Astellas and Seagen Receive Positive CHMP Opinion for PADCEV™ (enfortumab vedotin) in Locally Advanced or Metastatic Urothelial Cancer

- If approved, PADCEV would be the first medicine for patients in the EU who have received prior platinum-based chemotherapy and a PD-1/L1 inhibitor -

TOKYO and BOTHELL, Wash. – December 17, 2021 -- Astellas Pharma Inc. (TSE:4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") and Seagen Inc. (Nasdaq:SGEN) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion, recommending approval of the antibody-drug conjugate (ADC) PADCEV™ (enfortumab vedotin) as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a PD-1/L1 inhibitor.[1]

Urothelial cancer is the most common type of bladder cancer.[2] In Europe, an estimated 204,000 people were diagnosed with urothelial cancer in 2020, and more than 67,000 died as a result of the disease.[3] If approved by the European Commission (EC), enfortumab vedotin will be the first ADC authorized in the European Union for people living with advanced urothelial cancer.

"People with advanced bladder cancer have few treatment options after platinum-based chemotherapy and immunotherapy," said Ahsan Arozullah, M.D., M.P.H., Vice President, Medical Sciences-Oncology, Astellas. "The CHMP's positive opinion is an important step as we work to expand availability of enfortumab vedotin as quickly as possible."

The CHMP recommendation is based on data from the global phase 3 EV-301 trial, which evaluated enfortumab vedotin versus chemotherapy in adult patients with locally advanced or metastatic urothelial cancer who were previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor. Results from the trial, which had a primary endpoint of overall survival, were published in the *New England Journal of Medicine*.

The positive opinion from the CHMP will now be reviewed by the EC. EC decisions are valid in the European Union Member States, as well as Iceland, Norway and Liechtenstein.[4]

About Urothelial Cancer
Urothelial cancer is the most common type of bladder cancer (90 percent of cases), and can also be found in the renal pelvis (where urine collects inside the kidney), ureter (tube that connects the kidneys to the bladder) and urethra.[2] Globally, approximately 573,000 new cases of bladder cancer and 212,000 deaths are reported annually.[3]

About the EV-301 Trial
The EV-301 trial (NCT03474107) was 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.[5] The primary endpoint was overall survival and secondary endpoints included 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.

About Enfortumab Vedotin
Enfortumab vedotin is an antibody-drug conjugate (ADC) that is directed against Nectin-4, a protein located on the surface of cells and highly expressed in bladder cancer.[6,7] Nonclinical data suggest the anticancer activity of enfortumab vedotin 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).[6]

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® 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.[5]

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 (≥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 (≥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 (≥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 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 (≥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 (≥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%), AST increased and hyperglycemia (3% each). Adverse reactions leading to dose reduction occurred in 49% of patients; the most common (≥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 enfortumab vedotin, including its efficacy, safety and therapeutic uses; and the

potential to obtain regulatory approval of enfortumab vedotin in the European Union. 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 enfortumab vedotin may not ultimately be approved in the European Union as monotherapy for the treatment of adult patients with advanced urothelial cancer who have previously received platinum containing chemotherapy and a PD-1/L1 inhibitor in a timely manner or at all; and that setbacks in the development and commercialization of enfortumab vedotin could occur as a result of the difficulty and uncertainty of pharmaceutical product development, failure to establish sufficient efficacy in clinical trials, the risk of adverse events or safety signals, adverse regulatory actions or other factors. 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 June 30, 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.

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