

Patient case studies: Navigating challenging clinical scenarios

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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; EU, European Union; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; MHRA, Medicines and Healthcare products Regulatory Agency; P, pembrolizumab; PD-1/L1, programmed death-1/ligand-1; UC, urothelial carcinoma.

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

Date of preparation: July 2025 | Job code: MAT-NL-PAD-2025-00038

▼ 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

Personal honoraria for speaker, consultancy or advisory role

- Apogepha, AstraZeneca, Astellas, BMS, Eisai, Ipsen, Janssen, MSD, Novartis, Roche, Pfizer

Institutional financial interests that have been paid directly to my institution

- Eisai, Ipsen, Janssen, MSD, Novartis, Roche, Seagen, Pfizer

Other

- EAU RCC Guideline Vice Chairman, Steering Committee Member in BC, PC and RCC trials



Treatment with 1L EV+P following progression on adjuvant IO



Clinical
scenario 1

Patient profile: George



George

- Male
- **Age:** 47 years
- **ECOG PS:** 0
- **GFR:** 113 mL/min (no lab abnormalities)



Lifestyle: Married, one daughter aged 17 years, non-smoker

Employment status/job:
Works full time



Comorbidities: None

Concomitant medications: None

Patient history



Dec 2018

Initial presentation
with gross
haematuria



Jan 2019

TUR-B, histology;
urothelial
carcinoma, min. of
pT2, pTis, G3



Staging: CT-Thorax-
Abdomen-Pelvis: cN0 cM0



MTB:

**Neoadjuvant therapy or
proceed to cystectomy?**

Patient history



Feb 2019

Radical cystectomy,
orthotopic ileal
neobladder (I-Pouch),
urothelial carcinoma

TNM: pTis and pT3a, pN0, cM0, L0,
V0, Pn0, R1 (urethra, pTis), CPS 15



MTB:

Adjuvant therapy or follow-up?

Patient history



Apr 2019
**Adjuvant nivolumab
every 4 weeks for 12 cycles**



Apr 2020
End of nivolumab treatment

George progressed 18 months after initiating treatment with adjuvant nivolumab



18 months post-adjuvant nivolumab:
Presentation with metachronous mUC of the bladder with liver and retroperitoneal lymph node metastasis (liver, biopsy proven)



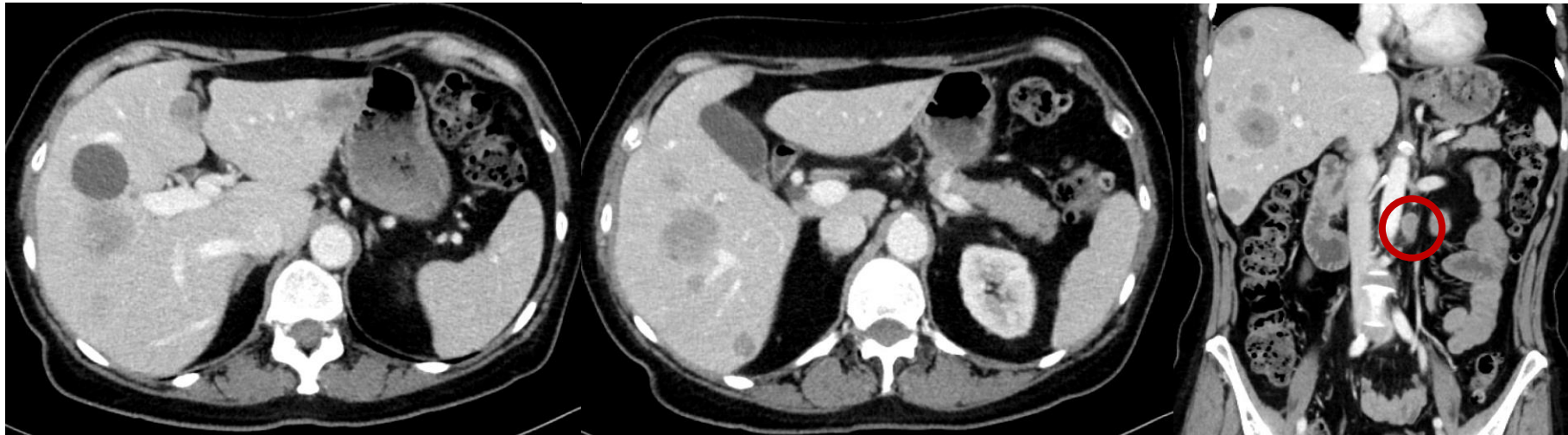
Non symptomatic

ECOG PS: 0

No autoimmune disorders, polyneuropathy or diabetes in medical history

Imaging confirmed disease progression

Nov 2021



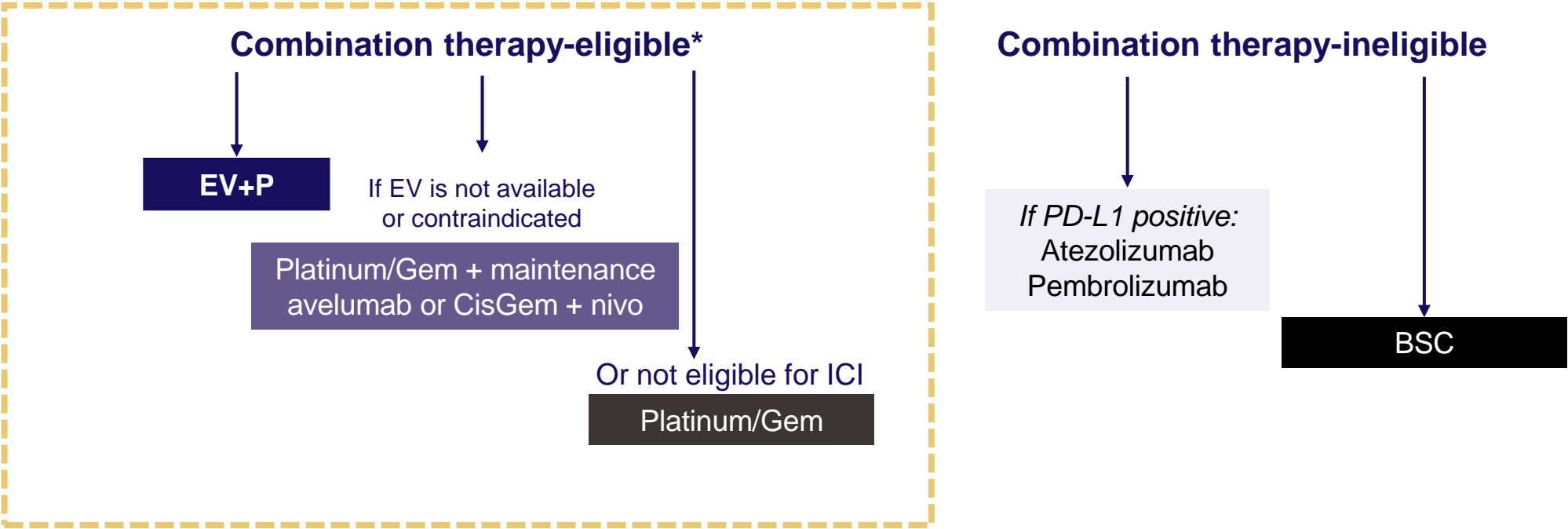
Fictitious patient case created for illustrative purposes.

Speaker's own images.

ECOG PS, Eastern Cooperative Oncology Group performance score; mUC, metastatic urothelial carcinoma.

George was evaluated to determine whether she was able to receive EV+P combination therapy

The EAU guidelines for unresectable/mUC treatment



George was considered suitable to receive EV+P, and 1L treatment with EV+P was the preferred choice vs. other options

Fictitious patient case created for illustrative purposes.

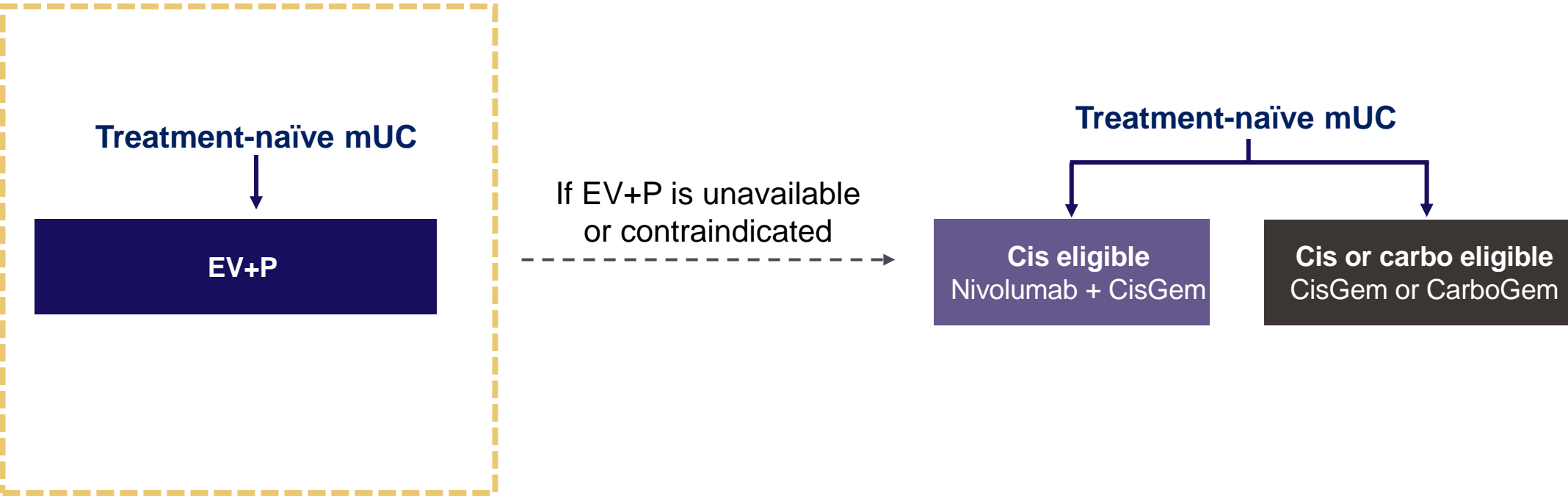
*PS 0–2, GFR >30 mL/min, adequate organ functions, for cisplatin: GFR >50 mL/min.

1L, first line; BSC, best supportive care; Cis, cisplatin; EAU, European Association of Urology; EV, enfortumab vedotin; Gem, gemcitabine; GFR, glomerular filtration rate; ICI, immune checkpoint inhibitor; mUC, metastatic urothelial carcinoma; nivo, nivolumab; P, pembrolizumab; PD-L1, programmed cell death ligand 1; PS, performance status.

EAU. Muscle-invasive and metastatic bladder cancer. Available at: <https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer>. Last accessed: June 2025.

George was evaluated to determine whether she was able to receive EV+P combination therapy

The ESMO guidelines for unresectable/mUC treatment



George was considered suitable to receive EV+P, and 1L treatment with EV+P was the preferred choice vs. other options

Reintroducing pembrolizumab based immunotherapy in advanced/mUC after prior exposure

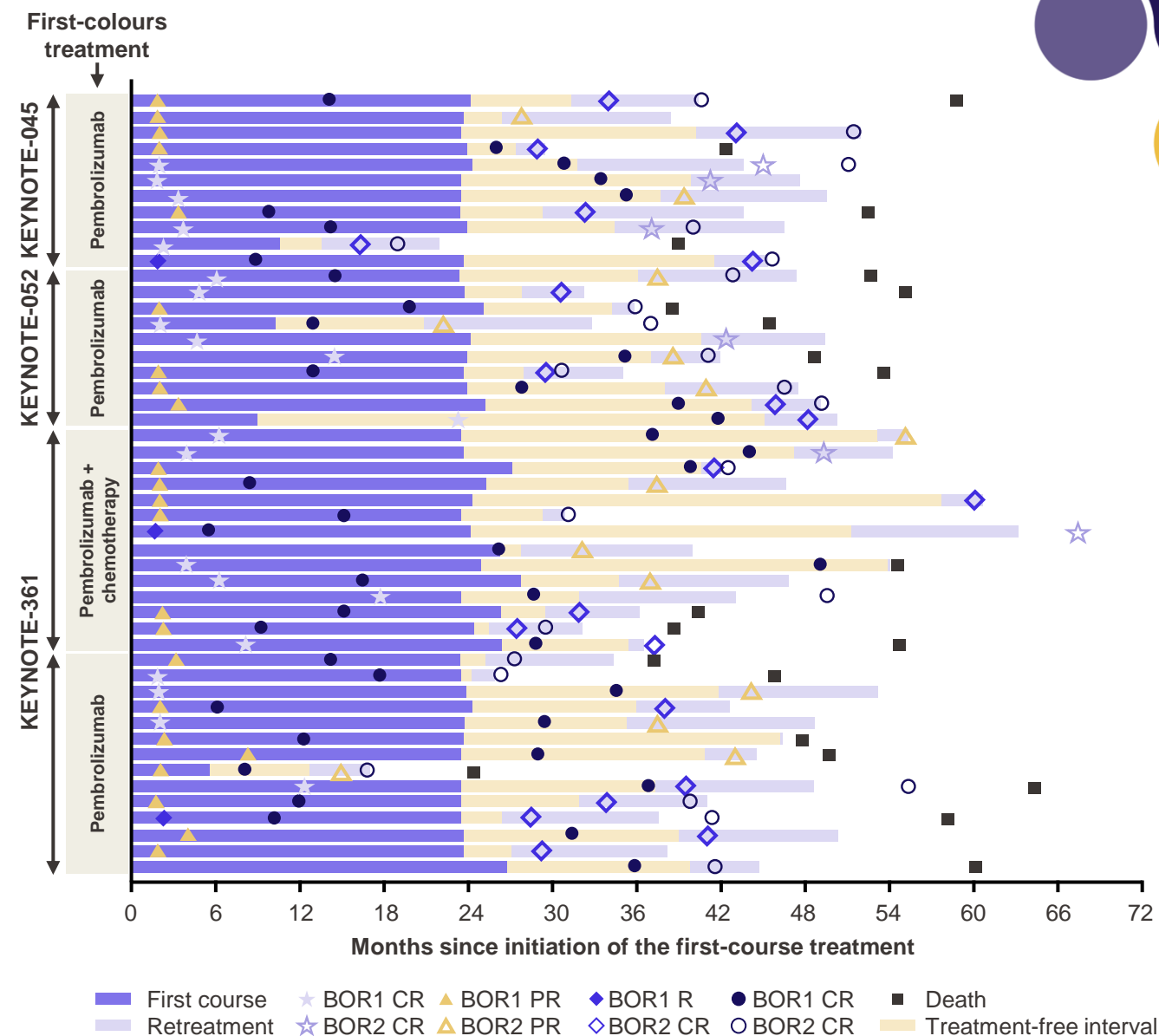
Post-hoc analysis evaluating pembrolizumab retreatment in patients with advanced/mUC who received pembrolizumab in KEYNOTE-52, KEYNOTE-45 or KEYNOTE-361, and either stopped pembrolizumab after a CR or completed pembrolizumab with an objective response or SD (analysis population n=49)

- **ORR:** 41%
- **mPFS:** 9.5 months
- **mOS:** 25.7 months

Median follow-up: 24.4 months.

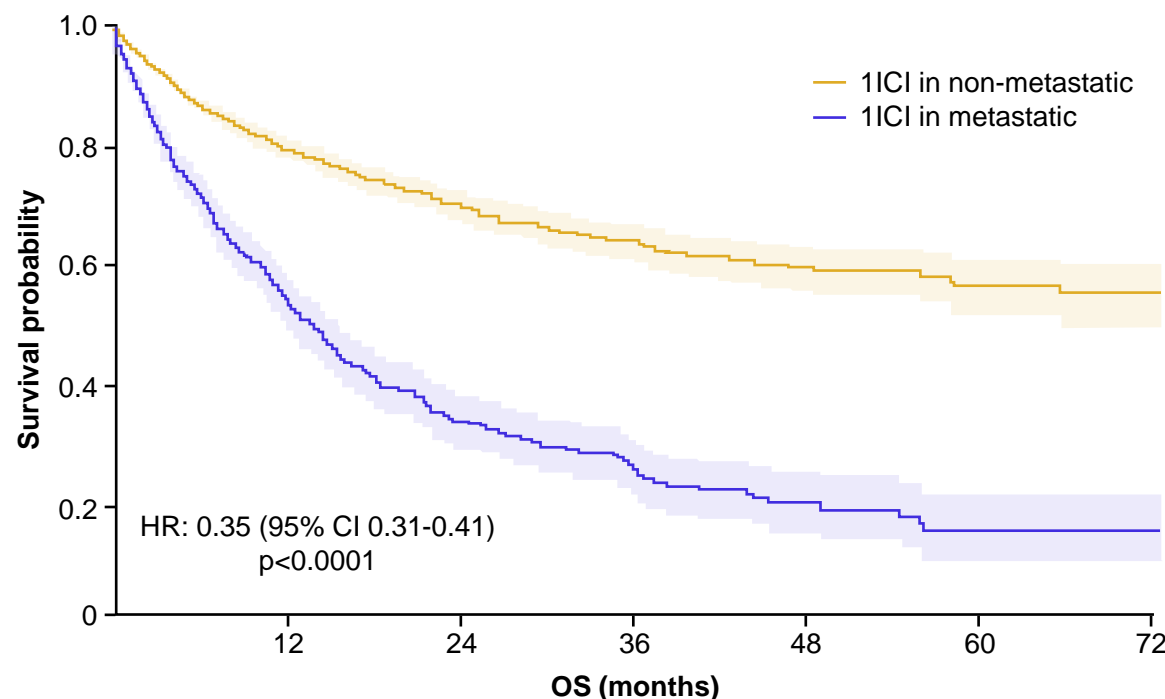
BOR, best overall response; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; mUC, metastatic urothelial carcinoma; PR, partial response; ORR, objective response rate; PD, progression of disease; SD, stable disease.

Koshkin VS et al. *Eur Urol* 2025;87:390–395.

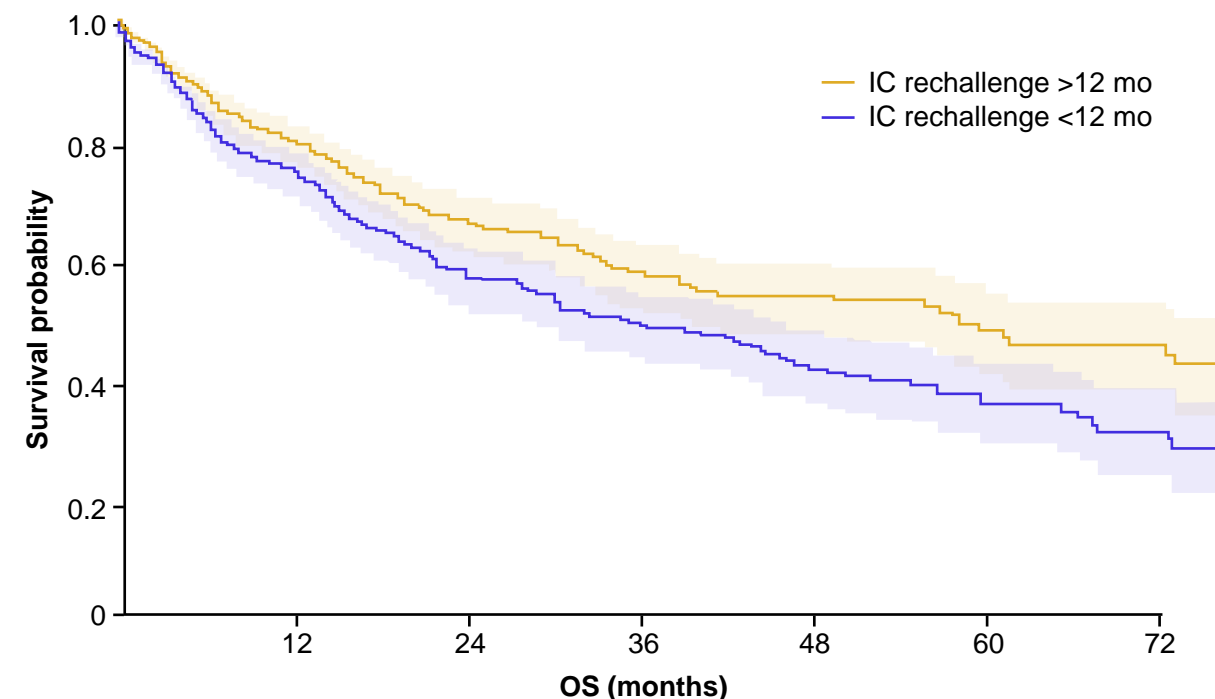


Reintroducing immunotherapy after prior exposure

International, retrospective, real-world study using the TriNetX network for a large-scale search of patients with UC who underwent two separate courses of ICI between Jan 2014–Oct 2024
(analysis population n=292)



1ICI in non-metastatic and 2ICI in mUC was associated with longer mOS than both ICI courses in mUC (72.0 vs. 13.8 months; HR: 0.35, [95% CI 0.31–0.41]; p<0.0001)



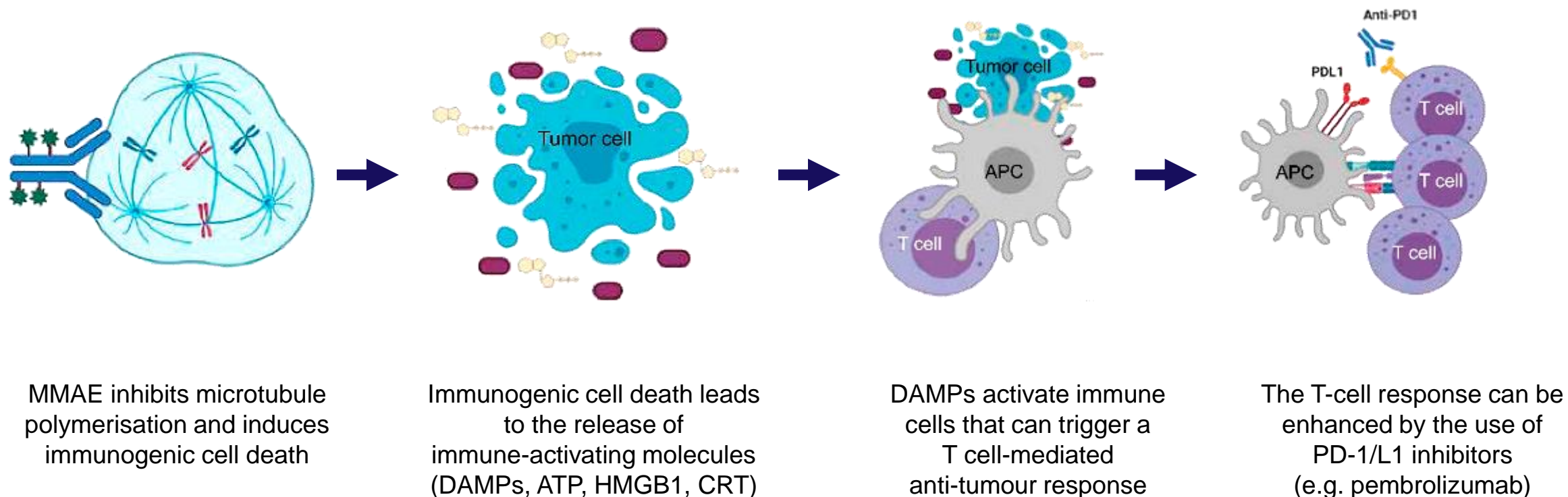
ICI rechallenge after a cut-off >12 months reached longer mOS than <12 months (34.6 vs. 11.7 months; HR:0.46 [95% CI 0.29–0.73]; p=0.027)

Median follow-up: 21.7 months.

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; mOS, median overall survival; mUC, metastatic urothelial carcinoma; OS, overall survival; UC, urothelial carcinoma.

Mairoano BA et al. Presented at ASCO GU 2025. Abstract 732.

Proposed MoA of EV+P: EV induces enhanced T-cell response in combination with P



Poll: Vote via the Onomi app!



When would you feel comfortable initiating treatment with EV+P?

- 1–6 months post-adjuvant IO
- 6–9 months post-adjuvant IO
- 9–12 months post-adjuvant IO
- >12 months post-adjuvant IO

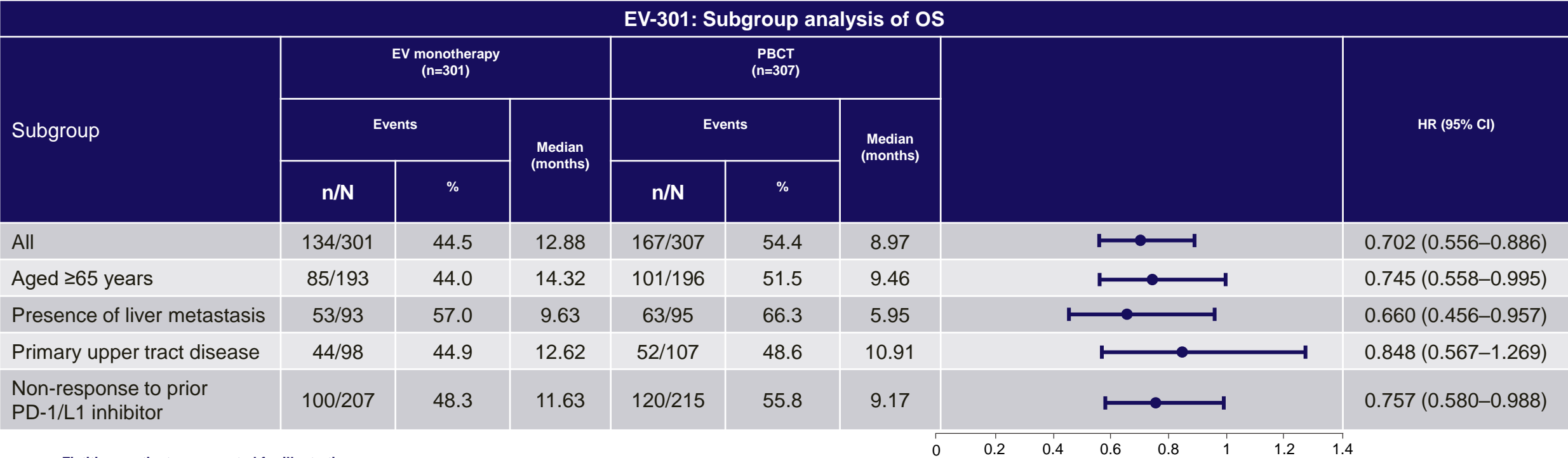


**Vote via the
Onomi app**



Alternative path: What if George had an aggressive progression pattern?

- Considerations for rapid progressive disease on adjuvant immunotherapy
- Hard-to-treat subgroups in EV-301 showed benefit for **EV monotherapy** in patients with IO failure

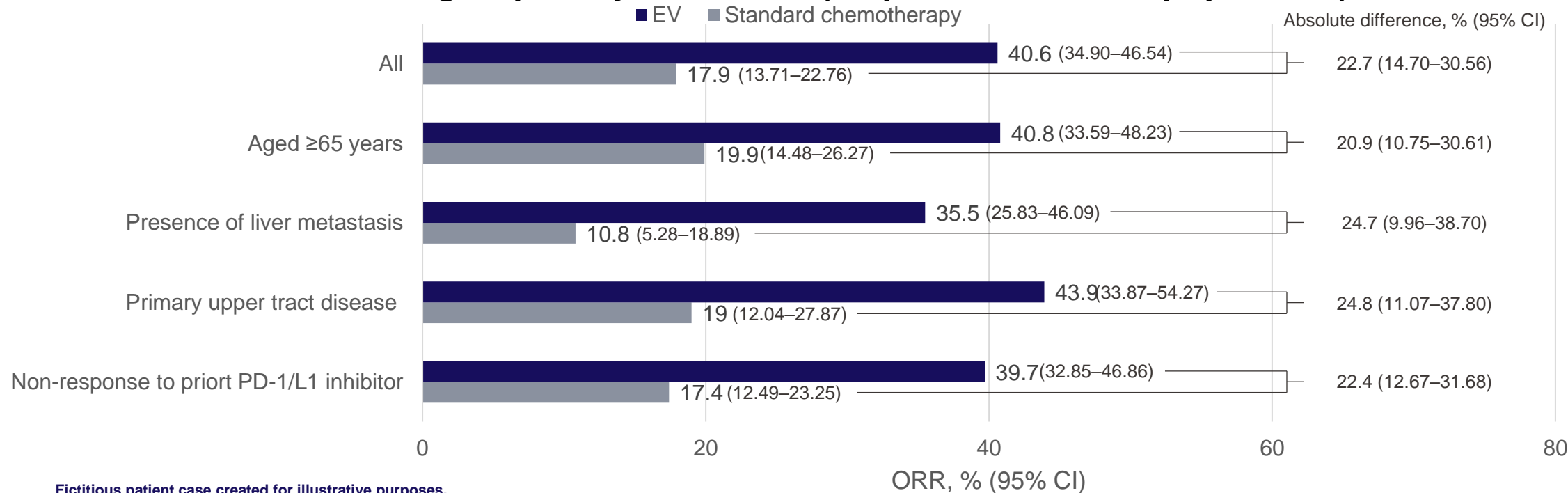


Fictitious patient case created for illustrative purposes.
Median follow-up: 11.1 months.
CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; IO, immunotherapy; OS, overall survival; PBCT, platinum-based chemotherapy; PD-1/L1, programmed cell death protein/ligand 1.
Rosenberg J et al. Presented at ESMO 2021. Abstract 1151.

Alternative path: What if George had an aggressive progression pattern?

- Considerations for rapid progressive disease on adjuvant immunotherapy
- Hard-to-treat subgroups in EV-301 showed benefit for **EV monotherapy** in patients with IO failure

EV-301: Subgroup analysis of ORR (response-evaluable population)



Fictitious patient case created for illustrative purposes.
Median follow-up: 11.1 months.
CI, confidence interval; EV, enfortumab vedotin; IO, immunotherapy; ORR, overall response rate; PD-1/L1, programmed cell death protein/ligand 1.
Rosenberg J et al. Presented at ESMO 2021. Abstract 1151.

George: Male patient, 47 years old

Nov 2021



MTB:

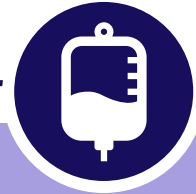
- CisGem?
- CisGem+ avemulab maintenance?
- CisGem+ nivo?
- EV+P?

Fictitious patient case created for illustrative purposes.

Speaker's own images.

EV, enfortumab vedotin; Cis, cisplatin; Gem, gemcitabine; MTB, multidisciplinary tumour board; Nivo, nivolumab; P, pembrolizumab.

George: Male patient, 47 years old

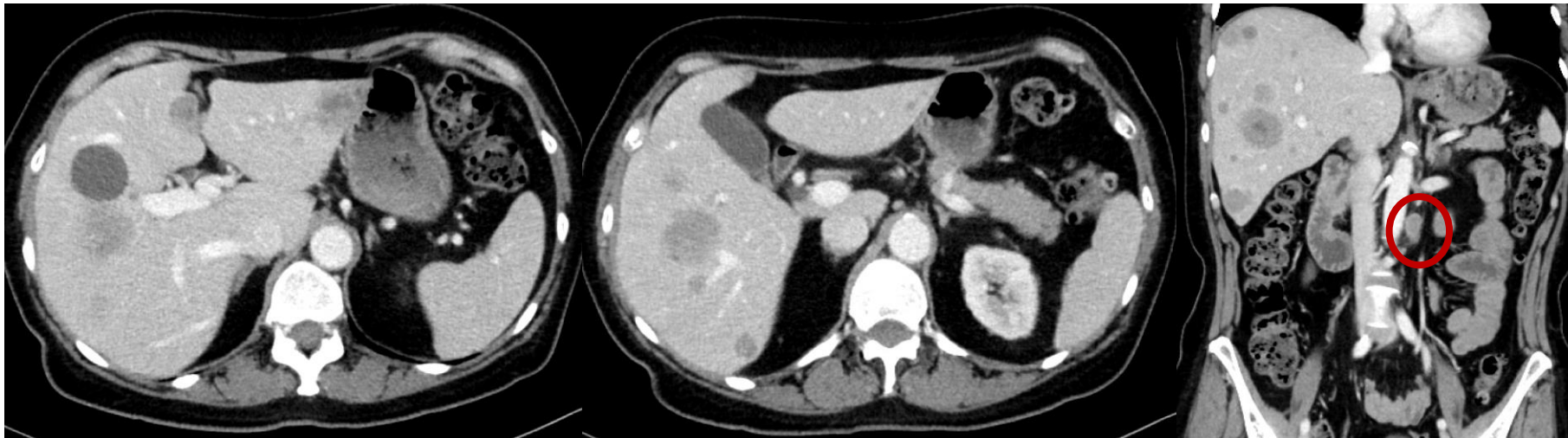


Nov 2021

**Initiated treatment with EV+P
(EV: 1.25mg/kg, P: 200 mg IV)**

Liver metastases:

Nov 2021

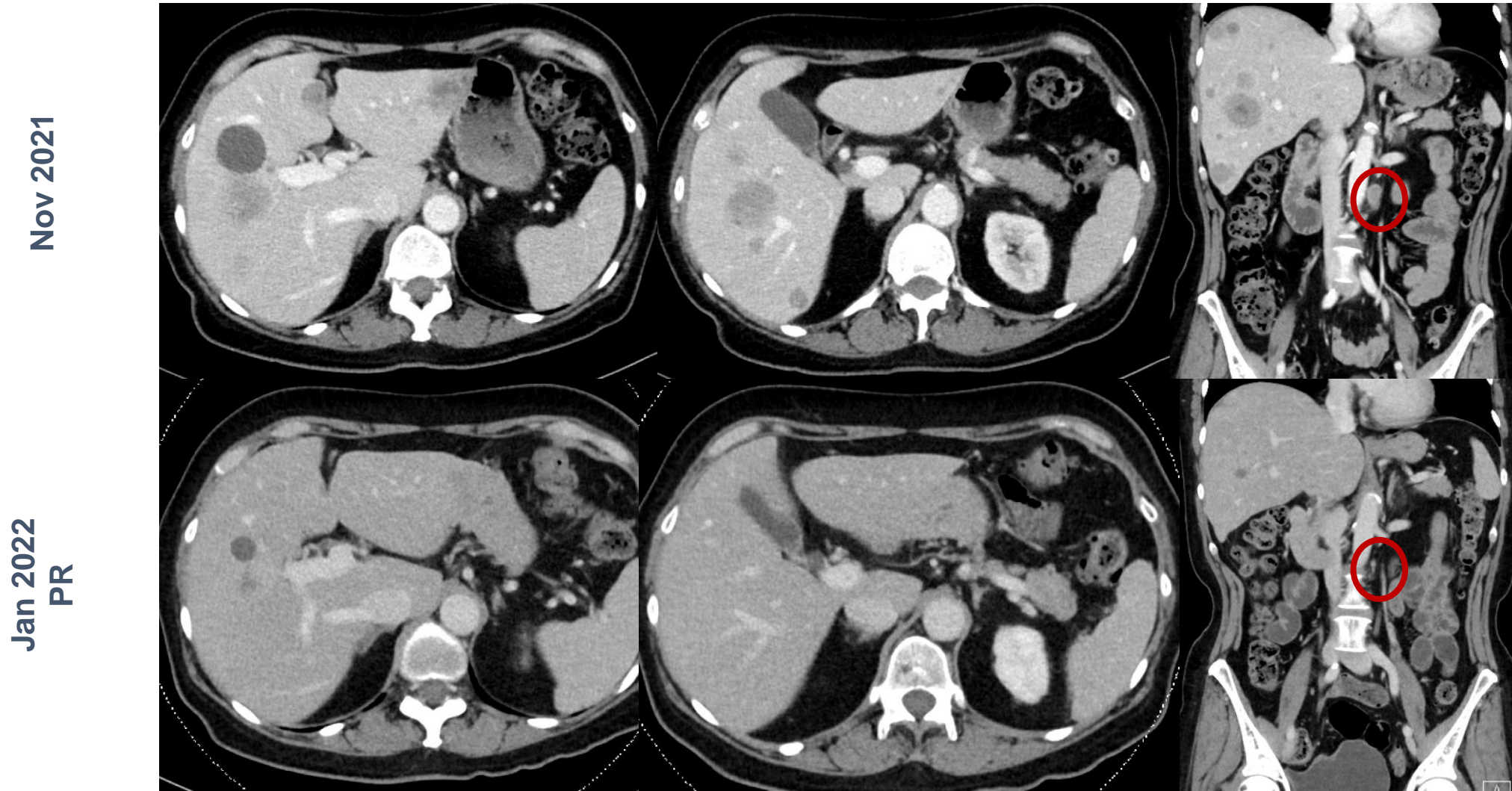


Fictitious patient case created for illustrative purposes.

Speaker's own images.

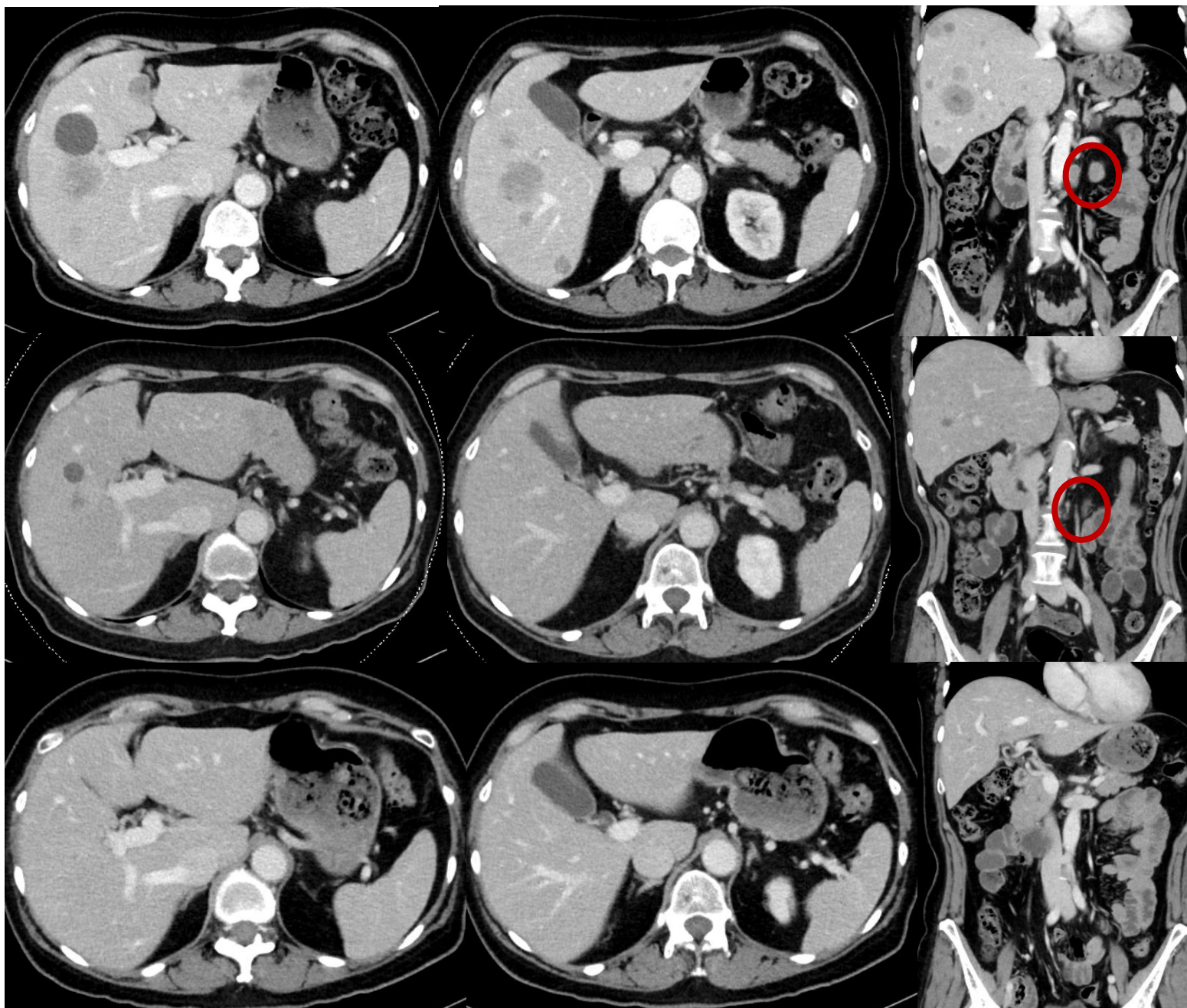
EV, enfortumab vedotin; P, pembrolizumab.

George: Male patient, 47 years old



Fictitious patient case created for illustrative purposes.
Speaker's own images.
PR, partial response.

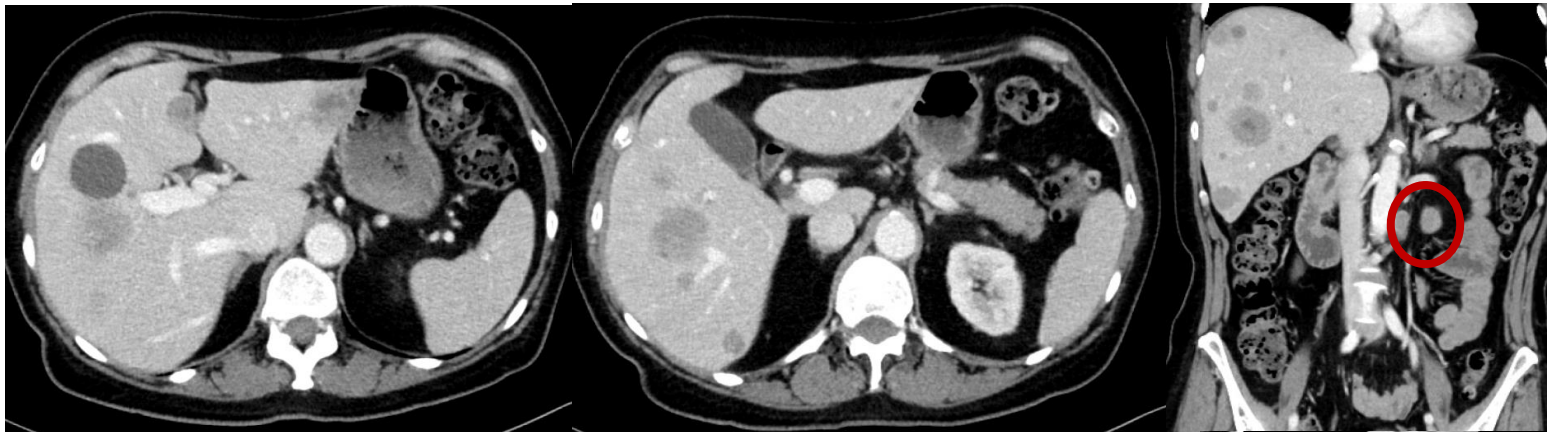
Nov 2021
Jan 2022 PR
May 2022 CR



Fictitious patient case created for illustrative purposes.
Speaker's own images.
CR, complete response; PR, partial response.

George: Male patient, 47 years old

Nov 2021
Baseline



May 2022
CR



- **Since May 2022:** Ongoing CR
- **Since Feb 2023:** Treatment modified due to polyneuropathy and dermatitis

George: Male patient, 47 years old



Treatment management:

- Treatment was **withheld** until **Grade ≤ 1**
- George was **referred to specialised care**
- Once **reduced to Grade 1**, treatment resumed by a dose reduction of one step to **1 mg/kg**

Dermatitis:



Summary



Patients in EV-302 were all naïve to ICI¹



EV+P is indicated for the first-line treatment of adult patients with unresectable/mUC who are eligible for platinum-containing chemotherapy²



There are no guidelines on use of EV+P following ICI given in early-stage disease; the indication does not restrict EV+P for patients with prior ICI in earlier stage disease²



The advice presented here is based on ICI sequencing evidence. It is important to continue evaluating RWE to further supplement guidance in the future³



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 maleimidecaproyl 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	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 (≥1/1,000 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 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:** **Immunoegnicity:** 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: Federal 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.ebnijwerkingmelden.be/ / www.notifierunneffettidesirable.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-fetal 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. bocoprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telitromycin, 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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