Informational Resource for Skin Reactions During Treatment With PADCEV®

A resource to assist with identifying and addressing skin reactions during treatment

PADCEV, as a single agent or in combination with pembrolizumab, can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Withhold PADCEV and consider referral for specialized care for suspected SJS, TEN, or for Grade 3 skin reactions. During each visit, closely monitor patients for signs and symptoms of new or worsening skin reactions, and consider dose interruption, dose reduction, or discontinuation of PADCEV when skin reactions occur. Dose modifications were common in the clinical trials of PADCEV and were an important way to treat certain adverse reactions.[1]

BOXED WARNING: SERIOUS SKIN REACTIONS

- **PADCEV (enfortumab vedotin-ejfv) 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.**

INDICATIONS

PADCEV, in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment, is indicated for the treatment of adult patients with muscle invasive bladder cancer (MIBC).

PADCEV, in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (la/mUC).

PADCEV, as a single agent, is indicated for the treatment of adult patients with la/mUC who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

Please refer to the Prescribing Information for a full list of potential adverse reactions.

Please see Important Safety Information and full Prescribing Information, including BOXED WARNING.

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Identification and PADCEV® dose modifications for skin reactions

ENCOURAGE PATIENTS TO IMMEDIATELY INFORM THEIR HEALTHCARE PROVIDER ABOUT ANY NEW OR WORSENING SIGNS OF SKIN REACTIONS[1]:

- Target lesions (skin reactions that look like rings)
- Rash or itching that continues to get worse
- Blistering or peeling of skin
- Painful sores or ulcers in mouth or nose, throat, or genital area
- Fever or flu-like symptoms
- Swollen lymph nodes

Identifying and addressing skin reactions early is important[1]

POTENTIAL SCREENING QUESTIONS TO ASSIST IN IDENTIFICATION OF SKIN REACTIONS[1]

- Are you experiencing any new or worsening rashes, blistering or peeling of skin?
- Have you had a fever or other flu-like symptoms?
- Have you noticed any sores or ulcers in your mouth or nose, throat, or genital area?

Consider asking screening questions to monitor patients for these signs and symptoms

PADCEV DOSE MODIFICATIONS FOR SKIN REACTIONS[1]

SEVERITY*	PADCEV DOSE MODIFICATION*
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**

WITHHOLD **RESUME** **DISCONTINUE**

*Grade 1 is mild; Grade 2 is moderate; Grade 3 is severe; Grade 4 is life-threatening.[1]

RECOMMENDED STARTING DOSE OF PADCEV AND DOSE REDUCTION SCHEDULE[1]

The recommended dose of PADCEV (as a single agent or in combination with pembrolizumab) is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg).

Starting dose	1st dose **reduction**	2nd dose **reduction**	3rd dose **reduction**
DOSE LEVEL: **1.25 mg/kg up to 125 mg**	DOSE LEVEL: **1 mg/kg up to 100 mg**	DOSE LEVEL: **0.75 mg/kg up to 75 mg**	DOSE LEVEL: **0.5 mg/kg up to 50 mg**

Refer to the PADCEV Prescribing Information for the recommended dosing schedule of PADCEV as a single agent or in combination with pembrolizumab. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

Starting with the first cycle and throughout treatment, closely monitor patients for skin reactions[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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 65% (all grades) of the 570 patients treated with PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC in clinical trials. The majority of the skin reactions that occurred with combination therapy included rash and maculo-papular rash. Grade 3-4 skin reactions occurred in 13% of patients (Grade 3: 12%, Grade 4: 1.1%), including maculo-papular rash, rash, SJS, dermatitis, exfoliative generalized dermatitis, toxic skin eruption, acute generalized exanthematous pustulosis, bullous dermatitis, erythema, macular rash, and pruritic rash. A fatal reaction of TEN occurred in one patient (0.2%). The median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 24 months). Skin reactions led to discontinuation of PADCEV in 8% of patients. Of the patients who experienced a skin reaction and had data regarding resolution (n=367), 87% had complete resolution and 13% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 31% (15/49) had Grade ≥2 skin reactions.

Skin reactions occurred in 70% (all grades) of the 564 patients treated with PADCEV in combination with intravenous pembrolizumab for the treatment of la/mUC in clinical trials. The majority of skin reactions that occurred 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,

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Skin reactions grading

CTCAE v6.0 grading scale for select skin reactions[2]

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dry skin	No associated erythema or pruritus	Associated with erythema or pruritus; limiting instrumental ADL*	—	—	—
Erythema multiforme	Not associated with skin tenderness	Associated with skin tenderness	Associated with oral or genital erosions	Associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL*	Widespread and constant; systemic corticosteroid or immunosuppressive therapy indicated; limiting sleep or self-care ADL†	—	—
Rash maculo-papular	Asymptomatic	Mild symptoms	Macules/papules covering >50% BSA; moderate or severe symptoms	Life-threatening consequences; urgent intervention indicated	Death
SJS	—	—	Skin sloughing covering <10% BSA	Skin sloughing covering ≥10% BSA; life-threatening consequences	Death
TEN	—	—	—	Skin sloughing covering ≥30% BSA with associated symptoms (eg, erythema, purpura, or epidermal detachment); life-threatening consequences	Death

Note: '—' indicates a grade is not available.[2]

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.[2]

†Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications.[2]

ADL=activities of daily living; **BSA**=body surface area; **CTCAE**=Common Terminology Criteria for Adverse Events; **ICU**=intensive care unit.

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Treatment considerations for skin reactions

CLINICAL CONSIDERATIONS FOR SKIN REACTIONS WHILE TREATING WITH PADCEV®

Inform patients that severe skin reactions, including SJS and TEN with fatal outcomes have occurred after administration of PADCEV, predominantly during the first cycle of treatment but may occur later. Educate patients on the potential for skin reactions, common signs or symptoms, and importance of immediately reporting[1]

Starting with the first cycle and throughout treatment, monitor patients for skin reactions[1]

Consider PADCEV dose modifications or appropriate treatment. As clinically indicated, consider topical corticosteroids and antihistamines[1]

Refer for specialized dermatology care for suspected SJS, TEN or for Grade 3 skin reactions.[1,3]

OTHER CONSIDERATIONS FOR SKIN REACTIONS WHILE ON ANTICANCER TREATMENTS[4]

Treatment strategies for rash:

- Applying fragrance-free, unscented, and hypoallergenic cream-based moisturizers to keep the area hydrated
- Consultation with their care team for specific recommendations on topical therapies, such as steroid creams or other anti-inflammatory ingredients
- Soaking in mixtures containing oatmeal, baking soda, or bath oil to help manage itchy or irritated skin
- Using cool cloths to help relieve pain and swelling

General advice for skin care during and after cancer treatment may include:

- Using mild soaps and skin cleansers
- Bathing with warm (not hot) water
- Applying sunscreen (SPF ≥30)
- Maintaining proper hydration
- Avoiding harsh chemicals that can irritate the skin

These considerations come from professionals and organizations that support cancer care; they are not based on studies with PADCEV.

SPF=sun protection factor.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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. 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. 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.

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without preexisting 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 DKA 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. 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.

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 intravenous pembrolizumab for the treatment of MIBC, 7% of the 570 patients treated with combination therapy had pneumonitis/ILD of any grade and 1.8% had Grade 3-4. The median time to onset of any grade pneumonitis/ILD was 3.2 months (range: 0.7 to 13 months).

When PADCEV was given in combination with intravenous pembrolizumab for the treatment of la/mUC, 10% of the 564 patients had pneumonitis/ILD of any grade and 4% had Grade 3-4. A fatal event of pneumonitis/ILD occurred in 2 patients (0.4%). 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.

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Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Peripheral neuropathy (PN) When PADCEV was given in combination with intravenous pembrolizumab for the treatment of MIBC, 42% of the 570 patients treated with combination therapy had PN of any grade, 14% had Grade 2 neuropathy, and 3% had Grade 3 neuropathy. The median time to onset of Grade ≥2 PN was 4.9 months (range: 0.2 to 23 months). Of the patients who experienced neuropathy and had data regarding resolution (n=239), 41% had complete resolution, and 59% of patients had residual neuropathy at last evaluation. Of the patients with residual neuropathy at last evaluation, 30% (42/142) had Grade ≥2 neuropathy.

When PADCEV was given in combination with intravenous pembrolizumab for the treatment of la/mUC, 67% of the 564 patients had PN of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The median time to onset of Grade ≥2 PN was 6 months (range: 0.3 to 25 months). 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.

PN 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. PN occurred in patients treated with PADCEV with or without preexisting PN. The median time to onset of Grade ≥2 PN was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients. 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 PN and consider dose interruption or dose reduction of PADCEV when PN occurs. Permanently discontinue PADCEV in patients who develop Grade ≥3 PN.

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.

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.

Embryo-fetal toxicity PADCEV can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment 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.

ADVERSE REACTIONS

Most common adverse reactions, including laboratory abnormalities (≥20%):

- **PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC:** decreased hemoglobin, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), rash, increased creatinine, decreased lymphocytes, fatigue, pruritus, decreased sodium, PN, increased potassium, diarrhea, alopecia, dysgeusia, decreased appetite, nausea, constipation, urinary tract infection (UTI), dry eye, increased glucose, decreased weight, decreased potassium, hyperglycemia, decreased phosphate, and decreased neutrophils.
- **PADCEV in combination with intravenous pembrolizumab for the treatment of la/mUC:** increased AST, increased creatinine, rash, increased glucose, PN, increased lipase, decreased lymphocytes, increased ALT, 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, UTI, and decreased platelets.
- **PADCEV as a single agent:** increased glucose, increased AST, decreased lymphocytes, increased creatinine, rash, fatigue, PN, decreased albumin, decreased hemoglobin, alopecia, decreased appetite, decreased neutrophils, decreased sodium, increased ALT, decreased phosphate, diarrhea, nausea, pruritus, increased urate, dry eye, dysgeusia, constipation, increased lipase, decreased weight, decreased platelets, abdominal pain, and dry skin.

EV-304 Study: Patients with cisplatin-eligible MIBC (PADCEV in combination with intravenous pembrolizumab)

- **Neoadjuvant phase:** Of a total of 403 patients, **serious adverse reactions** occurred in 27% of patients receiving PADCEV in combination with intravenous pembrolizumab; the most common (≥1.5%) were rash (3.2%), pneumonitis/ILD (2.2%), and diarrhea (1.7%). **Fatal adverse reactions** occurred in 1.7% of patients, including multiple organ dysfunction syndrome (0.5%) and COVID-19 pneumonia, cardiac arrest, pneumonia, septic shock, and urosepsis (0.2% each). Additional fatal adverse reactions were reported in 2 patients in the post-surgery phase before adjuvant treatment started, including pneumonia and sepsis (1 patient each). **Adverse reactions leading to discontinuation** of PADCEV in the neoadjuvant phase occurred in 21% of patients; the most common (≥1%) were PN (5%) and rash (3.5%). **Adverse reactions leading to dose interruption** of PADCEV in the neoadjuvant phase occurred in 35% of patients; the most common (≥2%) were rash (10%), increased ALT (4%), neutropenia (3.7%), hyperglycemia (3%). **Adverse reactions leading to dose reduction** of PADCEV in the neoadjuvant phase occurred in 15% of patients; the most common (≥1%) were rash (9%) and pruritus (2%). Of the 403 patients in the PADCEV in combination with intravenous pembrolizumab arm who received neoadjuvant treatment, thirteen (3.2%) patients did not receive surgery due to adverse reactions. The **adverse reactions that led to cancellation of surgery** were multiple organ dysfunction syndrome (0.5%) and adenocarcinoma of colon, COVID-19 pneumonia, cardiac arrest, chronic obstructive pulmonary disease, coronary artery disease, glomerulonephritis, immune-mediated lung disease, myocarditis, pneumonia, pneumonitis, and urosepsis (0.2% each). Of the 351 patients who received neoadjuvant treatment with PADCEV in combination with intravenous pembrolizumab and underwent radical cystectomy (RC), 26 (7%) patients experienced delay of surgery due to adverse reactions.
- **Adjuvant phase:** Of the 351 patients who underwent surgery, 225 patients received adjuvant treatment with PADCEV with or without intravenous pembrolizumab. Of the 126 patients who did not receive adjuvant PADCEV, discontinuation of PADCEV prior to the adjuvant phase was due to an adverse event in 65 patients. **Serious adverse reactions** occurred in 36% of patients receiving PADCEV; the most common (≥1.5%) included UTI (8%), sepsis (2.2%), and diarrhea, hyperglycemia, pneumonitis/ILD, and urosepsis (1.8% each). **Fatal adverse reactions** occurred in 3.1% of patients and included cardiac arrest, death, duodenal ulcer perforation, acute pancreatitis, renal failure, small cell lung cancer, and toxic shock syndrome (0.4% each). **Adverse reactions leading to discontinuation** of PADCEV in the adjuvant phase occurred in 16% of patients; the most common (≥1%) were rash (3.6%), PN (1.8%), and UTI (1.3%). **Adverse reactions leading to dose interruption** of PADCEV in the adjuvant phase occurred in 34% of patients; the most common (≥2%) were diarrhea and UTI (5% each), rash (4%), and COVID-19 (2.7%). **Adverse reactions leading to dose reduction** of PADCEV in the adjuvant phase occurred in 5% of patients; the most common (>1%) included rash (1.3%).

EV-303 Study: Patients with cisplatin-ineligible MIBC (PADCEV in combination with intravenous pembrolizumab)

- **Neoadjuvant phase:** Of a total of 167 patients, **serious adverse reactions** occurred in 27% of patients receiving PADCEV in combination with intravenous pembrolizumab; the most frequent (≥2%) were UTI (3.6%) and hematuria (2.4%). **Fatal adverse reactions** occurred in 1.2% of patients including myasthenia gravis and TEN (0.6% each). Additional fatal adverse reactions were reported in 2.7% of patients in the post-surgery phase before adjuvant treatment started, including sepsis and intestinal obstruction (1.4% each). **Adverse reactions leading to discontinuation** of PADCEV occurred in 22% of patients; the most common (≥1%) were rash (4.8%), PN (2.4%), and diarrhea, dysgeusia, fatigue, pruritus, and TEN (1.2% each). **Adverse reactions leading to dose interruption** of PADCEV occurred in 29% of patients; the most common (≥2%) were rash (8%), neutropenia (3.6%), hyperglycemia (3%), and fatigue and PN (2.4% each). **Adverse reactions leading to dose reduction** of PADCEV occurred in 13% of patients; the most common (≥1%) were rash (4.8%), pruritus (1.8%), and

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Important Safety Information (cont'd)

ADVERSE REACTIONS (cont'd)

PN, increased ALT, increased AST, decreased appetite, fatigue, neutropenia, and decreased weight (1.2% each). Seven (4.2%) patients did not receive surgery due to adverse reactions. The **most common adverse reactions that led to cancellation of surgery** were acute myocardial infarction, bile duct cancer, colon cancer, respiratory distress, UTI and deaths due to myasthenia gravis and TEN (0.6% each). Of the 146 patients who received neoadjuvant treatment with PADCEV in combination with intravenous pembrolizumab and underwent RC, six (4.1%) patients experienced delay of surgery due to adverse reactions.

- **Adjuvant phase:** Of the 146 patients who underwent surgery, 92 patients received adjuvant treatment with PADCEV with or without intravenous pembrolizumab. Of the 54 patients who did not receive adjuvant PADCEV, discontinuation of PADCEV prior to the adjuvant phase was due to an adverse event in 27 patients. **Serious adverse reactions** occurred in 43% of patients receiving PADCEV; the most frequent (≥2%) were UTI (8%), acute kidney injury, pyelonephritis, and urosepsis (4.3% each), and hypokalemia, intestinal obstruction, and sepsis (2.2% each). **Fatal adverse reactions** occurred in 8% of patients, including urosepsis, hemorrhage intracranial, death, myocardial infarction, multiple organ dysfunction syndrome, and pneumonia pseudomonal (1.1% each). **Adverse reactions leading to discontinuation** of PADCEV occurred in 28% of patients; the most common (≥2%) were PN (5%) and rash (4.3%). **Adverse reactions leading to dose interruption** of PADCEV occurred in 39% of patients; the most common (≥2%) were rash (7%), diarrhea and UTI (5% each), fatigue (4.3%), pruritus (3.3%), and PN and pyelonephritis (2.2% each). **Adverse reactions leading to dose reduction** of PADCEV occurred in 8% of patients; the most common (≥2%) was weight decreased (2.2%).

EV-302 Study: 440 patients with previously untreated la/mUC (PADCEV in combination with intravenous pembrolizumab)

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with intravenous pembrolizumab; the most common (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), UTI (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 intravenous 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 (≥2%) were PN (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 PN (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased ALT (3%), and pruritus (2.5%). **Adverse reactions leading to dose reduction** of PADCEV occurred in 42% of patients; the most common (≥2%) were rash (16%), PN (13%), and fatigue (2.7%).

EV-301 Study: 296 patients previously treated with a PD-1/L1 inhibitor and platinum-based chemotherapy for la/mUC (PADCEV monotherapy)

Serious adverse reactions occurred in 47% of patients treated with PADCEV; the most common (≥2%) were UTI, 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 (≥2%) were PN (5%) and rash (4%). **Adverse reactions leading to dose interruption** occurred in 61% of patients; the most common (≥4%) were PN (23%), rash (11%), and fatigue (9%). **Adverse reactions leading to dose reduction** occurred in 34% of patients; the most common (≥2%) were PN (10%), rash (8%), decreased appetite (3%), and fatigue (3%).

EV-201, Cohort 2 Study: 89 patients previously treated with a PD-1/L1 inhibitor and not eligible for cisplatin-based chemotherapy for la/mUC (PADCEV monotherapy)

Serious adverse reactions occurred in 39% of patients treated with PADCEV; the most common (≥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 (≥2%) was PN (7%). **Adverse reactions leading to dose interruption** occurred in 60% of patients; the most common (≥3%) were PN (19%), rash (9%), fatigue (8%), diarrhea (5%), increased AST (3%), and hyperglycemia (3%). **Adverse reactions leading to dose reduction** occurred in 49% of patients; the most common (≥3%) were PN (19%), rash (11%), and fatigue (7%).

DRUG INTERACTIONS

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 monomethyl auristatin E exposure, 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.

SPECIFIC POPULATIONS

Lactation Advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

Hepatic impairment Avoid the use of PADCEV in patients with moderate or severe hepatic impairment.

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References: 1. PADCEV. Package insert. Northbrook, IL: Astellas Pharma US, Inc; 2026. **2.** U.S. Department of Health and Human Services. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (MedDRA 28.0). Published July 22, 2025. Accessed October 8, 2025. **3.** Protocol for: Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med*. 2021;384(12):1125-1135. **4.** American Cancer Society. Rashes and skin changes. Updated September 12, 2024. Accessed May 9, 2025. https://www.cancer.org/cancer/managing-cancer/side-effects/hair-skin-nails/rashes-skin-changes.html

Please refer to the Prescribing Information for a full list of potential adverse reactions.

Please see Important Safety Information and full Prescribing Information, including BOXED WARNING.

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