

1. NAME OF THE MEDICINAL PRODUCT

PADCEV™ 20 mg powder for concentrate for solution for infusion

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: enfortumab vedotin

Each vial contains either 20 mg or 30 mg enfortumab vedotin. After reconstitution, each mL of solution contains 10 mg of enfortumab vedotin.

Enfortumab vedotin is an antibody-drug conjugate (ADC) comprised of a Nectin-4 directed, fully human Chinese Hamster Ovary (CHO)-expressed IgG1-kappa monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PADCEV is supplied as single-dose vials containing sterile, preservative-free, white to off-white lyophilized powder for reconstitution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

PADCEV is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy.

4.2 Posology and method of administration

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 package insert 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 in patients with locally advanced or metastatic urothelial cancer

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

Adverse reaction	Severity*	Dose modification*
Peripheral neuropathy	Grade 2	- Withhold until Grade ≤ 1 - For first occurrence, resume treatment at the same dose level - For a recurrence, withhold until Grade ≤ 1, then resume treatment reduced by one dose level (see Table 1)
	Grade ≥ 3	Permanently discontinue.

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

Special populations

Elderly

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

Patients with renal impairment

No dose adjustment is required 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).

Patients with hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment [total bilirubin of 1 to $1.5 \times$ upper limit of normal (ULN) and AST any, or total bilirubin $\leq$ 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).

Pediatric population

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

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.

4.3 Contraindications

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

4.4 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). 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).

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).

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).

Hyperglycemia

Hyperglycemia 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).

Hyperglycemia occurred more frequently in patients with pre-existing hyperglycemia or a high body mass index (≥ 30 kg/m²). Patients with baseline HbA1c $\geq 8\%$ 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 hyperglycemia. 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).

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). 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).

Ocular disorders

Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin (see section 4.8). 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). 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). 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 at least 4 months following the last dose of PADCEV.

Patient information leaflet

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 with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. Concomitant administration of enfortumab vedotin and CYP3A4 (substrates) metabolised medicinal products, has no clinically relevant risk of inducing pharmacokinetic interactions (see section 5.2).

Effects of other medicinal products on enfortumab vedotin

CYP3A4 inhibitors, substrates or inducers

Based on physiologically-based pharmacokinetic (PBPK) modeling, concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} and AUC exposure to a minor extent, with no change in ADC exposure. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities.

Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g., midazolam).

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).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Pregnancy testing is recommended for females of reproductive potential within 7 days prior to initiating treatment. Females of reproductive potential should be advised 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 up to at least 4 months following the last dose of PADCEV.

Pregnancy

PADCEV can cause fetal harm when administered to pregnant women based upon findings from animal studies. Embryo-fetal development studies in female rats have shown that intravenous

administration of enfortumab vedotin resulted in reduced numbers of viable fetuses, reduced litter size, and increased early resorptions (see section 5.3). PADCEV is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether enfortumab vedotin is excreted in human milk. 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.

Fertility

In rats, repeat dose administration of enfortumab vedotin, resulted in testicular toxicity and may alter male fertility. MMAE has been shown to have aneugenic properties (see section 5.3). Therefore, 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.

4.7 Effects on ability to drive and use machines

No studies with enfortumab vedotin and the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

Enfortumab vedotin as monotherapy

The safety of enfortumab vedotin was evaluated as monotherapy in 793 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), three phase 2 studies (EV-103, EV-201 and EV-203) and one phase 3 study (EV-301) (see Table 3). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 55.7 months).

The most common adverse reactions with enfortumab vedotin were alopecia (47.7%), decreased appetite (47.2%), fatigue (46.8%), diarrhea (39.1%), peripheral sensory neuropathy (38.5%), nausea (37.8%), pruritus (33.4%), dysgeusia (30.4%), anemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycemia (14.9%), dry eye (12.7%), alanine aminotransferase increased (12.7%) and rash (11.6%).

The most common serious adverse reactions ($\geq 2\%$) were diarrhea (2.1%) and hyperglycemia (2.1%). Twenty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction ($\geq 2\%$) 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 ($\geq 2\%$) 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%), anemia (3.2%), hyperglycemia (3.2%), neutrophil count decreased (3%), diarrhea (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 ($\geq 2\%$) 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 package insert 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%), diarrhea (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 ($\geq 2\%$) were diarrhea (3%) and pneumonitis (2.3%). Thirty-six percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reactions ($\geq 2\%$) 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 ($\geq 2\%$) leading to dose interruption were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhea (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 ($\geq 2\%$) leading to dose reduction 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 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	Anemia	Anemia
Not known ¹	Neutropenia, febrile neutropenia, neutrophil count decreased	Neutropenia, febrile neutropenia, neutrophil count decreased
Endocrine disorders		
Very common		Hypothyroidism
Metabolism and nutrition disorders		
Very common	Hyperglycemia, decreased appetite	Hyperglycemia, decreased appetite
Not known ¹	Diabetic ketoacidosis	Diabetic ketoacidosis
Nervous system disorders		
Very common	Peripheral sensory neuropathy, dysgeusia	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, hypoesthesia, gait	Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness

	Monotherapy	In combination with pembrolizumab
	disturbance, muscular weakness	
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation	Neurotoxicity, dysesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation
Eye disorders		
Very common	Dry eye	Dry eye
Respiratory, thoracic, and mediastinal disorders		
Very common		Pneumonitis/ILD ²
Common	Pneumonitis/ILD ²	
Gastrointestinal disorders		
Very common	Diarrhea, vomiting, nausea	Diarrhea, vomiting, nausea
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus, rash, rash maculo-papular, dry skin	Alopecia, pruritus, rash maculo-papular, dry skin, rash macular
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, 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, blood blister	Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis
Not known ¹	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural 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	Alanine aminotransferase increased, aspartate aminotransferase increased,

	Monotherapy	In combination with pembrolizumab
	aminotransferase increased, weight decreased	weight decreased
Common		Lipase increased
Injury, poisoning and procedural complications		
Common	Infusion related reaction	Infusion related reaction

¹Based on global post-marketing experience.

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

Description of selected adverse reactions

Immunogenicity

A total of 697 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-drug antibody (ADA), and in patients that were negative at baseline (N=681), a total of 24 (3.5%) were positive post baseline.

A total of 490 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ADA, and in patients that were negative at baseline (N=466), a total of 14 (3%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following enfortumab vedotin administration as monotherapy and in combination with pembrolizumab.

Due to the limited number of patients with antibodies against PADCEV, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics.

Skin reactions

In clinical studies of enfortumab vedotin as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 14% (108) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 8.2 months). Serious skin reactions occurred in 4.3% (34) of patients. Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥ 2 events.

In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥ 2 events.

Pneumonitis/ILD

In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.5%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months) and the median duration for pneumonitis/ILD was 1.6 months (range: 0.1 to 43.0 months). Of the 26 patients who experienced pneumonitis/ILD, 8 (30.8%) had resolution of symptoms.

In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 2.1% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months).

Hyperglycemia

In clinical studies of enfortumab vedotin as monotherapy, hyperglycemia (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 hyperglycemia occurred in 2.5% of patients, 7% of patients developed severe (Grade 3 or 4) hyperglycemia and 0.3% of patients experienced fatal events, one event each of hyperglycemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline hemoglobin A1C (HbA1c). The median time to onset of hyperglycemia was 0.5 months (range: 0 to 20.3 months). Of the patients who experienced hyperglycemia 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 months). 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01FX13

Mechanism of action

Enfortumab vedotin is an ADC targeting Nectin-4, an adhesion protein located on the surface of the 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 internalization 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. Combination of enfortumab vedotin with PD-1 inhibitors results in enhanced anti-tumour 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.

Pharmacodynamic effects

In an exposure-response analysis, a higher exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 hyperglycemia).

Cardiac electrophysiology

The effect of enfortumab vedotin on the duration of cardiac ventricular repolarization was evaluated in 17 patients with locally advanced or metastatic urothelial carcinoma who received enfortumab vedotin 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, enfortumab vedotin had no large effect on QTc prolongation (>20 msec).

Clinical efficacy and safety

Enfortumab vedotin in combination with pembrolizumab

Previously untreated unresectable or metastatic urothelial cancer

EV-302 (KEYNOTE-A39)

The efficacy of PADCEV in combination with pembrolizumab was evaluated in study EV-302 (KEYNOTE-A39), an open-label, randomized, phase 3, multicenter study that enrolled 886 patients with unresectable or metastatic urothelial cancer who had not received prior systemic therapy for locally advanced or metastatic disease. Patients that received neoadjuvant chemotherapy or patients that received adjuvant chemotherapy following cystectomy were included in the study if recurrence was >12 months from completion of therapy. Patients were considered cisplatin-ineligible if they had at least one of the following criteria: glomerular filtration rate (GFR) between 30-59 mL/min, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 , Grade ≥ 2 hearing loss or New York Heart Association (NYHA) Class III heart failure.

Patients were randomized 1:1 to receive either enfortumab vedotin in combination with pembrolizumab (arm A) or gemcitabine and platinum-based chemotherapy (cisplatin or carboplatin) (arm B). Patients in arm A received enfortumab vedotin 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 enfortumab vedotin. Patients in arm B received gemcitabine 1000 mg/m² administered on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m² or carboplatin (AUC = 4.5 or 5 mg/mL/min according to local guidelines) administered on Day 1 of a 21-day cycle. Treatment was continued until disease progression, unacceptable toxicity or completion of the maximum number of treatment cycles (chemotherapy, 6 cycles; pembrolizumab, 35 cycles; enfortumab vedotin, no set maximum).

Patients randomized to the gemcitabine and platinum-based chemotherapy arm were permitted to receive maintenance immunotherapy (e.g., avelumab). Randomization was stratified by cisplatin eligibility (eligible versus ineligible), PD-L1 expression (CPS $\geq$ 10 versus CPS<10), and presence of liver metastases (present versus absent). PD-L1 expression was based on the PD-L1 IHC 22C3 pharmDx kit.

Patients were excluded from the study if they had active CNS metastases, ongoing sensory or motor neuropathy Grade $\geq$ 2, uncontrolled diabetes defined as hemoglobin A1C (HbA1c) $\geq$ 8% or HbA1c $\geq$ 7% with associated diabetes symptoms, autoimmune disease or a medical condition that required immunosuppression, pneumonitis or other forms of interstitial lung disease.

The median age was 69 years (range: 22 to 91); 77% were male; and most were White (67%) or Asian (22%). Patients had a baseline 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 unresectable urothelial cancer. Seventy-two percent of patients had visceral metastasis at baseline including 22% with liver metastases. Eighty-five percent of patients had urothelial carcinoma (UC) histology, 6% had UC mixed squamous differentiation and 2% had UC mixed other histologic variants. Forty-six percent of patients were cisplatin-ineligible and 54% were cisplatin-eligible at time of randomization. Of the 877 patients tested who had tissue evaluable for PD-L1 expression, 58% of patients had tumours that expressed PD-L1 with a CPS $\geq$ 10 and 42% had tumours that expressed PD-L1 with a CPS $<$ 10. The median follow-up time was 17.3 months (range: 0.3 to 37.2).

The primary efficacy outcome measures were Overall Survival (OS) and Progression Free Survival (PFS) as assessed by BICR according to RECIST v1.1. Secondary efficacy outcome measures included Objective Response Rate (ORR) as assessed by BICR according to RECIST v1.1.

The study showed statistically significant improvements in OS, PFS and ORR for patients randomized to enfortumab vedotin in combination with pembrolizumab as compared to gemcitabine and platinum-based chemotherapy.

Table 4, Figures 1 and 2 summarize the efficacy results for EV-302.

Table 4. 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)	0.468 (0.376, 0.582)	
2-sided p-value ^c	$<$ 0.00001	
12-month OS (%) (95% CI) ^a	78.2 (73.9, 81.9)	61.4 (56.6, 65.9)
18-month OS (%) (95% CI) ^a	69.5 (64.4, 74.1)	44.7 (39.2, 50.1)
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)	0.450 (0.377, 0.538)	
2-sided p-value ^c	$<$ 0.00001	
12-month PFS (%) (95% CI) ^a	50.7 (45.6, 55.5)	21.6 (17.2, 26.2)

Endpoint	PADCEV + pembrolizumab n=442	Gemcitabine + platinum n=444
18-month PFS (%) (95% CI) ^a	43.9 (38.5, 49.1)	11.7 (8.0, 16.1)
Objective Response Rate (CR + PR) ^{d,f}		
Confirmed ORR (%) (95% CI) ^e	67.7 (63.1, 72.1)	44.4 (39.7, 49.2)
2-sided p-value ^g	<0.00001	
Duration of Response ^{d,f}		
Median in months (95% CI) ^a	NR (20.2, -)	7.0 (6.2, 10.2)

NR = Not reached.

- Based on the complementary log-log transformation method (Collett, 1994).
- Based on stratified Cox proportional hazards model. A hazard ratio <1 favors the enfortumab vedotin in combination with pembrolizumab arm.
- Based on stratified log-rank test.
- Evaluated by BICR using RECIST v1.1
- Based on the Clopper-Pearson method (Clopper 1934).
- Includes only patients with measurable disease at baseline (n=437 for enfortumab vedotin in combination with pembrolizumab, n=441 for gemcitabine plus platinum). The duration of response was estimated for responders.
- Based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases

Figure 1. Kaplan Meier plot of overall survival, EV-302

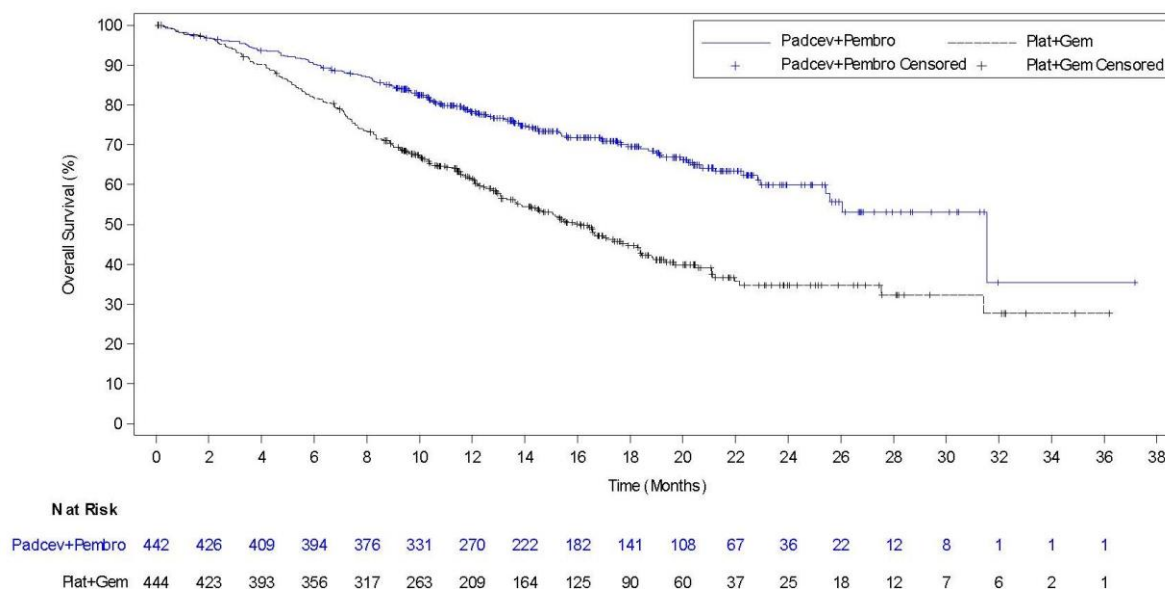
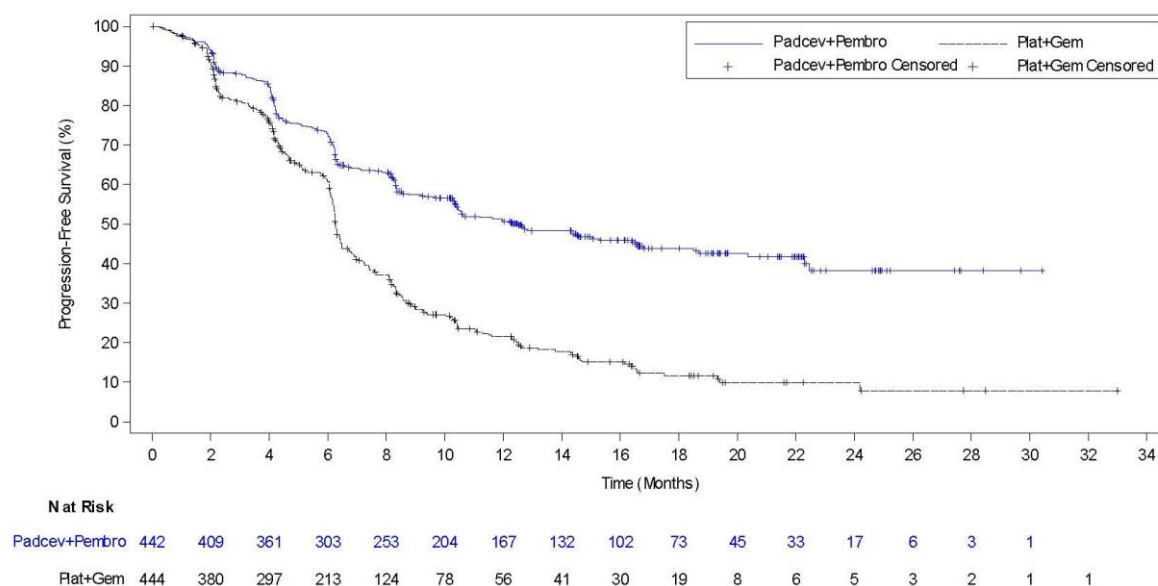


Figure 2. Kaplan Meier plot of progression-free survival, EV-302



Time to pain progression (TTPP) was defined as the time from date of randomization to date of pain progression based on BPI-SF Q3 (worst pain) and Q7 (medication received for pain). Enfortumab vedotin in combination with pembrolizumab demonstrated a median TTPP of 14.2 months compared with 10.0 months in patients treated with gemcitabine and platinum-containing chemotherapy and was not statistically significant (HR = 0.916; 2-sided p-value = 0.48). The least squares (LS) mean reduction in worst pain at week 26 was numerically greater in the enfortumab vedotin in combination with pembrolizumab arm (-0.61) than the gemcitabine and platinum-containing chemotherapy arm (-0.03) with an LS mean difference between treatment groups of -0.58.

Patients treated with enfortumab vedotin in combination with pembrolizumab maintained their health-related quality of life (HRQoL), as assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30). Mean change from baseline analyses numerically favored enfortumab vedotin in combination with pembrolizumab over gemcitabine and platinum-containing chemotherapy across QoL and functioning domains. These results should be interpreted in the context of the open-label study design with no adjustment for multiplicity.

Enfortumab vedotin as monotherapy

Previously treated locally advanced or metastatic urothelial cancer

EV-301

The efficacy of enfortumab vedotin as monotherapy was evaluated in EV-301, an open-label, randomized, phase 3, multicenter study that enrolled 608 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Patients were randomized 1:1 to receive either enfortumab vedotin 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 hemoglobin A1C (HbA1c) $\geq 8\%$ or HbA1c $\geq 7\%$ 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 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), Objective Response Rate (ORR) and Disease Control Rate (DcR) for patients randomized to enfortumab vedotin as compared to chemotherapy (PFS, ORR and DcR 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 randomized to the enfortumab vedotin 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 randomized to receive enfortumab vedotin experienced longer PFS compared to those randomized 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 randomized to receive enfortumab vedotin 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 enfortumab vedotin 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 tumor, prior lines of therapy in locally advanced or metastatic setting and best response to prior PD1 or PD-L1.

Table 5, Figure 3 and 4 summarize the efficacy results for EV-301.

Table 5. Efficacy results in EV-301

Endpoint	Enfortumab vedotin 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)

Endpoint	Enfortumab vedotin N=301	Chemotherapy N=307
12-month PFS (%) (95% CI)	21.7 (16.3, 27.7)	8.3 (4.61, 13.4)
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 (CR) (%)	4.9	2.7
Partial response rate (PR) (%)	35.8	15.2
Disease Control Rate (DcR) ^{†, ¶}		
DcR (%) (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)
1-sided p-value	<0.001 [§]	
Duration of Response		
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).

¶DCR was defined as the proportion of subjects who had a best overall response of confirmed CR, confirmed PR, or stable disease (≥7 weeks).

Figure 3. Kaplan Meier plot of overall survival

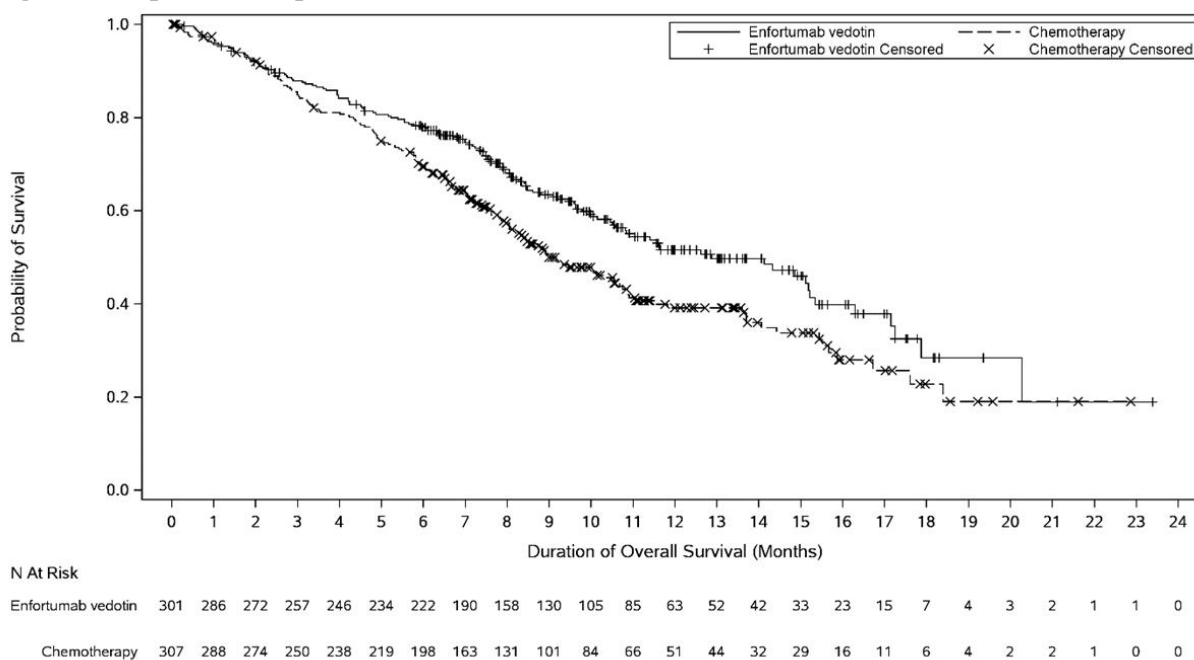
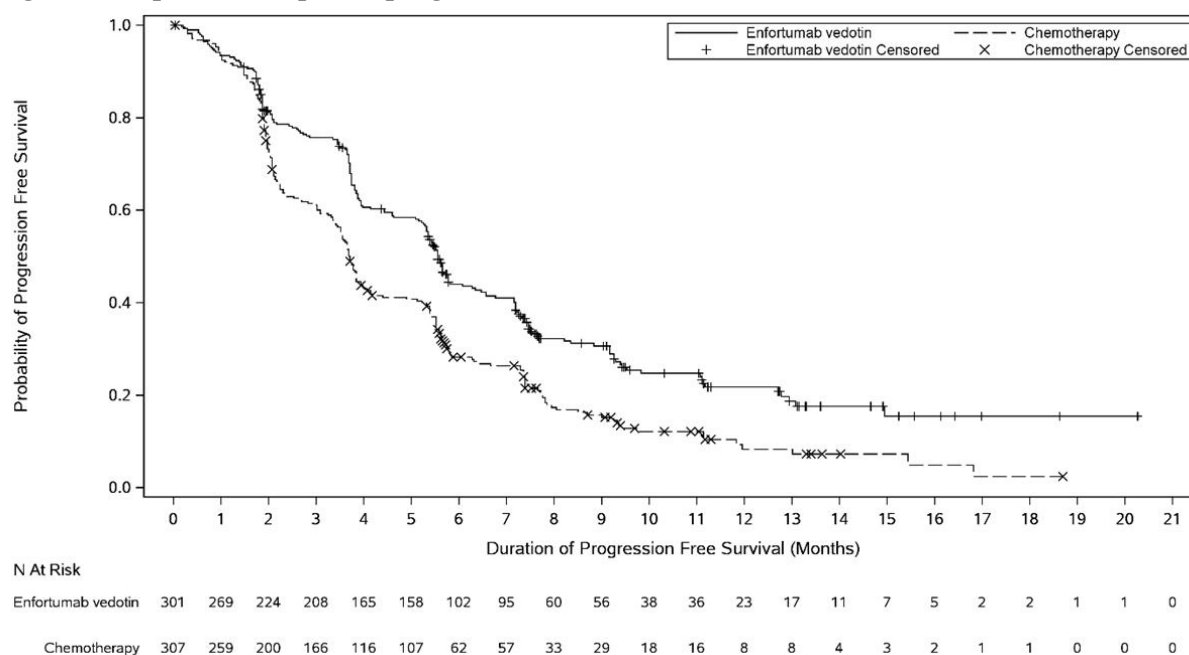


Figure 4. Kaplan Meier plot of progression free survival



Patient-reported quality of life (QoL) was assessed using the EORTC QLQ-C30. Over the first 12 weeks of treatment, patients treated with enfortumab vedotin maintained overall quality of life compared with baseline and had less variability compared to chemotherapy. Further, patients treated with enfortumab vedotin 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 enfortumab vedotin 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.

EV-201

The efficacy of enfortumab vedotin was evaluated in EV-201, a single-arm, multi-cohort, multicenter study that enrolled 219 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor. Patients were treated with 1.25 mg/kg enfortumab vedotin over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cohort 1 included 125 patients with locally advanced or metastatic urothelial cancer who were treated with enfortumab vedotin and received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. The ORR as established by blinded independent central review (BICR) in Cohort 1 was 44% (95% CI: 35.1, 53.2) with 15 (12%) CR, 40 (32%) PR, and a median DOR of 7.6 months (95% CI: 6.53, NE).

Cohort 2 of this study included 89 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor, are cisplatin ineligible and did not receive platinum in the locally advanced or metastatic setting.

Reasons for cisplatin ineligibility included: 66% with baseline creatinine clearance of < 60 mL/min, 7% with ECOG PS of 2, 15% with Grade 2 or greater hearing loss, and 12% with more than one cisplatin-ineligibility criteria. Seventy percent of patients had TCC and 17% had TCC with other histologic variants.

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

The median age was 75 years (range: 49 to 90 years), 74% were male and 70% were White. Most patients had an ECOG score of 1 (46.1%) or 0 (41.6%). Seventy-nine percent of patients had visceral metastases; 24% had liver metastases. A validated immunohistochemistry assay was used to assess patients with tumor tissue available and detected Nectin-4 expression in all, but one patient tested (79/80, 98.8%).

The median number of prior systemic therapies was 1 (range: 1 to 4). Fifty-one percent of patients received prior PD-1 inhibitor, 45% received prior PD-L1 inhibitor, and an additional 4% received both PD-1 and PD-L1 inhibitors. Seventy-five percent of patients did not respond to prior therapy with a PD-1 or PD-L1 inhibitor.

Efficacy was established by BICR based upon ORR and is presented in Table 6. The ORR was 50.6% (95% CI: 39.8, 61.3), the median time to response was 1.81 months (95% CI: 1.0 – 7.2) and the median duration of response was 13.8 months (95% CI: 6.41, -). The median follow-up time was 16.0 months. Responses were consistent across key patient subgroups including patients ≥ 75 years of age, patients with liver metastasis and patients who did not respond to prior PD-1 or PD-L1 inhibitor therapy.

Table 6. Efficacy results in EV-201, Cohort 2

Endpoint	Enfortumab vedotin 1.25 mg/kg N=89
ORR (%) (95% CI)	50.6 (39.8, 61.3)
Complete Response Rate (CR)	22.4%
Partial Response Rate (PR)	28.1%
Median Duration of Response, months (95% CI)	13.8 (6.41, -)

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 medicinal products. *In vitro* studies indicate that unconjugated MMAE is a substrate of P-glycoprotein.

Biotransformation

A small fraction of unconjugated MMAE released from enfortumab vedotin is metabolized. *In vitro* data indicate that the metabolism of unconjugated MMAE occurs primarily via oxidation by CYP3A4.

Elimination

The mean clearance of ADC and unconjugated MMAE in patients was 0.11 L/h and 2.11 L/h, respectively.

ADC elimination exhibited a multi-exponential decline with a half-life of 3.6 days.

Elimination of unconjugated MMAE appeared to be limited by its rate of release from enfortumab vedotin. Unconjugated MMAE elimination exhibited a multi-exponential decline with a half-life of 2.6 days.

Excretion

The excretion of unconjugated MMAE occurs mainly in feces 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 feces and urine as unchanged unconjugated

MMAE over a 1-week period. The majority of recovered unconjugated MMAE was excreted in feces (72%). A similar excretion profile is expected for unconjugated MMAE after enfortumab vedotin administration.

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.

Race and gender

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.

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 (CrCL >60–90 mL/min), moderate (CrCL 30–60 mL/min) and severe (CrCL 15–<30 mL/min) 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).

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 metastatic urothelial cancer, respectively, with mild hepatic impairment (total bilirubin of 1 to $1.5 \times$ ULN and AST any, or total bilirubin $\leq$ ULN and AST > ULN) compared to patients with normal hepatic function. Enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n=5) or severe hepatic impairment (n=1). The effect of moderate or severe hepatic impairment (total bilirubin $>1.5 \times$ ULN and AST any) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Physiologically based pharmacokinetic modeling predictions:

Concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} and AUC exposure to a minor extent, with no change in ADC exposure.

Concomitant use of enfortumab vedotin with rifampin (a combined P-gp and strong CYP3A inducer) is predicted to decrease unconjugated MMAE C_{max} and AUC exposure with moderate effect, with no change in ADC exposure. The full impact of rifampin on the C_{max} of unconjugated MMAE may be underestimated in the PBPK model.

Concomitant use of enfortumab vedotin is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate). *In vitro* studies using human liver microsomes indicate that unconjugated MMAE inhibits CYP3A4/5 but not other CYP450 isoforms. Unconjugated MMAE did not induce major CYP450 enzymes in human hepatocytes.

In vitro studies

In vitro studies indicate that unconjugated MMAE is a substrate and not an inhibitor of the efflux transporter P-glycoprotein (P-gp). *In vitro* studies determined that unconjugated MMAE was not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1 or OATP1B3), organic cation transporter 2 (OCT2), or organic anion transporter 1 or 3 (OAT1 or OAT3). Unconjugated MMAE was not an inhibitor of the bile salt export pump (BSEP), P-gp, BCRP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.

5.3 Preclinical safety data

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 in the micronucleus test in rats which is consistent with the pharmacological action of microtubule disrupting agents.

Skin lesions were noted in repeat dose studies in rats (4- and 13-weeks) and in monkeys (4-weeks). The skin changes were fully reversible by the end of a 6-week recovery period.

Hyperglycemia reported in the clinical studies was absent in both the rat and monkey toxicity studies and there were no histopathological findings in the pancreas of either species.

Fetal toxicity (reduced litter size or complete litter loss) was observed and decrease in the litter size was reflected in an increase in early resorptions. Mean fetal body weight in the surviving fetuses at the 2 mg/kg dose level were reduced compared with control.

Enfortumab vedotin associated fetal skeletal variations were considered developmental delays. A dose of 2 mg/kg (approximately similar to the exposure at the recommended human dose) resulted in maternal toxicity, embryo-fetal lethality and structural malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternbrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased fetal weight were observed.

Testicular toxicity observed, only in rats, was partially reversed by the end of a 24-week recovery period.

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

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

48 months

6.4 Special precautions for storage

Store at 2°C to 8°C.
Do not freeze.

6.5 Nature and contents of container

PADCEV 20 mg powder for concentrate for solution for infusion vial

10 mL Type I glass vial with gray bromobutyl rubber stopper, 20 mm aluminum seal with a green ring and green cap. Each carton contains 1 vial.

PADCEV 30 mg powder for concentrate for solution for infusion vial

10 mL Type I glass vial with gray bromobutyl rubber stopper, 20 mm aluminum seal with a silver ring and yellow cap. Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

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

Instructions for preparation and 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 enfortumab vedotin.
 - b) 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL enfortumab vedotin.
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 enfortumab vedotin 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 enfortumab vedotin.
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. Immediately 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.

Disposal

PADCEV is an antineoplastic product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Name and Address of Manufacturer

Manufactured by:

Simtra Deutschland GmbH

Kantstraße 2, 33790, Halle/Westfalen, Germany

Packed and released by:

Astellas Ireland Co. Limited,

Killorglin, Co. Kerry, V93 FC86 Ireland

DATE OF REVISION OF THE TEXT

03 March 2026

For any enquiry, please write to pv.my@astellas.com.

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