Patient Card and Patient Booklet:

The marketing of PADCEV is subject to a risk management plan (RMP) including a 'Patient Card' and 'Patient Booklet'. The 'Patient Card' and 'Patient Booklet', emphasize important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card and the booklet before starting treatment.

Prescriber guide:

This product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

1. NAME OF THE MEDICINAL PRODUCT

PADCEV™ 20 mg
Each single dose vial contains 20 mg enfortumab vedotin as lyophilized powder for reconstitution and dilution for intravenous infusion only.

PADCEV™ 30 mg
Each single dose vial contains 30 mg enfortumab vedotin as lyophilized powder for reconstitution and dilution for intravenous infusion only.

WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately 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; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (3.2), Warnings and Precautions (5.1) and Adverse Reactions (6.1)].***

2. THERAPEUTIC INDICATION

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

PADCEV, as a single agent, is indicated for the treatment of adult patients with locally advanced or mUC who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, or
- are ineligible for cisplatin-containing chemotherapy and have previously received a PD-1/PD-L1 inhibitor.

3. DOSAGE AND ADMINISTRATION

3.1 Recommended Dosage

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. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

The recommended dose of PADCEV as a single agent 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.

3.2 Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	**Severity**[1]	**Dose Modification**[1]
Skin Reactions[2] *[see Boxed Warning, Warnings and Precautions (5.1)]*	For persistent or recurrent Grade 2 skin reactions	Consider withholding until Grade ≤ 1, then resume treatment at the same dose level or dose reduce by one dose level.
	Grade 3 skin reactions	Withhold until Grade ≤ 1, then resume treatment at the same dose level or dose reduce by one dose level.
	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 2-4 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
Hyperglycemia *[see Warnings and Precautions (5.2)]*	Blood glucose > 250 mg/dL	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.
Pneumonitis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade ≥ 3	Permanently discontinue.

Adverse Reaction	Severity[1]	Dose Modification[1]
Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*	Grade 2	Withhold until Grade ≤ 1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤ 1, then resume treatment reduced by one dose level.
	Grade ≥ 3	Permanently discontinue.
Other nonhematologic toxicity *[see Adverse Reactions (6)]*	Grade 3	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic toxicity *[see Adverse Reactions (6)]*	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤ 1, then reduce dose by one dose level or discontinue treatment.

1. Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.
2. Referral to specialized care should be considered

Table 2. Recommended Dose Reduction Schedule

	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

3.3 Instructions for Preparation and Administration

- Administer PADCEV as an intravenous infusion only.
- PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

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

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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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.

Administration

13. Immediately administer the infusion over 30 minutes through an intravenous line.
14. If the infusion is not administered immediately, the prepared infusion bag should not be stored longer than 8 hours at 2°C to 8°C. DO NOT FREEZE.

DO NOT administer PADCEV as an intravenous push or bolus.
DO NOT mix PADCEV with, or administer as an infusion with, other medicinal products.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 9.

5. WARNINGS AND PRECAUTIONS

5.1 Skin Reactions

Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later.

Skin reactions occurred in 70% (all grades) of the 564 patients treated with PADCEV in combination with pembrolizumab in clinical trials. When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate compared to PADCEV as a single agent. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash and papular rash. Grade 3-4 skin reactions occurred in 17% of patients (Grade 3: 16%, Grade 4: 1%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.2%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Skin reactions led to discontinuation of PADCEV in 6% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced a skin reaction and had data regarding resolution (N = 391), 59% had complete resolution and 41% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 27% (43/159) had Grade ≥ 2 skin reactions.

Skin reactions occurred in 58% (all grades) of the 720 patients treated with PADCEV as a single agent in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 34% had pruritus. Grade 3-4 skin reactions occurred in 14% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 8 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=75), 24% of patients restarting at the same dose and 24% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 3.1% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced a skin reaction and had data regarding resolution (N =328), 58% had complete resolution and 42% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 39% (53/137) had Grade ≥ 2 skin reactions.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated.

For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤ 1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (3.2)]*.

5.2 Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV.

Patients with baseline hemoglobin A1C ≥ 8% were excluded from clinical trials.

In clinical trials of PADCEV as a single agent, 17% of the 720 patients treated with PADCEV developed hyperglycemia of any grade; 7% of patients developed Grade 3-4 hyperglycemia (Grade 3: 6.5%, Grade 4: 0.6%). Fatal events of hyperglycemia and diabetic ketoacidosis occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. The median time to onset of hyperglycemia was 0.5 months (range: 0 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.7% of patients *[see Adverse Reactions (6.1)]*. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. Of the patients who initiated insulin therapy for treatment of hyperglycemia, 66% (23/35) discontinued insulin by the time of last evaluation. *]*

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.

If blood glucose is elevated (> 250 mg/dL), withhold PADCEV *[see Dosage and Administration (3.2)]*.

5.3 Pneumonitis/Interstitial Lung Disease (ILD)

Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV.

When PADCEV was given in combination with pembrolizumab, 10% of the 564 patients treated with combination therapy had pneumonitis/ILD of any grade and 4% had Grade 3-4. A fatal event of pneumonitis/ILD occurred in two patients (0.4%). The incidence of pneumonitis/ILD, including severe events, occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26 months).

In clinical trials of PADCEV as a single agent, 3% of the 720 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of any grade pneumonitis/ILD was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD 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/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD *[see Dosage and Administration (3.2)]*.

5.4 Peripheral Neuropathy

When PADCEV was given in combination with pembrolizumab, 67% of the 564 patients treated with combination therapy had peripheral neuropathy of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of Grade ≥ 2 peripheral neuropathy was 6 months (range: 0.3 to 25 months) *[see Adverse Reactions (6.1)]*. Of the patients who experienced neuropathy and had data regarding resolution (N = 373), 13% had complete resolution, and 87% of patients had residual neuropathy at last evaluation. Of the patients with residual neuropathy at last evaluation, 45% (146/326) had Grade ≥ 2 neuropathy.

Peripheral neuropathy occurred in 53% of the 720 patients treated with PADCEV as a single agent in clinical trials including 38% with sensory neuropathy, 8% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions.

Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥ 2 peripheral neuropathy was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced neuropathy who had data regarding resolution (N = 296), 11% had complete resolution, and 89% had residual neuropathy at the time of their last evaluation. Of the patients with residual neuropathy at last evaluation, 50% (132/262) had Grade ≥ 2 neuropathy.

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs.

Permanently discontinue PADCEV in patients who develop Grade ≥ 3 peripheral neuropathy *[see Dosage and Administration (3.2)]*.

5.5 Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.

Dry eye symptoms occurred in 30% of patients, and blurred vision occurred in 10% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.7 months (range: 0 to 30.6 months).

Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

5.6 Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 1% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

5.7 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with

female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (10.1)]*.

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hyperglycemia *[see Warnings and Precautions (5.2)]*
- Pneumonitis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.3)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*
- Ocular Disorders *[see Warnings and Precautions (5.5)]*
- Infusion Site Extravasation *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV in combination with pembrolizumab at 1.25 mg/kg in 564 patients in EV-302 and EV-103 and PADCEV as a single agent at 1.25 mg/kg in 720 patients in EV-301, EV-201, EV-203 (NCT04995419), EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 564 patients receiving PADCEV in combination with pembrolizumab, 59% were exposed for ≥ 6 months, and 24% were exposed for ≥ 12 months. In this pooled population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were increased aspartate aminotransferase, increased creatinine, rash, increased glucose, peripheral neuropathy, increased lipase, decreased lymphocytes, increased alanine aminotransferase, decreased hemoglobin, fatigue, decreased sodium, decreased phosphate, decreased albumin, pruritus, diarrhea, alopecia, decreased weight, decreased appetite, increased urate, decreased neutrophils, decreased potassium, dry eye, nausea, constipation, increased potassium, dysgeusia, urinary tract infection and decreased platelets. Among 720 patients receiving PADCEV as a single agent, 37% were exposed for ≥ 6 months and 14% were exposed for ≥ 12 months. In this pooled population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were increased glucose, increased aspartate aminotransferase, decreased lymphocytes, increased creatinine, rash, fatigue, peripheral neuropathy, decreased albumin, decreased hemoglobin, alopecia, decreased appetite, decreased neutrophils, decreased sodium, increased alanine aminotransferase, decreased phosphate, diarrhea, nausea, pruritus, increased urate, dry eye, dysgeusia, constipation, increased lipase, decreased weight, decreased platelets, abdominal pain, dry skin.

The data described in the following section reflects exposure to PADCEV in combination with pembrolizumab from EV-302 and the dose escalation cohort, Cohort A and Cohort K of EV-103. Patients received PADCEV 1.25 mg/kg in combination with pembrolizumab until disease progression or unacceptable toxicity.

The data described in the following section also reflects exposure to PADCEV as a single agent from an open-label, randomized, trial (EV-301) and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort trial (EV-201). Patients received PADCEV 1.25 mg/kg until disease progression or unacceptable toxicity.

Previously Untreated Locally Advanced or Metastatic Urothelial Cancer

EV-302

The safety of PADCEV in combination with pembrolizumab was evaluated in an open-label, randomized, multicenter trial (EV-302) 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 reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥ 2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Fatal adverse reactions occurred in 3.9% of patients treated with PADCEV in combination with pembrolizumab including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Adverse reactions leading to discontinuation of PADCEV occurred in 35% of patients. The most common adverse reactions (≥ 2%) leading to discontinuation of PADCEV were peripheral neuropathy (15%), rash (4.1%) and pneumonitis/ILD (2.3%).

Adverse reactions leading to dose interruption of PADCEV occurred in 73% of patients. The most common adverse reactions (≥ 2%) leading to dose interruption of PADCEV were peripheral neuropathy (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased alanine aminotransferase (3%) and pruritus (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 42% of patients. The most common adverse reactions (≥ 2%) leading to dose reduction of PADCEV were rash (16%), peripheral neuropathy (13%) and fatigue (2.7%).

Table 3 summarizes the most common (≥ 15%) adverse reactions in EV-302.

Table 3. Adverse Reactions ≥ 15% (All Grades) in Patients Treated with PADCEV in Combination with Pembrolizumab in EV-302

	PADCEV in combination with pembrolizumab n=440		**Chemotherapy n=433**	
Adverse Reaction	**All Grades %**	**Grade 3-4 %**	**All Grades %**	**Grade 3-4 %**
Skin and subcutaneous tissue disorders				
Rash[1]	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
Dry skin	17	0.2	1	0
General disorders and administration site conditions				
Fatigue[1]	51	6	57	7
Pyrexia	18	0.7	16	1.2

Adverse Reaction	PADCEV in combination with pembrolizumab n=440		Chemotherapy n=433	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Nervous system disorders				
Peripheral neuropathy[1]	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Decreased weight	33	3.6	9	0.2
Eye disorders				
Dry eye[1]	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

1. Includes multiple terms.

Clinically relevant adverse reactions (< 15%) include vomiting (12%), pneumonitis/ILD (10%), hypothyroidism (10%), blurred vision (6%), skin hyperpigmentation (6%), infusion site extravasation (2%) and myositis (0.5%).

Table 4. Selected Laboratory Abnormalities Reported in ≥ 15% (All Grades) of Patients Treated with PADCEV in Combination with Pembrolizumab in EV-302

Laboratory Abnormality	PADCEV in combination with pembrolizumab		Chemotherapy	
	All Grades[1] %	Grade 3-4[1] %	All Grades[1] %	Grade 3-4[1] %
Chemistry				
Increased aspartate aminotransferase	75	5	39	3
Increased creatinine	71	3	68	3
Increased glucose	66	14	54	5
Increased alanine aminotransferase	59	5	49	3
Decreased sodium	46	13	47	13
Decreased phosphate	44	9	36	9
Decreased albumin	39	2	35	0.5
Decreased potassium	26	5	16	3
Increased potassium	24	1	36	4
Increased calcium	21	1	14	0.2
Hematology				
Decreased lymphocytes	58	15	59	17
Decreased hemoglobin	53	7	89	33
Decreased neutrophils	30	9	80	50

1. The denominator used to calculate the rate varied from 407 to 439 based on the number of patients with a baseline value and at least one post-treatment value.

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

EV-103

The safety of PADCEV was evaluated in combination with pembrolizumab in a multi cohort trial (EV-103) in 121 patients with locally advanced or metastatic urothelial cancer who were not eligible for cisplatin-containing chemotherapy and received at least one dose of PADCEV 1.25 mg/kg and pembrolizumab *[see Clinical Studies (12)]*. The median duration of exposure to PADCEV was 7 months (range: 0.6 to 33 months).

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥ 2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis/ILD (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%), and hypotension (2.5%).

Fatal adverse reactions occurred in 5% of patients treated with PADCEV in combination with pembrolizumab including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%).

Adverse reactions leading to discontinuation of PADCEV occurred in 36% of patients. The most common adverse reactions (≥ 2%) leading to discontinuation of PADCEV were peripheral neuropathy (20%) and rash (6%).

Adverse reactions leading to dose interruption of PADCEV occurred in 69% of patients. The most common adverse reactions (≥ 2%) leading to dose interruption of PADCEV were peripheral neuropathy (18%), rash (12%), increased lipase (6%), pneumonitis/ILD (6%), diarrhea (4.1%), acute kidney injury (3.3%), increased alanine aminotransferase (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), increased amylase (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 45% of patients. The most common adverse reactions (≥ 2%) leading to dose reduction of PADCEV were peripheral neuropathy (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

Table 5 summarizes the most common (≥ 20%) adverse reactions in EV-103.

Table 5. Adverse Reactions ≥ 20% (All Grades) in Patients Treated with PADCEV in Combination with Pembrolizumab in EV-103

	PADCEV in combination with pembrolizumab n=121	
Adverse Reaction	**All Grades %**	**Grade 3-4 %**
Skin and subcutaneous tissue disorders		
Rash[1]	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy[1]	65	3.3

Adverse Reaction	PADCEV in combination with pembrolizumab n=121	
	All Grades %	Grade 3-4 %
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Decreased weight	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

1. Includes: multiple terms.

Clinically relevant adverse reactions (< 20%) include vomiting (19.8%), pyrexia (18%), hypothyroidism (11%), pneumonitis/ILD (10%), skin hyperpigmentation (8%), myasthenia gravis (2.5%), myositis (3.3%), and infusion site extravasation (0.8%).

Table 6. Selected Laboratory Abnormalities ≥ 20% (All Grades) in Patients Treated with PADCEV in Combination with Pembrolizumab in EV-103

Laboratory Abnormality	PADCEV in combination with pembrolizumab	
	All Grades[1] %	Grade 3-4[2] %
Chemistry		
Increased glucose	74	13
Increased aspartate aminotransferase	73	9
Increased creatinine	69	3.3
Decreased sodium	60	19
Increased alanine aminotransferase	60	7
Increased lipase	59	32
Decreased albumin	59	4.2
Decreased phosphate	51	15
Decreased potassium	35	8
Increased potassium	27	1.7
Increased calcium	27	4.2
Hematology		
Decreased hemoglobin	69	15
Decreased lymphocytes	64	17
Decreased neutrophils	32	12

1. The denominator used to calculate the rate varied from 114 to 121 based on the number of patients with a baseline value and at least one post-treatment value.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

The safety of PADCEV was evaluated as a single agent in EV-301 in patients with locally advanced or metastatic urothelial cancer (n=296) who received at least one dose of PADCEV 1.25 mg/kg and who were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy *[see Clinical Studies (12)]*. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions (≥ 2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis/ILD and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions (≥ 2%) leading to discontinuation were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption occurred in 61% of patients; the most common adverse reactions (≥ 4%) leading to dose interruption were peripheral neuropathy (23%), rash (11%) and fatigue (9%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions (≥ 2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

Table 7 summarizes the most common (≥ 15%) adverse reactions in EV-301.

Table 7. Adverse Reactions (≥ 15%) in Patients Treated with PADCEV in EV-301

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	14	20	0.3
Alopecia	47	0	38	0
Pruritus	34	2	7	0
Dry skin	17	0	4	0
General disorders and administration site conditions				
Fatigue[1]	50	9	40	7
Pyrexia[1]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[1]	50	5	34	3
Dysgeusia[1]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[1]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[1]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[1]	25	2	35	5
Eye Disorders				
Dry eye[1]	24	0.7	6	0.3
Infections and infestations				
Urinary Tract Infection[1]	17	6	13	3
Vascular disorders				
Hemorrhage[1]	17	3	13	2
Investigations				
Decreased weight	16	0.3	7	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (< 15%) include vomiting (14%), increased aspartate aminotransferase (12%), hyperglycemia (10%), increased alanine aminotransferase (9%), skin hyperpigmentation (8%), pneumonitis/ILD (3%) and infusion site extravasation (0.7%).

Table 8. Selected Laboratory Abnormalities Reported in ≥ 15% (Grades 2-4) or ≥ 5% (Grade 3-4) of Patients Treated with PADCEV in EV-301

Laboratory Abnormality	PADCEV[1]		Chemotherapy[1]	
	Grades 2-4 %	Grade 3-4 %	Grades 2-4 %	Grade 3-4 %
Hematology				
Decreased lymphocytes	41	14	34	18
Decreased hemoglobin	28	4	42	14
Decreased neutrophils	27	12	25	17
Chemistry				
Decreased phosphate	39	8	24	6
Increased glucose (non-fasting)	33	9	27	6
Increased creatinine	18	2	13	0
Decreased potassium	16	2	7	3
Increased lipase	13	8	7	4
Decreased sodium	8	8	5	5

1. The denominator used to calculate the rate varied from 262 to 287 based on the number of patients with a baseline value and at least one post-treatment value.

EV-201, Cohort 1

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 1 in patients (n=125) with locally advanced or metastatic urothelial cancer who had received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy *[see Clinical Studies (12)]*. Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. The median duration of exposure to PADCEV was 4.6 months (range: 0.5-15.6).

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥ 3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, sepsis and pneumonitis/ILD (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). Adverse reactions leading to dose interruption occurred in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).

Table 9 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 1.

Table 9. Adverse Reactions Reported in ≥ 15% (All Grades) or ≥ 5% (Grade 3-4) of Patients Treated with PADCEV in EV-201 Cohort 1

Adverse Reaction	PADCEV n=125	
	All Grades %	Grade 3-4 %
General disorders and administration site conditions		
Fatigue[1]	56	6
Nervous system disorders		
Peripheral neuropathy[1]	56	4
Dysgeusia	42	0
Metabolism and nutrition disorders		
Decreased appetite	52	2
Skin and subcutaneous tissue disorders		
Rash[1]	52	13
Alopecia	50	0
Dry skin	26	0
Pruritus[1]	26	2
Gastrointestinal disorders		
Nausea	45	3
Diarrhea[1]	42	6
Vomiting	18	2
Eye disorders		
Dry eye[1]	40	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (< 15%) include skin hyperpigmentation (14%), herpes zoster (3%), pneumonitis/ILD (2%) and infusion site extravasation (2%).

Table 10. Selected Laboratory Abnormalities Reported in ≥ 15% (Grades 2-4) or ≥ 5% (Grade 3-4) of Patients Treated with PADCEV in EV-201, Cohort 1

Laboratory Abnormality	PADCEV	
	Grades 2-4[1] %	Grade 3-4[1] %
Hematology		
Decreased hemoglobin	34	10
Decreased lymphocytes	32	10
Decreased neutrophils	14	5
Chemistry		
Decreased phosphate	34	10
Increased glucose (non-fasting)	27	8
Increased creatinine	20	2
Decreased potassium	19[2]	1
Increased lipase	14	9

Laboratory Abnormality	PADCEV	
	Grades 2-4[1] %	Grade 3-4[1] %
Decreased sodium	8	8
Increased urate	7	7

1. Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available for 121 or 122 patients.
2. Includes Grade 1 (potassium 3.0-3.5 mmol/L) – Grade 4.

EV-201, Cohort 2

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 2 in patients with locally advanced or metastatic urothelial cancer (n=89) who received at least one dose of PADCEV 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and were not eligible for cisplatin-based chemotherapy. The median duration of exposure was 5.98 months (range: 0.3 to 24.6 months).

Serious adverse reactions occurred in 39% of patients treated with PADCEV. The most common serious adverse reactions (≥ 3%) were pneumonia, sepsis and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia and pneumonitis/ILD (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction (≥ 2%) leading to discontinuation was peripheral neuropathy (7%).

Adverse reactions leading to dose interruption occurred in 60% of patients; the most common adverse reactions (≥ 3%) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), increased aspartate aminotransferase (3%) and hyperglycemia (3%).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common adverse reactions (≥ 3%) leading to dose reduction were peripheral neuropathy (19%), rash (11%) and fatigue (7%).

Table 11 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

Table 11. Adverse Reactions ≥ 15% (All Grades) or ≥ 5% (Grades 3-4) in Patients Treated with PADCEV in EV-201, Cohort 2

Adverse Reaction	PADCEV n=89	
	All Grades (%)	Grades 3-4 (%)
Skin and subcutaneous tissue disorders		
Rash[1]	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy[1]	58	8
Dysgeusia[1]	29	0
General disorders and administration site conditions		
Fatigue[1]	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Gastrointestinal disorders		
Diarrhea[1]	36	8
Nausea	30	1
Investigations		
Decreased weight	35	1
Eye disorders		
Dry eye[1]	30	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (< 15%) include vomiting (13%), increased aspartate aminotransferase (12%), increased lipase (11%), increased alanine aminotransferase (10%), skin hyperpigmentation (4%), pneumonitis/ILD (4%) and infusion site extravasation (1%).

Table 12. Selected Laboratory Abnormalities Reported in ≥ 15% (Grades 2-4) or ≥ 5% (Grades 3-4) of Patients Treated with PADCEV in EV-201, Cohort 2

Laboratory Abnormality	PADCEV n=88[3]	
	Grades 2-4[4] %	Grade 3-4[5] %
Hematology		
Decreased lymphocytes	43	15
Decreased hemoglobin	34	5
Decreased neutrophils	20	9
Chemistry		
Increased glucose (non-fasting)	36	13

Laboratory Abnormality	PADCEV n=88[3]	
	Grades 2-4[4] %	Grade 3-4[5] %
Decreased phosphate	25	7
Increased creatinine	23	3
Increased lipase	18	11
Increased urate	9	9
Increased potassium	8	6
Decreased sodium	7	7

1. Based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of PADCEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Epidermal necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis *[see Warnings and Precautions (5.1)]*.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.
/https://sideeffects.health.gov.il

7. DRUG INTERACTIONS

7.1 Effects of Other Drugs on PADCEV

Dual P-gp and Strong CYP3A4 Inhibitors
Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated MMAE exposure *[see Clinical Pharmacology (10.3)]*, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (10.1)]*. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural

malformations and skeletal anomalies at maternal exposures similar to the exposures at the recommended human dose of 1.25 mg/kg *(see Data)*. Advise patients of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In a rat pilot embryo-fetal development study, administration of enfortumab vedotin on gestation day 6 and 13 during the period of organogenesis resulted in a complete litter loss in all pregnant rats at the maternally toxic dose of 5 mg/kg (approximately 3 times the exposure at the recommended human dose). A dose of 2 mg/kg (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 sternebrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased fetal weight were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment *[see Use in Specific Populations (8.1)]*.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Females

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), PADCEV may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (11.1)]*.

Males

Based on findings from animal studies, PADCEV may impair male fertility *[see Nonclinical Toxicology (11.1)]*.

8.4 Pediatric Use

Safety and effectiveness of PADCEV in pediatric patients have not been established.

8.5 Geriatric Use

Of the 564 patients treated with PADCEV in combination with pembrolizumab, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 39% (n=282) were 65-74 years and 24% (n=170) were 75 years or older. No overall differences in effectiveness were Of the 564 patients treated with PADCEV in combination with pembrolizumab, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 39% (n=282) were 65-74 years and 24% (n=170) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients.

Patients 75 years of age or older treated with PADCEV in combination with pembrolizumab experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Patients 75 years of age or older treated with PADCEV as a single agent experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 6% in patients younger than 75 years, and 11% in patients 75 years or older.

No significant difference was observed in the pharmacokinetics of PADCEV between patients 65 years and older and younger patients *[see Clinical Pharmacology (10.3)]*.

8.6 Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST). PADCEV has only been studied in a limited number of patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (10.3)]*. In another ADC that contains MMAE, the frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function.

9. DESCRIPTION

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). Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug-to-antibody ratio of approximately 3.8:1. The molecular weight is approximately 152 kDa.

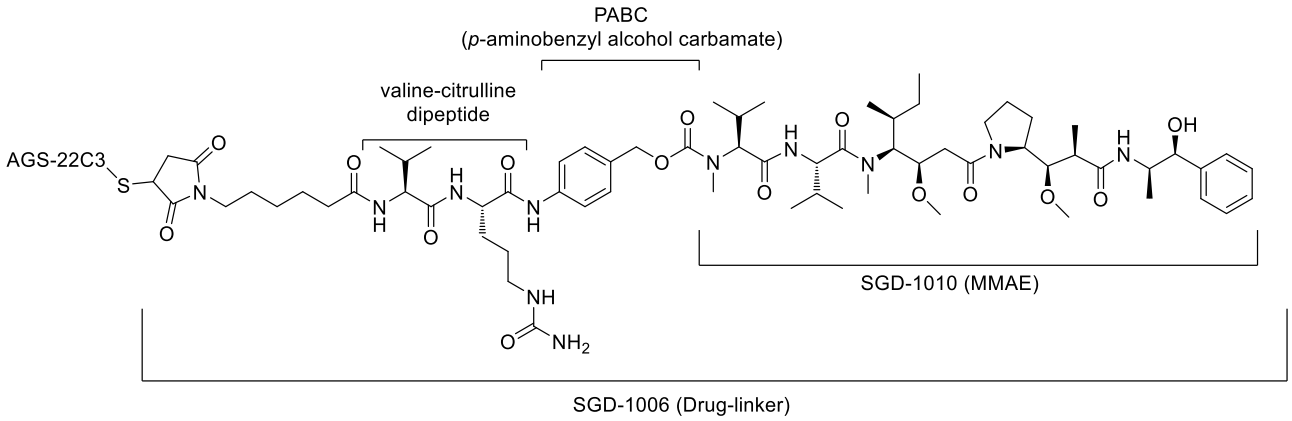


Figure 1. Structural Formula

Approximately 4 molecules of MMAE are attached to each antibody molecule. Enfortumab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells and the small molecule components are produced by chemical synthesis.

PADCEV (enfortumab vedotin) for injection is provided as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. PADCEV is supplied as a 20 mg per vial and a 30 mg per vial and requires reconstitution with Sterile Water for Injection, (2.3 mL and 3.3 mL, respectively) resulting in a clear to slightly opalescent, colorless to slightly yellow solution with a final concentration of 10 mg/mL *[see Dosage and Administration (3.3)]*. After reconstitution, each vial allows the withdrawal of 2 mL (20 mg) and 3 mL (30 mg). Each mL of reconstituted solution contains 10 mg of enfortumab vedotin, histidine (1.4 mg), histidine hydrochloride monohydrate (2.31 mg), polysorbate 20 (0.2 mg) and trehalose dihydrate (55 mg) with a pH of 6.0.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Enfortumab vedotin is an ADC. The antibody is a human IgG1 kappa directed against Nectin-4, an adhesion protein located on the surface of cells. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody 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. The combination of enfortumab vedotin with a PD-1 blocking antibody resulted in up-regulation of immune function and increased anti-tumor activity in syngeneic mouse tumor models expressing Nectin-4.

10.2 Pharmacodynamics

In an exposure-response analysis for safety, higher enfortumab vedotin exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 hyperglycemia). The exposure-response relationship for efficacy has not been fully characterized.

Cardiac Electrophysiology

At the recommended dose, PADCEV had no large QTc prolongation (> 20 msec).

10.3 Pharmacokinetics

Enfortumab vedotin (ADC) pharmacokinetics were characterized after single and multiple doses in patients with locally advanced or metastatic urothelial carcinoma and other solid tumors.

The pharmacokinetics of the ADC and unconjugated MMAE were consistent when assessed following PADCEV administration as a single agent and in combination with pembrolizumab after 1 treatment cycle.

The exposure parameters of the ADC and unconjugated MMAE (the cytotoxic component of enfortumab vedotin) are summarized in Table 13 below. Peak ADC concentrations were observed near the end of intravenous infusion while peak unconjugated MMAE concentrations were observed approximately 2 days after PADCEV dosing. Minimal accumulation of the ADC and unconjugated MMAE was observed following repeat administration of PADCEV in patients. Steady-state concentrations of the ADC were reached after 1 treatment cycle for the ADC as a single agent and in combination with pembrolizumab.

Table 13. Exposure parameters of the ADC and unconjugated MMAE after first treatment cycle of 1.25 mg/kg of PADCEV dose of Days 1, 8 and 15

	ADC Mean (± SD)	**Unconjugated MMAE Mean (± SD)**
C_{max}	28 (6.1) µg/mL	5.5 (3.0) ng/mL
$AUC_{0\text{-}28d}$	110 (26) µg·d/mL	85 (50) ng·d/mL
$C_{trough,0\text{-}28d}$	0.31 (0.18) µg/mL	0.81 (0.88) ng/mL

C_{max} = maximum concentration, $AUC_{0\text{-}28d}$ = area under the concentration-time curve from time zero to 28 days, $C_{trough,0\text{-}28d}$ = pre-dose concentration on day 28

Distribution

The estimated mean steady-state volume of distribution of the ADC was 12.8 L following administration of PADCEV. *In vitro*, plasma protein binding of unconjugated MMAE ranged from 68% to 82%.

Elimination

The ADC and unconjugated MMAE exhibited multi-exponential declines with an elimination half-life of 3.6 days and 2.6 days, respectively. The mean clearance (CL) of the ADC and unconjugated MMAE was 0.11 L/h and

2.11 L/h, respectively. Elimination of unconjugated MMAE appeared to be limited by its rate of release from the ADC.

Metabolism

Catabolism of the ADC has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. The ADC releases MMAE via proteolytic cleavage, and unconjugated MMAE is primarily metabolized by CYP3A4 *in vitro*.

Excretion

The excretion of the ADC is not fully characterized. Following a single-dose of another ADC that contains unconjugated MMAE, 17% of the total unconjugated MMAE administered was recovered in feces and 6% in urine over a 1-week period, primarily as unchanged form. A similar excretion profile of unconjugated MMAE is expected after PADCEV administration.

Specific Populations

No clinically significant differences in the pharmacokinetics of the ADC or unconjugated MMAE were identified based on age (24 to 90 years), sex, race (White, Asian, or Black), renal impairment and mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ ULN and AST > ULN) The effect of end stage renal disease with or without dialysis and moderate or severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) on the pharmacokinetics of the ADC or unconjugated MMAE is unknown.

Drug Interaction Trials

No clinical trials evaluating the drug-drug interaction potential of the ADC have been conducted.

Physiologically Based Pharmacokinetic (PBPK) Modeling Predictions:

Dual P-gp and Strong CYP3A4 Inhibitor: Concomitant use of PADCEV with ketoconazole (a dual P-gp and strong CYP3A4 inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%.

Dual P-gp and Strong CYP3A4 Inducer: Concomitant use of PADCEV with rifampin (a dual P-gp and strong CYP3A4 inducer) is predicted to decrease unconjugated MMAE C_{max} by 28% and AUC by 53%.

Sensitive CYP3A substrates: Concomitant use of PADCEV is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate).

In Vitro Studies

Transporter Systems: MMAE is a substrate of P-glycoprotein (P-gp) and is not an inhibitor of P-gp.

10.6 Immunogenicity

The observed incidence of anti-drug antibody (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of PADCEV or of other enfortumab vedotin products.

In the 0.3-to-55.7-month treatment periods with ADA sampling in eight clinical studies of PADCEV 1.25 mg/kg as a single agent on Days 1, 8 and 15 of a 28-day cycle and in combination with pembrolizumab on Days 1 and 8 of a 21-day cycle in patients with locally advanced or metastatic urothelial cancer *[see Clinical Studies (12)]*,

the incidence of anti-enfortumab vedotin antibody formation was 3.6% (22 of 617 patients who were tested for ADA) for PADCEV as a single agent and 3.0% (14 of 466 patients who were tested for ADA) for PADCEV in combination with pembrolizumab.

Because of the low occurrence of ADA, the effect of the ADA on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of PADCEV is unknown.

11. NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule-disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Fertility studies with enfortumab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies indicate the potential for enfortumab vedotin to impair female and male reproductive function and fertility.

In repeat-dose toxicology studies conducted in rats for up to 13 weeks, doses ≥ 2 mg/kg enfortumab vedotin (at exposures similar to the exposures at the recommended human dose) resulted in decreases in testes and epididymis weights, seminiferous tubule degeneration, spermatid/spermatocyte depletion in the testes and cell debris, sperm granuloma and hypospermia/abnormal spermatids in the epididymis. Findings in the testes and epididymis did not reverse by the end of the recovery period.

MMAE-containing ADCs have been associated with adverse ovarian effects when administered to sexually immature animals. Adverse effects included decrease in, or absence of, secondary and tertiary ovarian follicles after weekly administration to cynomolgus monkeys in studies of 4-week duration. These effects showed a trend towards recovery 6 weeks after the end of dosing; no changes were observed in primordial follicles.

12. CLINICAL STUDIES

12.1 Metastatic Urothelial Cancer

Previously Untreated Locally Advanced or Metastatic Urothelial Cancer

EV-302

The efficacy of PADCEV in combination with pembrolizumab was evaluated in EV-302 (NCT04223856), an open label, randomized, multicenter trial that enrolled 886 patients with locally advanced or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease. 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.

Patients were randomized 1:1 to receive either:

- PADCEV 1.25 mg/kg 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. Treatment was continued until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, pembrolizumab was continued for up to 2 years.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5) on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity for up to 6 cycles.

Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

The median age was 69 years (range: 22 to 91); 77% were male; 67% were White, 22% were Asian, 1% were Black or African American, and 10% were unknown or other; 12% were Hispanic or Latino. 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, including 72% with visceral and 22% with liver metastases, and 5% had locally advanced urothelial cancer. 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 considered cisplatin-ineligible and 54% were considered cisplatin-eligible at time of randomization.

The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures included objective response rate (ORR) as assessed by BICR.

The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients randomized to PADCEV in combination with pembrolizumab as compared to platinum-based chemotherapy. Efficacy results were consistent across all stratified patient subgroups. Table 14 and Figures 2-3 summarize the efficacy results for EV-302.

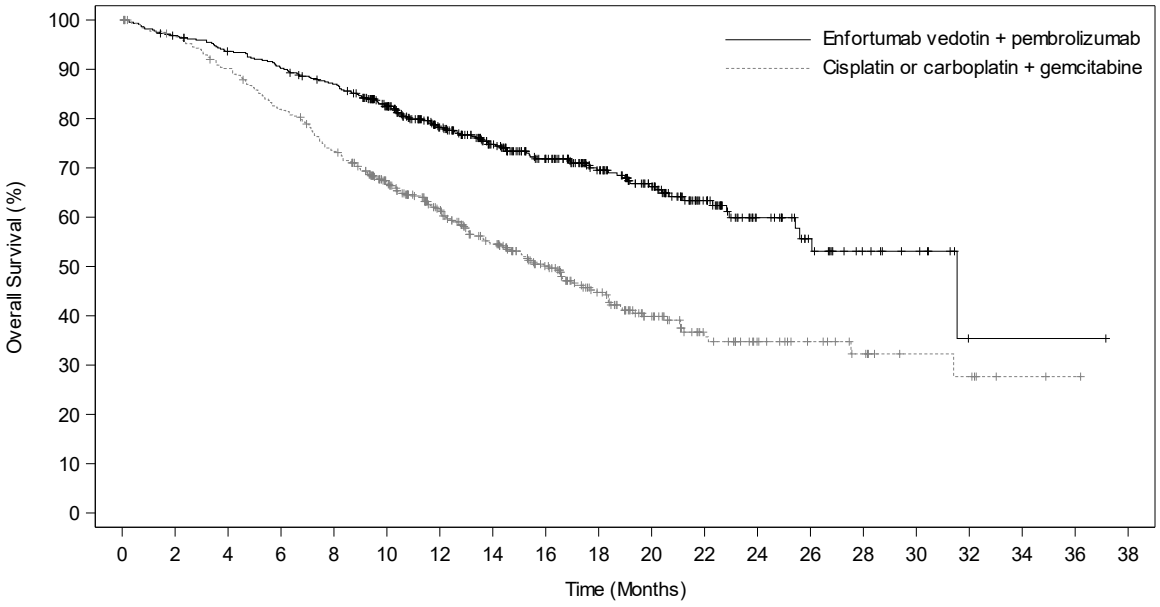
Table 14. Efficacy Results in EV-302

Endpoint	**PADCEV with pembrolizumab n=442**	**Cisplatin or carboplatin with gemcitabine n=444**
Overall Survival		
Number (%) of patients with events	133 (30.1)	226 (50.9)
Median in months (95% CI)	31.5 (25.4, NE)	16.1 (13.9, 18.3)
Hazard ratio (95% CI)[1]	0.47 (0.38, 0.58)	
p-value[2,3]	< 0.0001	
Progression Free Survival		
Number (%) of patients with events	223 (50.5)	307 (69.1)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)

Endpoint	PADCEV with pembrolizumab n=442	Cisplatin or carboplatin with gemcitabine n=444
Hazard ratio (95% CI)[1]	0.45 (0.38, 0.54)	
p-value[2,3]	< 0.0001	
Confirmed Objective Response Rate[4]		
ORR (%) (95% CI)	67.7 (63.1, 72.1)	44.4 (39.7, 49.2)
p-value[3,5]	< 0.0001	
Complete response rate (%)	29.1	12.5
Partial response rate (%)	38.7	32.0

NE = Not estimable.

1. Based on a stratified Cox proportional hazards model.
2. Based on stratified log-rank test.
3. Two-sided p-value.
4. Includes only patients with measurable disease at baseline (n=437 for PADCEV in combination with pembrolizumab, n=441 for chemotherapy).
5. Cochran-Mantel-Haenszel test (CMH) controlling for stratification factors.



N at Risk

Enfortumab vedotin + pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Cisplatin or carboplatin + gemcitabine	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

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

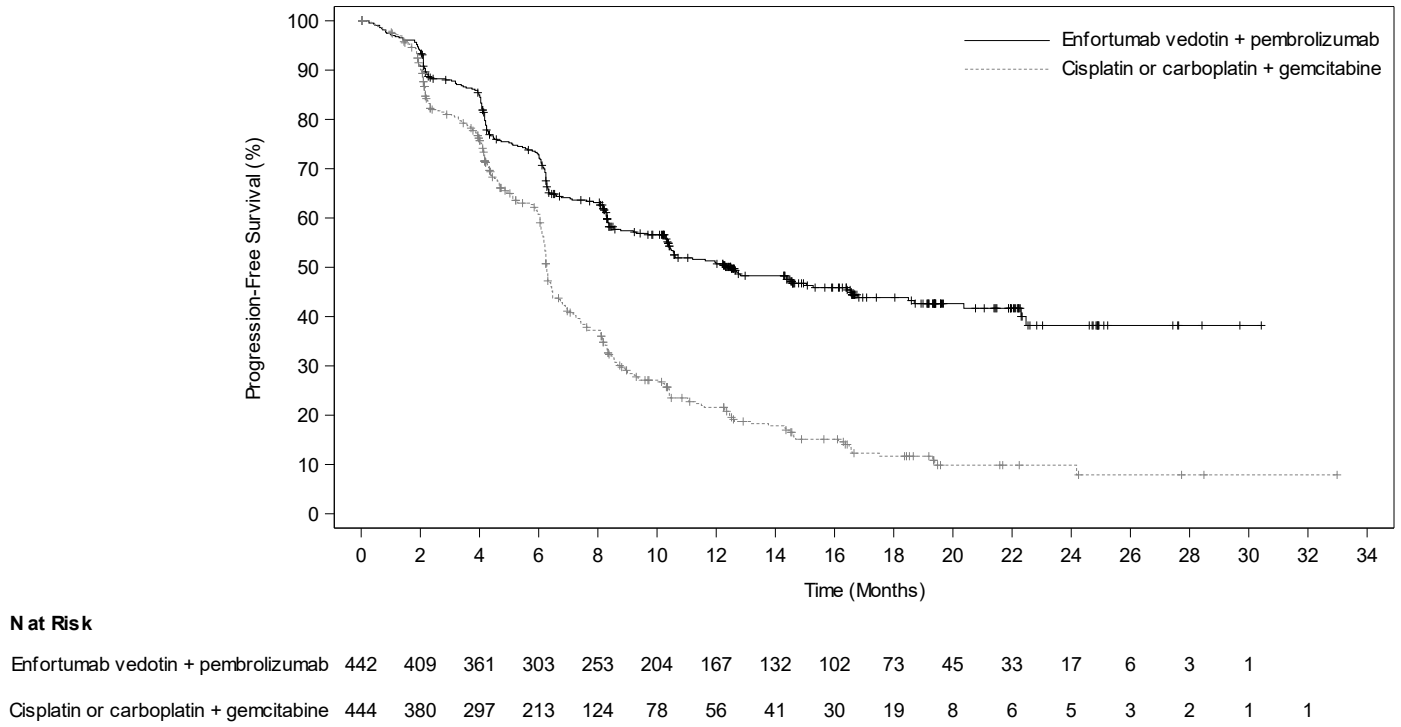


Figure 3. Kaplan Meier Plot of Progression-Free Survival, EV-302

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

EV-103

The efficacy of PADCEV in combination with pembrolizumab was evaluated in EV-103 (NCT03288545), an open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) trial 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 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 trial.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received PADCEV 1.25 mg/kg as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by pembrolizumab 200 mg as an IV infusion on Day 1 of a 21-day cycle approximately 30 minutes after PADCEV. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received PADCEV in combination with pembrolizumab. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White, 5% were Black, 4% were Asian and 6% were other, unknown or not reported. Ten percent of patients were Hispanic or Latino. Forty-five percent 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%. Reasons for cisplatin ineligibility included: 60% with baseline creatinine clearance of 30 – 59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss, and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline including 22% with liver metastases. Thirty-nine percent of patients had transitional cell carcinoma (TCC) histology; 13% had TCC with squamous differentiation and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1.

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).

Efficacy results are presented in Table 15 below.

Table 15. Efficacy Results in EV-103, Combined Dose Escalation Cohort, Cohort A, and Cohort K

	PADCEV in combination with pembrolizumab n=121
Confirmed ORR (95% CI)	68% (58.7, 76.0)
Complete response rate	12%
Partial response rate	55%

The median duration of response for the dose escalation cohort + Cohort A was 22.1 months (range: 1.0+ to 46.3+) and for Cohort K was not reached (range: 1.2 to 24.1+).

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The efficacy of PADCEV as a single agent was evaluated in EV-301 (NCT03474107), an open-label, randomized, multicenter trial that enrolled 608 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. Patients were randomized 1:1 to receive either PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle or investigator's choice of chemotherapy. Randomization was stratified by ECOG PS (0 vs 1), region of world (Western Europe vs US vs Rest of World), and presence of liver metastasis.

Patients were excluded if they had active central nervous system (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.

The median age was 68 years (range: 30 to 88 years) and 77% were male. Racial demographics were reported as White (52%), Asian (33%), Black (0.7%), Native Hawaiian or Other Pacific Islander (0.2%) or not reported (15%). Nine percent of patients were Hispanic or Latino. All patients had a baseline ECOG performance status of 0 (40%) or 1 (60%). Thirty-four percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Eighty percent of patients had visceral metastases including 31% with liver metastases. Seventy-six percent of patients had pure TCC histology; 14% had TCC with other histologic variants; and 10% had other tumor histologies including adenocarcinoma and squamous cell carcinoma. The median number of prior therapies was 2 (range 1 to ≥ 3). Sixty-three percent of patients received prior cisplatin-based regimens, 26% received prior

carboplatin-based regimens, and an additional 11% received both cisplatin and carboplatin-based regimens. Patients on the control arm received docetaxel (38%), paclitaxel (36%) or vinflunine (25%).

The major efficacy outcome measures were OS, PFS, and ORR assessed by investigator using RECIST v1.1. Efficacy results were consistent across all stratified patient subgroups.

Table 16 and Figures 4-5 summarize the efficacy results for EV-301.

Table 16. Efficacy Results in EV-301

Endpoint	PADCEV n=301	Chemotherapy n=307
Overall Survival[1]		
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)	0.70 (0.56, 0.89)	
p-value	0.0014	
Progression Free Survival[1]		
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)	0.62 (0.51, 0.75)	
p-value	< 0.0001	
Overall Response Rate (CR + PR)[2]		
ORR (%) (95% CI)	40.6 (34.9, 46.5)	17.9 (13.7, 22.8)
p-value	< 0.0001	
Complete response rate (%)	4.9	2.7
Partial response rate (%)	35.8	15.2

1. Based on log-rank test. Stratification factors were ECOG PS, region and liver metastasis.
2. Based on Cochran-Mantel-Haenszel test. Stratification factors were ECOG PS, region and liver metastasis.

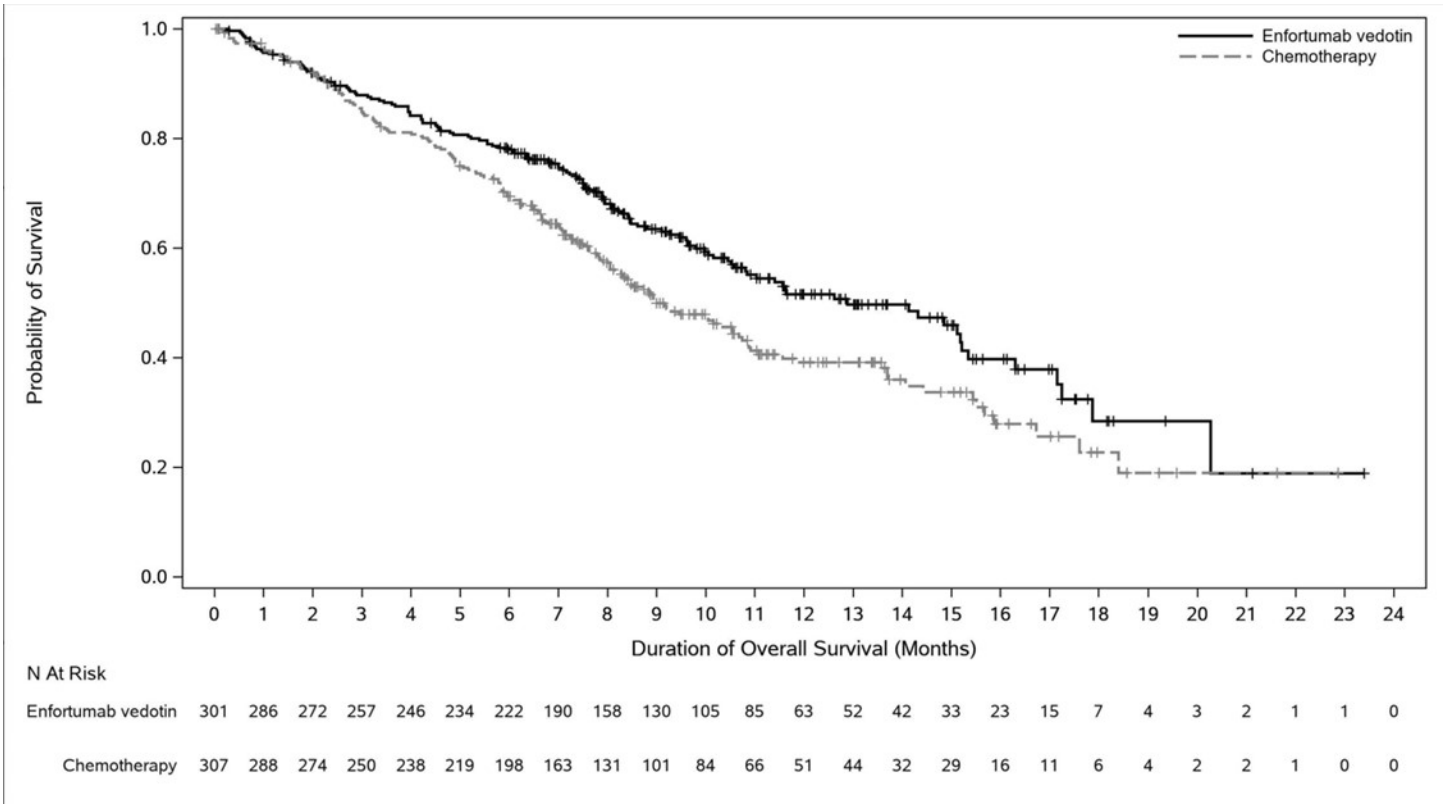


Figure 4. Kaplan Meier Plot of Overall Survival, EV-301

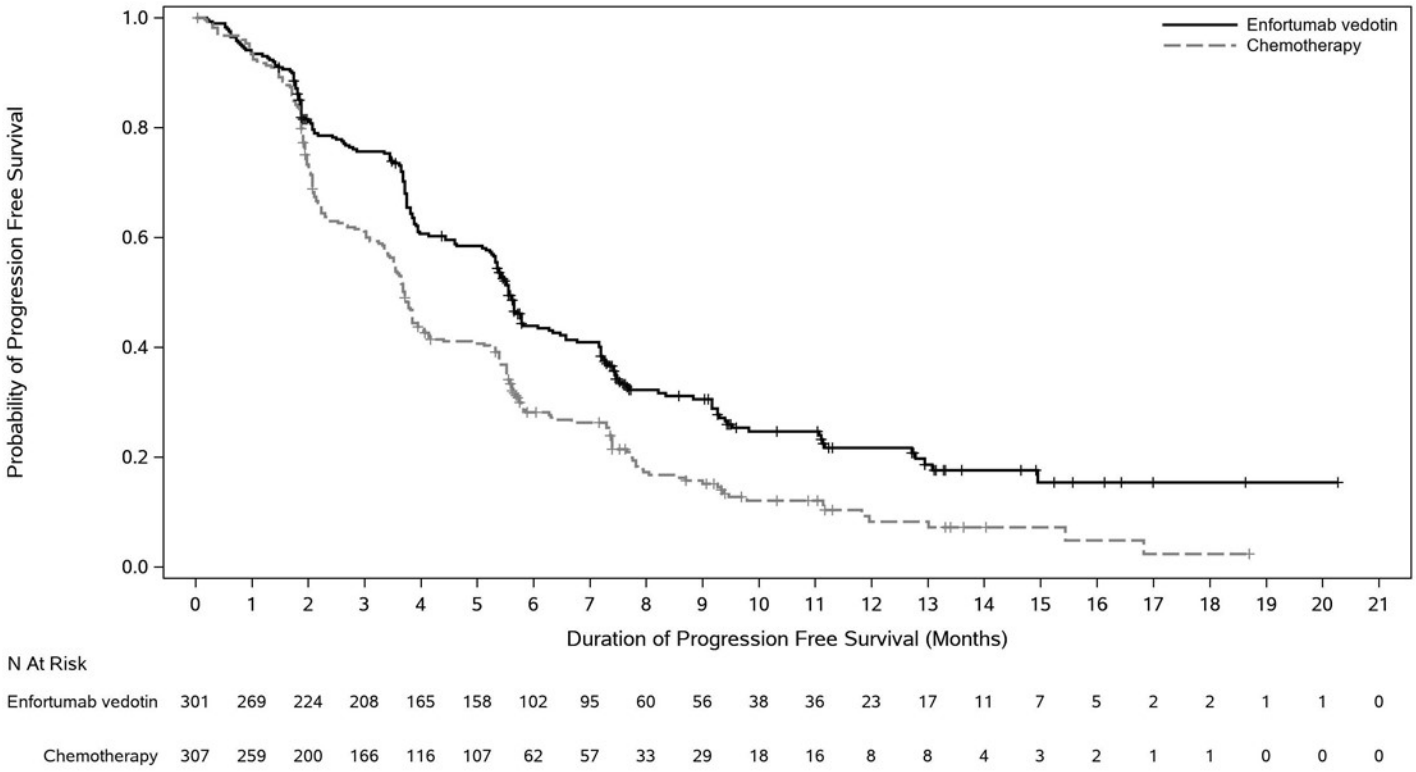


Figure 5. Kaplan Meier Plot of Progression Free Survival, EV-301

EV-201, Cohort 1

The efficacy of PADCEV as a single agent was also investigated in Cohort 1 of EV-201 (NCT03219333), a single-arm, multi-cohort, multicenter trial that enrolled 125 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. Patients were excluded if they had active central nervous system (CNS) metastases, ongoing sensory or motor neuropathy ≥ Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c ≥ 7% with associated diabetes symptoms.

PADCEV was administered at a dose of 1.25 mg/kg, as an intravenous (IV) infusion on days 1, 8, and 15 of each 28-day cycle.

The median age was 69 years (range: 40 to 84 years) and 70% were male. Racial demographics were reported as White (85%), Asian (9%), Black (2%), Other (0.8%) or not reported (4%). Four percent of patients were Hispanic or Latino. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (32%) or 1 (68%). Ninety percent of patients had visceral metastases including 40% with liver metastases. Approximately two-thirds (67%) of patients had pure transitional cell carcinoma (TCC) histology; 33% had TCC with other histologic variants. The median number of prior systemic therapies was 3 (range: 1 to 6). Sixty-six percent of patients received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 8% received both cisplatin and carboplatin-based regimens.

The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) assessed by BICR using RECIST v1.1.

Efficacy results are presented in Table 17.

Table 17. Efficacy Results in EV-201, Cohort 1 (BICR Assessment)

Endpoint	**PADCEV n=125**
Confirmed ORR (95% CI)	44% (35.1, 53.2)
Complete Response Rate (CR)	12%
Partial Response Rate (PR)	32%
Median[1] Duration of Response, months (95% CI)	7.6 (6.3, NE)

NE = not estimable

1. Based on patients (n=55) with a response by BICR.

Previously Treated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Cancer

EV-201, Cohort 2

The efficacy of PADCEV as a single agent was also evaluated in Cohort 2 of EV-201, a single-arm, multi-cohort, multicenter trial in 89 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and were cisplatin ineligible and did not receive platinum in the locally advanced or metastatic setting. Patients were excluded if they had active CNS metastases, ongoing sensory or motor neuropathy ≥ Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c ≥ 7% with associated diabetes symptoms.

PADCEV was administered at a dose of 1.25 mg/kg, as an intravenous (IV) infusion on days 1, 8, and 15 of each 28-day cycle.

The median age was 75 years (range: 49 to 90 years), 74% were male. Racial demographics were reported as White (70%), Asian (22%) or not reported (8%). One percent of patients were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (42%), 1 (46%) and 2 (12%). Forty-three percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Seventy-nine percent of patients had visceral metastases and 24% had liver metastases.

Reasons for cisplatin ineligibility included: 66% with baseline creatinine clearance of 30-59 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 histology; 13% had TCC with squamous differentiation and 17% had TCC with other histologic variants.

The median number of prior systemic therapies was 1 (range: 1 to 4).

Efficacy results are presented in Table 18 below.

Table 18. Efficacy Results in EV-201, Cohort 2 (BICR Assessment)

Endpoint	**PADCEV n=89**
Confirmed ORR (95% CI)	51% (39.8, 61.3)
Complete Response Rate (CR)	22%
Partial Response Rate (PR)	28%
Median[1] Duration of Response, months (95% CI)	13.8 (6.4, NE)

NE = not estimable

1. Based on patients (n=45) with a response by BICR.

13. REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

14. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PADCEV (enfortumab vedotin) 20 mg and 30 mg are supplied as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials. PADCEV vials are available in the following packages:

- Carton of one 20 mg single-dose vial
- Carton of one 30 mg single-dose vial

Storage

Store PADCEV vials refrigerated at 2ºC to 8ºC in the original carton. Do not freeze. Do not shake.

Special Handling

PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Shelf life
The expiry date of the product is indicated on the packaging materials.

Name of manufacturer:
Astellas Pharma US, Inc.
1 Astellas Way, Northbrook IL 60062, USA

Name of registration holder:
Astellas Pharma International B.V., 21 Ha'melacha St., Rosh Ha'Ayin 4809157, Israel.

MARKETING AUTHORISATION NUMBER(S)

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