data shown are for illustrative purposes only; direct comparisons should not be drawn

ORR, mPFS, and mOS are generally consistent with those in EV-302, although numerically lower in some real-world patient subsets[1–3]

A broader population of patients are receiving EV+P in the real-world setting vs. the EV-302 clinical trial[1–4]

We are currently awaiting more mature data for overall survival outcomes in the real-world setting

US real-world EV+P efficacy outcomes are consistent with EV-302

Median follow-up: UNITE: 5.5 months; Mayo Clinic: 7.1 months; EV-302: 29.1 months.
CI, confidence interval; EV, enfortumab vedotin; mFU, median follow-up; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; P, pembrolizumab; PFS, progression-free survival; RWE, real-world evidence; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.
1. Jindal T et al. Presented at ASCO GU 2025. Abstract 867; 2. Jain P et al. Presented at ASCO GU 2025. Abstract 745; 3. Powles T. Presented at ASCO GU 2025. Abstract 664; 4. Powles T et al. *N Engl J Med* 2024;390:875–888.

Did real-world use of EV+P reflect the EV-302 trial results?

UNITE/Mayo clinic data are not fully mature to assess OS, although more recent analyses preliminarily confirm expected outcomes[1–3]

Safety analysis was not available for the US data; however, no additional safety signals were identified in the European real-world data, and the **safety profile of EV+P was consistent with EV-302[1–3]**

As we continue to accumulate experience with EV+P in the **real-world patient population**, these data appear **consistent with efficacy outcomes from EV-302[1–5]**

EV, enfortumab vedotin; OS, overall survival; P, pembrolizumab.

1. Jindal T et al. Presented at ASCO GU 2025. Abstract 867; 2. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 3. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 4. Jain P et al. Presented at ASCO GU 2025. Abstract 745; 5. Powles T. Presented at ASCO GU 2025. Abstract 664.

Job code: MAT-NL-PAD-2025-00040

Genitourinary Masterclass

EV monotherapy in the real world: Insights from Europe and the US

Did real-world use of EV monotherapy reflect the EV-301 trial results?

EV as monotherapy is indicated for the treatment of adult patients with LA/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor.[1]

1L, first-line; EV, enfortumab vedotin; LA, locally advanced; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PD-1/L1, PD-1/L1, programmed cell death protein 1/ligand 1;

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry analysis evaluated clinical outcomes of patients receiving EV monotherapy: Overview

Design

Retrospective, multicentre, real-world study from 16 centres in Austria

Cohort

A total of 128 patients with advanced UC who had received EV monotherapy outside of a clinical trial setting

Aim

Investigate the **efficacy** and **tolerability** of **EV monotherapy** in a real-world setting

EV, enfortumab vedotin; UC, urothelial carcinoma.

Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry evaluated real-world outcomes of patients receiving EV: Baseline characteristics (1/2)

Demographics and clinical characteristics	N=128 n (%)*
Sex	
Female	34 (26.6)
Male	94 (73.4)
Age, years	
Median age (range)	69 (34–90)
<75	92 (71.9)
≥75	36 (28.1)
ECOG PS	
0	56 (43.8)
1	40 (31.3)
2	19 (14.8)
3	11 (8.6)
N/A	2 (1.6)
BMI, kg/m^2	
Median (range)	24 (15–54)
<30	105 (82.0)
≥30	20 (15.6)
N/A	3 (2.3)
Number of comorbidities	
0	42 (32.8)
1	29 (22.7)
≥2	57 (44.5)

Demographics and clinical characteristics	N=128 n (%)*
FGFR3 alterations	
Positive	18 (14.0)
Negative	63 (49.2)
N/A	47 (36.7)
Number of previous therapy lines (immunotherapy and chemotherapy)	
None†	3 (2.3)
1–2	94 (73.4)
3	17 (13.3)
4	8 (6.3)
N/A	6 (4.7)
Previous definitive therapy of primary tumour	
RC/NU	86 (67.2)
Radiochemotherapy	4 (3.1)
None	38 (29.7)
Previous systemic therapy	
Immunotherapy and chemotherapy	112 (87.5)
Immunotherapy only	4 (3.1)
Chemotherapy only	3 (2.3)
N/A	8 (6.3)
Neo/adjuvant therapy	
Received	27 (21.1)
None	94 (73.4)
N/A	7 (5.5)

Percentages may not equal 100 due to rounding.*Values are n (%) unless otherwise specified;
†Three patients received EV as first-line therapy.
BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; N/A, not available; NU, nephroureterectomy; RC, radical cystectomy; UC, urothelial carcinoma.
Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry evaluated real-world outcomes of patients receiving EV: Baseline characteristics (2/2)

Demographics and clinical characteristics	N=128 n (%)
Comorbidities	
Diabetes mellitus	25 (29.1)
Severe CKD (GFR <30 ml/min)	9 (10.5)
Moderate CKD (GFR <60 ml/min)	46 (53.5)
Cardiac disorder	43 (50.0)
Pulmonary disease	21 (24.4)
Peripheral vascular disease	19 (22.1)
Cerebrovascular disease	9 (10.5)
Liver disease	5 (5.8)
Histology subtype of primary disease	
Pure UC*	113 (88.3)
Mixed type	10 (7.8)
Squamous cell carcinoma	3 (2.3)
Nested	1 (0.8)
Ductus-bellini	1 (0.8)

Demographics and clinical characteristics	N=128 n (%)
Location of metastases	
Lymph nodes	105 (82.0)
Lymph nodes only	32 (25.0)
Lung	44 (34.4)
Liver	39 (30.5)
Bone	39 (30.5)
Brain	7 (5.5)
Other†	26 (20.3)
PD-L1 status	
CPS ≥10	30 (23.4)
CPS <10	60 (46.9)
N/A	38 (29.7)

Percentages may not equal 100 due to rounding.
*Inclusive of one patient with sarcomatoid differentiation; †Others including peritoneum (10), local relapse (10), adrenal gland (9), skin (2), and penile (1).
CKD, chronic kidney disease; CPS, combined positive score; EV, enfortumab vedotin; GFR, glomerular filtration rate; PD-L1, programmed cell death ligand 1; UC, urothelial carcinoma.
Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry evaluated real-world outcomes of patients receiving EV: Efficacy outcomes

Efficacy parameter	N=128
mFU, months	6.2
OS	
Median, months (range)	10.75 (0–42.7)
1-year OS, % (95% CI)	42.0 (31.4–42.5)
PFS	
Median, months (range)	4.8 (0–42.7)
1-year PFS, % (95% CI)	26.0 (17.5–34.6)
DCR, % (95% CI)	46.9 (38.5–55.5)
ORR, % (95% CI)	31.3 (23.9–39.8)
Best response, n %	
CR	11 (8.6)
PR	29 (22.7)
SD	20 (15.6)
PD	45 (35.1)
N/A	9 (7.0)

No differences in efficacy were observed by sex, BMI, PD-L1 status, number of comorbidities, prior treatment lines, or tumour histology patient subgroups

- Patients without liver lesions had a significantly longer mPFS (6.5 vs. 3.0 m; p=0.0027) and mOS (13.8 vs. 7.5 m; p=0.0187) than patients with liver lesions
- Patients with lower ECOG PS (0–1) experienced significant benefit in ORR 40.0% vs. 12.0%; p=0.007), mPFS (5.3 vs. 2.4 m; p<0.0001) and mOS (11.8 vs. 2.8 m;p<0.0001) versus ECOG PS 2–3

No significant differences were observed in OS between patients with reduced EV dose after experiencing AEs compared to those who received the full dose continuously (13.8 vs 9.7 m; p=0.1178)

Median follow-up: 6.2 months.

AE, adverse event; BMI, body mass index; CI, confidence interval; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; m, month; mFU, median follow-up; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; N/A, not applicable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease.

Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Job code: MAT-NL-PAD-2025-00040

The Austrian patient registry evaluated real-world outcomes of patients receiving EV: Safety outcomes

TRAEs (N=128)	Any grade, n (%)	Grade ≥3, n (%)
Any event	97 (75.8)	33 (25.8)
Skin disorder	46 (35.9)	7* (5.4)
Gastrointestinal disorder	35 (27.3)	4 (3.1)
Peripheral sensory neuropathy	33 (25.8)	7 (5.4)
General deterioration	19 (14.8)	2† (1.5)
Blood and lymphatic disorder	13 (10.2)	N/A
Eye disorder	13 (10.2)	0
Cardiac disorder	5 (3.9)	1‡ (0.7)
Endocrine disorder (hyperglycaemia)	4 (3.1)	0
Respiratory disorder	4 (3.1)	3¶ (2.3)
Psychiatric disorder	4 (3.1)	0
Infectious disease	11 (8.6)	5§ (3.9)
Others††	16 (12.5)	0

Number of patients with TRAEs of special interest:

- Grade ≥3 SJS: 3 (2.3%)
- Grade 3/4 ILD-pneumonitis: 3 (2.3%)
- Grade 5 AE (heart attack and TEN): 2 (1.6%), the latter considered to be EV-related by the treating physician

No additional safety signals associated with EV monotherapy were identified in the Austrian patient registry analysis

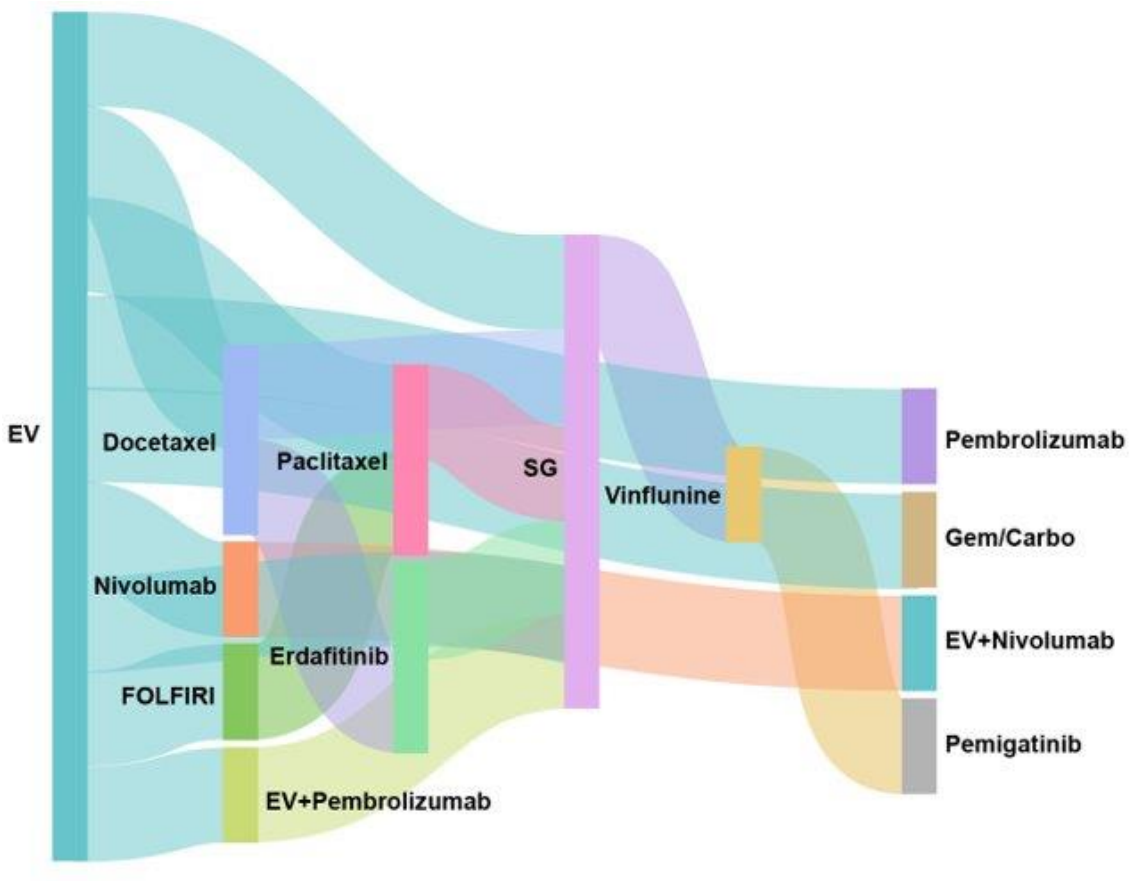
Median follow-up: 6.2 months.
Percentage may not equal to 100 because of rounding;
TRAEs were defined as treatment-relaed adverse events which were graded as per CTCAE version 5.0, as determined by the treating physician.
*Including Grade ≥3 SJ (n=2) and fatal Grade 5 TEN (n=1); †Including Grade ≥3 fatigue (n=1) and Grade ≥3 loss of appetite (n=1); ‡Fatal event (heart attack) assessed as not related to EV therapy by the treating physician; ¶Including Grade ≥3 ILD (n=3); §Including infections of the urinary tract (n=2), the respiratory tract (n=2) and the gastrointestinal tract (n=1); ††Others included hyponatremia (n=2), vertigo (n=2), hypocalcaemia (n=1), tumour lysis syndrome (n=1), and DVT (n=1).
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DVT. deep vein thrombosis; EV, enfortumab vedotin; ILD, interstitial lung disease; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TRAE, treatment-related adverse event.
Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Job code: MAT-NL-PAD-2025-00040

Subsequent therapies in the Austrian patient registry

Treatment received by patients after discontinuation of EV treatment	
Chemotherapy (n=10)	Vinflunine (n=4)
	Paclitaxel (n=2)
	Docetaxel (n=2)
	FOLFIRI (n=1)
	Carboplatin + gemcitabine (n=1)
Antibody–drug conjugate targeting TROP-2 (n=6)	Sacituzumab-govitecan (n=6)
Immune checkpoint inhibitor (n=5)	Nivolumab (n=1)
	Nivolumab + EV (n=1)
	Pembrolizumab (n=2)
	Pembrolizumab + EV (n=1)
FGFR inhibitor (n=4)	Erdafitinib (n=3)
	Pemigatinib (n=1)

Therapy lines following EV monotherapy



Not all agents used as subsequent therapies are licensed for UC in UK/EMEA. Please check the SmPC for the indication of all agents

Carbo, carboplatin; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; Gem, gemcitabine; TROP-2, trophoblast surface antigen-2; SG, sacituzumab govitecan.

Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Job code: MAT-NL-PAD-2025-00040

The GUARDIANS analysis evaluated real-world outcomes of patients receiving EV monotherapy in Germany and Switzerland: Overview

Design

Retrospective, multicentre, real-world study including 25 Swiss and German hospitals and private practices

Cohort

A total of 188 patients with LA/mUC who received EV monotherapy

Aim

Assess **efficacy** and **safety** of **EV monotherapy** in a European cohort of real-world patients

EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma.

Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553.

Job code: MAT-NL-PAD-2025-00040

The GUARDIANS analysis evaluated real-world outcomes of patients receiving EV monotherapy in Germany and Switzerland: Baseline characteristics

Demographics and clinical characteristics	N=188 n (%)*
Age, years	
Median (range)	66 (31–89)
≥75	42 (22.3)
Sex, male	127 (76.6)
ECOG PS	
0	68 (19.1)
1	73 (38.8)
2	20 (10.6)
≥3	6 (3.2)
Missing	21 (11.2)
Number of previous treatment lines	
0	1 (0.5)
1	8 (4.3)
2	99 (52.7)
3	48 (25.5)
4	26 (13.8)
5	6 (3.2)

Demographics and clinical characteristics	N=188 n (%)
Previous treatment	
PBCT	177 (94.1)
Cisplatin	146 (77.7)
Carboplatin	40 (21.3)
Vinflunine	54 (28.7)
Taxane	33 (17.6)
ICI	165 (87.8)
Pembrolizumab	97 (51.6)
Avelumab	47 (25.0)
Nivolumab	22 (11.7)
Atezolizumab	10 (5.3)
FGFR inhibitor	7 (3.7)
Sacituzumab govitecan	2 (1.1)

*Values presented are n (%) unless specified otherwise.
ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; ICI, immune checkpoint inhibitor; PBCT, platinum-based chemotherapy.
Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553.

Job code: MAT-NL-PAD-2025-00040

The GUARDIANS analysis evaluated real-world outcomes of patients receiving EV monotherapy in Germany and Switzerland: Efficacy outcomes

Efficacy parameter[1]	N=188, n (%)
mOS, months (95% CI)	12.00 (9.65–14.35)
mPFS, months (95% CI)	7.00 (5.43–8.57)
mFU, months	11.0
Best overall response, n (%) CR PR SD PD Unknown/could not be evaluated	 8 (4.3) 79 (42.0) 22 (11.7) 53 (28.2) 11 (5.9)
ORR, n (%)	87 (46.3)
DCR, n (%)	109 (58.0)

Median follow-up: 11 months.

CI, confidence interval; CR, complete response; DCR, disease control rate; EV, enfortumab vedotin; mFU, median follow-up; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1. Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553.

Job code: MAT-NL-PAD-2025-00040

Summary of European RWE efficacy outcomes with EV

European RWE data

Parameter	Austrian registry (N=128)[1]	GUARDIANS (N=188)[2]
Median age, years	69	66
Age ≥75 years, %	28.1	22.3
ECOG PS 0–1, %	75.1	69.6
ECOG PS 2, %	14.8	10.6
ECOG PS 3, %	8.6	3.2
Missing, %	–	11.2
Hepatic metastases, n (%)	39 (30.5)	–
Prior therapy lines ≥3, %	19.5	42.6
Outcomes, %		
ORR	31.3	46.3
CR	8.6	4.3
PR	22.7	42.0
DCR	46.9	58.0
mOS, months	10.8	12.0
mPFS, months	4.8	7.0

EV-301 clinical trial data

Parameter	EV-301 (N=301)[3]
Median age, years	68
Age ≥75 years, %	17.3
ECOG PS 0–1, %	100
ECOG PS 2, %	–
ECOG PS 3, %	–
Missing, %	–
Hepatic metastases, n (%)	93 (30.9)
Prior therapy lines ≥3, %	13.0
Outcomes, %	
ORR	41.3
CR	6.9
PR	34.4
DCR	71.9
mOS, months	12.9
mPFS, months	5.6

Data shown are for illustrative purposes only; direct comparisons should not be drawn

The European real-world studies demonstrated real-world efficacy consistent with data from EV-301

Median follow-up: Austrian registry: 6.2 months; GUARDIANS: 11.0 months; EV-301: 23.8 months.

CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance score; EV, enfortumab vedotin; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PD, progressive disease; PR, partial response; RWE, real-world evidence.

1. Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278; 2. Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553; 3. Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

The UNITE study evaluated real-world outcomes of patients receiving EV monotherapy in the US: Overview

Design

Retrospective, multicentre, real-world study from 16 centres in the US

Cohort

A total of 260 patients with advanced UC who received EV monotherapy

Aim

Assess **outcomes, AEs**, and **biomarkers** in LA/mUC treated patients with targeted therapies (including EV-based regimens)

Median time from the initial diagnosis to the date of advanced disease was 10.9 months. Median follow-up from the initial UC diagnosis to the last follow-up was 35.9 months.
AE, adverse event; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; UC, urothelial carcinoma; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.
Koshkin VS et al. *Cancer* 2022;128:1194–1205.

The UNITE study evaluated real-world outcomes of patients receiving EV monotherapy in the US: Baseline characteristics

Baseline characteristic	EV monotherapy (N=260)
Median age, years	71
Sex, %	
Male	79
ECOG PS, %	
0	29
1	50
2–4	21
Location of primary tumour, %	
Bladder	73
Upper urinary tract	25
Urethra	<1
Unknown	2

Baseline characteristic	EV monotherapy (N=260)
Histology, %	
Pure urothelial	68
Mixed urothelial predominant	27
Mixed variant predominant	2
Pure variant	1
Unknown	2
Metastatic disease sites, %	
LN or locoregional recurrence only	20
Liver	32
Visceral non-liver	48
Lines of therapy for metastatic disease before receiving EV, %*	
None	5
1	28
2	42
3	18
≥4	7

*PBCT and immunotherapy are indicated as neoadjuvant treatments in MIBC[2]

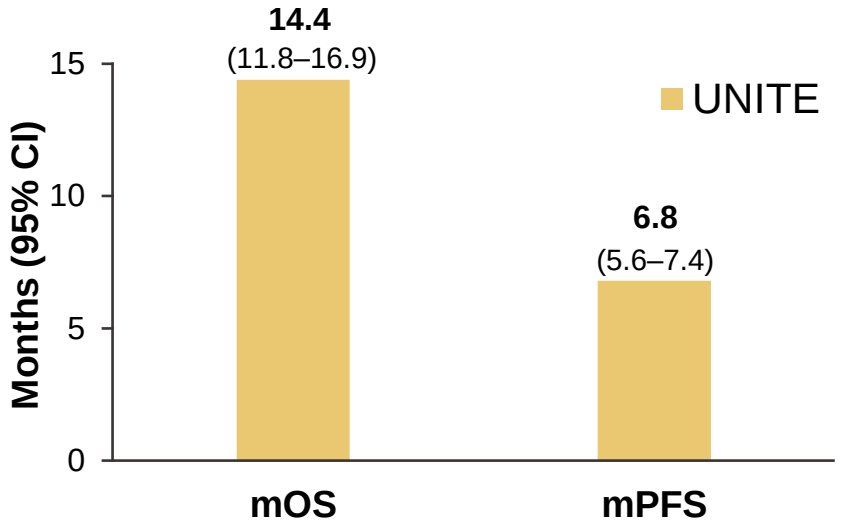
Median time from the initial diagnosis to the date of advanced disease was 10.9 months. Median follow-up from the initial UC diagnosis to the last follow-up was 35.9 months.

ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; LN, lymph node; MIBC, muscle-invasive bladder cancer; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

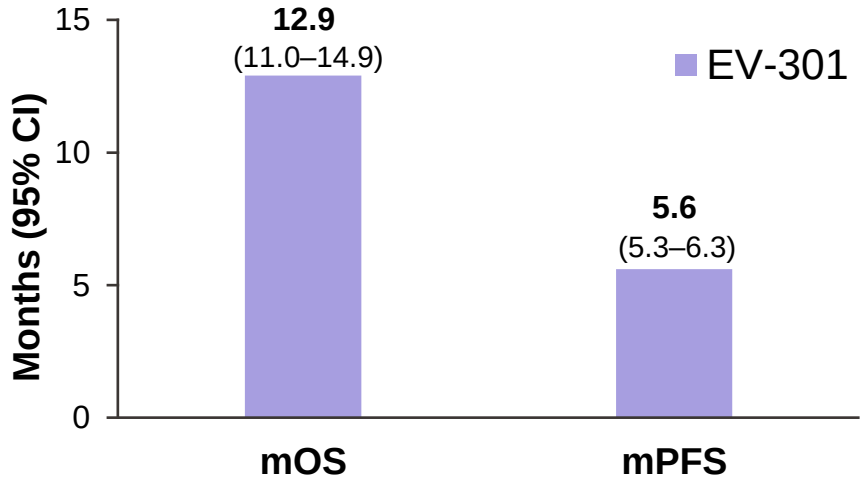
1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. EAU. Muscle-invasive and metastatic bladder cancer. Available at: https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. Last accessed: June 2025.

The UNITE study evaluated real-world outcomes of patients receiving EV monotherapy in the US: Efficacy outcomes

Efficacy outcomes for patients receiving EV from RWE[1]



Efficacy outcomes for patients receiving EV in EV-301[2]



UNITE and EV-301 are two different studies with distinct populations and so , cannot be compared directly

ORR 52%

ORR 41.3%

Clinical outcomes for patients treated with EV in the US were similar to outcomes in EV-301[1,2]

Median follow-up was 35.9 months in UNITE and 23.8 months in EV-301.[1,2]
CI, confidence interval; EV, enfortumab vedotin; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; RWE, real-world evidence; UC, urothelial carcinoma; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.
1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

Job code: MAT-NL-PAD-2025-00040

The UNITE study: EV showed similar efficacy for patient subgroups underrepresented or not included in EV-301

Patient subgroup[1]	Patients, n	ORR, % (95% CI)
ECOG PS		
0–1	173	56 (48–63)
2–3	34	41 (25–59)
Baseline neuropathy		
No	139	48 (40–57)
Yes	71	62 (50–73)
Baseline diabetes mellitus		
No	183	51 (44–59)
Yes	29	59 (39–76)
Renal function at baseline		
GFR ≥30 mL/min	187	54 (47–61)
GFR <30 mL/min	25	40 (22–61)
Patient age, years		
<75	139	53 (45–62)
≥75	69	51 (39–63)
Primary tumour location		
Bladder primary	151	50 (42–58)
Upper tract primary	56	61 (47–73)
FGFR3		
Wild type	102	54 (44–64)
Altered	28	57 (37–75)
Histology		
Pure urothelial	142	58 (49–66)
Variant histology component	66	42 (31–55)

ORRs in all subgroups were ≥40%[1]

Consistent responses were observed in populations that were not included in EV-301[1,2]

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; GFR, glomerular filtration rate; ORR, observed response rate; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.

1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. Powles T et al. *N Eng J Med* 2021;384:1125–1135.

Outcomes in patients with variant histology receiving EV monotherapy

Updated analysis including 566 patients treated with EV monotherapy:

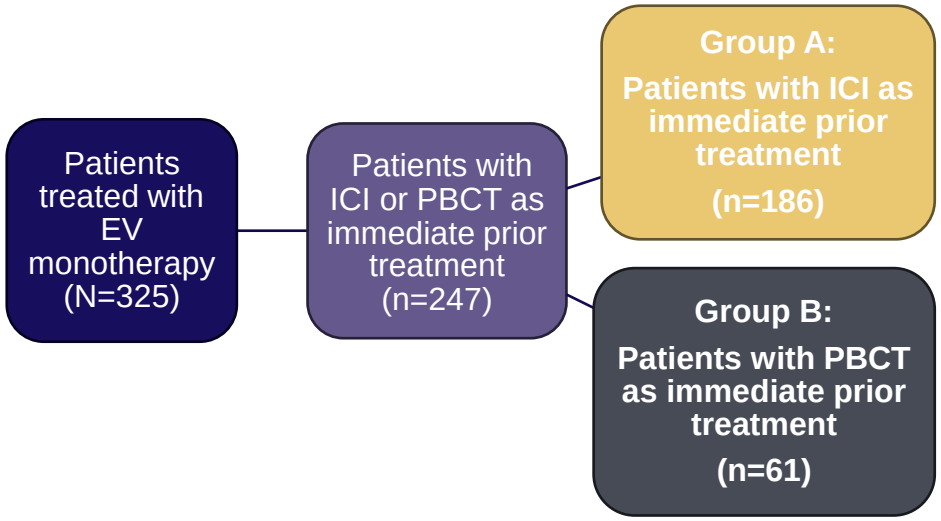
- There were 366 patients with pure urothelial histology: ORR 52%
- There were 200 patients with variant histology component: ORR 44%

Observed response rate based on variant histology component (N=200)

Variant histology	N	Overall ORR, % (n/n)	Urothelial predominant (<50% variant), n	Urothelial predominant ORR, % (n/n)	Variant predominant (50–99% variant), n	Variant predominant ORR, % (n/n)	Pure variant (100% variant), n	Pure variant ORR, % (n/n)
Squamous	94	47 (36/76)	70	55 (31/56)	17	33 (5/15)	7	0 (0/5)
Micropapillary	41	35 (12/34)	35	38 (11/29)	6	20 (1/5)	0	-
Plasmacytoid	23	53 (9/17)	18	64 (9/14)	2	Not evaluable	3	0 (0/3)
Sarcomatoid	21	47 (8/17)	15	38 (5/13)	4	100 (3/3)	2	0 (0/1)
Adenocarcinoma /glandular	9	56 (5/9)	8	63 (5/8)	1	0 (0/1)	0	-
NE/small cell	9	0 (0/8)	3	0 (0/3)	4	0 (0/3)	2	0 (0/2)
Nested	2	50 (1/2)	1	0 (0/1)	1	100 (1/1)	0	-
Lipid cell variant	1	100 (1/1)	1	100 (1/1)	0	-	0	-

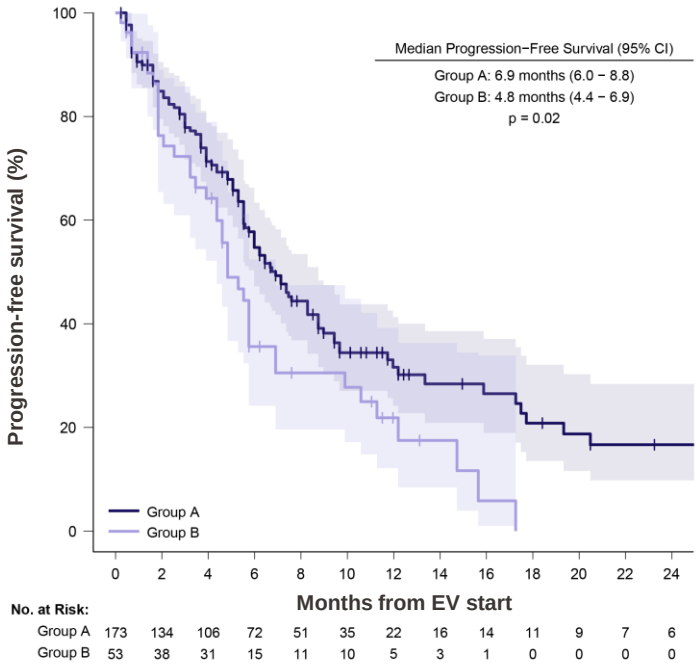
EV, enfortumab vedotin; NE, neuroendocrine; ORR, observed response rate.
Jindal T et al. Presented at ASCO GU 2024. Abstract #652.

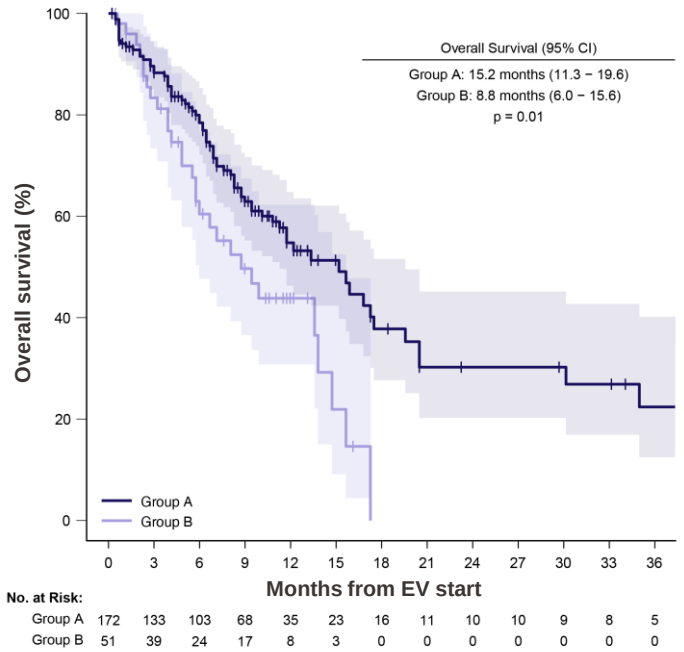
EV outcomes based on prior treatment in UNITE study



	Efficacy in patients with prior treatment			
	Overall (N=247)	Group A (n=186)	Group B (n=61)	P-value (A vs. B)
mOS, months	13.0	15.2	8.8	0.01
mPFS, months	6.0	6.9	4.8	0.02
ORR	52%	58%	37%	0.02

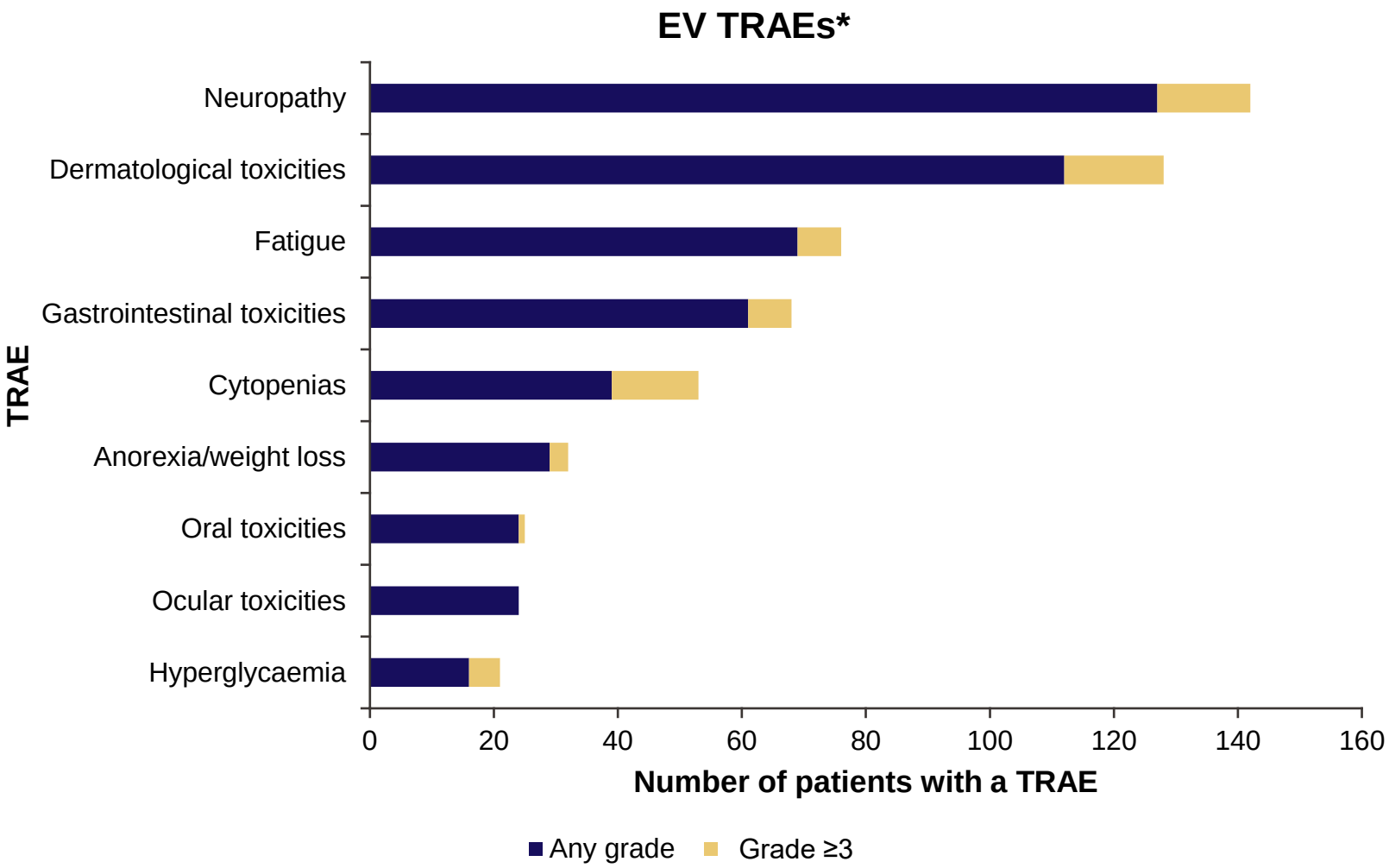
PFS and OS with EV in Group A (IC Ias immediate prior treatment) and Group B (PBCT as immediate prior treatment)





EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; mOS, median overall survival; mPFS, median progression-free survival, ORR, objective response rate; PBCT, platinum-based chemotherapy.
Koshkin V et al, Presented at ASCO GU 2023. Abstract 514

TRAEs reported with EV monotherapy in the UNITE study



371/539† patients had TRAEs attributed to EV

*Grade 5 TRAEs: sepsis (2), neutropenic sepsis (1), neutropenic fever (1), SJS (1); †Cohort included 539 patients treated with EV monotherapy in the Unite study.
EV, enfortumab vedotin; SJS, Stevens–Jonhson syndrome; TRAE, treatment-related adverse event; UNITE, Urothelial Cancer Network to Investigate Therapeutic Experiences.
Nizam et al, Presented at ESMO 2023. Abstract 2394P.

Did real-world use of EV monotherapy reflect the EV-301 trial results?

- Clinical outcomes with EV monotherapy in real-world cohorts are consistent with data from EV-301[1–4]
- Real-world data from Europe and the US show the potential efficacy of EV monotherapy, even in heavily pretreated patients[1–3]
- No additional safety signals associated with EV monotherapy were identified in the European and US analysis[1,5]
- EV monotherapy benefit extends to patient subsets excluded from EV-301 but frequently encountered in clinical practice (e.g., patients with low GFR)[3,4]

ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate.

1. Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278; 2. Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553; 3. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 4. Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054; 5. Nizam et al, Presented at ESMO 2023. Abstract 2394P.

Summary

RWE can help support findings from RCTs by providing insights to a broader patient population[1]

RWE on EV monotherapy and EV in combination with P in Europe and the US provided efficacy data consistent with data from EV-302 and EV-301, with no additional safety signals identified[2–8]

These findings demonstrate the value of EV outside of the RCT setting, and longer follow-up will provide greater insights into the real-world effectiveness of EV+P[2–8]

Ongoing insights from the clinical use of EV+P will enhance our ability to manage this treatment effectively, helping deliver the highest quality care to patients[9]

EV, enfortumab vedotin; P, pembrolizumab; RCT, randomised controlled trial; RWE, real-world evidence.

1. Azoulay L. *Oncologist* 2022;27:e731–e738; 2. Niedersüß-Beke D et al. Presented at ASCO GU 2025. Abstract 736; 3. Zschäbitz S et al. Presented at ASCO GU 2025. Abstract 715; 4. Jindal T et al. Presented at ESMO 2024. Abstract FPN1988P; 5. Jain P et al. Presented at ASCO GU 2025. Abstract 745; 6. Niedersüß-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278; 7. Zschäbitz S et al. Presented at ASCO GU 2024. Abstract 553; 8. Koshkin V et al, *Cancer* 2022:128:1194–1205; 9. Speaker's own opinion.

Genitourinary Masterclass

astellas

Please refer to the EMA SmPC for PADCEV™ (enfortumab vedotin) via the following link: https://www.ema.europa.eu/en/documents/product-information/padcev-epar-product-information_en.pdf

Please scan the QR code to access the UK aPI for PADCEV

Please scan the QR code to access the NL SmPC for PADCEV

PADCEV is subject to medicinal prescription.
Astellas Pharma B.V., Sylviusweg 62, 2333 BE Leiden, The Netherlands

EMA, European Medicines Agency; aPI, abbreviated Prescribing Information; SmPC, Summary of Product Characteristics.

ABBREVIATED SUMMARY OF PRODUCT CHARACTERISTICS

For full prescribing information refer to the Summary of Product Characteristics (SPC).

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. **NAME OF THE MEDICINAL PRODUCT:** Padcev 20 mg powder for concentrate for solution for infusion **&** Padcev 30 mg powder for concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION: Padcev 20 mg powder for concentrate for solution for infusion: One vial of powder for concentrate for solution for infusion contains 20 mg enfortumab vedotin. Padcev 30 mg powder for concentrate for solution for infusion: One vial of powder for concentrate for solution for infusion contains 30 mg enfortumab vedotin. After reconstitution, each mL of solution contains 10 mg of enfortumab vedotin. Enfortumab vedotin is comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker. For the full list of excipients, see section 6.1 of the SPC.

PHARMACEUTICAL FORM: Powder for concentrate for solution for infusion. White to off-white lyophilized powder.

CLINICAL PARTICULARS: Therapeutic indications: Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy. Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor (see section 5.1 of the SPC). **Posology and method of administration**: Treatment with Padcev should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Ensure good venous access prior to starting treatment (see section 4.4 of the SPC). Posology: As monotherapy, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SPC for additional dosing information of pembrolizumab.

Table 1. Recommended dose reductions of enfortumab vedotin for adverse reactions

	Dose level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Dose modifications

Table 2. Dose interruption, reduction and discontinuation of enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer

Adverse reaction	Severity*	Dose modification*
Skin reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialised care.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
	Grade 2 worsening Grade 2 with fever Grade 3	• Withhold until Grade ≤1. • Referral to specialised care should be considered. • Resume at the same dose level or consider dose reduction by one dose level (see Table 1).
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL). • Resume treatment at the same dose level.
Pneumonitis/ interstitial lung disease (ILD)	Grade 2	• Withhold until Grade ≤1, then resume at the same dose or consider dose reduction by one dose level (see Table 1).
	Grade ≥3	Permanently discontinue.
Peripheral neuropathy	Grade 2	• Withhold until Grade ≤1. • For first occurrence, resume treatment at the same dose level. • For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level (see Table 1).
	Grade ≥3	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe and Grade 4 is life threatening.

Special populations: *Elderly*: No dose adjustment is necessary in patients ≥65 years of age. *Renal impairment*: No dose adjustment is necessary in patients with mild [creatinine clearance (CrCL) >60–90 mL/min], moderate (CrCL 30–60 mL/min) or severe (CrCL 15–<30 mL/min) renal impairment. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see section 5.2 of the SPC). *Hepatic impairment*: No dose adjustment is necessary in patients with mild hepatic impairment [total bilirubin of 1 to 1.5 × upper limit of normal (ULN) and AST any, or total bilirubin ≤ ULN and AST > ULN]. Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given. *Paediatric population:* There is no relevant use of enfortumab vedotin in the paediatric population for the indication of locally advanced or metastatic urothelial cancer.

Method of administration

Padcev is for intravenous use. The recommended dose must be administered by intravenous infusion over 30 minutes. Enfortumab vedotin must not be administered as an intravenous push or bolus injection. For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6 of the SPC. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use**: Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Skin reactions: Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Mild to moderate skin reactions, predominantly rash maculo-papular, have been reported with enfortumab vedotin. The incidence of skin reactions occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue Padcev for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see section 4.2 of the SPC). Pneumonitis/ILD: Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin. The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold Padcev for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue Padcev for Grade ≥3 pneumonitis/ILD (see section 4.2 of the SPC). Hyperglycaemia: Hyperglycaemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with enfortumab vedotin (see section 4.8 of the SPC). Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m²). Patients with baseline HbA1c ≥8% were excluded from clinical studies. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), Padcev should be withheld until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate (see section 4.2 of the SPC). Serious infections: Serious infections such as sepsis (including fatal outcomes) have been reported in patients treated with Padcev. Patients should be carefully monitored during treatment for the emergence of possible serious infections. Peripheral neuropathy: Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions (see section 4.8 of the SPC). Patients with preexisting peripheral neuropathy Grade ≥2 were excluded from clinical studies. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin (see Table 1). Padcev should be permanently discontinued for Grade ≥3 peripheral neuropathy (see section 4.2 of the SPC). Ocular disorders: Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin (see section 4.8 of the SPC). Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen. Infusion site extravasation: Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred (see section 4.8 of the SPC). Ensure good venous access prior to starting Padcev and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions. Embryo-foetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus (see sections 4.6 and 5.3 of the SPC). Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 6 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 months following the last dose of Padcev. Patient information pack: The prescriber must discuss the risks of Padcev therapy, including combination therapy with pembrolizumab, with the patient. The patient should be provided with the patient information leaflet and patient card with each prescription. **Interactions:** Formal drug–drug interaction studies with enfortumab vedotin have not been conducted. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities. Strong CYP3A4 inducers may decrease the exposure of unconjugated MMAE with moderate effect (see section 5.2 of the SPC). **Undesirable effects**: Summary of the safety profile: *Enfortumab vedotin as monotherapy*: The safety of enfortumab vedotin was evaluated as monotherapy in 793 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), three phase 2 studies (EV-103, EV-201 and EV-203) and one phase 3 study (EV-301) (see Table 3). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 55.7 months). The most common adverse reactions with enfortumab vedotin were alopecia (47.7%), decreased appetite (47.2%), fatigue (46.8%), diarrhoea (39.1%), peripheral sensory neuropathy (38.5%), nausea (37.8%), pruritus (33.4%), dysgeusia (30.4%), anaemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycaemia (14.9%), dry eye (12.7%), alanine aminotransferase increased (12.7%) and rash (11.6%). The most common serious adverse reactions (≥2%) were diarrhoea (2.1%) and hyperglycaemia (2.1%). Twenty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (4.8%). Adverse reactions leading to dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (14.8%), fatigue (7.4%), rash maculo-papular (4%), aspartate aminotransferase increased (3.4%), alanine aminotransferase increased (3.2%), anaemia (3.2%), hyperglycaemia (3.2%), neutrophil count decreased (3%), diarrhoea (2.8%), rash (2.4%) and peripheral motor neuropathy (2.1%). Thirty-eight percent of patients required a dose reduction due to an adverse reaction; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (10.3%), fatigue (5.3%), rash maculo-papular (4.2%) and decreased appetite (2.1%). *Enfortumab vedotin in combination with pembrolizumab*: When enfortumab vedotin is administered in combination with pembrolizumab, refer to the SmPC for pembrolizumab prior to initiation of treatment. The safety of enfortumab vedotin was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in one phase 2 study (EV-103) and one phase 3 study (EV-302) (see Table 3). Patients were exposed to enfortumab vedotin in combination with pembrolizumab for a median duration of 9.4 months (range: 0.3 to 34.4 months). The most common adverse reactions with enfortumab vedotin in combination with pembrolizumab were peripheral sensory neuropathy (53.4%), pruritus (41.1%), fatigue (40.4%), diarrhoea (39.2%), alopecia (38.5%), rash maculo-papular (36%), weight decreased (36%), decreased appetite (33.9%), nausea (28.4%), anaemia (25.7%), dysgeusia (24.3%), dry skin (18.1%), alanine aminotransferase increased (16.8%), hyperglycaemia (16.7%), aspartate aminotransferase increased (15.4%), dry eye (14.4%), vomiting (13.3%), rash macular (11.3%), hypothyroidism (10.5%) and neutropenia (10.1%). The most common serious adverse reactions (≥2%) were diarrhoea (3%) and pneumonitis (2.3%). Thirty-six percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reactions (≥2%) leading to discontinuation were peripheral sensory neuropathy (12.2%) and rash maculo-papular (2%). Adverse reactions leading to dose interruption of enfortumab vedotin occurred in 72% of patients. The most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhoea (4.8%), fatigue (3.7%), pneumonitis (3.7%), hyperglycaemia (3.4%), neutropenia (3.2%), alanine aminotransferase increased (3%), pruritus (2.3%) and anaemia (2%). Adverse reactions leading to dose reduction of enfortumab vedotin occurred in 42.4% of patients. The most common adverse reactions (≥2%) leading to dose reduction were peripheral sensory neuropathy (9.9%), rash maculo-papular (6.4%), fatigue (3.2%), diarrhoea (2.3%) and neutropenia (2.1%). Tabulated summary of adverse reactions: Adverse reactions observed during clinical studies of enfortumab vedotin as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of enfortumab vedotin are listed in this section by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions in patients treated with enfortumab vedotin

	Monotherapy	In combination with pembrolizumab
Infections and infestations		
Common	Sepsis	Sepsis
Blood and lymphatic system disorders		
Very common	Anaemia	Anaemia
Not known[1]	Neutropenia, febrile neutropenia, neutrophil count decreased	Neutropenia, febrile neutropenia, neutrophil count decreased
Endocrine disorders		
Very common		Hypothyroidism
Metabolism and nutrition disorders		
Very common	Hyperglycaemia, decreased appetite	Hyperglycaemia, decreased appetite
Not known[1]	Diabetic ketoacidosis	Diabetic ketoacidosis
Nervous system disorders		
Very common	Peripheral sensory neuropathy, dysgeusia	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness	Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation	Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation
Eye disorders		
Very common	Dry eye	Dry eye
Respiratory, thoracic, and mediastinal disorders		
Very common		Pneumonitis/ILD[2]
Common	Pneumonitis/ILD[2]	
Gastrointestinal disorders		
Very common	Diarrhoea, vomiting, nausea	Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus, rash, rash maculo-papular, dry skin	Alopecia, pruritus, rash maculo-papular, dry skin, rash macular
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular	Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash papular, rash pruritic, rash vesicular, erythaema multiforme, dermatitis
Uncommon	Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister	Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis
Not known[1]	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema
Musculoskeletal and connective tissue disorders		
Common		Myositis
General disorders and administration site conditions		
Very common	Fatigue	Fatigue
Common	Infusion site extravasation	Infusion site extravasation
Investigations		
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased
Common		Lipase increased
Injury, poisoning and procedural complications		
Common	Infusion related reaction	Infusion related reaction

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organising pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity and sarcoidosis.

Description of selected adverse reactions: *Immunogenicity:* A total of 697 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-drug antibody (ADA), and in patients that were negative at baseline (N=681), a total of 24 (3.5%) were positive post baseline. A total of 490 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ADA, and in patients that were negative at baseline (N=466), a total of 14 (3%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following enfortumab vedotin administration as monotherapy and in combination with pembrolizumab. Due to the limited number of patients with antibodies against Padcev, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics. *Skin reactions*: In clinical studies of enfortumab vedotin as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 14% (108) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 8.2 months). Serious skin reactions occurred in 4.3% (34) of patients. Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥2 events. In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥2 events. *Pneumonitis/ILD*: In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.5%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months) and the median duration for pneumonitis/ILD was 1.6 months (range: 0.1 to 43.0 months). Of the 26 patients who experienced pneumonitis/ILD, 8 (30.8%) had resolution of symptoms. In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 2.1% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months). *Hyperglycaemia*: In clinical studies of enfortumab vedotin as monotherapy, hyperglycaemia (blood glucose >13.9 mmol/L) occurred in 17% (133) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Serious events of hyperglycaemia occurred in 2.5% of patients, 7% of patients developed severe (Grade 3 or 4) hyperglycaemia and 0.3% of patients experienced fatal events, one event each of hyperglycaemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycaemia increased consistently in patients with higher body mass index and in patients with higher baseline haemoglobin A1C (HbA1c). The median time to onset of hyperglycaemia was 0.5 months (range: 0 to 20.3). Of the patients who experienced hyperglycaemia and had data regarding resolution (N=106), 66% had complete resolution, 19% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 34% of patients with residual hyperglycaemia at last evaluation, 64% had Grade ≥2 events. *Peripheral neuropathy*: In clinical studies of enfortumab vedotin as monotherapy, peripheral neuropathy occurred in 53% (422) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Five percent of patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 peripheral neuropathy was 5 months (range: 0.1 to 20.2). Of the patients who experienced neuropathy and had data regarding resolution (N=340), 14% had complete resolution, 46% had partial improvement, and 41% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade ≥2 events. *Ocular disorders*: In clinical studies of enfortumab vedotin as monotherapy, 30% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.5% of patients and 0.1% of patients permanently discontinued treatment due to dry eye. Severe (Grade 3) dry eye only occurred in 3 patients (0.4%). The median time to onset of dry eye was 1.7 months (range: 0 to 30.6 months). Special populations: *Elderly*: Enfortumab vedotin in combination with pembrolizumab has been studied in 173 patients <65 years and 391 patients ≥65 years. Generally, adverse event frequencies were higher in patients ≥65 years of age compared to <65 years of age, particularly for serious adverse events (56.3%, and 35.3%, respectively) and Grade ≥3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator. **Overdose:** There is no known antidote for overdosage with enfortumab vedotin. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.6 days (ADC) and 2.6 days (MMAE).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

België/Belgique: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten / Agence fédérale des médicaments et des produits de santé; www.fagg.be / www.afmps.be; Afdeling Vigilantie / Division Vigilance: Website/Site internet: www.eenbijwerkingmelden.be / www.notifierunneffetindesirable.be; e-mail: adr@fagg-afmps.be

Ireland: HPRA Pharmacovigilance, Website: www.hpra.ie or Astellas Pharma Co. Ltd. Tel: +353 1 467 1555, E-mail: irishdrugsafety@astellas.com.

Nederland: Nederlands Bijwerkingen Centrum Lareb; Website: www.lareb.nl

Luxembourg/Luxemburg : Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé ; Site internet : www.guichet.lu/pharmacovigilance

MARKETING AUTHORISATION HOLDER:
Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands

MARKETING AUTHORISATION NUMBERS: EU/1/21/1615/001 & EU/1/21/1615/002

DATE OF REVISION OF THE TEXT: December 2024
Job Bag Number: MAT-BX-PAD-2025-00004

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
Ireland: Astellas Pharma Co. Ltd., Tel.: +353 1 467 1555. SPC may be found at www.medicines.ie.
Delivery Status: subject to medical prescription.
Astellas Pharma B.V.,
NL: Sylviusweg 62, 2333BE Leiden, Netherlands
BE/LU: Medialaan 50, 1800 Vilvoorde, Belgium
IE: Legal classification: S1A.

Prescribing Information: PADCEV™▼ (enfortumab vedotin) 20 mg and 30 mg powder for concentrate for solution for infusion

For full prescribing information refer to the Summary of Product Characteristics (SPC).

Presentation: One vial of PADCEV powder for concentrate for solution for infusion contains either 20 mg or 30 mg enfortumab vedotin. After reconstitution, each ml of solution contains 10 mg of enfortumab vedotin. Enfortumab vedotin is comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker.

Indications: PADCEV, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy. PADCEV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor (see section 5.1 of the SPC).

Posology and method of administration: Treatment with PADCEV should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. PADCEV is for intravenous use. It must not be administered as an intravenous push or bolus injection. Good venous access prior to starting treatment should be ensured (see section 4.4 of the SPC). As monotherapy, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg). It must be administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SmPC for additional dosing information of pembrolizumab. For information on recommended dose reductions of enfortumab vedotin for adverse reactions as well as instructions on dose modifications (interruption, reduction and discontinuation) in patients experiencing adverse reactions refer to section 4.2 of the SPC. Special Populations: *Elderly:* No dose adjustment is necessary in patients ≥65 years of age (see section 5.2 of the SPC). *Renal impairment:* No dose adjustment is necessary in patients with mild [creatinine clearance (CrCL) >60-90 mL/min], moderate (CrCL 30–60 mL/min) or severe (CrCL 15–<30 mL/min) renal impairment. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see section 5.2 of the SPC). *Hepatic impairment:* No dose adjustment is necessary in patients with mild hepatic impairment [total bilirubin of 1 to 1.5 × upper limit of normal (ULN) and aspartate transaminase (AST) any, or total bilirubin ≤ ULN and AST > ULN]. Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given (see section 5.2 of the SPC). *Paediatric population:* There is no relevant use of enfortumab vedotin in the paediatric population for the indication of locally advanced or metastatic urothelial cancer.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC.

Special warnings and precautions for use: Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Skin reactions: Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Mild to moderate skin reactions, predominantly rash maculo-papular, have been reported with enfortumab vedotin. The incidence of skin reactions occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue PADCEV for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see section 4.2 of the SPC). Pneumonitis/Interstitial Lung Disease (ILD): Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin. The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold PADCEV for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV for Grade ≥3 pneumonitis/ILD (see section 4.2 of the SPC). Hyperglycaemia: Hyperglycaemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre- existing diabetes mellitus, treated with enfortumab vedotin (see section 4.8 of the SPC). Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m^2). Patients with baseline HbA1c ≥8% were excluded from clinical studies. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), PADCEV should be withheld until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate (see section 4.2 of the SPC). Serious infections: Serious infections such as sepsis (including fatal outcomes) have been reported in patients treated with PADCEV. Patients should be carefully monitored during treatment for the emergence of possible serious infections. Peripheral neuropathy: Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions (see section 4.8 of the SPC). Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical studies. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin. PADCEV should be permanently discontinued for Grade ≥3 peripheral neuropathy (see section 4.2 of the SPC). Ocular disorders: Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin (see section 4.8 of the SPC). Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen. Infusion site extravasation: Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred (see section 4.8 of the SPC). Ensure good venous access prior to starting PADCEV and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions. Embryo-foetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus (see sections 4.6 and 5.3 of the SPC). Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 6 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 months following the last dose of PADCEV. Patient information pack: The prescriber must discuss the risks of PADCEV therapy, including combination therapy with pembrolizumab, with the patient. The patient should be provided with the patient information leaflet and patient card with each prescription.

Effects on ability to drive and use machines: PADCEV has no or negligible influence on the ability to drive and use machines.

Interactions: Formal drug–drug interaction studies with enfortumab vedotin have not been conducted. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities. Strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE with moderate effect (see section 5.2 of the SPC).

Fertility, pregnancy and lactation: Women of childbearing potential/ Contraception in males and females: Refer to 'Special warnings and precautions for use' section above. Pregnancy: PADCEV can cause foetal harm when administered to pregnant women based upon findings from animal studies. PADCEV is not recommended during pregnancy and in women of childbearing potential not using effective contraception. Breast-feeding: Breast-feeding should be discontinued during PADCEV treatment and for at least 6 months after the last dose. Fertility: Men being treated with this medicinal product are advised to have sperm samples frozen and stored before treatment. There are no data on the effect of PADCEV on human fertility.

Undesirable effects: Summary of the safety profile: *Enfortumab vedotin as monotherapy*: The safety of enfortumab vedotin was evaluated as monotherapy in 793 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), three phase 2 studies (EV-103, EV-201 and EV-203) and one phase 3 study (EV-301) (see Table 3 in section 4.8 of the SPC). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 55.7 months). The most common adverse reactions with enfortumab vedotin were alopecia (47.7%), decreased appetite (47.2%), fatigue (46.8%), diarrhoea (39.1%), peripheral sensory neuropathy (38.5%), nausea (37.8%), pruritus (33.4%), dysgeusia (30.4%), anaemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycaemia, (14.9%), dry eye (12.7%), alanine aminotransferase increased (12.7%) and rash (11.6%). The most common serious adverse reactions (≥2%) were diarrhoea (2.1%) and hyperglycaemia (2.1%). Twenty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (4.8%). Adverse reactions leading to dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (14.8%), fatigue (7.4%), rash maculo-papular (4%), aspartate aminotransferase increased (3.4%), alanine aminotransferase increased (3.2%), anaemia (3.2%), hyperglycaemia (3.2%), neutrophil count decreased (3%), diarrhoea (2.8%), rash (2.4%) and peripheral motor neuropathy (2.1%). Thirty-eight percent of patients required a dose reduction due to an adverse reaction; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (10.3%), fatigue (5.3%), rash maculo-papular (4.2%) and decreased appetite (2.1%). *Enfortumab vedotin in combination with pembrolizumab:* When enfortumab vedotin is administered in combination with pembrolizumab, refer to the SPC for pembrolizumab prior to initiation of treatment. The safety of enfortumab vedotin was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in one phase 2 study (EV-103) and one phase 3 study (EV-302) (see Table 3). Patients were exposed to enfortumab vedotin in combination with pembrolizumab for a median duration of 9.4 months (range: 0.3 to 34.4 months). The most common adverse reactions with enfortumab vedotin in combination with pembrolizumab were peripheral sensory neuropathy (53.4%), pruritus (41.1%), fatigue (40.4%), diarrhoea (39.2%), alopecia (38.5%), rash maculo-papular (36%), weight decreased (36%), decreased appetite (33.9%), nausea (28.4%), anaemia (25.7%), dysgeusia (24.3%), dry skin (18.1%), alanine aminotransferase increased (16.8%), hyperglycaemia (16.7%), aspartate aminotransferase increased (15.4%), dry eye (14.4%), vomiting (13.3%), rash macular (11.3%), hypothyroidism (10.5%) and neutropenia (10.1%). The most common serious adverse reactions (≥2%) were diarrhoea (3%) and pneumonitis (2.3%). Thirty-six percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reactions (≥2%) leading to discontinuation were peripheral sensory neuropathy (12.2%) and rash maculo-papular (2%). Adverse reactions leading to dose interruption of enfortumab vedotin occurred in 72% of patients. The most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhoea (4.8%), fatigue (3.7%), pneumonitis (3.7%), hyperglycaemia (3.4%), neutropenia (3.2%), alanine aminotransferase increased (3%), pruritus (2.3%) and anaemia (2%). Adverse reactions leading to dose reduction of enfortumab vedotin occurred in 42.4% of patients. The most common adverse reactions (≥2%) leading to dose reduction were peripheral sensory neuropathy (9.9%), rash maculo-papular (6.4%), fatigue (3.2%), diarrhoea (2.3%) and neutropenia (2.1%). Summary of adverse reactions: Adverse reactions observed during clinical studies of enfortumab vedotin as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of enfortumab vedotin are listed in this section according to Medical Dictionary for Regulatory Activities (MedDRA) system organ classification by frequency category. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). *Infections and infestations:* (monotherapy and in combination with pembrolizumab) Common: Sepsis. *Blood and lymphatic system disorders:* (monotherapy and in combination with pembrolizumab) Very common: Anaemia. Not known[1]: Neutropenia, febrile neutropenia, neutrophil count decreased. *Endocrine disorders:* (in combination with pembrolizumab) Very common: Hypothyroidism. *Metabolism and nutrition disorders:* (monotherapy and in combination with pembrolizumab) Very common: Hyperglycaemia, decreased appetite. Not known[1]: Diabetic ketoacidosis. *Nervous system disorders:* (monotherapy and in combination with pembrolizumab) Very common: Peripheral sensory neuropathy, dysgeusia. (monotherapy) Common: Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness. (in combination with pembrolizumab) Common: Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness. (monotherapy) Uncommon: Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation. (in combination with pembrolizumab) Uncommon: Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation. *Eye disorders:* (monotherapy and in combination with pembrolizumab) Very common: Dry eye. *Respiratory, thoracic, and mediastinal disorders:* (in combination with pembrolizumab) Very common: Pneumonitis/ILD[2]. (monotherapy) Common: Pneumonitis/ILD[2]. *Gastrointestinal disorders:* (monotherapy and in combination with pembrolizumab) Very common: Diarrhoea, vomiting, nausea. *Skin and subcutaneous tissue disorders:* (monotherapy) Very common: Alopecia, pruritus, rash, rash maculo-papular, dry skin. (in combination with pembrolizumab) Very common: Alopecia, pruritus, rash maculo-papular, dry skin, rash macular. (monotherapy) Common: Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular. (in combination with pembrolizumab) Common: Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash papular, rash pruritic, rash vesicular, erythaema multiforme, dermatitis. (monotherapy) Uncommon: Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister. (in combination with pembrolizumab) Uncommon: Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis. (monotherapy and in combination with pembrolizumab) Not known[1]: TEN, SJS, epidermal necrosis, skin hyperpigmentation, skin discoloration, pigmentation disorder, symmetrical drug-related intertriginous and flexural exanthaema. *Musculoskeletal and connective tissue disorders:* (in combination with pembrolizumab) Common: Myositis. *General disorders and administration site conditions:* (monotherapy and in combination with pembrolizumab) Very common: Fatigue. (monotherapy and in combination with pembrolizumab) Common: Infusion site extravasation. *Investigations:* (monotherapy and in combination with pembrolizumab) Very common: Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased. (in combination with pembrolizumab) Common: Lipase increased. *Injury, poisoning and procedural complications:* (monotherapy and in combination with pembrolizumab) Common: Infusion related reaction.

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organizing pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity and sarcoidosis.

Description of selected adverse reactions. *Immunogenicity:* A total of 697 patients were tested for immunogenicity to enfortumab vedotin1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-drug antibody (ADA), and in patients that were negative at baseline (N=681), a total of 24 (3.5%) were positive post baseline. A total of 490 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ADA, and in patients that were negative at baseline (N=466), a total of 14 (3%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following enfortumab vedotin administration as monotherapy and in combination with pembrolizumab. Due to the limited number of patients with antibodies against PADCEV, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics. *Skin reactions:* In clinical studies of enfortumab vedotin as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 14% (108) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 8.2 months). Serious skin reactions occurred in 4.3% (34) of patients. Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥2 events. In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥2 events. *Pneumonitis/ILD:* In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.5%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months) and the median duration for pneumonitis/ILD was 1.6 months (range: 0.1 to 43.0 months). Of the 26 patients who experienced pneumonitis/ILD, 8 (30.8%) had resolution of symptoms. In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 2.1% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months). *Hyperglycaemia:* In clinical studies of enfortumab vedotin as monotherapy, hyperglycaemia (blood glucose >13.9 mmol/L) occurred in 17% (133) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Serious events of hyperglycaemia occurred in 2.5% of patients, 7% of patients developed severe (Grade 3 or 4) hyperglycaemia and 0.3% of patients experienced fatal events, one event each of hyperglycaemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycaemia increased consistently in patients with higher body mass index and in patients with higher baseline haemoglobin A1C (HbA1c). The median time to onset of hyperglycaemia was 0.5 months (range: 0 to 20.3). Of the patients who experienced hyperglycaemia and had data regarding resolution (N=106), 66% had complete resolution, 19% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 34% of patients with residual hyperglycaemia at last evaluation, 64% had Grade ≥2 events. *Peripheral neuropathy:* In clinical studies of enfortumab vedotin as monotherapy, peripheral neuropathy occurred in 53% (422) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Five percent of patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 peripheral neuropathy was 5 months (range: 0.1 to 20.2). Of the patients who experienced neuropathy and had data regarding resolution (N=340), 14% had complete resolution, 46% had partial improvement, and 41% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade ≥2 events. *Ocular disorders:* In clinical studies of enfortumab vedotin as monotherapy, 30% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.5% of patients and 0.1% of patients permanently discontinued treatment due to dry eye. Severe (Grade 3) dry eye only occurred in 3 patients (0.4%). The median time to onset of dry eye was 1.7 months (range: 0 to 30.6 months). *Special populations:* Elderly: Enfortumab vedotin in combination with pembrolizumab has been studied in 173 patients <65 years and 391 patients ≥65 years. Generally, adverse event frequencies were higher in patients ≥65 years of age compared to <65 years of age, particularly for serious adverse events (56.3%, and 35.3%, respectively) and Grade ≥3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator. Prescribers should consult the full SPC in relation to other adverse reactions.

Overdose: There is no known antidote for overdosage with enfortumab vedotin. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.6 days (ADC) and 2.6 days (MMAE).

Cost (excluding VAT): PADCEV 20 mg powder for concentrate for solution for infusion x 1 vial: £578
PADCEV 30 mg powder for concentrate for solution for infusion x 1 vial: £867

Legal classification: POM

Marketing Authorisation numbers:

PADCEV 20 mg powder for concentrate for solution for infusion PLGB 00166/0432.
PADCEV 30 mg powder for concentrate for solution for infusion PLGB 00166/0433.

Marketing Authorisation Holder:

Astellas Pharma Ltd. 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX.

Date of Preparation of Prescribing Information: February 2025

Job Bag Number: MAT-GB-PAD-2025-00017

Further information available from: Astellas Pharma Ltd, Medical Information 0800 783 5018. For full prescribing information, refer to the SPC, which may be found at: https://www.medicines.org.uk/emc.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.