

## Press Release

### **PADCEV™ (enfortumab vedotin-ejfv) Plus KEYTRUDA® (pembrolizumab) sBLA Granted FDA Priority Review for Treatment of Certain Patients with Muscle-Invasive Bladder Cancer**

*Results from the pivotal EV-303 trial demonstrated that, when used before and after surgery, the combination reduced the risk of recurrence, progression or death by 60% and the risk of death by 50% in cisplatin-ineligible patients with muscle-invasive bladder cancer*

*If approved, PADCEV plus KEYTRUDA could fundamentally change the treatment approach for patients with this disease*

**TOKYO, October 22, 2025** – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, “Astellas”) today announced that the U.S. Food and Drug Administration (FDA) accepted for priority review a supplemental Biologics License Application (sBLA) for PADCEV™ (enfortumab vedotin-ejfv) in combination with KEYTRUDA® (pembrolizumab) as a neoadjuvant treatment (before surgery) and then continued after radical cystectomy as adjuvant treatment (after surgery) for patients with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy.

Under the Prescription Drug User Fee Act (PDUFA), the FDA has set a target action April 7, 2026.

The sBLA submission was based on results from the pivotal Phase 3 EV-303 clinical trial (also known as KEYNOTE-905) evaluating PADCEV, a Nectin-4 directed antibody-drug conjugate, in combination with KEYTRUDA, a PD-1 inhibitor, as neoadjuvant and adjuvant treatment versus surgery alone, the current standard of care. Detailed results from EV-303, which showed the combination reduced the risk of recurrence, progression or death by 60% and the risk of death by 50% compared to surgery alone, were presented at [the 2025 European Society of Medical Oncology \(ESMO\) Congress](#). The safety results in EV-303 were consistent with those previously reported for this combination, and no new safety signals were identified.

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### **About the EV-303/KEYNOTE-905 Trial**

The EV-303 trial (also known as KEYNOTE-905) is an ongoing, open-label, randomized, three-arm, controlled, Phase 3 study evaluating neoadjuvant and adjuvant PADCEV in combination with KEYTRUDA or neoadjuvant and adjuvant KEYTRUDA versus surgery alone in patients with MIBC who are either not eligible for or declined cisplatin-based chemotherapy. Patients were randomized to receive either neoadjuvant and adjuvant KEYTRUDA (arm A), surgery alone (arm B) or neoadjuvant and adjuvant PADCEV in combination with KEYTRUDA (arm C).<sup>1</sup>

The primary endpoint of this trial is event-free survival (EFS) between arm C and arm B, defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes radical cystectomy (RC) surgery or failure to undergo RC surgery in participants with residual disease, gross residual disease left behind at the time of surgery, local or distant recurrence as assessed by imaging and/or biopsy or death due to any cause. Key secondary endpoints include overall survival (OS) and pathologic complete response (pCR) rate between arm C and arm B, as well as EFS, OS and pCR rate between arm A and arm B.<sup>1</sup>

For more information on the global EV-303 trial, go to [clinicaltrials.gov](https://clinicaltrials.gov).

### **About Muscle-Invasive Bladder Cancer**

Bladder cancer is the ninth most common cancer worldwide, diagnosed in more than 614,000 people each year globally, including an estimated 85,000 people in the U.S.<sup>2,3</sup> MIBC represents approximately 30% of all bladder cancer cases.<sup>4</sup> The standard treatment for patients with MIBC is neoadjuvant cisplatin-based chemotherapy followed by surgery, which has been shown to prolong survival.<sup>5</sup> However, up to half of patients with MIBC are not eligible to receive cisplatin and face limited treatment options, typically undergoing surgery without any systemic treatment.<sup>6</sup>

### **About PADCEV™ (enfortumab vedotin)**

PADCEV™ (enfortumab vedotin) is a first-in-class antibody-drug conjugate (ADC) that is directed against Nectin-4, a protein located on the surface of cells and highly expressed in bladder cancer.<sup>7</sup> Nonclinical data suggest the anticancer activity of PADCEV is due to its binding to Nectin-4-expressing cells, followed by the internalization and release of the anti-tumor agent monomethyl auristatin E (MMAE) into the cell, which result in the cell not reproducing (cell cycle arrest) and in programmed cell death (apoptosis).<sup>8</sup>

PADCEV plus KEYTRUDA is approved for the treatment of adult patients with locally advanced or metastatic urothelial cancer (la/mUC) regardless of cisplatin eligibility in the United States, the European Union, Japan and a number of other countries around the world. PADCEV is also approved as a single agent for the treatment of adult patients with la/mUC who have previously received a PD-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.<sup>8</sup>

### **PADCEV (enfortumab vedotin-ejfv) U.S. Indication & Important Safety Information**

#### **BOXED 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.

### **Indication**

PADCEV™, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced 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, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

### **PADCEV 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 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.

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.

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 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 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 at 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 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.

**Peripheral neuropathy (PN)** When PADCEV was given in combination with pembrolizumab, 67% of the 564 patients treated with combination therapy had PN of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The incidence of PN 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  $\geq 2$  PN was 6 months (range: 0.3 to 25 months).

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  $\geq 2$  PN was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients.

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  $\geq 3$  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 ( $\geq 20\%$ ) (PADCEV in combination with pembrolizumab)**

Increased aspartate aminotransferase (AST), increased creatinine, rash, increased glucose, PN, increased lipase, decreased lymphocytes, increased alanine aminotransferase (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, urinary tract infection and decreased platelets.

**Most common adverse reactions, including laboratory abnormalities ( $\geq 20\%$ ) (PADCEV monotherapy)**

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, dry skin.

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

**Serious adverse reactions** occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions ( $\geq 2\%$ ) 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 ( $\geq 2\%$ ) leading to discontinuation** of PADCEV 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 ( $\geq 2\%$ ) leading to dose interruption** of PADCEV were PN (22%), rash (16%), COVID19 (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 adverse reactions ( $\geq 2\%$ ) leading to dose reduction** of PADCEV were rash (16%), PN (13%) and fatigue (2.7%).

**EV-103 Study: 121 patients with previously untreated la/mUC who were not eligible for cisplatin-containing chemotherapy (PADCEV in combination with pembrolizumab)**

**Serious adverse reactions** occurred in 50% of patients treated with PADCEV in combination with pembrolizumab; the most common ( $\geq 2\%$ ) 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 ( $\geq 2\%$ ) were PN (20%) and rash (6%). **Adverse reactions leading to dose interruption** of PADCEV occurred in 69% of patients; the most common ( $\geq 2\%$ ) were PN (18%), rash (12%), increased lipase (6%), pneumonitis/ILD (6%), diarrhea (4.1%), acute kidney injury (3.3%), increased ALT (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), increased amylase (2.5%), anemia (2.5%), COVID19 (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 ( $\geq 2\%$ ) were PN (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

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

**Serious adverse reactions** occurred in 47% of patients treated with PADCEV; the most common ( $\geq 2\%$ ) 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 ( $\geq 2\%$ ) were PN (5%) and rash (4%). **Adverse reactions leading to dose interruption** occurred in 61% of patients; the most common ( $\geq 4\%$ ) were PN (23%), rash (11%), and fatigue (9%). **Adverse reactions leading to dose reduction** occurred

in 34% of patients; the most common ( $\geq 2\%$ ) were PN (10%), rash (8%), decreased appetite, and fatigue (3% each).

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

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

**For more information, please see the U.S. full Prescribing Information including BOXED WARNING for PADCEV [here](#).**

**About Astellas**

Astellas is a global life sciences company committed to turning innovative science into VALUE for patients. We provide transformative therapies in disease areas that include oncology, ophthalmology, urology, immunology and women's health. Through our research and development programs, we are pioneering new healthcare solutions for diseases with high unmet medical need. Learn more at [www.astellas.com](http://www.astellas.com).

**About the Pfizer, Astellas and Merck Collaboration**

Seagen and Astellas entered a clinical collaboration agreement with Merck to evaluate the combination of Seagen's and Astellas' PADCEV™ (enfortumab vedotin-efv) and Merck's KEYTRUDA® (pembrolizumab) in patients with previously untreated metastatic urothelial cancer. Pfizer Inc. successfully completed its acquisition of Seagen on December 14, 2023. KEYTRUDA is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside of the United States and Canada).

**Cautionary Notes**

*In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency*

exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties. Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

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<sup>6</sup> Esteban-Villarrubia J, Torres-Jiménez J, Bueno-Bravo C, García-Mondaray R, Subiela JD, Gajate P. Current and Future Landscape of Perioperative Treatment for Muscle-Invasive Bladder Cancer. *Cancers (Basel)*. 2023 Jan 17;15(3):566. doi: 10.3390/cancers15030566. PMID: 36765525; PMCID: PMC9913718.

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<sup>8</sup> PADCEV [package insert]. Northbrook, IL: Astellas Pharma US, Inc.