

Maximising outcomes in advanced UC: The critical importance of putting first things 1st

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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.¹

Please note: This indication has received EMA approval; reimbursement in some EU countries is still pending.

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, locally advanced; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; UC, urothelial carcinoma.

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

Date of preparation: July 2025 | Job code: MAT-NL-PAD-2025-00029



This medicinal product is subject to additional monitoring.

NL: 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.

Nederland: Nederlands Bijwerkingen Centrum Lareb;

Website: www.lareb.nl

UK: 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 Store or Apple App Store.

Adverse events should also be reported to Astellas Pharma Ltd on 0800 783 5018



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



astellas

Speaker disclosures

Advisory Boards:

- Amgen, Astellas, AstraZeneca, BMS, Ipsen, Janssen, Lilly, Merck, MSD, Novartis, Roche, Pfizer, Sanofi

Lectures/travel expenses/congress support:

- Amgen, Astellas, AstraZeneca, BMS, Eisai, Ipsen, Janssen, Merck, MSD, Pierre Fabre, Roche, Sanofi

Financing of scientific studies in the context of industry-sponsored studies:

- AstraZeneca, AvenCell, BMS, Lilly, MSD, Pfizer, Roche, Sanofi

There are now multiple options to consider for 1L advanced UC*

**PBCT +
avelumab
maintenance**

*JAVELIN
Bladder 100¹*

No disease progression[†]
following 1L PBCT

**Nivolumab +
CisGem**

CheckMate 901²

Cisplatin eligible

EV+P

EV-302³

Platinum eligible

Patient populations

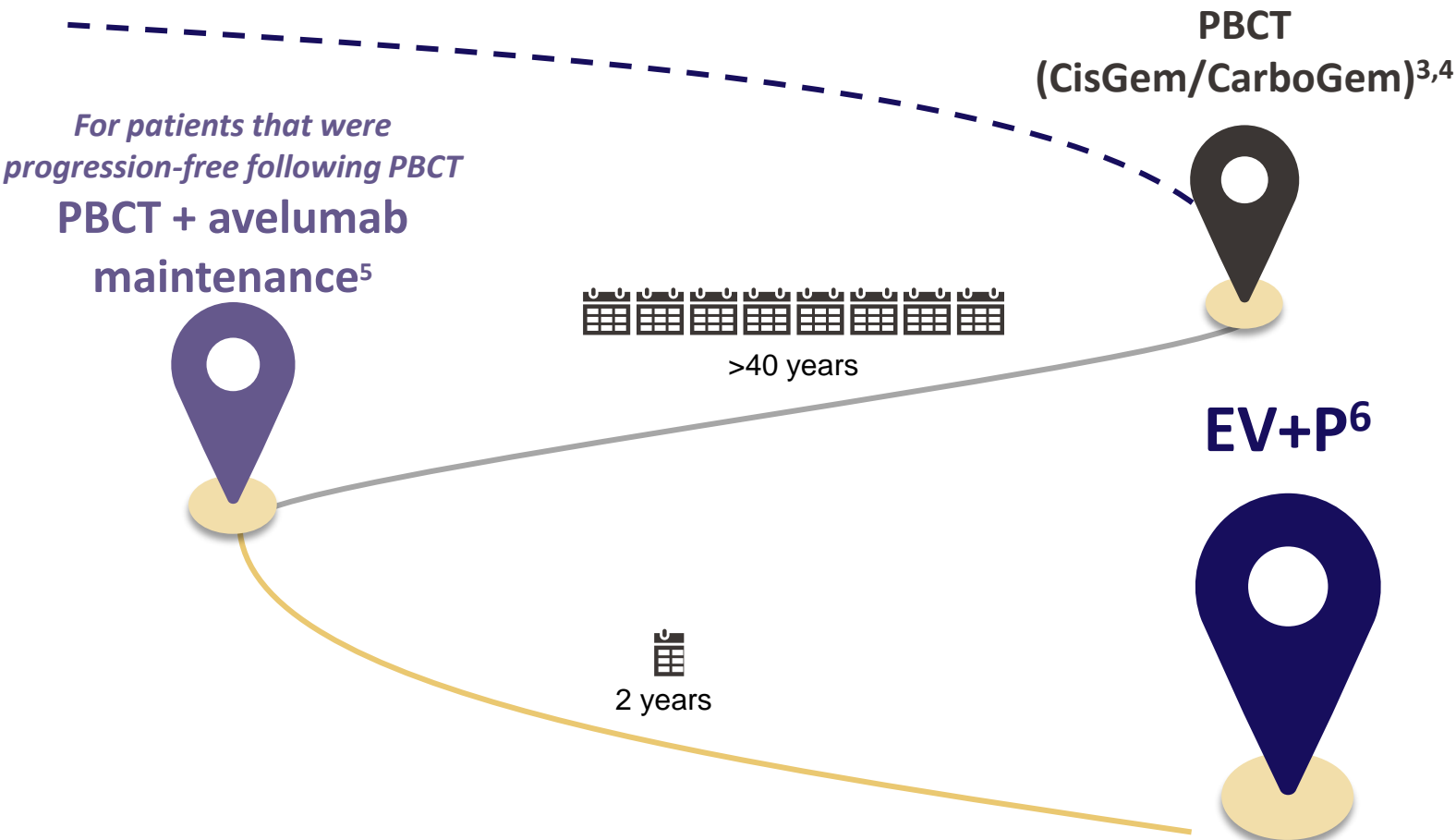
*Please refer to the relevant Summary of Product Characteristics for license, prescribing and safety information; [†]Complete response, partial response, or stable disease.

1L, first line; Cis, cisplatin; EV+P, enfortumab vedotin plus pembrolizumab; Gem, gemcitabine; m, metastatic; PBCT, platinum-based chemotherapy; UC, urothelial carcinoma.

1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789; 3. Powles T et al. *N Engl J Med* 2024;390:875–888.

The approval of EV+P transformed the 1L treatment landscape for advanced UC, becoming the new SOC^{1,2}

Evolution of the SOC for 1L treatment of advanced UC*



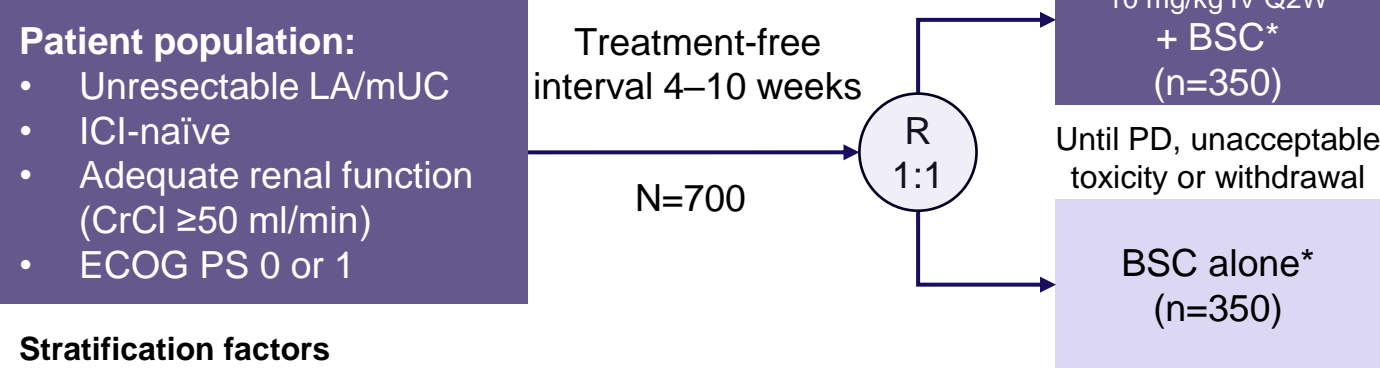
*Please refer to the relevant Summary of Product Characteristics for license, prescribing and safety information.

1L, first-line; Carbo, carboplatin; Cis, cisplatin; EV, enfortumab vedotin; Gem, gemcitabine; P, pembrolizumab; PBCT, platinum-based chemotherapy; SOC, standard of care; UC, urothelial carcinoma.

1. European Association of Urology. Muscle-invasive and metastatic bladder cancer. Available at: <https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer>. Last accessed: June 2025; 2. Li H et al. *ESMO Real World Data Digital Oncol* 2025;doi:10.1016/j.esmow.2024.100110 [Epub ahead of print]; 3. von der Maase H et al. *J Clin Oncol* 2000;18:3068–3077; 4. De Santis M et al. *J Clin Oncol* 2012;30:191–199; 5. Pfizer. Press release. January 2021. Available at: [pfizer.com/news/press-release/press-release-detail/european-commission-approves-bavencior-avelumab-first-line](https://www.pfizer.com/news/press-release/press-release-detail/european-commission-approves-bavencior-avelumab-first-line). Last accessed: May 2025; 6. EMA. Summary of opinion. July 2024. Available at: [ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-padcev-ii-13_en.pdf](https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-padcev-ii-13_en.pdf). Last accessed: June 2025.

JAVELIN Bladder 100: Avelumab maintenance vs. BSC alone

Study design^{1,2}



Stratification factors

- Best response to 1L PBCT (CR or PR vs. SD)
- Metastatic site (visceral vs. non-visceral)

Primary endpoint

- OS

Primary analysis populations

- All randomised patients
- PD-L1+ population

Secondary endpoints

- PFS and objective response per RECIST 1.1
- Time to response, DOR, and disease control
- Safety and tolerability

JAVELIN Bladder 100 ¹		Select baseline characteristics [†] (avelumab arm) ²	
Patient population	<ul style="list-style-type: none">• ECOG PS 0/1• Prior to initiating avelumab: received 4–6 cycles of PBCT and did not have disease progression	Type of PBCT, %	CisGem: 52.3; CarboGem: 42
Comparator	BSC (unblinded)	ECOG PS, %	0: 60.9; ≥1: 39.1
Primary endpoint	OS	Best response to 1L PBCT, %	CR: 25.7; PR: 46.6; SD: 27.7
		Visceral metastases, %	54.6
		PD-L1 positivity, %	54.0

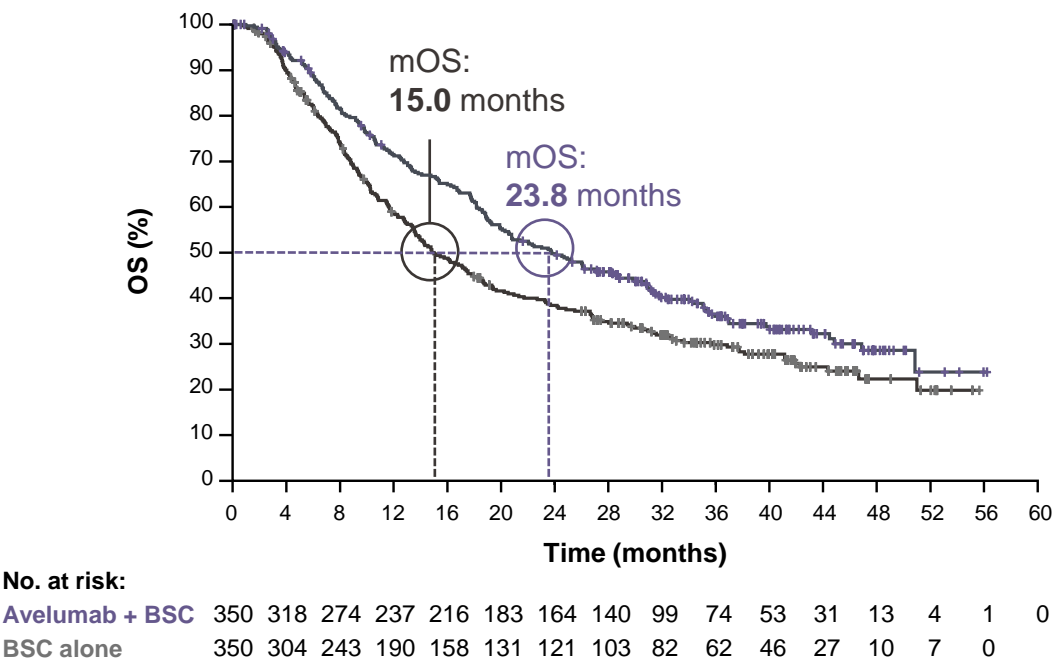
*Administered according to local practice based on clinical judgment and the patient's condition. BSC included antibiotic agents, nutritional support, hydration and pain management; other systemic anti-tumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was permitted;[†] From ≥2 years of follow-up.²

1L, first line; BSC, best supportive care; Carbo, carboplatin; Cis, cisplatin; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; ICI, immune checkpoint inhibitor; IV, intravenous; LA, locally advanced; m, metastatic; OS, overall survival; PBCT, platinum-based chemotherapy; PD, progressive disease; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; UC, urothelial carcinoma.

1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *N Engl J Med* 2020;383:1218–1230 (Protocol); 3. Powles T et al. *J Clin Oncol* 2023;41:3486–3492.

JAVELIN Bladder 100: A significant improvement in OS and PFS were seen with avelumab + BSC vs. BSC alone¹

OS in the overall trial population¹



	Avelumab + BSC	BSC	HR (95% CI) p-value
mOS, ¹ months	23.8	15	0.76 (0.63–0.91) 0.0036
mPFS, ¹ months	5.5	2.1	0.54 (0.46–0.64) <0.0001
ORR, ² %	9.7	1.4	–
CR, ² %	6.0	0.9	–
AE/TRAE ^{1*} Any grade, % Grade 3 or 4, %	98.3/78.2 53.8/19.5	NA [†]	–
TRAE leading to discontinuation, ⁴ %	11.6	NA [‡]	–
QOL ⁵ (FBISI-18, EQ-5D-5L, TTD)	Results were similar between both arms		

An improvement in OS was seen for PBCT + maintenance avelumab, in a highly selective patient population^{1,2}

Because the trial met its objective in the initial analysis (data cut-off: October 21, 2019),¹ updated analysis are considered exploratory, and all p-values are descriptive.
*In patients with ≥12 months of avelumab treatment. [†]Safety data from the primary analysis were 77.7% for any grade AE or 25.5% for ≥ Grade 3 AEs. [‡]TRAEs leading to discontinuation in the primary analysis were 0% in BSC arm. ²Avelumab + BSC median follow-up: 38.0 months; BSC median follow-up: 39.6 months.
AE, adverse event; BSC, best supportive care; CI, confidence interval; CR, complete response; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level Questionnaire; FBISI-18, National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Bladder Symptom Index-18; HR, hazard ratio; (m)OS, (median) overall survival; mPFS, median progression-free survival; NA, not available; ORR, overall response rate; QOL, quality of life; TRAE, treatment-related adverse event; TTD, time to deterioration.
1. Powles T et al. *J Clin Oncol* 2023;41:3486–3492; 2. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 3. Powles T et al. *N Engl J Med* 2020;383:1218–1230 (supplementary appendix); 4. Powles T et al. *J Clin Oncol* 2023;41:3486–3492 (supplementary appendix); 5. Grivas P et al. *Eur Urol* 2023;83:320–328.

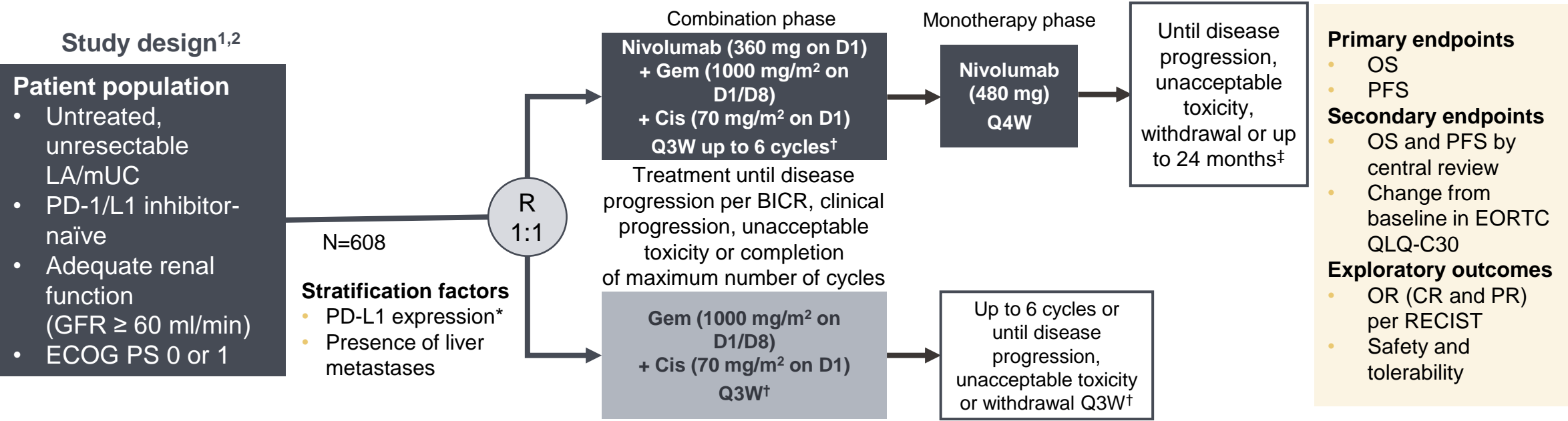
JAVELIN Bladder 100: Long-term safety data were consistent with observations from previous analyses¹



AE occurrence, ² n (%)	Avelumab maintenance (n=344)*†		AE occurrence, ² n (%)	Avelumab maintenance (n=344)*†	
	Any grade	Grade ≥3		Any grade	Grade ≥3
Overall	338 (98.3)	185 (53.8)	Nausea	55 (16.0)	1 (0.3)
Arthralgia	68 (19.8)	2 (0.6)	Decreased appetite	48 (14.0)	1 (0.3)
Fatigue	65 (18.9)	6 (1.7)	Cough	46 (13.4)	1 (0.3)
Pruritus	64 (18.6)	1 (0.3)	Vomiting	46 (13.4)	4 (1.2)
Asthenia	62 (18.0)	0	Anaemia	44 (12.8)	14 (4.1)
Diarrhoea	61 (17.7)	2 (0.6)	Hypothyroidism	43 (12.5)	1 (0.3)
Urinary tract infection	61 (17.7)	15 (4.4)	Rash	41 (11.9)	2 (0.6)
Constipation	60 (17.4)	2 (0.6)	Haematuria	38 (11.0)	6 (1.7)
Back pain	59 (17.2)	4 (1.2)	Abdominal pain	35 (10.2)	2 (0.6)
Pyrexia	56 (16.3)	1 (0.3)			

*Long-term safety was not analysed in the BSC alone arm because the majority of patients had already discontinued by the time of the previously reported analysis, and data would be unlikely to change with additional follow-up;²
†The most common AEs of any grade and Grade ≥3 AEs with maintenance avelumab and BSC are shown (any grade in ≥10% or Grade ≥3 in ≥5% of patients).²
AE, adverse event; BSC, best supportive care.
1. Powles T et al. *J Clin Oncol* 2023;41:3486–3492; 2. Powles T et al. *J Clin Oncol* 2023;41:3486–3492 (supplementary appendix).

CheckMate 901: Nivolumab + CisGem vs. CisGem alone

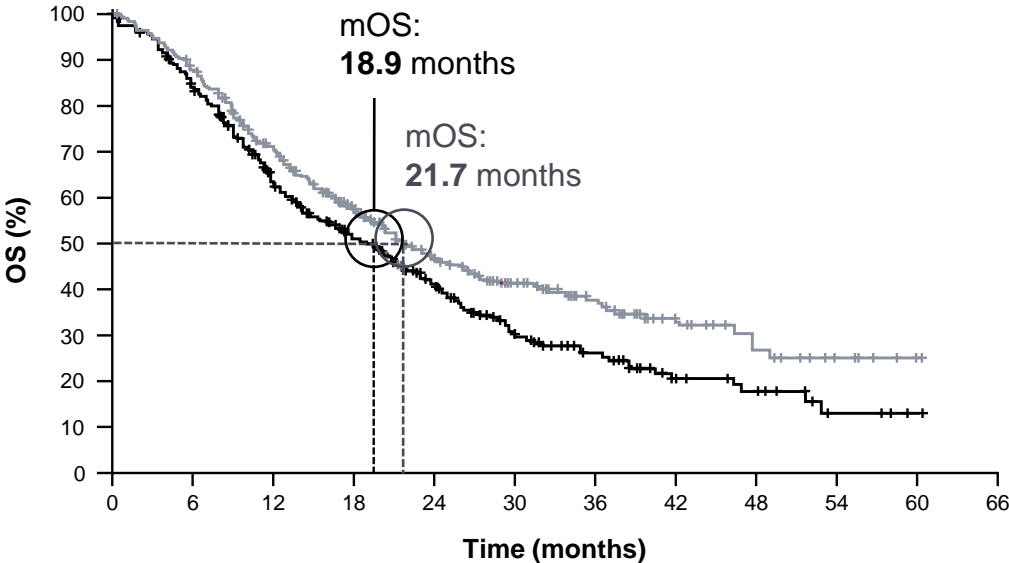


CheckMate-901 ¹		Select baseline characteristics (Nivo/Cis/Gem), all values in % ^{1,2}	
Patient population	<ul style="list-style-type: none">• ECOG PS 0, 1• Cis eligible	Cis eligible, %	100
Comparator	<ul style="list-style-type: none">• CisGem (max. 6 cycles)• Subsequent therapy: Avelumab maintenance (9%)/Atezolizumab (2%)²	Renal pelvis/other tumour type at initial diagnosis, %	10.9/11.8
Primary endpoints	OS; PFS by BICR	Liver metastasis at initial diagnosis, %	21.1
		PD-L1-positive expression, %	36.5

*Per PD-L1 pharmDx IHC assay.¹†Patients who discontinued cisplatin could be switched to CarboGem for the remainder of the platinum-doublet cycles (up to six in total); ‡A maximum of 24 months from first dose of nivolumab administered as part of the Nivo + CisGem combination.¹
BICR, blinded independent central review; Carbo, carboplatin; Cis, cisplatin; CR, complete response; D, day; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; GFR, glomerular filtration rate; Gem, gemcitabine; IHC, immunohistochemistry; LA, locally advanced; m, metastatic; Nivo, nivolumab; OR, overall response; OS, overall survival; PD-1/PD-L1, programmed cell death protein/ligand 1; PFS, progression-free survival; PR, partial response; PS, performance status; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; UC, urothelial carcinoma.
1. van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789; 2. van der Heijden MS et al. Presented at ESMO 2023. LBA7.

CheckMate 901: Nivolumab + CisGem was associated with significant improvements in OS and PFS vs. CisGem alone

OS in the ITT population



No. at risk:

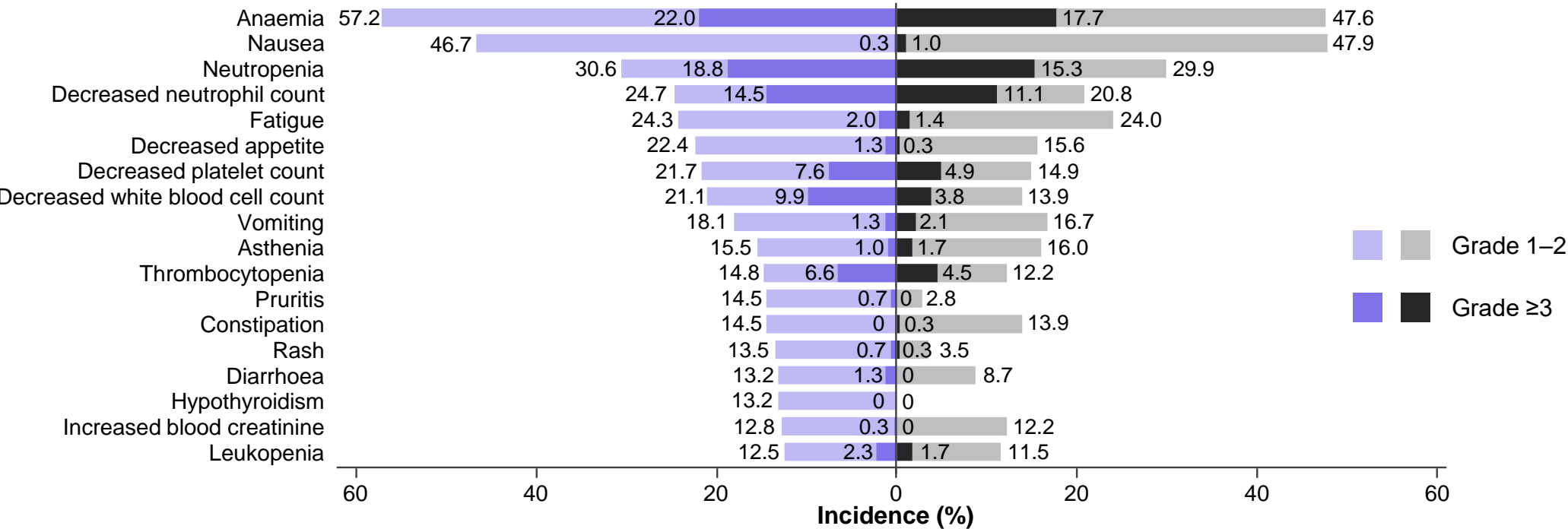
Nivo + CisGem	304	264	196	142	97	69	48	25	15	7	2	0
CisGem	304	242	166	122	82	49	33	17	13	4	1	0

	Nivo + CisGem	CisGem	HR (95% CI) p-value
mOS, months	21.7	18.9	0.78 (0.63–0.96) 0.02
mPFS, months	7.9	7.6	0.72 (0.59–0.88) 0.001
ORR, %	57.6	43.1	–
CR, %	21.7	11.8	–
TRAE Any grade, % Grade ≥3, %	97.4 61.8	92.7 51.7	–
TRAE leading to discontinuation, %	21.1	17.4	–
QOL (EORTC QLQ-C30)	Stable, with no change of more than 10 points through Week 16 in both groups		

Median follow-up: 33.6 months.¹
AE, adverse event; CI, confidence interval; Cis, cisplatin; CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; Gem, gemcitabine; HR, hazard ratio; ITT, intention to treat; (m)OS, (median) overall survival; mPFS, median progression-free survival; Nivo, nivolumab; ORR, objective response rate; QOL, quality of life; TRAE, treatment-related adverse event.
van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789.

CheckMate 901: The safety profile of nivolumab + CisGem was consistent with the established safety profiles of these agents in previous trials

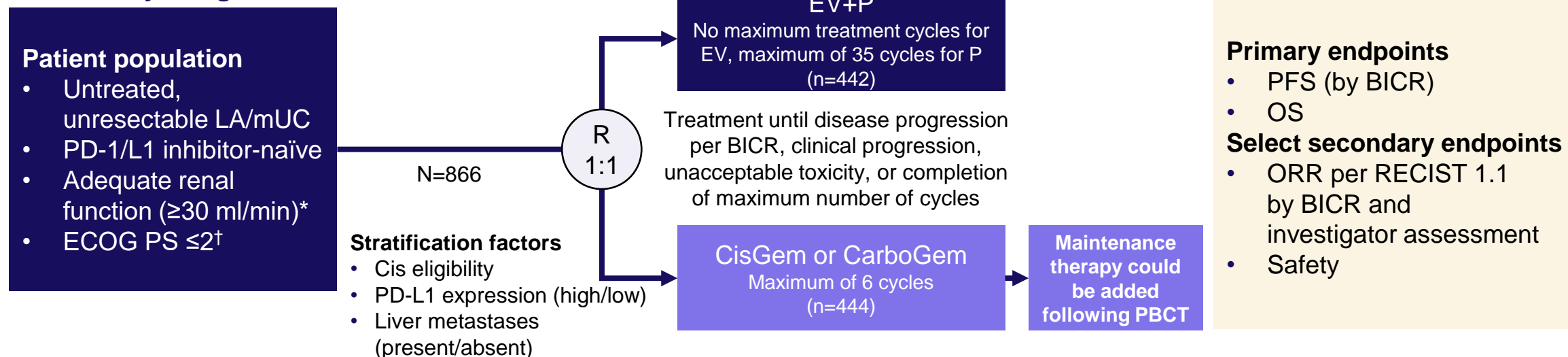
TRAE occurrence* (any grade in ≥10% of patients)	Nivo + CisGem (n=304)		CisGem (n=288)	
	Any grade	Grade ≥3†	Any grade	Grade ≥3†
Overall, %	97.4	61.8	92.7	51.7
Leading to discontinuation, %	21.1	11.2	17.4	7.6



*Includes events that occurred in treated patients between the first dose and 30 days after the last dose of study therapy. The tornado plot displays individual, treatment-related of any grade occurring in ≥10% of treated patients in either arm; †One Grade 5 event occurred in each arm (sepsis in the Nivo+ CisGem arm and acute kidney injury in the CisGem arm).
Cis, cisplatin; Gem, gemcitabine; Nivo, nivolumab; TRAE, treatment-related adverse event.
van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789.

EV-302: Enfortumab vedotin + pembrolizumab vs. PBCT

Study design^{1,2}



EV-302/KEYNOTE-A39 ^{1,2}	
Patient population	<ul style="list-style-type: none"> • ECOG PS ≤ 2 • GFR ≥ 30 ml/min
Comparator	<ul style="list-style-type: none"> • CisGem or CarboGem (max. 6 cycles) • Avelumab maintenance (~30% of population)
Primary endpoint	PFS by BICR; OS

Select baseline characteristics (EV+P) ¹	
Cis eligible, %	54.3
Upper tract, %	30.5
Visceral metastases, %	71.9
Liver metastases, %	22.6
High PD-L1 positive expression (CPS ≥ 10), %	58.0

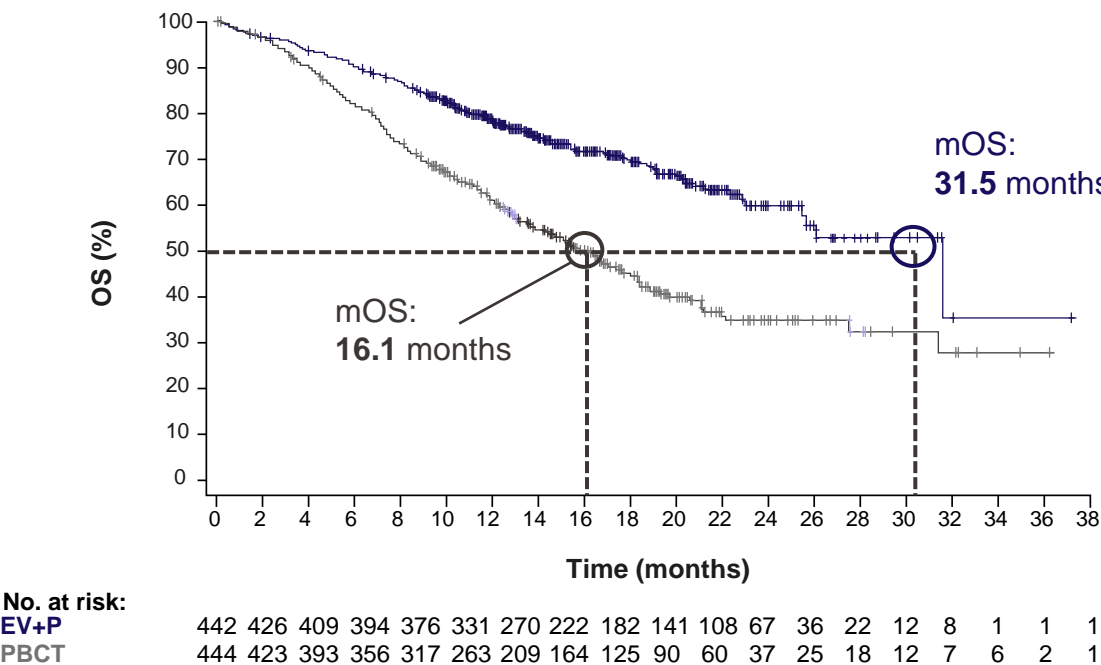
* GFR ≥ 30 ml/min Measured by the Cockcroft–Gault formula, modification of Diet in Renal Disease or 24-hour urine test;² [†]Patients with an ECOG PS of 2 were required to meet additional criteria: haemoglobin ≥ 10 g/dL, GFR ≥ 50 ml/min, may not have NYHA Class III heart failure.²

BICR, blinded independent central review; Carbo, carboplatin; Cis, cisplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; Gem, gemcitabine; GFR, glomerular filtration rate; LA, locally advanced; m, metastatic; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-1/PD-L1, programmed cell death protein/ligand 1; PFS, progression-free survival; PS, performance status; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; UC, urothelial carcinoma.

1. Powles T et al. *N Engl J Med* 2024;390:875–888; 2. Powles T et al. *N Engl J Med* 2024;390:875–888 (supplementary appendix).

EV-302 primary analysis: OS and PFS were nearly doubled with EV+P vs. PBCT

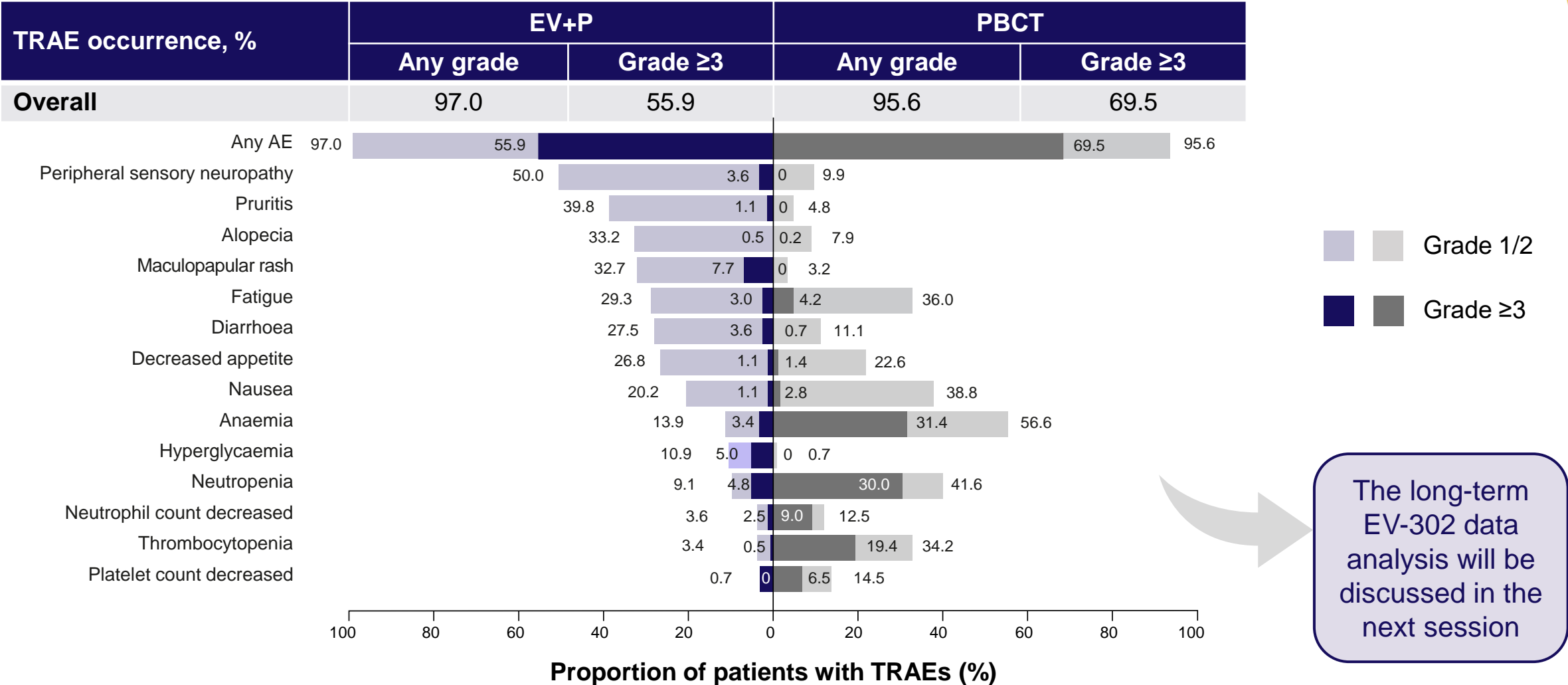
OS in the overall population (primary analysis)¹



	EV+P	PBCT	HR (95% CI) p-value
mOS, ¹ months	31.5	16.1	0.47 (0.38–0.58) <0.001
mPFS, ¹ months	12.5	6.3	0.45 (0.38–0.54) <0.001
ORR, ¹ %	67.7	44.4	–
CR, ¹ %	29.1	12.5	–
TRAE ¹ Any grade, % Grade ≥3, %	97.0 55.9	95.6 69.5	–
TRAE leading to discontinuation, ¹ %	EV or P: 35.0; EV 29.5; P 21.4	18.5	–
QOL, ² (EORTC QLQ-C30)	Least squares mean change from baseline up to week 26 favoured EV+P		
mTTCD, ² months (95% CI)	5.9 (4.50–10.02)	3.2 (1.84–NE)	–

Median follow-up: 17.2 months.
AE, adverse event; CI, confidence interval; Cis, cisplatin; CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; NE, not evaluable; ORR, objective response rate; P, pembrolizumab; PBCT, platinum-based chemotherapy; QOL, quality of life; TRAE, treatment-related adverse event; mTTCD, median time to confirmed deterioration.
1. Powles T et al. *N Engl J Med* 2024;390:875–888; 2. Gupta S et al. *Lancet Oncol* 2025;26:795–805.

EV-302 primary analysis: EV+P had an overall lower rate of Grade ≥3 AEs vs. PBCT

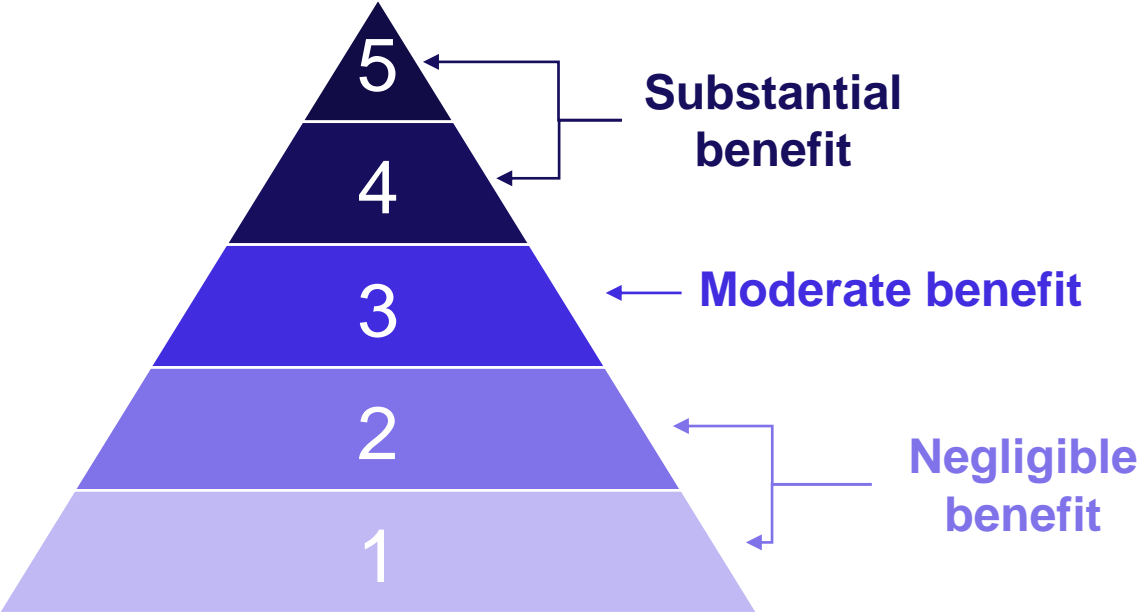


The long-term EV-302 data analysis will be discussed in the next session

TRAEs shown in the figure are any grade by preferred term in ≥20% of patients for any grade in either arm; Grade ≥3 TRAEs shown occurred in ≥5% of the patients in either treatment group.
AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab; PBCT, platinum-based chemotherapy; TRAE, treatment-related adverse event.
Powles T et al. *N Engl J Med* 2024;390:875–888

The ESMO-MCBS is a validated and reproducible tool to assess the magnitude of clinical benefit for cancer medicines

ESMO-MCBS score implications (non-curative setting)



If median OS with the standard treatment >12 months ≤24 months

GRADE 4	HR ≤0.70 <u>AND</u> gain ≥5 months	<input type="checkbox"/>
	Increase in 3 year survival alone ≥10%	<input type="checkbox"/>
GRADE 3	HR ≤0.70 <u>AND</u> gain ≥3-<5 months	<input type="checkbox"/>
GRADE 2	HR ≤0.70 <u>AND</u> gain ≥1.5-<3 months	<input type="checkbox"/>
	HR >0.70-0.75 <u>AND</u> gain ≥1.5 months	<input type="checkbox"/>
GRADE 1	HR > 0.75 <u>OR</u> gain <1.5 months	<input type="checkbox"/>

Mark with ✓ if relevant

Preliminary magnitude of clinical benefit grade (highest grade scored)	4	3	2	1
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Non-curative setting grading - 5 and 4 (substantial benefit), 3 (moderate benefit), 2 and 1 (negligible benefit)

Quality of life/Grade 3-4 toxicities* assessment

Does secondary endpoint QoL show improvement? ☐

Are there statistically significantly less grade 3-4 toxicities impacting on daily well-being?* ☐

*This does not include alopecia, myelosuppression, but rather chronic nausea, diarrhoea, fatigue, etc.

Mark with ✓ if relevant

Adjustments

- 01. Upgrade 1 level if improved QoL and/or less grade 3-4 toxicities impacting daily well-being are shown
- 02. If there is a long term plateau in the survival curve, and OS advantage continues to be observed at 5 years, also score according to form 1 (treatments with curative potential) and present both scores i.e. A/4.

Non-curative setting grading 4-5 indicates a substantial magnitude of clinical benefit

Final adjusted magnitude of clinical benefit grade	5	4	3	2	1
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ESMO, European Society for Medical Oncology; HR, hazard ratio; MCBS, Magnitude of Clinical Benefit Scale; OS, overall survival; QoL, quality of life.
ESMO guidelines. ESMO MCBS booklet. Available at: [ESMO-MCBS Booklet](#). Last accessed: May 2025.

The ESMO-MCBS shows that treatment with EV+P leads to meaningful improvements in patient outcomes

	PBCT + avelumab maintenance <i>JAVELIN Bladder 100</i> ¹	Nivo + CisGem <i>CheckMate 901</i> ²	EV+P <i>EV-302</i> ³
Trial population	No disease progression* following 1L PBCT	Cisplatin eligible	Cisplatin eligible
Score card ID	220	416	433
Outcome data			
PFS control (months)	-	7.6	6.3
PFS gain (months)	-	0.3	6.2
PFS, HR (CI)	-	0.72 (0.59–0.88)	0.45 (0.38–0.54)
OS control (months)	15.0	18.9	16.1
OS gain (months)	8.8	2.8	15.4
OS, HR (CI)	0.76 (0.63–0.91)	0.78 (0.63–0.96)	0.47 (0.38–0.58) interim at 73% of info
Adjustments			
QoL	No QoL benefit	No QoL benefit	QoL data pending
Final ESMO-MCBS score (F2a)	Non-curative, 4	Non-curative, 2	Non-curative, 4

Please interpret with caution. In the absence of head-to-head studies these data should not be compared directly. Data are for illustrative purposes only.

*Complete response, partial response, or stable disease.⁴

1L, first line; CI, confidence intervals; Cis, cisplatin; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy; PFS, progression-free survival; QoL, quality of life.

1. ESMO. ESMO-MCBS Scorecards for solid tumours – avelumab. Available at: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-220-1>. Last accessed: May 2025;

2. ESMO. ESMO-MCBS Scorecards for solid tumours – nivolumab. Available at: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-416-1>. Last accessed: May 2025;

3. ESMO. ESMO-MCBS Scorecards for solid tumours – enfortumab. Available at: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-433-1>. Last accessed: May 2025;

4. Powles T et al. *N Engl J Med* 2020;383:1218–1230.

The ESMO-MCBS shows that treatment with EV+P leads to meaningful improvements in patient outcomes

	PBCT + avelumab maintenance <i>JAVELIN Bladder 100</i> ¹	Nivo + CisGem <i>CheckMate 901</i> ²	EV+P <i>EV-302</i> ³
Trial population	No disease progression* following 1L PBCT	Cisplatin eligible	Cisplatin eligible
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Outcome data			
PFS control (months)	-	7.6	6.3
PFS gain (months)	-	0.3	6.2
PFS, HR (CI)	-	0.72 (0.59–0.88)	
OS control (months)	15.0	18.9	
OS gain (months)	8.8	2.8	
OS, HR (CI)	0.76 (0.63–0.91)	0.78 (0.63–0.96)	
Adjustments			
QoL	No QoL benefit	No QoL benefit	QoL data pending
Final ESMO-MCBS score (F2a)	Non-curative, 4	Non-curative, 2	Non-curative, 4

QoL data was pending at the time of creation of this version of the MCBS scorecard. QoL data has recently been reported for EV-302⁵

Please interpret with caution. In the absence of head-to-head studies these data should not be compared directly. Data are for illustrative purposes only.

*Complete response, partial response, or stable disease.⁴

1L, first line; CI, confidence intervals; Cis, cisplatin; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; EV, enfortumab vedotin; Gem, gemcitabine; HR, hazard ratio; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy; PFS, progression-free survival; QoL, quality of life.

1. ESMO. ESMO-MCBS Scorecards for solid tumours – avelumab. Available at: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-220-1>. Last accessed: May 2025;

2. ESMO. ESMO-MCBS Scorecards for solid tumours – nivolumab. Available at: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-416-1>. Last accessed: May 2025;

3. ESMO. ESMO-MCBS Scorecards for solid tumours – enfortumab. Available at: <https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/scorecard-433-1>. Last accessed: May 2025;

4. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 5. Gupta S et al. *Lancet Oncol* 2025;26:795–805.

The ESMO-MCBS shows that treatment with EV+P leads to meaningful improvements in patient outcomes

	PBCT + avelumab main JAVELIN	Nivo + CisGem	EV+P EV-302 ³
Trial population	No disease followi		Cisplatin eligible
Score card ID			433
Outcome data			
PFS control (months)			6.3
PFS gain (months)	-	0.3	6.2
PFS, HR (CI)	-	0.72 (0.59–0.88)	0.45 (0.38–0.54)
OS control (months)	15.0	18.9	16.1
OS gain (months)	8.8	2.8	15.4
OS, HR (CI)	0.76 (0.63–0.91)	0.65 (0.51–0.83)	0.47 (0.38–0.58) interim at 73% of info
Adjustments			
QoL	No QoL be	it	QoL data pending
Final ESMO-MCBS score (F2a)	Non-curative, 2	Non-curative, 2	Non-curative, 4

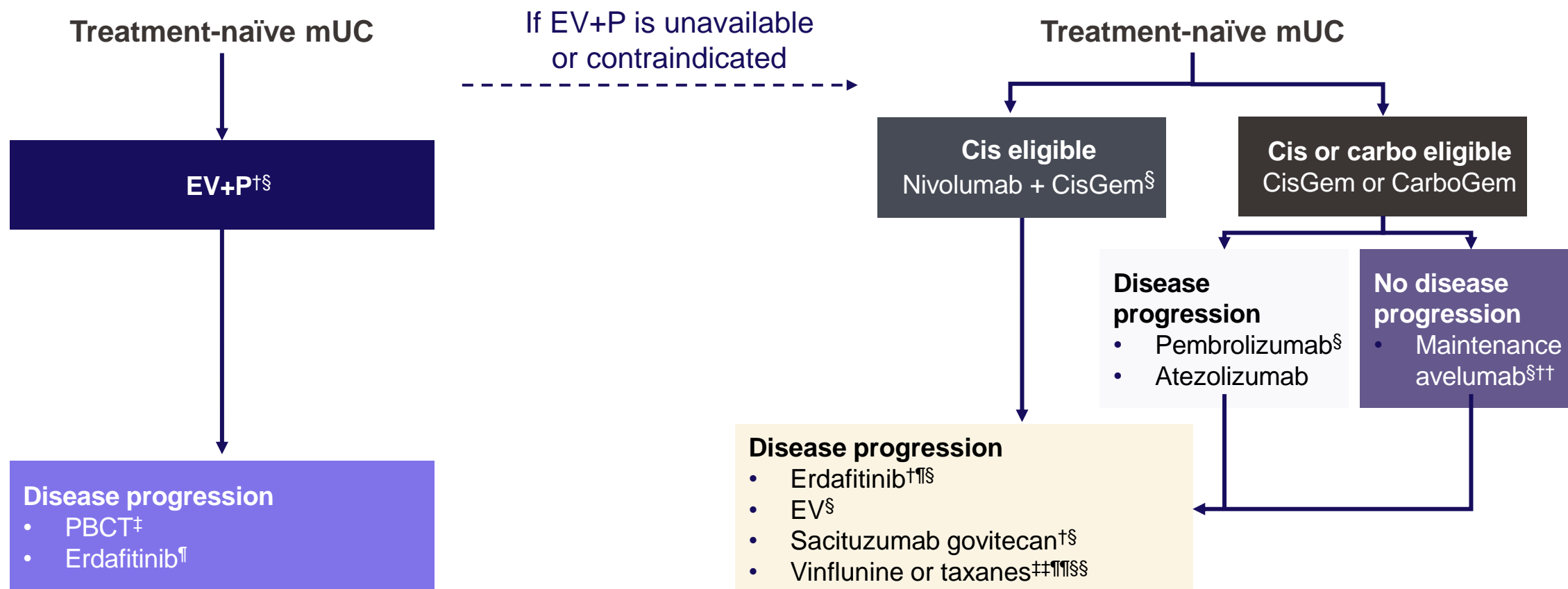
The MCBS shows the added **benefit of treatment compared with the SOC** at the time of the trial



How could this evolve with additional trial data?

Please interpret with caution. In the absence of head-to-head studies these data should not be compared directly. Data are for illustrative purposes only.

ESMO clinical practice guidelines recommend EV+P for the 1L treatment of unresectable/mUC*



*Disclaimer: The ESMO Clinical Practice Guideline aligns with the EU regulatory approval for pembrolizumab ‘for the 1L treatment of unresectable or metastatic UC in adults’

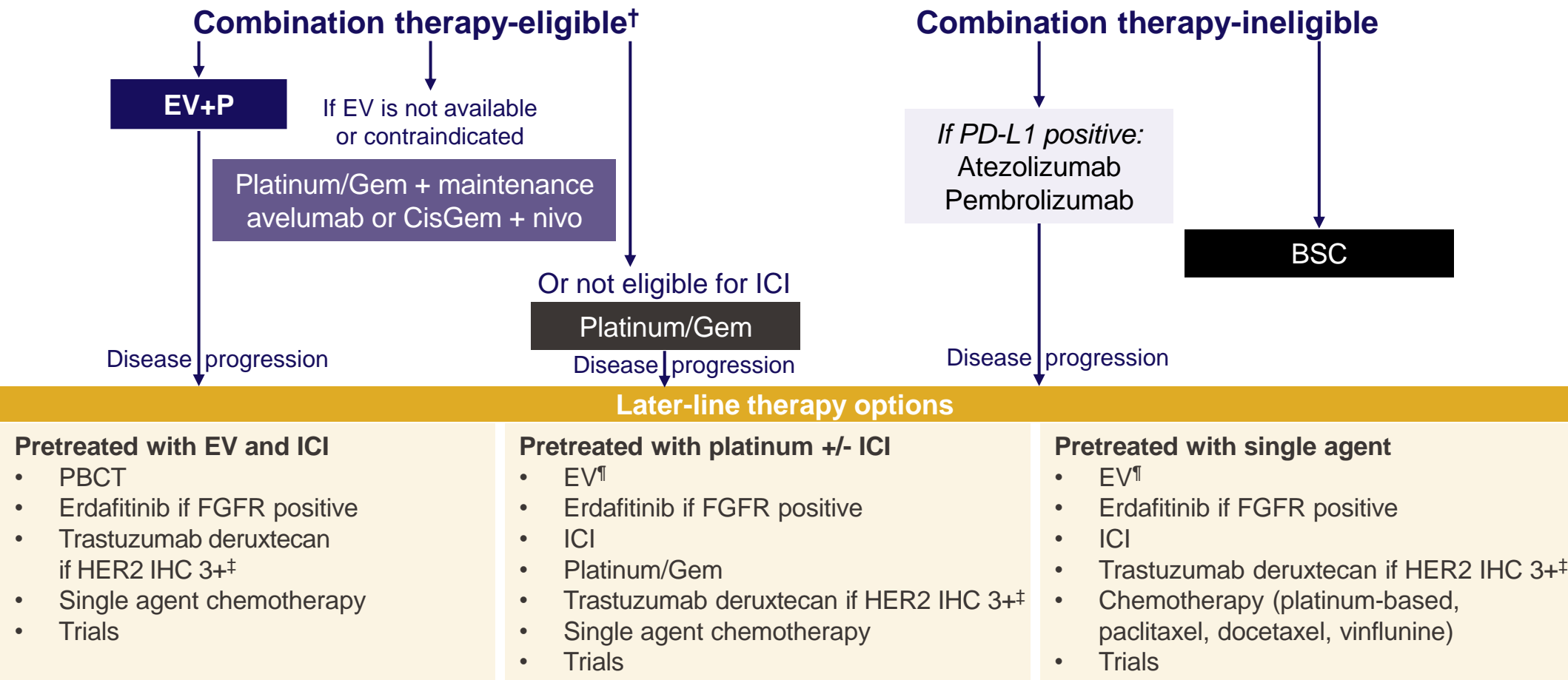
Figure adapted from Powles T et al. 2024.

†FDA approved and EMA approved; ‡Rechallenge with single-agent ICI is not encouraged without further evidence; ¶In tumours with selected FGFR DNA fusions and mutations; §ESMO-MCBS v1.1 was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>); ¶¶This should be assessed within 10 weeks of completion of chemotherapy; ¶¶Rechallenge with platinum-based chemotherapy may be considered if progression occurred 12 months after the end of previous PBCT or 12 months after the end of previous PBCT and maintenance avelumab; ¶¶Platinum doublets to be considered if the treatment-free interval from the last PBCT is >1 year; §§To be considered when other therapies are not available.

1L, first line; Carbo; carboplatin; Cis, cisplatin; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; EV, enfortumab vedotin; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; Gem, gemcitabine; ICI, immune checkpoint inhibitor; m, metastatic; MCBS, Magnitude of Clinical Benefit Scale; P, pembrolizumab; PBCT, platinum-based chemotherapy; UC, urothelial carcinoma.

Powles T et al. *Ann Oncol* 2024;35:485–490.

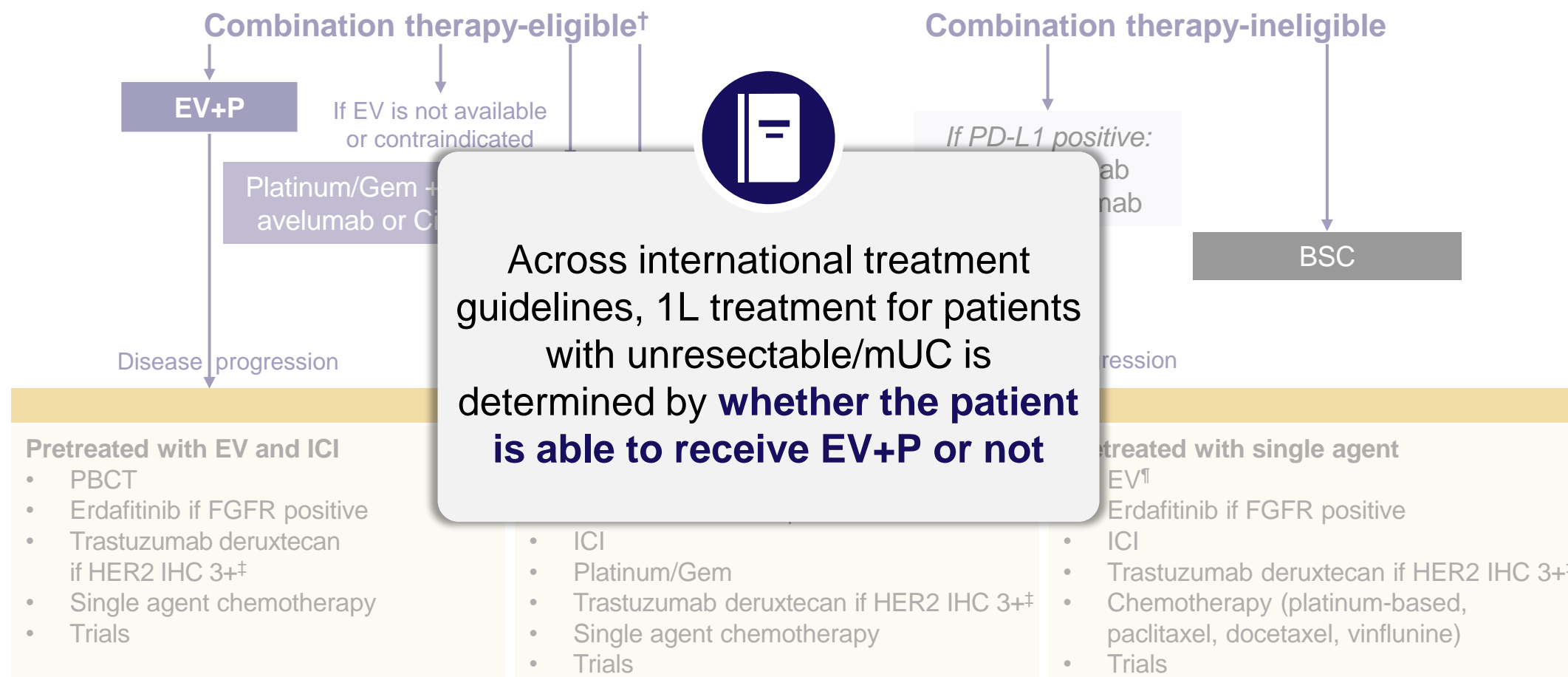
EAU clinical guidelines recommend EV+P for the 1L treatment of unresectable/mUC*



***Disclaimer:** The EAU Clinical Guideline aligns with the EU regulatory approval for pembrolizumab ‘for the 1L treatment of unresectable or metastatic UC in adults’

Figure adapted from 2025 EAU Muscle-invasive and Metastatic Bladder Cancer Guidelines. †PS 0–2, GFR >30 ml/minute, adequate organ functions, for Cis: GFR >50 ml/minute; ‡Not an EMA-approved indication. Approved by the FDA if no satisfactory alternative treatment options; ¶The indication for EV monotherapy as per the SmPC requires patients to have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor. 1L, first-line; BSC, best supportive care; Cis, cisplatin; EAU, European Association of Urology; EMA, European Medicines Agency; EV, enfortumab vedotin; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; Gem, gemcitabine; GFR, glomerular filtration rate; ICI, immune checkpoint inhibitor; mUC, metastatic urothelial carcinoma; nivo, nivolumab; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-1/PD-L1, programmed cell death protein/ligand 1; PS, performance status; SmPC, Summary of Product Characteristics. European Association of Urology. Muscle-invasive and metastatic bladder cancer. Available at: <https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer>. Last accessed: May 2025.

EAU clinical guidelines recommend EV+P for the 1L treatment of unresectable/mUC*



Summary



Currently, there are **multiple options available** for the 1L treatment of patients with unresectable/mUC^{1,2}



The approval of EV+P **transformed the 1L treatment landscape** for patients with unresectable/mUC^{2,3}



EV+P is the recommended SOC in 1L unresectable/mUC in patients who are platinum-eligible, per multiple international treatment guidelines including ESMO and EAU guidelines^{1,2}

1L, first line; EAU, European Association of Urology; ESMO, European Society for Medical Oncology; EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PBCT, platinum-based chemotherapy; SOC, standard of care.

1. Powles T et al. *Ann Oncol* 2024;35:485–490; 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; Last accessed: May 2025; 3. Li H et al. *ESMO Real World Data Digital Oncol* 2025;doi:10.1016/j.esmow.2024.100110 [Epub ahead of print].



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

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



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



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

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 maleimidoacaproyl 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. While 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*
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialised care.
Skin reactions	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
	Grade 2 worsening Grade 2 with fever Grade 3	<ul style="list-style-type: none">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)	<ul style="list-style-type: none">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	<ul style="list-style-type: none">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	<ul style="list-style-type: none">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 and/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 treated 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-fetal toxicity and contraception: Pregnant women should be informed of the potential risk to a fetus (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 (47.4%), decreased appetite (47.2%), fatigue (46.8%), diarrhoea (39.1%), peripheral sensory neuropathy (36.5%), 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 (≥1/1000 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 known¹	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 known¹	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/ILD²
Common	Pneumonitis/ILD²	
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, rash maculo-papular, dry skin, rash macular
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythema, rash erythematous, rash macular, rash papular, rash pruritic, rash vesicular	Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythema, rash erythematous, rash papular, rash pruritic, rash vesicular, erythema multiforme, dermatitis
Uncommon	Dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, bull blister	Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis
Not known¹	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthema	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthema
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

¹Based on global post-marketing experience.

²Includes: 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 overdose with enfortumab vedotin. In case of overdose, 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.eunijwerkingmelden.be/ / www.notifierunneffectedesirabe.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: Mediaalane 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 x 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/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 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-fœtal 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. bupropion, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicity. 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 known¹: 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 known¹: 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, hypoesthesia, gait disturbance, muscular weakness. (in combination with pembrolizumab) Common: Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoesthesia, 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/ILD². (monotherapy) Common: Pneumonitis/ILD². *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, erythema, rash erythematous, 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, erythema, rash erythematous, rash papular, rash pruritic, rash vesicular, erythema multiforme, dermatitis. (monotherapy) Uncommon: Dermatitis exfoliative generalised, erythema 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 known¹: TEN, SJS, epidermal necrosis, skin hyperpigmentation, skin discoloration, pigmentation disorder, symmetrical drug-related intertriginous and flexural exanthema. *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.

¹Based on global post-marketing experience.

²Includes: 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 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. Prescribers should consult the full SPC in relation to other adverse reactions.

Overdose: There is no known antidote for overdose with enfortumab vedotin. In case of overdose, 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: £587

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.

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