Press Release

Japan's Ministry of Health, Labour and Welfare Approves PADCEV™ (enfortumab vedotin) with KEYTRUDA® (pembrolizumab) for First-Line Treatment of Radically Unresectable Urothelial Carcinoma

- Approval based on the EV-302 trial where the treatment combination nearly doubled median overall survival and significantly extended progression free survival compared to platinum-containing chemotherapy, the current standard of care for first-line treatment of radically unresectable urothelial carcinoma[1]-

- Approval follows priority review designation from the Ministry of Health, Labour and Welfare, granted on the basis of the clinical usefulness of the treatment combination and the seriousness of the disease for which it is intended[2] -

TOKYO, September 24, 2024 – Astellas Pharma Inc. (TSE:4503, President and CEO: Naoki Okamura, "Astellas") today announced that Japan's Ministry of Health, Labour and Welfare (MHLW) has approved PADCEV™ (enfortumab vedotin [genetical recombination]) with MSD's KEYTRUDA® (pembrolizumab [genetical recombination]) as a combination therapy for the first-line treatment of adult patients with radically unresectable urothelial carcinoma. This is the first approved combination treatment for radically unresectable urothelial carcinoma in Japan to offer an alternative to platinum-containing chemotherapy, the current standard of care for first-line treatment.

In Japan, bladder cancer is the 9th most common cancer, with over 34,500 new cases diagnosed and 11,000 deaths reported from the disease in 2022.[3] Particularly poor outcomes are associated with the latter stages of the disease, with global five-year survival rates of 39% and 8% for locally advanced and metastatic urothelial cancer, respectively.[4]

The approval by the MHLW was supported by results from the Phase 3 EV-302 clinical trial (also known as KEYNOTE-A39) which explored the efficacy and safety of enfortumab vedotin in combination with pembrolizumab in patients with previously untreated locally advanced or metastatic urothelial cancer (la/mUC). Results showed that the treatment combination resulted in a median overall survival of 31.5 months (95% CI: 25.4-NR) compared to 16.1 months (95% CI: 13.9-18.3) with platinum-containing 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 progression-free survival 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). The safety results in EV-302 are consistent with those previously reported for this combination in EV-103 in cisplatin-ineligible patients with la/mUC. The most common (≥3%) Grade 3 or higher adverse events (AEs) related to treatment with enfortumab vedotin in combination with pembrolizumab were maculo-papular rash, hyperglycemia, neutropenia, peripheral sensory neuropathy, diarrhea, and anemia. No new safety issues were identified. 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.*[1]

Ahsan Arozullah, M.D., M.P.H., Senior Vice President, Head of Oncology Development, Astellas
"Today's approval by Japan's MHLW expands the benefits of treatment with enfortumab vedotin in combination with pembrolizumab to patients living with radically unresectable urothelial carcinoma in Japan. These patients will now have an alternative to platinum-containing chemotherapy to treat this devastating disease, helping to improve patient outcomes, extend lives and give further hope to the patients and families that we serve."

In addition to this latest approval, enfortumab vedotin in combination with pembrolizumab was approved by the European Commission in August 2024 for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer, who are eligible for platinum-containing chemotherapy. Furthermore, in December 2023, the U.S. Food and Drug Administration approved the use of the combination therapy for adult patients with locally advanced or metastatic urothelial cancer.

Astellas has already reflected the impact from the approval for enfortumab vedotin in Japan in its financial forecast for the current fiscal year ending March 31, 2025.

+++

About EV-302
The EV-302 trial is an open-label, randomized, controlled Phase 3 study, evaluating enfortumab vedotin in combination with pembrolizumab versus platinum-containing chemotherapy in patients with previously untreated la/mUC. The study 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 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 published in the *New England Journal of Medicine*.[1]

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.[5] Urothelial cancer accounts for 90% of global bladder

cancers and can also be found in the renal pelvis, ureter, and urethra.[6,7] If bladder cancer has spread to surrounding organs or muscles, it is called locally advanced disease.[8] If the cancer has spread to other parts of the body, it is called metastatic disease.[9] Globally, approximately 12% of cases are locally advanced or metastatic urothelial cancer at diagnosis.[10]

About PADCEV™ (enfortumab vedotin [genetical recombination])
PADCEV (enfortumab vedotin [genetical recombination]) 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.[11,12] Non-clinical 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).[11]

PADCEV is indicated in Japan as monotherapy for the treatment of adult patients with radically unresectable urothelial carcinoma that has progressed after anti-cancer chemotherapy, and in combination with KEYTRUDA® (pembrolizumab) for the first-line treatment of adult patients with radically unresectable urothelial carcinoma.[13]

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).

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-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.

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.

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.

Important Safety Information
For important Safety Information for PADCEV, please see the Package Insert.

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.

###

Contacts for inquiries or additional information:
For Media
Astellas Pharma Inc.
Corporate Communications
+81-3-3244-3201

For Investors
Astellas Pharma Inc.
Investor Relations
+81-3-3244-3202

[1] Powles T, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024;390:875-888.
[2] Pharmaceuticals and Medical Devices Agency. Drug Reviews. Available at: https://www.pmda.go.jp/english/review-services/reviews/0001.html. Last accessed: September 2024.
[3] International Agency for Research on Cancer. Global Cancer Observatory. Cancer Today: 2022. Available at: https://gco.iarc.who.int. Last accessed: August 2024.
[4] National Cancer Institute. Bladder Cancer Prognosis and Survival Rates. Available at: https://www.cancer.gov/types/bladder/survival. Last accessed: September 2024.
[5] National Cancer Institute. What is bladder cancer? (February 2023) Available at: https://www.cancer.gov/types/bladder. Last accessed: September 2024.
[6] Leow JJ, et al. Optimal management of upper tract urothelial carcinoma: Current perspectives. *Onco Targets Ther*. 2020;13:1-15.
[7] Petros FG. Epidemiology, clinical presentation, and evaluation of upper-tract urothelial carcinoma. *Transl Androl Urol*. 2020;9(4):1794-8.

[8] National Cancer Institute. NCI dictionary of cancer terms: Locally advanced cancer. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/locally-advanced-cancer. Last accessed: September 2024.
[9] American Cancer Society. If you have bladder cancer. (March 2024). Available at: https://www.cancer.org/cancer/types/bladder-cancer/if-you-have-bladder-cancer.html. Last accessed: September 2024.
[10] National Cancer Institute. Cancer stat facts: bladder cancer. Available at: https://seer.cancer.gov/statfacts/html/urinb.html. Last accessed: September 2024.
[11] European Medicines Agency. PADCEV EMA SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/padcev-epar-product-information_en.pdf. Last accessed: September 2024.
[12] Challita-Eid PM, 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.
[13] Astellas Press Release. Japan's MHLW Approves PADCEV® (enfortumab vedotin) for Advanced Urothelial Cancer. Available at: https://www.astellas.com/en/news/17206. Last accessed: September 2024.