Press Release

Astellas Receives Positive CHMP Opinion for PADCEV™ (enfortumab vedotin) in combination with KEYTRUDA® (pembrolizumab) for First-Line Treatment of Advanced Bladder Cancer

- If approved, enfortumab vedotin in combination with pembrolizumab will be the first and only treatment to offer an alternative to platinum-containing chemotherapy, the current standard of care for those with unresectable or metastatic urothelial cancer

- Positive opinion is based on Phase 3 EV-302 clinical trial results which showed enfortumab vedotin in combination with pembrolizumab nearly doubled median overall survival compared to platinum-containing chemotherapy[1]

TOKYO, July 26, 2024 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") 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 PADCEV™ (enfortumab vedotin, an antibody-drug conjugate [ADC]) in combination with KEYTRUDA® (pembrolizumab, a PD-1 inhibitor) for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer, who are eligible for platinum-containing chemotherapy.[2]

Ahsan Arozullah, MD, MPH, Senior Vice President and Head of Oncology Development, Astellas
"Treatment options available to patients with unresectable or metastatic urothelial cancer are currently limited mainly to platinum-containing chemotherapy. The data underpinning the CHMP's approval recommendation show that this combination could change how clinicians manage first-line treatment of this disease. We are delighted that the CHMP recognized the potential for enfortumab vedotin in combination with pembrolizumab as first-line treatment for patients with unresectable or metastatic urothelial cancer."

The positive CHMP opinion is based on data from the Phase 3 EV-302 clinical trial (also known as KEYNOTE-A39) which showed enfortumab vedotin in combination with pembrolizumab significantly extends overall survival (OS) and progression-free survival (PFS) compared to platinum-containing chemotherapy in patients with previously untreated locally advanced or metastatic urothelial cancer (la/mUC). Treatment with the combination resulted in a median OS of 31.5 months (95% CI: 25.4-NR) compared to 16.1 months (95% CI: 13.9-18.3) with chemotherapy, representing a 53% reduction in risk of death (Hazard Ratio [HR]=0.47; 95% Confidence Interval [CI]:

0.38-0.58; P<0.00001). The median PFS of 12.5 months (95% CI: 10.4-16.6) with the combination compared to 6.3 months (95% CI: 6.2-6.5) with chemotherapy represents a 55% reduction in the risk of cancer progression or death (HR=0.45; 95% CI: 0.38-0.54; P<0.00001). During the EV-302 trial, approximately 30% of patients completed treatment with chemotherapy and then went on to receive maintenance therapy with avelumab, a PD-L1 inhibitor, which is reflective of current real world clinical practice.[1] Results were presented at the 2023 European Society for Medical Oncology (ESMO) Congress and published in the *New England Journal of Medicine*.

Europe has the highest rate of new bladder cancer cases in the world.[3] Every year, more than 165,000 people are diagnosed with the disease in the European Union (EU), and it claims the lives of over 50,000 people.[3]

Not only does bladder cancer affect a person's physical functioning throughout the disease journey, patients and caregivers also report significant impacts on quality of life and mental well-being which are often exacerbated by late detection and challenging pathways to diagnosis.[4]

The positive opinion will now be reviewed by the European Commission (EC), which has the authority to approve medicines in all 27 EU member states as well as Iceland, Liechtenstein and Norway.[5]

In December 2023, the U.S. Food and Drug Administration (FDA) approved enfortumab vedotin in combination with pembrolizumab for the treatment of adult patients with la/mUC.[6] In April 2022, the EC approved enfortumab vedotin as a monotherapy for the treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.[7]

Astellas has already reflected the impact from this result in its financial forecast for the current fiscal year ending March 31, 2025.

For more information, please see the press release "European Medicines Agency Validates Type II Variation Application for PADCEV™ (enfortumab vedotin) with KEYTRUDA® (pembrolizumab) for First-Line Treatment of Advanced Bladder Cancer" issued on January 29, 2024.

About EV-302

EV-302 is an ongoing, open-label, randomized, controlled Phase 3 trial, evaluating enfortumab vedotin in combination with pembrolizumab versus platinum-containing chemotherapy in patients with previously untreated la/mUC. The trial enrolled 886 patients with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemotherapy regardless of PD-L1 status. Patients were randomized to receive either enfortumab vedotin in combination with pembrolizumab or platinum-containing chemotherapy. The dual primary endpoints of this trial are OS and PFS per RECIST v1.1 by blinded independent central review (BICR). Select secondary endpoints include ORR per RECIST v1.1 by BICR, DOR per RECIST v1.1 by BICR, and safety.[1]

The most common (≥3%) Grade 3 or higher adverse events related to treatment with enfortumab vedotin and pembrolizumab were maculo-papular rash, hyperglycemia, neutropenia, peripheral sensory neuropathy, diarrhea, and anemia. The safety results in EV-302 are consistent with those previously reported with this combination in EV-103 in cisplatin-ineligible patients with la/mUC. No new safety issues were identified.[1]

The EV-302 trial is part of an extensive clinical program evaluating this combination in multiple stages of urothelial cancer and other solid tumors. Findings from EV-302 were presented at the 2023 European Society for Medical Oncology (ESMO) Congress and were published in the *New England Journal of Medicine*.

For more information on the EV-302 trial (NCT04223856) go to https://clinicaltrials.gov.

About Bladder and Urothelial Cancer
Urothelial cancer, or bladder cancer, begins in the urothelial cells, which line the urethra, bladder, ureters, renal pelvis, and some other organs.[8] Urothelial cancer accounts for 90% of all bladder cancers and can also be found in the renal pelvis, ureter, and urethra.[9,10] If cancer is not able to be treated with surgery, it is called unresectable.[11] If cancer has spread to surrounding organs or muscles, it is called locally advanced disease.[12] If cancer has spread to other parts of the body, it is called metastatic disease.[13] Approximately 12% of cases are unresectable locally advanced or metastatic urothelial cancer at diagnosis.[14]

Bladder cancer is diagnosed in approximately 614,000 people and causes 220,000 deaths worldwide each year.[15] In Europe, bladder cancer is the fifth most common cancer;[16] more than 165,000 people are diagnosed with the disease in the EU each year.[3] Continuous treatment and surveillance makes bladder cancer one of the most expensive cancer types over the lifetime of a patient and, in fact, have been shown to be the costliest cancer when compared to other malignancies.[17]

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.[7,18] 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).[7]

PADCEV is currently indicated in the EU as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.[7]

Ongoing Investigational Trials
EV-302 (NCT04223856) is an open-label, randomized, controlled Phase 3 trial, evaluating enfortumab vedotin in combination with pembrolizumab versus platinum-containing chemotherapy in patients with previously untreated locally advanced or metastatic urothelial cancer (la/mUC) who were eligible for cisplatin- or carboplatin-containing chemotherapy regardless of PD-L1 status.

EV-103 (NCT03288545) is an ongoing, multi-cohort, open-label, multicenter Phase 1b/2 trial investigating enfortumab vedotin alone or in combination with pembrolizumab and/or chemotherapy in first- or second-line settings in patients with la/mUC and in patients with muscle-invasive bladder cancer (MIBC).

EV-104 (NCT05014139) is a Phase 1 trial exploring enfortumab vedotin in patients with non-muscle invasive bladder cancer (NMIBC). The trial will be conducted in two-parts, assessing dose escalation and dose expansion with enfortumab vedotin when administered intravesically as a monotherapy.

Enfortumab vedotin in combination with pembrolizumab is being investigated in an extensive program in multiple stages of urothelial cancer, including two Phase 3 clinical trials in MIBC in EV-304 (NCT04700124, also known as KEYNOTE-B15) and EV-303 (NCT03924895, also known as KEYNOTE-905). The use of enfortumab vedotin in combination with pembrolizumab in second-line urothelial cancer and MIBC has not been proven safe or effective.

EV-202 (NCT04225117) is an ongoing, multi-cohort, open-label, multicenter Phase 2 trial investigating enfortumab vedotin alone in patients with previously treated advanced solid tumors. This trial also has a cohort that is investigating enfortumab vedotin in combination with pembrolizumab in patients with previously untreated recurrent / metastatic head and neck squamous cell carcinoma.

EV-203 (NCT04995419) is a Phase 2, multicenter, single-arm bridging trial in China designed to evaluate the efficacy, safety, and pharmacokinetic performance of enfortumab vedotin as treatment for patients in China. A total of 40 patients were enrolled in the trial.

Important Safety Information
For Important Safety Information for enfortumab vedotin please see the full Summary of Product Characteristics at: https://www.ema.europa.eu/en/documents/product-information/padcev-epar-product-information_en.pdf

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 the Astellas, Pfizer and MSD Collaboration
Astellas and Pfizer have a clinical collaboration agreement with MSD to evaluate the combination of Astellas' and Pfizer's PADCEV™ (enfortumab vedotin) and MSD's KEYTRUDA® (pembrolizumab) in patients with previously untreated metastatic urothelial cancer. 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).

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.

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