Astellas and Seagen Announce U.S. FDA Acceptance of Two Supplemental Biologics License Applications for PADCEV® (enfortumab vedotin-ejfv) in Locally Advanced or Metastatic Urothelial Cancer

- Priority Review Granted with Action Date of August 17 -

- Australia and Canada Regulators Will Review Applications as Part of FDA's Project Orbis -

TOKYO and BOTHELL, Wash. – April 19, 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) filed two supplemental Biologics License Application (sBLA) submissions for PADCEV® (enfortumab vedotin-ejfv) for review as part of the Real-Time Oncology Review (RTOR) pilot program. The applications were granted Priority Review, with a target action date of August 17, 2021. The review of both applications will also be conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence.

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. Project Orbis provides a framework for concurrent submission and review of oncology drugs among participating international partners. The first sBLA is based on the phase 3 EV-301 trial and seeks to convert PADCEV's accelerated approval to regular approval. The second sBLA, based on the pivotal trial EV-201's cohort 2, requests an expansion of the current indication to include patients with locally advanced or metastatic urothelial cancer who have been previously treated with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and are ineligible for cisplatin. Results from EV-301 were published in the *New England Journal of Medicine*. Results from EV-301 and EV-201 cohort 2 were presented at the 2021 American Society of Clinical Oncology Genitourinary Cancers Symposium.

"With our recent regulatory submissions, we intend to provide the highest level of clinical evidence supporting PADCEV use – overall survival data from a randomized phase 3 trial – and expand availability in multiple countries where there is unmet medical need," said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head, Astellas.

"These FDA filings, along with regulatory submissions outside of the United States under our collaboration with Astellas, are important steps in our shared goal of bringing PADCEV to more patients with advanced urothelial cancer," said Roger Dansey, M.D., Chief Medical Officer of Seagen.

Health authorities in Australia and Canada will evaluate data from EV-301 and EV-201 for initial registrations under Project Orbis. In March, the companies announced regulatory submissions in Japan and the European Union.

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.[1] Globally, approximately 573,000 new cases of bladder cancer and more than 212,000 deaths are reported annually.[2]

In 2019, PADCEV received accelerated approval in the U.S. 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. PADCEV is currently only approved for use in the U.S.

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 approximately 600 patients with locally advanced or metastatic urothelial cancer who were previously treated with a PD-1/L1 inhibitor and a platinum-based therapy.[3] 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.

About the EV-201 Trial
The EV-201 trial (NCT03219333) is a single-arm, dual-cohort, 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 128 patients in cohort 1 and 91 patients in cohort 2 at multiple centers internationally.[4] 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.

PADCEV (enfortumab vedotin-ejfv) U.S. Important Safety Information

Warnings and Precautions

Skin reactions: Severe cutaneous adverse reactions, including fatal cases of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (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 54% of the 310 patients treated with PADCEV in clinical trials. Twenty-six percent (26%) of patients had maculopapular rash and 30% had pruritus. Grade 3-4 skin reactions occurred in 10% of patients and included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In one clinical trial, the median time to onset of severe skin reactions was 0.8 months (range: 0.2 to 5.3). Of the patients who experienced rash, 65% had complete resolution and 22% had partial improvement.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines as clinically indicated. Withhold PADCEV and consider referral for specialized care for severe (Grade 3) skin reactions, suspected SJS, or TEN. Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia occurred in patients treated with PADCEV, including death and diabetic ketoacidosis, in those with and without pre-existing diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In one clinical trial, 8% of patients developed Grade 3-4 hyperglycemia. Patients with baseline hemoglobin A1C ≥8% were excluded. 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.

Peripheral neuropathy (PN), predominantly sensory, occurred in 49% of the 310 patients treated with PADCEV in clinical trials; 2% experienced Grade 3 reactions. In one clinical trial, peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 was 3.8 months (range: 0.6 to 9.2). Neuropathy led to treatment discontinuation in 6% of patients. At the time of their last evaluation, 19% had complete resolution, and 26% had partial improvement. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy.

Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes. Dry eye symptoms occurred in 36% of patients, and blurred vision occurred in 14% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.9 months (range: 0.3 to 6.2). 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 310 patients, 1.3% of patients experienced skin and soft tissue 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. One percent (1%) of patients 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

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, and sepsis (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). Adverse reactions leading to dose interruption occurred in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).

The most common adverse reactions (≥20%) were fatigue (56%), peripheral neuropathy (56%), decreased appetite (52%), rash (52%), alopecia (50%), nausea (45%), dysgeusia (42%), diarrhea (42%), dry eye (40%), pruritus (26%) and dry skin (26%). The most common Grade ≥3 adverse reactions (≥5%) were rash (13%), diarrhea (6%) and fatigue (6%).

Lab Abnormalities

In one clinical trial, Grade 3-4 laboratory abnormalities reported in ≥5% were: lymphocytes decreased (10%), hemoglobin decreased (10%), phosphate decreased (10%), lipase increased (9%), sodium decreased (8%), glucose increased (8%), urate increased (7%), neutrophils decreased (5%).

Drug Interactions

Effects of other drugs on PADCEV Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with 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 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 collaboration that was entered into in 2007 and expanded in 2009.

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 potential conversion of PADCEV's current accelerated approval in the U.S. to regular approval and the potential expansion of the current PADCEV label to include patients with locally advanced or metastatic urothelial cancer who have been previously treated with a PD-1/L1 inhibitor and are ineligible for cisplatin; the potential to obtain regulatory approvals in Japan, the European Union, Australia and Canada; and 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 the sBLA submissions based on the EV-301 and EV-201 second cohort clinical trials may not be ultimately approved by the FDA in a timely manner or at all; that the results of the EV-301 clinical trial may not be sufficient to convert PADCEV's accelerated approval in the U.S. to regular approval and that the results of the second cohort of the EV-201 clinical trial may not be sufficient to support the requested label expansion; that, even if PADCEV receives regular approval and even if the PADCEV label is expanded based on the results of the second cohort of the EV-201 clinical trial, the product labeling may not be as broad or desirable as requested or anticipated; and that regulatory approvals of PADCEV in Japan, the European Union, Australia and Canada may not be obtained or may not be obtained with product labeling that is as broad or desirable as requested or anticipated, 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 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 Annual Report on Form 10-K for the year ended December 31, 2020 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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