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™ 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 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

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, 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*	Dose Modification*
Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
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 *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold until Grade ≤ 1 for persistent or recurrent Grade 2 pneumonitis, consider dose reduction by one dose level.
	Grade >3	Permanently discontinue.
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.

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

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 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculopapular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients *[see Adverse Reactions (6.1)]*.

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

Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for severe (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, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3 months). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients. *[see Adverse Reactions (6.1)]*.

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

Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis 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 persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis *[see Dosage and Administration (3.2)]*.

5.4 Peripheral Neuropathy

Peripheral neuropathy occurred in 52% of the 680 patients treated with PADCEV in clinical trials including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% 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 4.6 months (range: 0.1 to 5.8 months). Neuropathy led to treatment discontinuation in 5% of patients [*see Adverse Reactions (6.1)*].

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 that 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 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 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 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 680 patients, 1.6% 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 approximately 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 *[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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 680 patients in EV-301, EV-201, EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 680 patients receiving PADCEV, 36% were exposed for ≥ 6 months and 9% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin.

The data described in the following sections reflect exposure to PADCEV from an open-label, randomized, study (EV-301); and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort study (EV-201). Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The safety of PADCEV was evaluated 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 (14)]*. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19.4 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 (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis 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 3 summarizes the most common (≥15%) adverse reactions in EV-301.

Table 3. 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[2]	50	9	40	7
Pyrexia[3]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[4]	50	5	34	3
Dysgeusia[5]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[6]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[7]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[8]	25	2	35	5
Eye Disorders				
Dry eye[9]	24	0.7	6	0.3
Blood and lymphatic system disorders				
Anemia	20	6	30	12
Infections and infestations				
Urinary Tract Infection[10]	17	6	13	3
Vascular disorders				
Hemorrhage[11]	17	3	13	2
Investigations				
Weight decreased	16	0.3	7	0

[1]Includes: blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, drug eruption, eczema, erythema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, stomatitis.
[2]Includes: fatigue, asthenia
[3]Includes: pyrexia, hyperthermia, hyperpyrexia, body temperature increased
[4]Includes: burning sensation, demyelinating polyneuropathy, dysesthesia, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy, gait disturbance, polyneuropathy, sensory loss
[5]Includes: dysgeusia, ageusia, hypogeusia
[6]Includes: diarrhea, colitis, enterocolitis
[7]Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain
[8]Includes: myalgia, arthralgia, back pain, bone pain, pain in extremity, musculoskeletal pain, arthritis, neck pain, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort

[9]Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, Meibomian gland dysfunction, ocular discomfort, punctate keratitis

[10]Includes: urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, streptococcal urinary tract infection, escherichia urinary tract infection, pyelonephritis acute, escherichia pyelonephritis, urinary tract infection fungal, cystitis, urinary tract infection staphylococcal, urinary tract infection pseudomonal

[11]Includes: hematuria, rectal hemorrhage, gastrointestinal hemorrhage, epistaxis, upper gastrointestinal hemorrhage, tumor hemorrhage, hemoptysis, vaginal hemorrhage, anal hemorrhage, hemorrhagic stroke, urethral hemorrhage, infusion site hemorrhage, conjunctival hemorrhage, hemorrhagic ascites, hemorrhoidal hemorrhage

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

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

	PADCEV[1]		Chemotherapy[1]	
Laboratory Abnormality	**Grades 2-4 %**	**Grade 3-4 %**	**Grades 2-4 %**	**Grade 3-4 %**
Hematology				
Lymphocytes decreased	41	14	34	18
Hemoglobin decreased	28	4	42	14
Neutrophils decreased	27	12	25	17
Chemistry				
Phosphate decreased	39	8	24	6
Glucose increased (non-fasting)	33	9	27	6
Creatinine increased	18	2	13	0
Potassium decreased	16	2	7	3
Lipase increased	13	8	7	4
Sodium decreased	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 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 (14)]*. 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 (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%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were fatigue peripheral neuropathy (12%), decreased appetite rash (6%), alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin. The most common Grade ≥3 adverse reaction (≥5%) were rash, diarrhea, and fatigue (4%).

Table 5 summarizes the All Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 1.

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

	PADCEV n=125	
Adverse Reaction	**All Grades %**	**Grade 3-4 %**
Any	**100**	**73**
General disorders and administration site conditions		
Fatigue[1]	56	6
Nervous system disorders		
Peripheral neuropathy[2]	56	4
Dysgeusia	42	0
Metabolism and nutrition disorders		
Decreased appetite	52	2
Skin and subcutaneous tissue disorders		
Rash[3]	52	13
Alopecia	50	0
Dry skin	26	0
Pruritus[4]	26	2
Gastrointestinal disorders		
Nausea	45	3
Diarrhea[5]	42	6
Vomiting	18	2
Eye disorders		
Dry eye[6]	40	0

[1]Includes: asthenia and fatigue
[2]Includes: hypoesthesia, gait disturbance, muscular weakness, neuralgia, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy and peripheral sensorimotor neuropathy.
[3]Includes: dermatitis acneiform, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, skin exfoliation, stasis dermatitis, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and urticaria.
[4]Includes: pruritus and pruritus generalized
[5]Includes: colitis, diarrhea and enterocolitis

[6]Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased

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

Table 6. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-201, Cohort 1

	PADCEV	
Laboratory Abnormality	**Grades 2-4[1] %**	**Grade 3-4[1] %**
Hematology		
Hemoglobin decreased	34	10
Lymphocytes decreased	32	10
Neutrophils decreased	14	5
Chemistry		
Phosphate decreased	34	10
Glucose increased (non-fasting)	27	8
Creatinine increased	20	2
Potassium decreased	19[2]	1
Lipase increased	14	9
Sodium decreased	8	8
Urate increased	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 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 (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%), aspartate aminotransferase increased (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 7 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

Table 7. 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[2]	58	8
Dysgeusia[3]	29	0
General disorders and administration site conditions		
Fatigue[4]	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Blood and lymphatic disorders		
Anemia	38	11
Gastrointestinal disorders		
Diarrhea[5]	36	8
Nausea	30	1
Investigations		
Weight decreased	35	1
Eye disorders		
Dry eye[6]	30	0

[1]Includes: blister, conjunctivitis, dermatitis bullous, dermatitis exfoliative generalized, eczema, erythema, erythema multiforme, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, stomatitis

[2]Includes: demyelinating polyneuropathy, gait disturbance, hypoesthesia, motor dysfunction, muscle atrophy, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy

[3]Includes: dysgeusia, ageusia, hypogeusia

[4]Includes: fatigue, asthenia

[5]Includes: diarrhea, colitis, enterocolitis

[6]Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased

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

Table 8. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grades 3-4) of Patients Treated with PADCEV in EV-201, Cohort 2

	PADCEV N=88[1]	
Laboratory Abnormality	**Grades 2-4[1] %**	**Grade 3-4[1] %**
Hematology		
Lymphocytes decreased	43	15
Hemoglobin decreased	34	5
Neutrophils decreased	20	9
Chemistry		
Glucose increased (non-fasting)	36	13
Phosphate decreased	25	7
Creatinine increased	23	3
Lipase increased	18	11
Urate increased	9	9
Potassium increased	8	6
Sodium decreased	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)]*.

Blood and lymphatic system disorders: Neutropenia, febrile neutropenia, and neutrophil count decreased.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the trials described below with the incidence of antibodies in other trials or other enfortumab vedotin products may be misleading.

Following administration A total of PADCEV 1.25 mg/kg; 16/590 (2.7%)365 patients tested for immunogenicity to PADCEV; 4 patients (1%) were confirmed to be transiently positive for anti-therapeutic antibody (ATA) against enfortumab vedotinand 1 patient (0.3%) was confirmed to be persistently positive for ATA at one or moreany post-baseline time points. Due to the limited number No impact of patients with ATA

against enfortumab vedotin, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety and or pharmacokinetics was observed.

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 unconjugatedfree 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 approximately 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 (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 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 at least 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

Males

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

8.4 Pediatric Use

PADCEV is not indicated for use in children and adolescents under 18 years old.

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

8.5 Geriatric Use

Of the 680 patients treated with PADCEV in clinical trials, 440 (65%) were 65 years or older and 168 (25%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients 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 AST any). PADCEV has only not been studied in a limited number of patients with moderate hepatic

impairment (n=3) and has not been evaluated in patients with severe hepatic impairment *[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. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST any, or total bilirubin ≤ULN and AST >ULN).

8.7 Renal Impairment

No dose adjustment is required in patients with mild (CrCL >60-90 mL/min), moderate (CrCL 30-60 mL/min) or severe (CrCL <30 mL/min) renal impairment *[see Clinical Pharmacology (10.3)]*.

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.

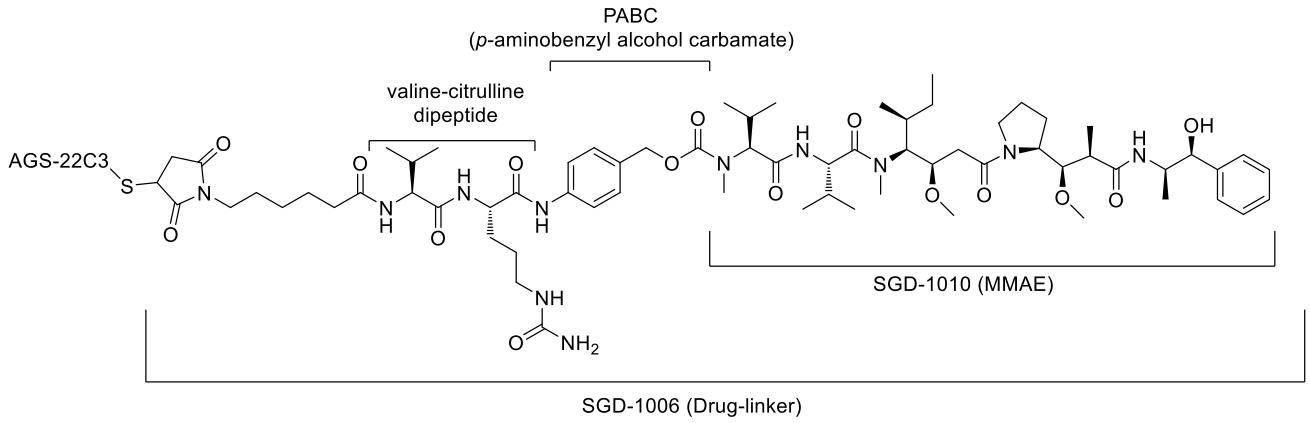


Figure 1. Structural Formula

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 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 apoptotic cell death.

10.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

10.3 Pharmacokinetics

Population pharmacokinetic analysis included data from 748 patients based five studies and one Phase 2 study. Enfortumab vedotin pharmacokinetics were characterized after single and multiple doses in patients with locally advanced or metastatic urothelial carcinoma and other solid tumors.

The exposure parameters of ADC and unconjugated MMAE (the cytotoxic component of enfortumab vedotin) are summarized in Table 9 below. Peak ADC concentrations were observed near the end of intravenous infusion while peak MMAE concentrations were observed approximately 2 days after enfortumab vedotin dosing. Minimal accumulation of the ADC and MMAE was observed following repeat administration of enfortumab vedotin in patients. Steady-state concentrations of ADC and MMAE were reached after 1 treatment cycle.

Table 9. Exposure parameters of ADC and unconjugated MMAE after first treatment cycle of 1.25 mg/kg of enfortumab vedotin 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_{0-28d}	110 (26) µg·d/mL	85 (50) ng·d/mL
$C_{trough,0-28d}$	0.31 (0.18) µg/mL	0.81 (0.88) ng/mL

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

Distribution

The estimated mean steady-state volume of distribution of ADC was 12.8 liters following administration of enfortumab vedotin. Plasma protein binding of MMAE ranged from 68% to 82%, *in vitro*.

Elimination

ADC and MMAE exhibited multi-exponential declines with an elimination half-life of 3.6 days and 2.6 days, respectively. The mean clearance (CL) of enfortumab vedotin and unconjugated MMAE in patients was 0.11 L/h and 2.11 L/h, respectively, in patients. Elimination of MMAE appeared to be limited by its rate of release from enfortumab vedotin.

Metabolism

Enfortumab vedotin catabolism 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. Enfortumab vedotin releases MMAE via proteolytic cleavage, and MMAE is primarily metabolized by CYP3A4 *in vitro*.

Excretion

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

Specific Populations

Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of enfortumab vedotin were observed based on age (24 to 90 years), sex, or race/ethnicity (Caucasian, Asian, Black, or others).

Hepatic Impairment

Based on population pharmacokinetics analysis, there was a 37% $AUC_{0\text{-}28d}$ increase in unconjugated MMAE exposure observed in patients with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ULN and AST >ULN, n=65) compared to normal hepatic function. Enfortumab vedotin has only been studied in limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment. The effect of moderate or severe hepatic impairment (AST or ALT >2.5 x ULN or total bilirubin >1.5 x ULN and AST any) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Renal Impairment

The pharmacokinetics of enfortumab vedotin and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to patients with mild (creatinine clearance; CrCL >60–90 mL/min; n=272), moderate (CrCL 30–60 mL/min; n=315) and severe (CrCL <30 mL/min; n=25) renal impairment. No significant differences in exposure (AUC) of ADC and MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. The effect of end stage renal disease with or without dialysis on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Drug Interaction Trials

No clinical trials evaluating the drug-drug interaction potential of enfortumab vedotin have been conducted. To characterize the drug-drug interaction potential of free MMAE, clinical studies with another ADC that contains MMAE are described below.

Physiologically Based Pharmacokinetic (PBPK) Modeling Predictions:

Dual P-gp and Strong CYP3A4 Inhibitor: Concomitant use of enfortumab vedotin 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 enfortumab vedotin 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 CYP3A4 Substrates: Concomitant use of enfortumab vedotin 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), but not an inhibitor of P-gp.

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 in rats indicate the potential for enfortumab vedotin to impair 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.

12 CLINICAL STUDIES

12.1 Metastatic Urothelial Cancer

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

EV-301

The efficacy of PADCEV was evaluated in EV-301 (NCT03474107), an open-label, 201 (NCT03219333), single-arm, 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 Eastern Cooperative Oncology Group (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 transitional cell carcinoma (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 overall survival (OS), progression free survival (PFS), and overall response rate (ORR) assessed by investigator using RECIST v1.1. Efficacy results were consistent across all stratified patient subgroups.

Table 10 and Figures 2-3 summarize the efficacy results for EV-301.

Table 10. 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 2. Kaplan Meier Plot of Overall Survival

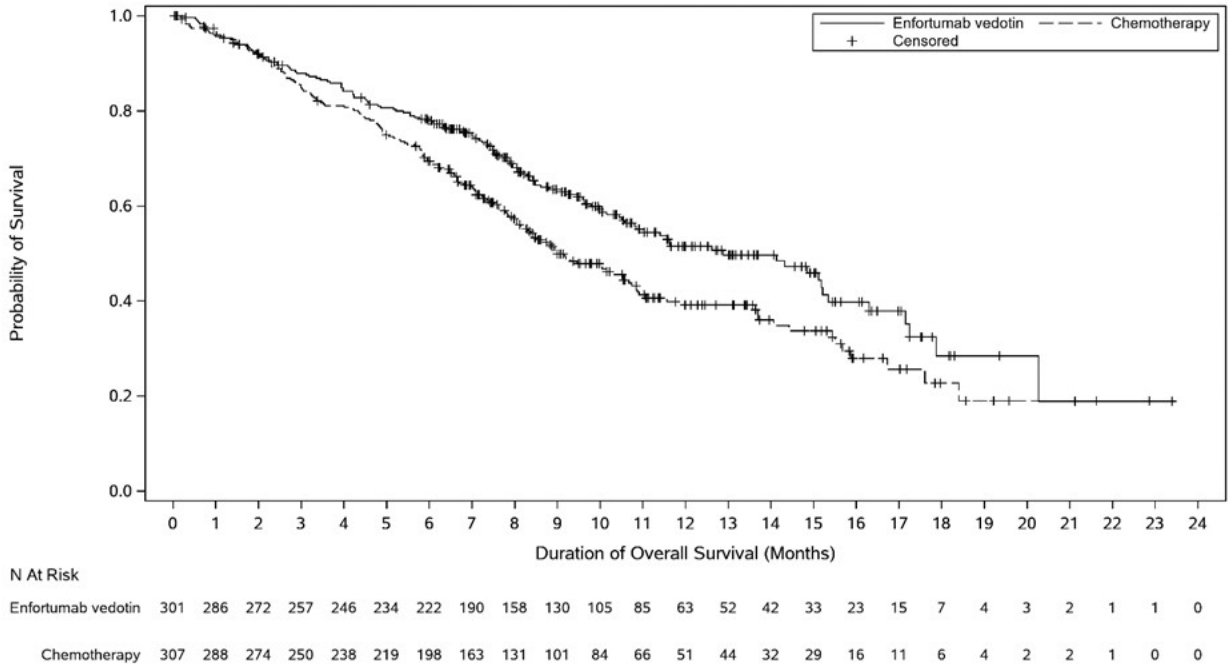
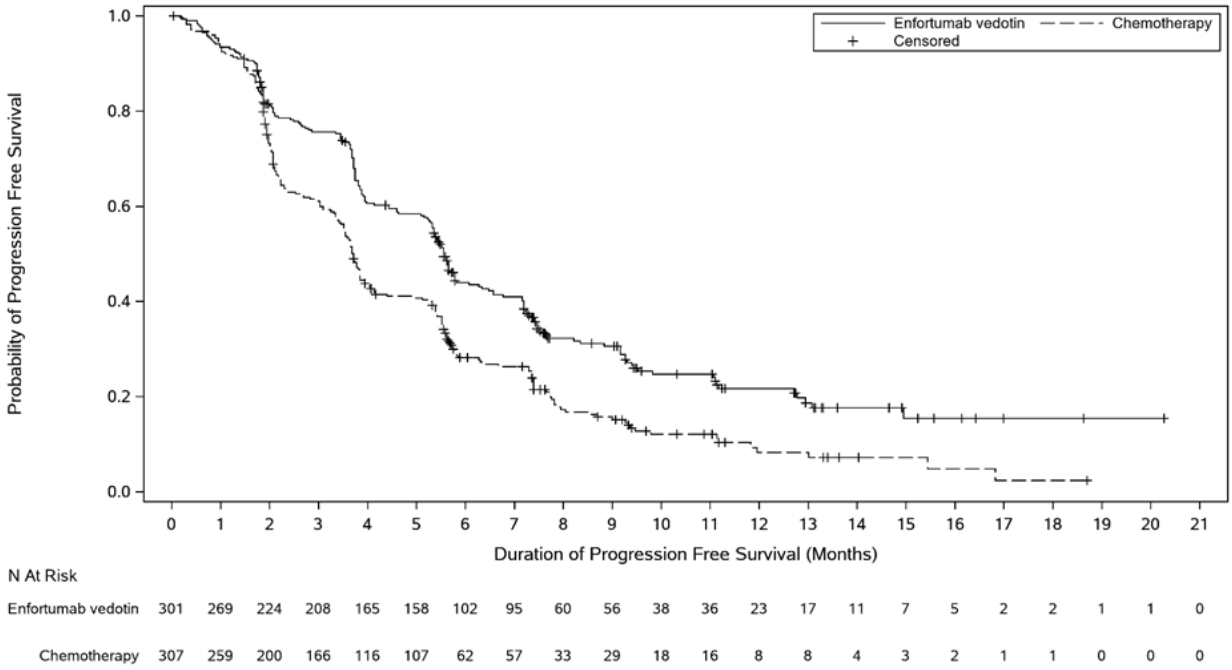


Figure 3. Kaplan Meier Plot of Progression Free Survival



EV-201, Cohort 1

The efficacy of PADCEV was also investigated in Cohort 1 of EV-201, 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 Latinowere Caucasian. 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. An immunohistochemistry clinical trial assay was used to assess patients with tumor tissue available, and detected Nectin-4 expression in all patients tested (n=120). The median number of prior systemic therapies was 3 (range: 1 to 6). Forty-six percent of patients received prior PD-1 inhibitor, 42% received prior PD-L1 inhibitor, and an additional 13% received both PD-1 and PD-L1 inhibitorsSixty-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 blinded independent central review (BICR) using RECIST v1.1.

Efficacy results are presented in Table 11.

Table 6. Efficacy Results in EV201 (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.

Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of PADCEV 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 12 below.

Table 12. 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 HOW SUPPLIED/STORAGE AND HANDLING

13.1 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

13.2 Storage

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

13.3 Special Handling

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

13.4 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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