▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - PADCEV™ (ENFORTUMAB VEDOTIN)

WARNING

SERIOUS SKIN REACTIONS

- PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).
- Withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.
- Permanently discontinue PADCEV in patients with confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions.

(See sections 4.2 Dose and method of administration, and 4.4 Special warnings and precautions for use.)

1 NAME OF THE MEDICINE

Enfortumab vedotin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for infusion contains either 20 mg or 30 mg enfortumab vedotin. After reconstitution, each mL contains 10 mg of enfortumab vedotin.

Enfortumab vedotin is a Nectin-4 targeted antibody drug conjugate (ADC) comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable vc maleimidocaproyl linker.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for injection vial. White to off-white lyophilized powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PADCEV, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC).

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Prior to administration, the PADCEV vial is reconstituted with Sterile Water for Injection (SWFI). The reconstituted solution is transferred to an intravenous infusion bag containing either sterile 5% Dextrose Injection, sterile 0.9% Sodium Chloride Injection or sterile Lactated Ringer's Injection for administration.

Product is for single use in one patient only. Discard any residue.

Treatment with PADCEV should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

Dosage

The recommended dose of PADCEV as monotherapy 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 PADCEV 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 a 21-day cycle until disease progression or unacceptable toxicity. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

Table 1. Recommended Dose Reduction Schedule for Adverse Events

	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. PADCEV dose interruption, reduction and discontinuation recommendations in patients with LA or mUC

Adverse Reaction	**Severity***	**Dose Modification***
Skin Reactions	Grade 2 worsening skin reactions	Consider withholding PADCEV until toxicity is Grade ≤1.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤1, then resume at the same dose level or consider dose reduction by one dose level (see Table 1).

Adverse Reaction	Severity*	Dose Modification*
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Immediately withhold until diagnosis established. If not SJS/TEN see Grade 3 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL). Resume treatment at the same dose level.
Pneumonitis/interstitial lung disease	Grade 2	Withhold until Grade ≤1, then resume at the same dose level or consider dose reduction by one dose level (see Table 1).
	Grade ≥3	Permanently discontinue.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤1. For first occurrence, resume treatment at the same dose level. For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level (see Table 1).
	Grade ≥3	Permanently discontinue.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Elderly

No dose adjustment is required in patients ≥65 years of age (see section 5.2 Pharmacokinetic properties).

Children

The safety and efficacy of PADCEV in pediatric patients have not been established.

Patients with 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. PADCEV has not been evaluated in patients with end stage renal disease (see section 5.2 Pharmacokinetic properties).

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. PADCEV has only been evaluated in a limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment. As there is limited to no data available, use PADCEV with caution in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST of any level) (see section 5.2 Pharmacokinetic properties).

Method of administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer drugs.

2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

3. Calculate the recommended dose based on the patient's weight to determine the number and strength (20 mg or 30 mg) of vials needed.

4. Reconstitute each vial as follows and, if possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilized powder:

   a. 20 mg vial: Add 2.3 mL of SWFI, resulting in 10 mg/mL PADCEV.

   b. 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL PADCEV.

5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle for at least 1 minute until the bubbles are gone. DO NOT SHAKE THE VIAL. Do not expose to direct sunlight.

6. Visually inspect the solution for particulate matter and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless to light yellow and free of visible particles. Discard any vial with visible particles or discoloration.

7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, reconstituted vials may be stored for up to 24 hours in refrigeration at 2°C to 8°C. DO NOT FREEZE. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.

9. Dilute PADCEV with either 5% Dextrose Injection, 0.9% Sodium Chloride Injection or Lactated Ringer's Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL PADCEV.

10. Mix diluted solution by gentle inversion. DO NOT SHAKE THE BAG. Do not expose to direct sunlight.

11. Visually inspect the infusion bag for any particulate matter or discoloration prior to use. The reconstituted solution should be clear to slightly opalescent, colorless to light yellow and free of visible particles. DO NOT USE the infusion bag if particulate matter or discoloration is observed.

12. Discard any unused portion left in the single-dose vials.

13. The prepared infusion bag should not be stored longer than 16 hours under refrigeration at 2°C to 8°C including infusion time. DO NOT FREEZE.

Administration

14. Administer the infusion over 30 minutes through an intravenous line. DO NOT administer as an IV push or bolus.

15. DO NOT co-administer other drugs through the same infusion line.

4.3 CONTRAINDICATIONS

PADCEV is contraindicated in patients with known hypersensitivity to enfortumab vedotin or to any of the excipients in the formulation (Refer to Section 6.1 – List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Skin Reactions

Skin reactions are anticipated on-target events, as Nectin-4 is expressed in the skin.

Skin reactions, predominantly mild to moderate rash maculo-papular, have occurred with PADCEV. The incidence of skin reactions occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as monotherapy (see section 4.8 Adverse effects (Undesirable effects)). Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with PADCEV, predominantly during the first cycle of treatment.

Starting with the first cycle and throughout treatment, monitor patients for skin reactions. Consider appropriate treatment such as topical corticosteroids and antihistamines for mild to moderate skin reactions. For Grade 2 worsening skin reactions, consider withholding PADCEV until toxicity is Grade ≤1. For severe (Grade 3) skin reactions, suspected SJS or TEN, withhold PADCEV and consider referral for specialized care. Permanently discontinue PADCEV for confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions (see section 4.2 Dose and method of administration).

Hyperglycaemia

Hyperglycaemia and diabetic ketoacidosis (DKA) including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV. Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m^2) (see section 4.8 Adverse effects (Undesirable effects)). Blood glucose levels should be monitored regularly in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated (>13.9 mmol/L; >250 mg/dL), withhold PADCEV (see sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic Properties).

Pneumonitis/interstitial lung disease

Severe, life-threatening or fatal pneumonitis/interstitial lung disease occurred in patients treated with PADCEV. In clinical trials of PADCEV as monotherapy, 2.1% of the 793 patients treated with PADCEV had pneumonitis and 0.6% had interstitial lung disease. Less than 1% of patients experienced severe (Grade 3 or -4) pneumonitis or interstitial lung disease (Grade 3: 0.5%, Grade 4: 0.3%). The median time to onset of pneumonitis or interstitial lung disease was 2.7 months (range: 0.6 to 6.0 months). Two patients (0.3%) on trial also experienced fatal events.

The incidence of pneumonitis/interstitial lung disease, including severe events occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as monotherapy (see section 4.8 Adverse effects (Undesirable effects)). Monitor patients for signs and symptoms indicative of pneumonitis/interstitial lung disease such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations. Withhold PADCEV for patients who develop Grade 2 pneumonitis/interstitial lung disease and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/interstitial lung disease (see section 4.2 Dose and method of administration).

Peripheral neuropathy

Peripheral neuropathy, predominantly sensory, has occurred with PADCEV, including Grade ≥3 reactions. Monitor patients for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of PADCEV (see sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic properties).

Ocular disorders

Ocular disorders, predominantly dry eye, occurred in patients treated with PADCEV. Severe (Grade 3) ocular disorders only occurred in 3 patients (0.4%).

Monitor patients for ocular disorders such as dry eye. Consider artificial tears for prophylaxis of dry eye and refer patient for ophthalmologic evaluation if ocular symptoms do not resolve or worsen.

Infusion Site Extravasation

Skin and soft tissue injury following PADCEV administration has been observed when extravasation occurred. 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.

Use in hepatic impairment

Based on population pharmacokinetics analysis using data from clinical studies in patients with metastatic UC, there was no significant differences in enfortumab vedotin exposure and a 37% and 16% increase in unconjugated MMAE average concentrations in patients with previously treated and previously untreated locally advanced or mUC, respectively, with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST of any level, or total bilirubin ≤ ULN and AST > ULN, n=65) compared to patients with normal hepatic function. As PADCEV has only been studied in a limited number of patients with moderate hepatic impairment (n=3) and has not been evaluated in patients with severe hepatic impairment (total bilirubin >1.5 × ULN and AST of any level), use PADCEV with caution in these patients.

Use in renal impairment

No significant differences in the safety and efficacy of PADCEV in patients with mild (creatinine clearance; CrCL >60–90 mL/min), moderate (CrCL 30–60 mL/min) and severe (CrCL 15-<30 mL/min) renal impairment were observed. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see sections 4.2 Special populations and 5.2 Pharmacokinetics in special populations).

Embryofetal Toxicity and Contraception

Pregnant women should be informed of the potential risk to a fetus (see section 4.6 Fertility, pregnancy and lactation). Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with PADCEV, to use effective contraception during treatment and for at least 7 months after stopping treatment. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 6 months after the last dose of PADCEV.

Use in the elderly

No overall differences in safety or efficacy were observed between patients ≥65 years of age and younger patients (see sections 4.2 Special populations and 5.2 Pharmacokinetics in special populations).

Paediatric use

There is no relevant use of enfortumab vedotin in the paediatric population for the indication of LA or mUC.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. To evaluate the drug-drug interaction potential of unconjugated MMAE, physiologically-based pharmacokinetic (PBPK) modeling was conducted to predict the drug-drug interaction potential of enfortumab vedotin following co-administration with other drugs.

Effects of other Medicines on PADCEV

Drug interactions with co-medications that are CYP3A4 inhibitors

Concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%, with no change in ADC exposure. Closely monitor for adverse reactions when PADCEV is given concomitantly with strong CYP3A4 inhibitors (see section 5.2 Pharmacokinetics in special populations).

Co-administration with other CYP substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of MMAE-mediated inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. Unconjugated MMAE does not induce CYP1A2, CYP2B6 or CYP3A4/5.

Co-administration with drugs that are substrates of transporters

In vitro data indicate that unconjugated MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations. Unconjugated MMAE was not a substrate or inhibitor for the BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OCT2 or OAT3 transporters. Unconjugated MMAE was also not an inhibitor of BSEP or OCT1.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of PADCEV on human male and female fertility have not been studied. MMAE, the cytotoxic moiety of enfortumab vedotin, acts via an aneugenic mechanism and may affect fertility. Results from a repeat-dose toxicity study in rats indicate the potential for enfortumab vedotin to impair male reproductive function and fertility.

In rats given weekly IV doses of ≥2 mg/kg enfortumab vedotin resulting in systemic exposures below the clinical exposure levels at the recommended clinical dose resulted in dose-dependent testicular seminiferous tubule degeneration with abnormal lumen contents and hypospermia. These findings were partially reversed following a 24-week treatment-free period. Repeat dose studies in female rats at IV doses ≤5 mg/kg enfortumab vedotin (resulting in subclinical exposures) showed no histological abnormalities in female reproductive organs however, dedicated fertility studies have not been conducted. Therefore, men being treated with PADCEV are advised to have sperm samples frozen and stored before treatment. Men being treated with PADCEV are advised to use effective contraception during treatment with PADCEV and not to father a child during treatment and for up to 6 months following the last dose. Effects on spermatogenesis cannot be excluded after a 6-month treatment-free period.

While not observed with enfortumab vedotin, ovarian effects were observed in repeat dose toxicity studies of other MMAE-containing ADCs. A mild to moderate decrease in, or absence of, secondary and tertiary ovarian follicles was observed in young female cynomolgus monkeys at doses ≥3 mg/kg weekly for 4 weeks. No changes were observed in primordial follicles. Effects on the secondary and tertiary ovarian follicles showed evidence of recovery 6 weeks after the end of dosing.

Use in pregnancy – Pregnancy Category D

There are no adequate or well-controlled studies with PADCEV in pregnant women. However, based on its mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. PADCEV is contraindicated in pregnancy. MMAE, the main cytotoxic moiety of enfortumab vedotin, was shown to cross the placenta in rats. In pregnant rats, administration of MMAE (0.2 mg/kg IV) or enfortumab vedotin (2.5 mg/kg IV) during the period of organogenesis, caused embryofetal lethality and toxicity and included an increased incidence of resorptions, pre- and post-implantation loss, and decreased litter size. There was also a reduction in mean fetal weight and an increased incidence of fetal malformations (protruding tongue, malrotated hindlimbs, gastroschisis, agnathia, situs inversus, and malformed mandible, misaligned, fused and/or absent caudal vertebrae, split vertebrae, and shortened long bone, malrotated hindlimb, absent 4th digit of the forepaw asymmetric, fused, incompletely ossified and misshapen sternebrae, misshapen cervical arch and unilateral ossification of the thoracic centra). These adverse embryofetal development effects occurred at exposures less than that expected in patients receiving enfortumab vedotin. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with PADCEV. Consider obtaining a pregnancy test in females of childbearing potential within 7 days prior to initiating treatment with PADCEV. Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for at least 7 months after the last dose. PADCEV should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If PADCEV is used during pregnancy or if the patient becomes pregnant while receiving PADCEV, the patient should be clearly advised on the potential risk to the fetus. See the 'Effects on fertility' section above pertaining to advice for women whose male partners are being treated with PADCEV.

Use in lactation

It is unknown whether enfortumab vedotin or the cytotoxic moiety, MMAE, are excreted in human milk. No studies have been conducted to assess the impact of PADCEV on milk production or its presence in breast milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants due to PADCEV, a risk to breast-fed children cannot be excluded. Breastfeeding should be discontinued during PADCEV treatment and for at least 6 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

PADCEV as monotherapy

The safety of PADCEV was evaluated as monotherapy in 793 patients who received at least one dose of PADCEV 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). Patients were exposed to PADCEV for a median duration of 4.7 months (range: 0.3 to 55.7 months).

Serious adverse events occurred in 46% of patients; the most common serious adverse reactions (≥2%) were diarrhoea (2%) and hyperglycaemia (2%). Permanent discontinuation

occurred in 21% of patients; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (5%). Dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (15%), fatigue (7%), rash maculo-papular (4%), aspartate aminotransferase increased (3%), alanine aminotransferase increased (3%), anaemia (3%), diarrhoea (3%), hyperglycaemia (3%), neutrophil count decreased (3%), rash (2%) and peripheral motor neuropathy (2%). Dose reduction occurred in 38% of patients; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (10%), fatigue (5%), rash maculo-papular (4%) and decreased appetite (2%).

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies 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 (≥10%), Integrated Safety Set and EV-301 Study, Monotherapy

	Integrated Safety Set[b]		**EV-301[c]**			
	PADCEV n=793		**PADCEV n=296**		**Chemotherapy n=291**	
Adverse Reaction[a]	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Skin and subcutaneous tissue disorders						
Alopecia	378 (47.7)	0	139 (47)	0	110 (37.8)	0
Pruritus	265 (33.4)	14 (1.8)	102 (34.5)	5 (1.7)	20 (6.9)	0
Rash	92 (11.6)	13 (1.6)	50 (16.9)	5 (1.7)	16 (5.5)	0
Rash maculo-papular	187 (23.6)	43 (5.4)	50 (16.9)	22 (7.4)	6 (2.1)	0
Dry skin	173 (21.8)	1 (0.1)	50 (16.9)	0	11 (3.8)	0
General disorders and administration site conditions						
Fatigue	371 (46.8)	59 (7.4)	107 (36.1)	20 (6.8)	78 (26.8)	14 (4.8)
Metabolism and nutrition disorders						
Hyperglycaemia	118 (14.9)	57 (7.2)	31 (10.5)	21 (7.1)	6 (2.1)	2 (0.7)
Decreased appetite	374 (47.2)	31 (3.9)	121 (40.9)	16 (5.4)	78 (26.8)	7 (2.4)
Nervous system disorders						
Peripheral sensory neuropathy	305 (38.5)	25 (3.2)	102 (34.5)	9 (3)	66 (22.7)	6 (2.1)
Dysgeusia	241 (30.4)	0	74 (25)	0	23 (7.9)	0
Gastrointestinal disorders						
Diarrhoea	310 (39.1)	36 (4.5)	103 (34.8)	11 (3.7)	66 (22.7)	5 (1.7)
Vomiting	148 (18.7)	12 (1.5)	42 (14.2)	4 (1.4)	44 (15.1)	3 (1)
Nausea	300 (37.8)	14 (1.8)	89 (30.1)	3 (1)	74 (25.4)	5 (1.7)
Blood and lymphatic system disorders						
Anaemia	231 (29.1)	77 (9.7)	59 (19.9)	19 (6.4)	87 (29.9)	34 (11.7)

Adverse Reaction[a]	Integrated Safety Set[b] PADCEV n=793		EV-301[c] PADCEV n=296		EV-301[c] Chemotherapy n=291	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Investigations						
Alanine aminotransferase increased	101 (12.7)	7 (0.9)	27 (9.1)	2 (0.7)	4 (1.4)	1 (0.3)
Aspartate aminotransferase increased	135 (17.0)	13 (1.6)	36 (12.2)	3 (1)	5 (1.7)	0
Weight decreased	200 (25.2)	7 (0.9)	47 (15.9)	1 (0.3)	20 (6.9)	0
Eye disorders						
Dry eye	101 (12.7)	0	19 (6.4)	0	3 (1)	0

a. Preferred terms in MedDRA (v26.0).
b. The above-mentioned listed adverse reactions have been observed during clinical studies (EV-101, EV-102, EV-103, EV-201, EV-203 and EV-301 data cutoffs 16-Dec-2022, 25-Feb-2019, 13-Mar-2023, 13-Mar-2023, 13-Mar-2023, 13-Mar-2023, respectively).
c. Data cutoff 15-Jul-2020.

Clinically relevant adverse reactions (<10%) and frequencies of patients who received PADCEV as monotherapy included:

Blood and lymphatic system disorders

Not known: Neutropenia†, febrile neutropenia†, neutrophil count decreased†

General disorders and administration site conditions

Common: Infusion site extravasation

Nervous system disorders

Common: Neuropathy peripheral, 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

Respiratory, thoracic, and mediastinal disorders

Not known: Pneumonitis†, interstitial lung disease†

Skin and subcutaneous tissue disorders

Common: Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular
Uncommon: Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister
Not known: Toxic epidermal necrolysis†, Stevens-Johnson syndrome†, epidermal necrosis†, symmetrical drug-related intertriginous and flexural exanthaema†

†Adverse reactions of an unknown frequency have been identified during post approval use of enfortumab vedotin. Because these reactions were reported voluntarily from a population of

uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

PADCEV in combination with pembrolizumab

The safety of PADCEV was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of PADCEV 1.25 mg/kg in combination with pembrolizumab in one phase 2 study (EV-103) and one phase 3 study (EV-302).

In EV-302, the safety of PADCEV in combination with pembrolizumab was evaluated in an open-label, randomised, multicentre trial in patients with locally advanced or metastatic urothelial cancer. Patients received either PADCEV 1.25 mg/kg and pembrolizumab (n=440) or gemcitabine and platinum chemotherapy (either cisplatin or carboplatin) (n=433). Among patients who received PADCEV and pembrolizumab, the median duration of exposure for PADCEV was 7 months (range: 0.3 to 31.9 months).

Serious adverse events occurred in 49.8% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were diarrhoea (3.0%) pneumonitis/ILD (2.3%).

Fatal adverse reactions occurred in 3.9% of patients treated with PADCEV in combination with pembrolizumab including pneumonitis/ILD (0.2%).

Permanent discontinuation of PADCEV occurred in 35.8% of patients. The most common adverse reactions (≥2%) leading to permanent discontinuation of PADCEV were peripheral sensory neuropathy (12.2%) and rash maculo-papular (2.0%).

Dose interruption of PADCEV occurred in 72% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhoea (4.8%), fatigue (3.7%), pneumonitis/ILD (3.7%), hyperglycaemia (3.4%), neutropenia (3.2%), alanine aminotransferase increased (3%), pruritus (2.3%) and anaemia (2.0%).

Dose reduction of PADCEV occurred in 42.4% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were peripheral sensory neuropathy (9.9%), rash maculo-papular (6.4%), fatigue (3.2%), diarrhea (2.3%) and neutropenia (2.1%).

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies 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 4. Adverse Reactions (≥20%), Integrated Safety Set and EV-302 Study, Combination with Pembrolizumab

Adverse Reaction[a]	Integrated Safety Set[b]		EV-302[c]			
	PADCEV with pembrolizumab n=564		PADCEV with pembrolizumab n=440		Gemcitabine +platinum n=433	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Skin and subcutaneous tissue disorders						
Alopecia	217 (38.5)	2 (0.4)	152 (34.5)	2 (0.5)	34 (7.9)	1 (0.2)
Pruritus	232 (41.1)	9 (1.6)	182 (41.4)	5 (1.1)	29 (6.7)	0
Rash[d]	384 (68.1)	89 (15.8)	297 (67.5)	64 (14.5)	64 (14.8)	0
General disorders and administration site conditions						
Fatigue[d]	303 (53.7)	41 (7.3)	225 (51.1)	27 (6.1)	246 (56.8)	28 (6.5)
Metabolism and nutrition disorders						
Decreased appetite	191 (33.9)	9 (1.6)	145 (33.0)	8 (1.8)	112 (25.9)	8 (1.8)
Nervous system disorders						
Peripheral neuropathy[d]	376 (66.7)	38 (6.7)	293 (66.6)	34 (7.7)	60 (13.9)	0
Dysgeusia	137 (24.3)	0	93 (21.1)	0	37 (8.5)	0
Gastrointestinal disorders						
Diarrhoea	221 (39.2)	29 (5.1)	166 (37.7)	20 (4.5)	69 (15.9)	6 (1.4)
Nausea	160 (28.4)	8 (1.4)	116 (26.4)	7 (1.6)	178 (41.1)	12 (2.8)
Blood and lymphatic system disorders						
Anaemia	145 (25.7)	49 (8.7)	108 (24.5)	31 (7.0)	267 (61.7)	148 (34.2)
Investigations						
Weight decreased	203 (36.0)	22 (3.9)	145 (33.0)	16 (3.6)	38 (8.8)	1 (0.2)
Eye disorders						
Dry eye[d]	156 (27.7)	0	107 (24.3)	0	9 (2.1)	0

a. Preferred terms in MedDRA (v26.0).
b. The above-mentioned listed adverse reactions have been observed during clinical studies EV-103 dose escalation cohort + cohort A+ cohort K, data cutoff 13Mar2023 and EV-302, data cutoff 8Aug2023.
c. Data cut off 8Aug2023.
d. Includes multiple terms.

Clinically relevant adverse reactions (<20%) and frequencies of patients who received PADCEV with pembrolizumab included:

Blood and lymphatic system disorders
Not known: Neutropenia†

Endocrine disorders
Very Common: Hypothyroidism

Respiratory, thoracic, and mediastinal disorders
Common: Pneumonitis
Not known: Interstitial lung disease†

Gastrointestinal disorders
Very Common: Vomiting

General disorders and administration site conditions
Common: Infusion site extravasation

Metabolism and nutrition disorders
Very common: Hyperglycaemia

Skin and subcutaneous tissue disorders
Very Common: Dry skin

Musculoskeletal and connective tissue disorders
Common: Myositis

Investigations
Very Common: Alanine aminotransferase increased, Aspartate aminotransferase increased

†Adverse reactions of an unknown frequency have been identified during post approval use of enfortumab vedotin. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Description of selected adverse reactions

Skin Reactions
In clinical studies of PADCEV as monotherapy, skin reactions occurred in 452 (57%) of the 793 patients treated with PADCEV 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 108 (14%) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The time to onset of severe skin reactions ranged from 0.1 to 8.2 months (median 0.7 months).

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 PADCEV in combination with pembrolizumab, skin reactions occurred in 392 (70%) 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 97 (17%) patients (Grade 3: 16%, Grade 4: 1%). The time to onset of severe skin reactions ranged from 0.1 to 17.2 months (median 1.7 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.

Hyperglycaemia
In clinical studies of PADCEV as monotherapy, hyperglycaemia occurred in 133 (17%) of the 793 patients treated with PADCEV 1.25 mg/kg. Severe (Grade 3 or 4) hyperglycaemia occurred

in 58 patients (Grade 3: 6.6%, Grade 4: 0.8%). Two patients experienced fatal events, one event each of hyperglycaemia and diabetic ketoacidosis. The incidence of Grade 3 or 4 hyperglycaemia increased consistently in patients with higher body mass index and in patients with higher baseline haemoglobin A1C. The time to onset of hyperglycaemia ranged from 0 to 20.3 months (median 0.5 months). Patients with baseline haemoglobin A1C ≥8% were excluded from clinical studies.

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.

Pneumonitis/interstitial lung disease
In clinical studies of PADCEV as monotherapy, pneumonitis occurred in 17 (2.1%) and interstitial lung disease occurred in 5 (0.6%) of the 793 patients treated with PADCEV 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis or interstitial lung disease (Grade 3: 0.5%, Grade 4: 0.3%). The time to onset of pneumonitis or interstitial lung disease ranged from 0.6 to 6.0 months (median 2.7 months).

In clinical studies of PADCEV in combination with pembrolizumab, pneumonitis occurred in 41 (7%) and interstitial lung disease occurred in 5 (1%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis occurred in 11 patients (Grade 3: 1.6%, Grade 4: 0.4%) and interstitial lung disease occurred in 4 patients (Grade 3: 0.7%). One patient experienced a fatal event of pneumonitis. The time to onset of pneumonitis or interstitial lung disease ranged from 0.3 to 26.2 months (median 4.0 months).

Peripheral Neuropathy
In clinical studies of PADCEV as monotherapy, peripheral neuropathy occurred in 422 (53%) of the 793 patients treated with PADCEV 1.25 mg/kg. Forty-one (5%) patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The time to onset of Grade ≥2 peripheral neuropathy ranged from 0.1 to 20.2 months (median 5.0 months). Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical studies.

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 PADCEV as monotherapy, 19 (2%) patients interrupted, and 1 (0.1%) patient permanently discontinued treatment for ocular disorders. Severe (Grade 3) ocular disorders only occurred in 3 patients (0.4%). Dry eye symptoms were experienced by 101 (13%) of patients during treatment with PADCEV 1.25 mg/kg and the time to onset ranged from 0 to 30.6 months (median 1.7 months) (see section 4.4 Special warnings and precautions for use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

The clinical pharmacology of enfortumab vedotin was evaluated in patients with solid tumours who received enfortumab vedotin administered by intravenous infusion.

Pharmacodynamic effects

In an exposure-response analysis for safety, a higher exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 peripheral neuropathy, Grade ≥3 hyperglycaemia). In an exposure-response analysis for efficacy, higher early exposures were associated with increased overall survival (OS), progression free survival (PFS), and objective response rate (ORR) across the entire range of enfortumab vedotin exposures compared to chemotherapy. Dose modifications to manage adverse events after attaining a response did not appear to negatively impact PFS or OS.

Cardiac Electrophysiology
The effect of PADCEV on the duration of cardiac ventricular repolarization was evaluated in 17 patients with LA or metastatic urothelial carcinoma who received PADCEV on Days 1, 8, and 15 of each 28-day cycle. Based on concentration – QTcF modeling, a population mean change in QTcF interval (change from baseline QTcF; upper 1-sided 95% CI) of 6.17 (10.5) msec was estimated to occur at a geometric mean C_{max} of 20.1 mcg/mL for the ADC. For MMAE, a population mean change in QTcF interval (upper 1-sided 95% CI) of -3.14 (9.52) msec was estimated to occur at a geometric mean C_{max} of 3.94 ng/mL. At the recommended dose of 1.25 mg/kg, PADCEV had no large effect on QTc prolongation (>20 msec).

Mechanism of action

Enfortumab vedotin is an ADC targeting Nectin-4, an adhesion protein located on the surface of epithelial cells including urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent, MMAE, via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalisation of the ADC-Nectin-4

complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis, and immunogenic cell death. MMAE released from enfortumab vedotin targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death. The combination of enfortumab vedotin with PD-1 inhibitors results in enhanced anti-tumor activity, consistent with the complementary mechanisms of MMAE induced cell cytotoxicity and induction of immunogenic cell death, plus the up-regulation of immune function by PD-1 inhibition.

Clinical studies

Urothelial Cancer

PADCEV in combination with Pembrolizumab

Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

EV-302

The efficacy of PADCEV in combination with pembrolizumab was evaluated in a phase 3, open label, randomised, multicentre study that enrolled 886 patients with locally advanced or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease.

Patients were randomised 1:1 to receive either PADCEV in combination with pembrolizumab or platinum-based chemotherapy (gemcitabine with cisplatin or carboplatin). Patients in arm A received PADCEV 1.25 mg/kg as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by pembrolizumab 200 mg on Day 1 of a 21-day cycle approximately 30 minutes after PADCEV. Patients in arm B received gemcitabine 1000 mg/m^2 administered on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5 according to local guidelines) administered on Day 1 of a 21-day cycle. Randomisation was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as haemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.

The median age was 69 years (range: 22 to 91); 77% were male; and most were White (68%) or Asian (22%). Patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (49%), 1 (47%) or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer and 5% of patients had locally advanced urothelial cancer. Seventy-two percent of patients had visceral metastasis at baseline including 23% with liver metastases. Eighty-five percent of patients had urothelial carcinoma (UC) histology including 6% with UC mixed squamous differentiation and 2% with UC mixed other histologic variants. Forty-six percent of patients were cisplatin-ineligible and 54% were cisplatin-eligible at time of randomisation. A total of 800 out of 886 patients had evaluable Nectin-4 results; of these 800 patients, 791 (99%) had detectable Nectin-4 (H-score > 0) as assessed by a validated immunohistochemistry (IHC) assay. Of the 877 patients tested who had tissue evaluable for PD-L1 expression, 58% of patients had tumors

that expressed PD-L1 with a CPS ≥10 and 42% had tumors that expressed PD-L1 with a CPS <10.

At the time of the primary analysis, 33% of patients in the PADCEV in combination with pembrolizumab arm and no patients in the platinum-based chemotherapy arm remained on treatment. Thirty-two percent of patients in the PADCEV in combination with pembrolizumab arm received subsequent therapy; 25% of patients received platinum-based chemotherapy as first subsequent therapy after progression. Seventy-one percent of patients in the platinum-based chemotherapy arm received subsequent therapy; 59% of patients received a PD-1 or PD-L1 inhibitor, including 30% of patients who received avelumab maintenance therapy, as first subsequent therapy after progression.

The median follow-up time for this study was 17.2 months (range: 0.1 to 37.2).
The median time to response in patients who received PADCEV in combination with pembrolizumab was 2.1 months (range: 1.3 to 12.3).

Table 5. Efficacy Results in EV-302

Endpoint	**PADCEV+pembrolizumab n=442**	**Gemcitabine +platinum n=444**
Overall Survival		
Number (%) of patients with events	133 (30.1)	226 (50.9)
Median in months (95% CI)[a]	31.5 (25.4, -)	16.1 (13.9, 18.3)
Hazard ratio[b] (95% CI)[a]	0.468 (0.376, 0.582)	
2-sided p-value[c]	<0.00001	
Progression Free Survival[d,]		
Number (%) of patients with events	223 (50.5)	307 (69.1)
Median in months (95% CI) [a]	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio[b] (95% CI) [a]	0.450 (0.377, 0.538)	
2-sided p-value[c]	<0.00001	
Objective Response Rate (CR + PR)[d, f]		
ORR (%) (95% CI)[e]	67.7 (63.1, 72.1)	44.4 (39.7, 49.2)
2-sided p-value[g]	<0.00001	
Complete response rate (%)	127 (29.1)	55 (12.5)
Partial response rate (%)	169 (38.7)	141 (32.0)
Duration of Response[d,f]		
Median in months (95% CI) [a]	NR (20.2, -)	7.0 (6.2, 10.2)

NR = Not reached.

a. Based on the complementary log-log transformation method (Collett, 1994).
b. Based on stratified Cox proportional hazards model. A hazard ratio <1 favors the PADCEV in combination with pembrolizumab arm.
c. Based on using stratified log-rank test.
d. Evaluated by BICR using RECIST v1.1.

e. Based on the Clopper-Pearson method (Clopper 1934).

f. Includes only patients with measurable disease at baseline (n=437 for PADCEV in combination with pembrolizumab, n=441 for gemcitabine plus platinum). The duration of response was estimated for responders.

g. Based on Cochran-Mantel-Haenszel test controlling for stratification factors (cisplatin eligibility, PD-L1 expression, and liver metastases) at randomisation.

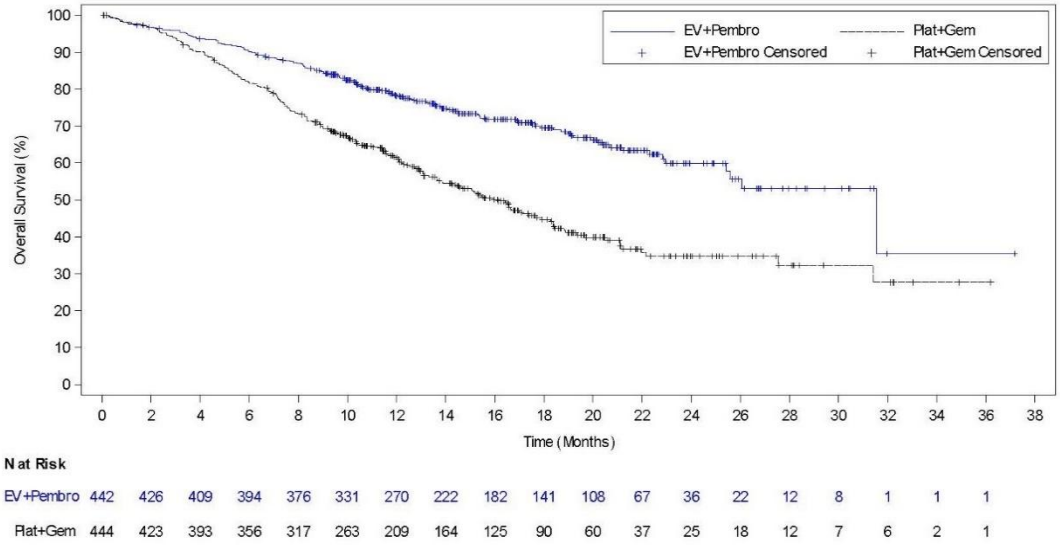


Figure 1. Kaplan Meier Plot of Overall Survival, EV-302

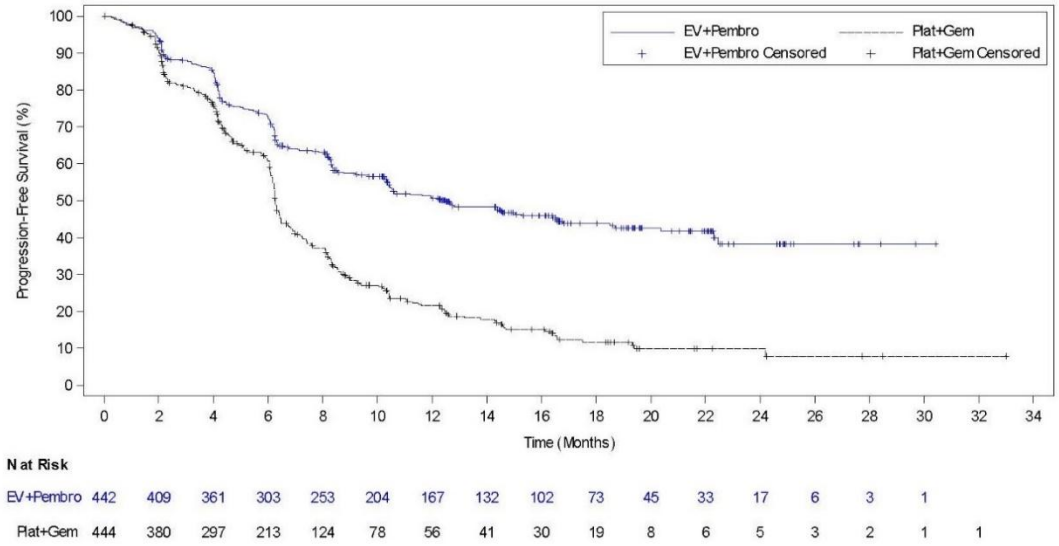


Figure 2. Kaplan Meier Plot of Progression-Free Survival, EV-302

Cisplatin Ineligible Patients with Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma

EV-103

The efficacy of PADCEV in combination with pembrolizumab was evaluated in a phase 2, open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) study in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease.

Patients in the dose escalation cohort (n=5) and Cohort A (n=40) received PADCEV 1.25 mg/kg in combination with pembrolizumab 200 mg. Patients in Cohort K received PADCEV 1.25 mg/kg as a single agent (n=73) or in combination with pembrolizumab 200 mg (n=76).

Patients received PADCEV 1.25 mg/kg as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by pembrolizumab 200 mg on Day 1 of a 21-day cycle approximately 30 minutes after PADCEV until disease progression or unacceptable toxicity.

Reasons for cisplatin ineligibility in patients enrolled in EV-103 included: ECOG PS of 2, creatinine clearance ≥30 and <60 mL/min, hearing loss/dysfunction and/or age.

Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.

A total of 121 patients received PADCEV 1.25 mg/kg in combination with pembrolizumab. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White; and 45% of patients had an ECOG performance status of 1 and 15% had an ECOG performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 98% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Eighty four percent of patients had visceral metastasis at baseline including 22% with liver metastases. Of the 108 patients tested who had tissue evaluable for PD-L1 expression, 43% of patients had tumors that expressed PD-L1 with a CPS ≥10 and 57% had tumors that expressed PD-L1 with a CPS <10. The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range: 0.7 to 52.4) and for Cohort K was 14.8 months (range: 0.6 to 26.2).

Confirmed ORR was evaluated by BICR using RECIST v1.1. The median time to response was 1.94 months (range: 1.1 to 13.2) for the dose escalation cohort + Cohort A and was 2.07 months (range: 1.1 to 6.6) for Cohort K.

Table 6. Efficacy Results in EV-103

	Padcev in combination with pembrolizumab	
	Dose Escalation Cohort + Cohort A n=45	**Cohort K n=76**
Confirmed ORR (95% CI)	73.3% (58.1, 85.4)	64.5% (52.7, 75.1)
Complete response rate	15.6%	10.5%
Partial response rate	57.8%	53.9%
Median Duration of Response, months (range)	22.1 (1.0+, 46.3+)	NR (1.2, 24.1+)
% with duration ≥6 months[a]	67%	71%

NR = Not reached

a. Based on observed duration of response

In the combined efficacy analysis of the dose escalation cohort, Cohort A and Cohort K, (n=121), confirmed ORR was 68% (95% CI: 58.7, 76.0) with complete and partial response rates of 12% and 55%, respectively. Among the responding patients, 80% had responses of 6 months or longer (based on observed duration of response).

PADCEV as monotherapy

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

EV-301

The efficacy of PADCEV as monotherapy was evaluated in study EV-301, an open-label, randomised, phase 3, multicentre study that enrolled 608 patients with LA or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Patients were randomised 1:1 to receive either PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle or one of the following chemotherapies as decided by the investigator: docetaxel (38%), paclitaxel (36%), or vinflunine (25%).

Patients were excluded from the study if they had active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as haemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

The median age was 68 years (range: 30 to 88 years), 77% were male, and most patients were White (52%) or Asian (33%). All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (40%) or 1 (60%). Eighty percent of patients had visceral metastases including 31% with liver metastases. Seventy-six percent of patients had urothelial carcinoma/transitional cell carcinoma (TCC) histology and 14% had urothelial carcinoma mixed. A total of 527 out of 608 subjects had evaluable Nectin-4 results; of these 527 subjects, 516 (98%) had detectable Nectin-4 (H-score >0) as assessed by a validated immunohistochemistry (IHC) assay. A total of 76 (13%) of patients received ≥3 lines of prior systemic therapy. Fifty-two percent (314) of patients received prior PD-1 inhibitor, 47% (284)

received prior PD-L1 inhibitor, and an additional 1% (9) patients received both PD-1 and PD-L1 inhibitors. Sixty-nine percent of patients did not respond to prior therapy with a PD-1 or PD-L1 inhibitor. Sixty-three percent (383) of patients received prior cisplatin-based regimens, 26% (159) received prior carboplatin-based regimens, and an additional 11% (65) received both cisplatin and carboplatin-based regimens.

The study demonstrated statistically significant improvements in Overall Survival (OS), Progression Free Survival (PFS), and Objective Response Rate (ORR) for patients randomised to PADCEV as compared to chemotherapy (PFS and ORR were evaluated by investigator assessment using RECIST v1.1). The median follow-up time for this study was 11.1 months (95% CI: 10.6 to 11.6). Patients randomised to the PADCEV arm had a statistically significant improvement in OS compared to the chemotherapy arm with a median OS of 12.9 months versus 9 months, respectively (HR=0.702; 95% CI: 0.556, 0.886; 1-sided p-value: 0.00142). Patients randomised to receive PADCEV experienced longer PFS compared to those randomised to receive chemotherapy with a median PFS of 5.6 months versus 3.7 months, respectively (HR=0.615; 95% CI: 0.505, 0.748; 1-sided p-value: <0.00001). Among the 288 patients randomised to receive PADCEV with measurable disease at baseline, the ORR was 40.6% (117/288) (95% CI: 34.90, 46.54) compared with chemotherapy with an ORR of 17.9% (53/296) (95% CI: 13.71, 22.76). The median time to response in the PADCEV arm was 1.87 months (95% CI: 1.1 to 5.7). Efficacy results were consistent across patient subgroups including age, geographic region, baseline ECOG PS, liver metastasis, preselected control therapy, primary site of tumour, prior lines of therapy in LA or metastatic setting and best response to prior PD1 or PD-L1.

Table 7 and Figures 3 and 4 summarise the efficacy results for EV-301.

Table 7. Efficacy Results in EV-301

Endpoint	PADCEV n=301	Chemotherapy n=307
Overall Survival		
Number (%) of patients with events	134 (44.5)	167 (54.4)
Median in months (95% CI)	12.9 (10.6, 15.2)	9.0 (8.1, 10.7)
Hazard ratio (95% CI)	0.702 (0.556, 0.886)	
1-sided p-value	0.00142*	
6-month OS (%) (95% CI)	77.9 (72.7, 82.3)	69.5 (63.9, 74.4)
12-month OS (%) (95% CI)	51.5 (44.6, 58.0)	39.2 (32.6, 45.6)
Progression Free Survival†		
Number (%) of patients with events	201 (66.8)	231 (75.2)
Median in months (95% CI)	5.6 (5.3, 5.8)	3.7 (3.5, 3.9)
Hazard ratio (95% CI)	0.615 (0.505, 0.748)	
1-sided p-value	<0.00001‡	
6-month PFS (%) (95% CI)	44.0 (38.0, 49.8)	28.2 (22.9, 33.8)
12-month PFS (%) (95% CI)	21.7 (16.3, 27.7)	8.3 (4.61, 13.4)

Endpoint	PADCEV n=301	Chemotherapy n=307
Objective Response Rate (CR + PR)†		
ORR (%) (95% CI)	40.6 (35.0, 46.5)	17.9 (13.7, 22.8)
1-sided p-value	<0.001§	
Complete response rate (%)	4.9	2.7
Partial response rate (%)	35.8	15.2
Duration of Response for responders		
Median in months (95% CI)	7.4 (5.6, 9.5)	8.1 (5.7, 9.6)

*pre-determined efficacy boundary = 0.00679, 1-sided (adjusted by observed deaths of 301).
†evaluated by investigator assessment using RECIST v1.1.
‡pre-determined efficacy boundary = 0.02189, 1-sided (adjusted by observed PFS1 events of 432).
§pre-determined efficacy boundary = 0.025, 1-sided (adjusted by 100% information fraction).

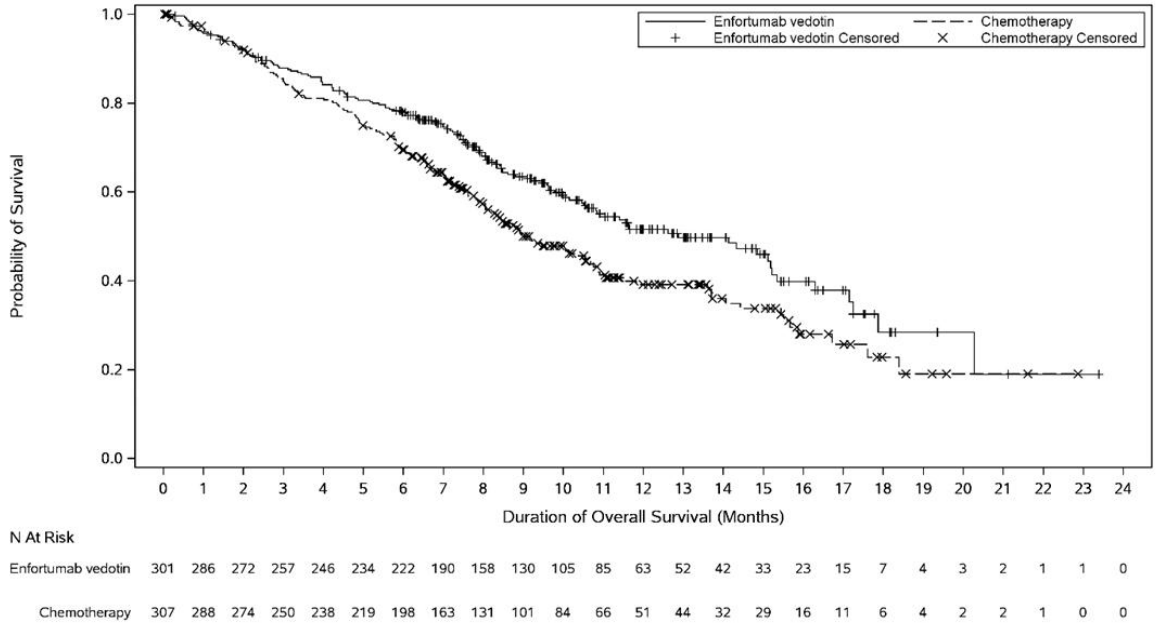


Figure 3. Kaplan Meier Plot of Overall Survival, EV-301

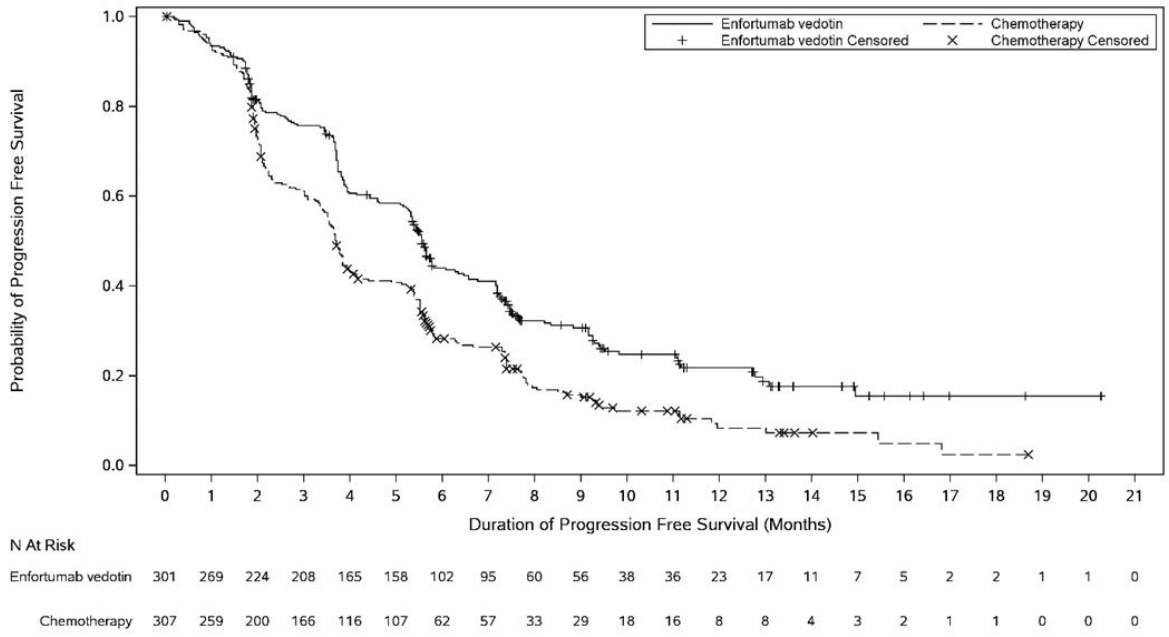


Figure 4. Kaplan Meier Plot of Progression Free Survival, EV-301

Patient-reported quality of life (QoL) was assessed using the EORTC QLQ-C30. Over the first 12 weeks of treatment, patients treated with PADCEV maintained overall quality of life compared with baseline and had less variability compared to chemotherapy. Further, patients treated with PADCEV had statistically significant improvements in pain compared to chemotherapy, with an average difference in change from baseline of -5.73 (2-sided $p<0.05$) at week 12. Fifty-two percent of patients treated with PADCEV and 29% of patients treated with chemotherapy achieved a clinically meaningful confirmed improvement in pain (odds ratio [95% CI]: 2.76, [1.81; 4.22]) over the study period. These results should be interpreted in the context of the open-label study design with no adjustment for multiplicity.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

The mean estimate of steady-state volume of distribution of ADC was 12.8 L following 1.25 mg/kg of enfortumab vedotin. *In vitro*, the binding of unconjugated MMAE to human plasma proteins ranged from 68% to 82%. Unconjugated MMAE is not likely to displace or to be displaced by highly protein-bound drugs. Unconjugated MMAE does not significantly partition into human red blood cells *in vitro*; the ratio of amount in blood to amount in plasma concentration is 0.926 to 0.976.

Metabolism

Enfortumab vedotin is expected undergo catabolism in patients, resulting in the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites. *In vitro* data indicate that the metabolism of unconjugated MMAE occurs primarily via oxidation by CYP3A4.

Excretion

The excretion of unconjugated MMAE occurs mainly in faeces with a smaller proportion in urine. After a single dose of another ADC that contained unconjugated MMAE, approximately 24% of the total unconjugated MMAE administered was recovered in faeces and urine as unchanged MMAE over a 1-week period. The majority of recovered unconjugated MMAE was excreted in faeces (72%). A similar excretion profile is expected for unconjugated MMAE after enfortumab vedotin administration.

Immunogenicity

A total of 697 patients were tested for immunogenicity to PADCEV 1.25 mg/kg; 16 patients were confirmed to be positive at baseline for anti-therapeutic antibody (ATA), and in patients that were negative at baseline (n=681), a total of 24 (3.5%) were positive postbaseline. 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 ATA, and in patients that were negative at baseline (n=466), a total of 14 (3.0%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following PADCEV 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 or safety.

Pharmacokinetic Characteristics in Special Populations

Elderly: Population pharmacokinetic analysis indicates that age [range: 24 to 90 years; 60% (450/748) >65 years, 19% (143/748) >75 years] does not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Gender and race: Based on population pharmacokinetic analysis, race [69% (519/748) White, 21% (158/748) Asian, 1% (10/748) Black and 8% (61/748) others or unknown] and gender [73% (544/748) male] do not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Patients with hepatic impairment: Based on population pharmacokinetics analysis using data from clinical studies in patients with metastatic UC, there was no significant differences in ADC exposure and a 37% and 16% increase in unconjugated MMAE average concentrations in patients with previously treated and previously untreated locally advanced or mUC, respectively, with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST of any level, or total bilirubin ≤ ULN and AST > ULN, n=65) compared to patients with normal hepatic function. As enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n=3) and has not been evaluated in patients with severe hepatic impairment (total bilirubin >1.5 × ULN and AST of any level), use PADCEV with caution in these patients.

Patients with renal impairment: The pharmacokinetics of ADC and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to patients with mild (creatinine clearance; CrCL >60–90 mL/min; n=272), moderate (CrCL 30–60 mL/min; n=315) and severe (CrCL 15–<30 mL/min; n=25) renal impairment. No significant differences in AUC

exposure of ADC or unconjugated MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min).

5.3 PRECLINICAL SAFETY DATA

No dedicated preclinical safety studies were conducted with enfortumab vedotin in combination with pembrolizumab.

Genotoxicity

No dedicated genotoxicity studies have been performed with enfortumab vedotin. Genotoxicity studies showed that MMAE had no discernible genotoxic potential in a reverse mutation test in bacteria (Ames test) or in a L5178Y $TK^{+/-}$ mouse lymphoma mutation assay. MMAE did induce chromosomal aberrations through an aneugenic mechanism in the micronucleus test in rats which is consistent with the pharmacological action of microtubule-disrupting agents.

Carcinogenicity

Carcinogenicity studies with enfortumab vedotin or the small molecule cytotoxic agent (MMAE) have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 20

6.2 INCOMPATIBILITIES

Do not co-administer other drugs through the same infusion line.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze).

6.5 NATURE AND CONTENTS OF CONTAINER

Clear 10 mL Type I glass vial
Gray bromobutyl rubber stopper
20 mg vial, 20 mm aluminium seal with a green ring and green cap
30 mg vial, 20 mm aluminium seal with a silver ring and yellow cap

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

PADCEV is an antineoplastic product. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

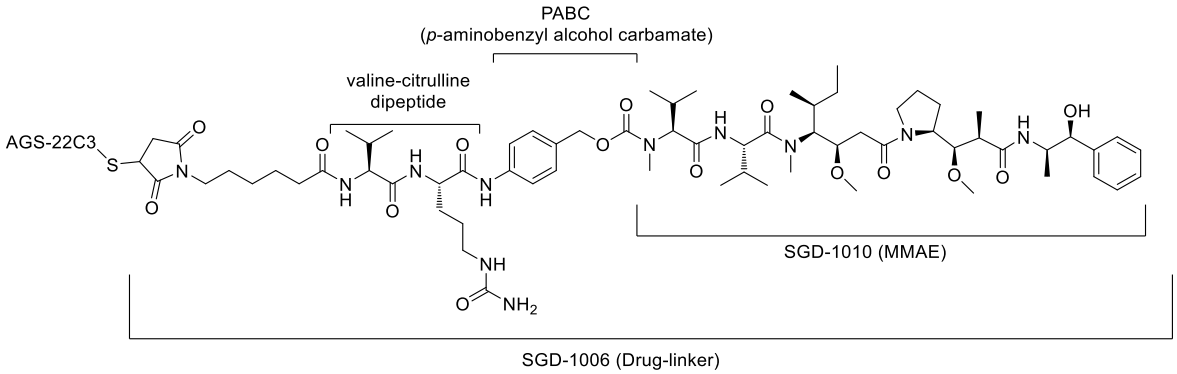
6.7 PHYSICOCHEMICAL PROPERTIES

Enfortumab vedotin is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker (SGD-1006).

Pharmacotherapeutic group: Nectin-4-directed antibody drug conjugate.

ATC code: L01FX13

Chemical structure



The molecular formula is C6754H10442N1750O2144S46 and molecular weight is approximately 152 kDa.

CAS number

1346452-25-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

7 July 2022

10 DATE OF REVISION

17 February 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	**Added indication for combination with pembrolizumab**
4.2	Added dosage information for combination with pembrolizumab Added handling precautions when preparing the administration solution
4.4	Added skin reactions when used in combination with pembrolizumab Updated pneumonitis/interstitial lung disease frequencies in monotherapy and added information when used in combination with pembrolizumab Updated ADC exposure information in patient with hepatic impairment
4.6	Added ovarian toxicity observed in toxicity studies of other MMAE-containing ADCs
4.8	Updated pooled ADR frequencies of monotherapy Added ADR information when used in combination with pembrolizumab
5.1	Added description of exposure-response analysis for efficacy Added description of mechanism of action regarding combination with pembrolizumab Added efficacy information for combination with pembrolizumab (EV-302 and EV-103)
5.2	Added immunogenicity information when used in combination with pembrolizumab Updated ADC exposure information in patient with hepatic impairment
5.3	Added note for combination with pembrolizumab