



U.S. FDA Grants Regular Approval and Expands Indication for PADCEV® (enfortumab vedotin-ejfv) for Patients with Locally Advanced or Metastatic Urothelial Cancer

***- Regular Approval Based on Overall Survival Results from Confirmatory EV-301 Trial -
- First and Only FDA-Approved Therapy for Urothelial Cancer Patients Who Are
Cisplatin-Ineligible and Have Previously Received One or More Prior Therapies, Based on
Cohort 2 of Pivotal EV-201 Trial -***

TOKYO and BOTHELL, Wash.– July 9, 2021 -- Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) and Seagen Inc. (Nasdaq:SGEN) today announced the U.S. Food and Drug Administration (FDA) granted PADCEV® (enfortumab vedotin-ejfv) regular approval in the U.S., in addition to approving a new indication for adult patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy. Cisplatin-ineligible patients typically have limited treatment options and a poor prognosis.

In 2019, the FDA granted accelerated approval for PADCEV for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy before (neoadjuvant) or after (adjuvant) surgery, or in a locally advanced or metastatic urothelial cancer setting. The conversion from accelerated approval to regular approval and the label expansion were based on two supplemental Biologics License Applications (sBLAs) reviewed under the Real-Time Oncology Review (RTOR) pilot program.

“The FDA’s decision to convert accelerated approval to regular approval was based on data from the Phase 3 EV-301 trial, which had a primary endpoint of overall survival for patients treated with PADCEV versus chemotherapy,” said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head, Astellas. “With PADCEV, for the first time, physicians can treat advanced urothelial cancer following treatment with a platinum-containing therapy and immunotherapy using an FDA-approved therapy that has demonstrated an overall survival benefit compared with chemotherapy.”

The EV-301 trial compared PADCEV to chemotherapy in adult patients (n=608) with locally advanced or metastatic urothelial cancer who were previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor. At the time of pre-specified interim analysis, patients who received PADCEV (n=301) in the trial lived a median of 3.9 months longer than those who received chemotherapy (n=307). Median overall survival was 12.9 vs. 9.0 months, respectively [Hazard Ratio=0.70 (95% Confidence Interval [CI]: 0.56, 0.89), p=0.001]. The most common all-grade adverse reactions (≥20%) included rash, fatigue, peripheral neuropathy, alopecia, decreased appetite, diarrhea, pruritus, nausea, constipation, dysgeusia, musculoskeletal pain, dry eye, pyrexia, abdominal pain and anemia.

“PADCEV is the first and only FDA-approved therapy for patients with locally advanced or metastatic urothelial cancer who have received immunotherapy and cannot receive cisplatin,” said Roger Dansey, M.D., Chief Medical Officer, Seagen. “Because of the FDA’s Real-Time Oncology Review, we’re able to make PADCEV available as early as possible to these patients, who have limited treatment options due to their age or comorbid conditions.”

Cohort 2 of the EV-201 trial evaluated PADCEV in patients (n=89) with locally advanced or metastatic urothelial cancer who had been previously treated with a PD-1/L1 inhibitor, had not received a platinum-containing chemotherapy in this setting, and were ineligible for cisplatin. After a median follow-up of 16 months, 51 percent of patients who received PADCEV had an objective response [95% CI: 39.8, 61.3] per blinded independent central review, with a median duration of response of 13.8 months [95% CI: 6.4, not reached]. The most common all-grade adverse reactions ($\geq 20\%$) included rash, peripheral neuropathy, alopecia, fatigue, decreased appetite, anemia, diarrhea, pruritus, weight decreased, nausea, dry eye and dysgeusia.

“Almost half of advanced bladder cancer patients cannot receive cisplatin-based chemotherapy. Many of these patients will receive first-line immunotherapy. If their cancer does not respond -- or if it progresses after prior response to immunotherapy -- there is an urgent need for more treatment options as there is currently no standard of care,” said Evan Y. Yu, M.D., Division of Oncology, Department of Medicine, University of Washington School of Medicine and a lead investigator for the EV-201 trial, in which all patients were previously treated with immunotherapy. “A new regulatory approval for enfortumab vedotin is an important clinical advance and can help serve this unmet need.”

Please see **Important Safety Information including BOXED WARNING** at the end of this press release.

Globally, approximately 573,000 new cases of bladder cancer and more than 212,000 deaths are reported annually.¹ PADCEV is the subject of a robust development program aimed at addressing unmet needs across the continuum of urothelial cancer and in other solid tumors.

The FDA’s RTOR program aims to explore a more efficient review process to ensure that safe and effective treatments are available to patients as early as possible. The agency’s review was also conducted as part of Project Orbis, an initiative of the FDA Oncology Center of Excellence that provides a framework for concurrent submission and review of oncology drugs among participating international health authorities. Through Project Orbis, health authorities in Australia and Canada are continuing to review data from EV-301 and EV-201 for initial registrations.

About the EV-301 Trial

The EV-301 trial ([NCT03474107](#)) is a global, multicenter, open-label, randomized phase 3 trial designed to evaluate enfortumab vedotin versus physician's choice of chemotherapy (docetaxel, paclitaxel or vinflunine) in 608 patients with locally advanced or metastatic urothelial cancer who were previously treated with a PD-1/L1 inhibitor and platinum-based therapies.² The primary endpoint is overall survival and secondary endpoints include progression-free survival, overall response rate, duration of response and disease control rate, as well as assessment of safety/tolerability and quality-of-life parameters. Results were published in the [New England Journal of Medicine](#).

About the EV-201 Trial

The EV-201 trial ([NCT03219333](#)) is a single-arm, multi-cohort, multicenter, pivotal phase 2 clinical trial of enfortumab vedotin for patients with locally advanced or metastatic urothelial cancer who have been previously treated with a PD-1 or PD-L1 inhibitor, including those who have also been treated with a platinum-containing chemotherapy (Cohort 1) and those who have not received a platinum-containing chemotherapy in this setting and who are ineligible for cisplatin (Cohort 2). The trial enrolled 125 patients in Cohort 1 and 89 patients in Cohort 2 at multiple centers internationally.³ The primary endpoint is confirmed objective response rate per blinded independent central review. Secondary endpoints include assessments of duration of response, disease control rate, progression-free survival, overall survival, safety and tolerability. Results of Cohort 2 were published in the [Lancet Oncology](#).

About PADCEV® (enfortumab vedotin-ejfv)

PADCEV 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.^{4,5} 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).⁴ PADCEV is co-developed by Astellas and Seagen.

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.

U.S. 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, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.⁴

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 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculo-papular 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). 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. 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 or TEN or for severe (Grade 3) skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN, or for 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, 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). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients. 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 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). 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.

Peripheral neuropathy (PN) 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. PN occurred in patients treated with PADCEV with or without preexisting PN. The median time to onset of Grade ≥2 PN was 4.6 months (range: 0.1 to 15.8 months). Neuropathy led to treatment discontinuation in 5% of patients. Monitor patients for symptoms of new or worsening peripheral neuropathy 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 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.

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.

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 ($\geq 20\%$)

Rash, aspartate aminotransferase (AST) increased, glucose increased, creatinine increased, fatigue, PN, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase (ALT) increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin.

EV-301 Study: 296 patients previously treated with a PD-1/L1 inhibitor and platinum-based chemotherapy.

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 (1.0%), 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 ($\geq 2\%$) 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). Clinically relevant adverse reactions ($< 15\%$) include vomiting (14%), AST increased (12%), hyperglycemia (10%), ALT increased (9%), pneumonitis (3%) and infusion site extravasation (0.7%).

EV-201, Cohort 2 Study: 89 patients previously treated with a PD-1/L1 inhibitor and not eligible for platinum-based chemotherapy.

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 (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%), AST increased 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%). Clinically relevant adverse reactions ($< 15\%$) include vomiting (13%), AST increased (12%), lipase increased (11%), ALT increased (10%), pneumonitis (4%) and infusion site extravasation (1%).

Drug Interactions

Effects of other drugs on PADCEV (*Dual P-gp and Strong CYP3A4 Inhibitors*)

Concomitant use with a 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 at least 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 full Prescribing Information including BOXED WARNING for PADCEV [here](#).

About Astellas

Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+[®] healthcare solutions that combine our expertise and knowledge with cutting-edge technology in different fields of external partners. Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into value for patients. For more information, please visit our website at <https://www.astellas.com/en>.

About Seagen

Seagen Inc. is a global biotechnology company that discovers, develops and commercializes transformative cancer medicines to make a meaningful difference in people's lives. Seagen is headquartered in the Seattle, Washington area, and has locations in California, Canada, Switzerland and the European Union. For more information on our marketed products and robust pipeline, visit www.seagen.com and follow @SeagenGlobal on Twitter.

About the Astellas and Seagen Collaboration

Astellas and Seagen are co-developing enfortumab vedotin under a 50:50 worldwide development and commercialization collaboration. In the United States, Astellas and Seagen co-promote enfortumab vedotin under the brand name PADCEV[®] (enfortumab vedotin-ejfv). In the Americas outside the US, Seagen holds responsibility for commercialization activities and regulatory filings. Outside of the Americas, Astellas holds responsibility for commercialization activities and regulatory filings.

Astellas 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.

Seagen Forward Looking Statements

Certain statements made in this press release are forward looking, such as those, among others, relating to the therapeutic potential of PADCEV, including its efficacy, safety and therapeutic uses. Actual results or developments may differ materially from those projected or implied in these forward-looking statements. Factors that may cause such a difference include, without limitation, the possibility that utilization and adoption of PADCEV in its additional labeled indication by prescribing physicians may be limited by physician awareness, the extent of reimbursement, impacts related to the COVID-19 pandemic

or other factors; and that setbacks in the development and commercialization of PADCEV could occur as a result of the difficulty and uncertainty of pharmaceutical product development, the failure of ongoing and subsequent clinical trials to establish sufficient efficacy, the risk of adverse events or safety signals or as a result of adverse regulatory actions. More information about the risks and uncertainties faced by Seagen is contained under the caption “Risk Factors” included in the company’s Quarterly Report on Form 10-Q for the quarter ended March 31, 2021 filed with the Securities and Exchange Commission. Seagen disclaims any intention or obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Astellas Contacts:

For Media

Chris Goldrick
Associate Director, Portfolio Communications
(847) 224-3014
chris.goldrick@astellas.com

For Investors

Astellas Pharma Inc.
Corporate Advocacy & Relations
TEL: +81-3-3244-3201

Seagen Contacts:

For Media

David Caouette
Vice President, Corporate Communications
(310) 430-3476
dcaouette@seagen.com

For Investors

Peggy Pinkston
Senior Vice President, Investor Relations
(425) 527-4160
ppinkston@seagen.com

References

¹ World Health Organization, International Agency for Research on Cancer. Globocan 2020 world fact sheet. <https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>. Accessed June 29, 2021.

² Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med*. 2021; 10.1056/NEJMoa2035807.

³ Yu EY, Petrylak DP, O’Donnell PH, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicenter, single-arm, phase 2 trial. *The Lancet Oncology*. 2021: S1470-2045(21)00094-2.

⁴ PADCEV [package insert]. Northbrook, Ill.: Astellas Pharma US, Inc.

⁵ Challita-Eid P, Satpayev D, Yang P, et al. Enfortumab Vedotin Antibody-Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models. *Cancer Res* 2016;76(10):3003-13.