European Medicines Agency Accepts Marketing Authorization Application for Enfortumab Vedotin

- Enfortumab vedotin to be reviewed under accelerated assessment for the treatment of locally advanced or metastatic urothelial cancer -

TOKYO and BOTHELL, Wash. – March 26, 2021 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") and Seagen Inc. (Nasdaq:SGEN) today announced that a marketing authorization application (MAA) for enfortumab vedotin was accepted by the European Medicines Agency (EMA). The MAA requests review of enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. If approved, enfortumab vedotin would be the first antibody-drug conjugate (ADC) available in the European Union for people living with urothelial cancer.

Enfortumab vedotin will be reviewed under accelerated assessment, which means the EMA's Committee for Medicinal Products for Human Use (CHMP) can reduce the timeframe for evaluation.

The MAA is based on 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 for patients treated with PADCEV versus chemotherapy, were published in the *New England Journal of Medicine*.

"In the European Union, it is estimated that 118,000 people are diagnosed with urothelial cancer each year, and 52,000 die as a result of the disease," said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head, Astellas. "People with advanced urothelial cancer face an urgent need for new treatment options, which is reflected in the CHMP's decision to grant accelerated assessment. We will continue to work with the CHMP toward our goal of securing marketing authorization as soon as possible."

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.[1] Globally, approximately 549,000 new cases of bladder cancer and 200,000 deaths are reported annually.[2] In Europe, it is estimated that 118,000 patients are diagnosed with this form of cancer and 52,000 deaths are reported annually.[3]

Locally advanced and metastatic urothelial cancer is an aggressive disease that is associated with poor survival and high healthcare costs.[4] Five-year relative survival rates for metastatic disease are estimated to be approximately 7 percent.[5]

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 platinum-based therapies. 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.[6]

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.[7,8] 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).[8]

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 the Astellas and Seagen Collaboration
Astellas and Seagen Inc. 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 for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and who have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, 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, the risk of adverse events or safety signals, failure to establish sufficient efficacy in clinical trials, 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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