



Astellas and Seagen Announce Positive Topline Results For PADCEV[®] (enfortumab vedotin-ejfv) with KEYTRUDA[®] (pembrolizumab) as First-Line Treatment for Advanced Urothelial Cancer

– Companies plan to discuss results with regulatory authorities –

TOKYO and BOTHELL, Wash.--July 26, 2022—Astellas Pharma Inc. (TSE:4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) and Seagen Inc. (Nasdaq:SGEN) today announced positive topline results from the phase 1b/2 EV-103 clinical trial (also known as KEYNOTE-869) Cohort K evaluating PADCEV[®] (enfortumab vedotin-ejfv) in combination with Merck’s anti-PD-1 therapy KEYTRUDA[®] (pembrolizumab) as first-line treatment in patients with unresectable locally advanced or metastatic urothelial cancer (la/mUC) who are ineligible to receive cisplatin-based chemotherapy. Merck is known as MSD outside the United States and Canada.

In patients treated with enfortumab vedotin and pembrolizumab, results demonstrated a 64.5% confirmed objective response rate (ORR) (95% CI: 52.7 to 75.1) per blinded independent central review (BICR), the primary endpoint of Cohort K. The median duration of response (DOR) per BICR was not reached. The most frequently reported treatment-emergent adverse events Grade 3 or greater that occurred in more than 5% of patients were rash maculo-papular, anemia, lipase increased, urinary tract infection, hyperglycemia, fatigue, neutropenia, hematuria, diarrhea, acute kidney injury, hyponatremia, chronic kidney disease, weight decreased, syncope, hypophosphatemia, pneumonitis, sepsis, and alanine aminotransferase increased. Overall, the results are generally consistent with previously reported efficacy and safety results of the EV-103 dose-escalation cohort and expansion Cohort A.¹ Additional Cohort K results will be reported at an upcoming scientific congress.

EV-103 Cohort K is a randomized cohort investigating enfortumab vedotin alone or in combination with pembrolizumab as first-line treatment in patients with unresectable la/mUC who are ineligible to receive cisplatin-based chemotherapy. Secondary endpoints include ORR per investigator assessment; DOR, disease control rate and progression-free survival per BICR and investigator assessment; overall survival; and assessment of safety.

Please see Important Safety Information at the end of this press release, including BOXED WARNING for enfortumab vedotin.

“Approximately half of patients with advanced urothelial carcinoma are ineligible for cisplatin-based chemotherapy,” said Ahsan Arozullah, M.D., M.P.H., Senior Vice President and Head of Development Therapeutic Areas, Astellas. “We intend to discuss Cohort K results with regulatory authorities as we seek to develop a new first-line treatment combination for these patients.”

“We are encouraged by the positive topline results of Cohort K for the combination of enfortumab vedotin and pembrolizumab in first-line locally advanced or metastatic urothelial cancer, and we look forward to sharing results at an upcoming medical meeting,” said Roger Dansey, M.D., interim CEO and Chief Medical Officer, Seagen.

Astellas, Seagen and Merck are investigating enfortumab vedotin plus pembrolizumab as part of an extensive collaboration, which also includes three Phase 3 studies: the EV-302/KEYNOTE-A39 trial intended to confirm these results, as well as EV-304/KEYNOTE-B15 and EV-303/KEYNOTE-905 in muscle-invasive bladder cancer.

In February 2020, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for enfortumab vedotin in combination with pembrolizumab for patients with unresectable la/mUC who are ineligible to receive cisplatin-based chemotherapy in the first-line setting. The designation is based on results from the dose-escalation cohort and expansion Cohort A of the phase 1b/2 trial, EV-103 ([NCT03288545](#)), evaluating patients with la/mUC who are ineligible to receive cisplatin-based chemotherapy treated in the first-line setting with enfortumab vedotin in combination with pembrolizumab.

About Bladder and Urothelial Cancer

It is estimated that approximately 83,730 people in the U.S. were diagnosed with bladder cancer in 2021.² Urothelial cancer accounts for 90% of all bladder cancers and can also be found in the renal pelvis, ureter and urethra.³ Globally, approximately 573,000 new cases of bladder cancer and 212,000 deaths are reported annually.⁴

About the EV-103 Trial (Cohort K)

The EV-103 trial ([NCT03288545](#)) is an ongoing, multi-cohort, open-label, multicenter phase 1b/2 trial of enfortumab vedotin alone or in combination with pembrolizumab and/or chemotherapy in first- or second-line settings in patients with locally advanced or metastatic urothelial cancer (la/mUC) and in patients with muscle-invasive bladder cancer.

Cohort K of the EV-103 trial is investigating enfortumab vedotin alone (n=73) or in combination with pembrolizumab (n=76) in adult patients with unresectable la/mUC who are ineligible for cisplatin-based chemotherapy and have received no prior treatment for la/mUC. The enfortumab vedotin monotherapy study arm is intended to characterize the activity of enfortumab vedotin alone in this patient population. Key outcome measures of EV-103 Cohort K are objective response rate (ORR) per blinded independent central review (BICR) using RECIST 1.1 and assessment of safety.

About PADCEV

PADCEV (enfortumab vedotin-ejfv) 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.⁵ Nonclinical data suggest the anticancer activity of PADCEV 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 $\geq 8\%$ 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 ($\geq 20\%$)

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 ($\geq 2\%$) 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 ($\geq 2\%$) were PN (5%) and rash (4%). Adverse reactions

leading to dose interruption occurred in 61% of patients; the most common ($\geq 4\%$) were PN (23%), rash (11%) and fatigue (9%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common ($\geq 2\%$) 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 ($\geq 3\%$) 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 ($\geq 2\%$) was PN (7%). Adverse reactions leading to dose interruption occurred in 60% of patients; the most common ($\geq 3\%$) 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 ($\geq 3\%$) 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 the company's marketed products and robust pipeline, visit www.seagen.com and follow @SeagenGlobal on Twitter.

About the Astellas, Seagen and Merck Collaboration

Astellas and Seagen entered a clinical collaboration agreement with Merck to evaluate the combination of Astellas' and Seagen's PADCEV[®] (enfortumab vedotin-ejfv) and Merck'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.

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 PADCEV alone or in combination, its possible efficacy, safety and therapeutic uses, plans to discuss Cohort K results with regulatory authorities and clinical development plans including planned and ongoing clinical trials. 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 data from the EV-103 trial may not be sufficient to support any regulatory approval; the risk of adverse events, including the potential for newly-emerging safety signals; adverse regulatory actions; delays, setbacks or failures in clinical development activities, the submission of regulatory applications and the regulatory review process for a variety of reasons, including the inherent difficulty and uncertainty of pharmaceutical product development; possible required modifications to clinical trials; the inability to provide information and institute safety mitigation measures as may be required by the FDA or other regulatory authorities from time to time; failure to properly conduct or manage clinical trials; and failure of clinical results to support continued development or regulatory approvals. 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 March 31, 2022 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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¹ C.J. Hoimes, J.E. Rosenberg et.al. EV-103: Initial results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. *Annals of Oncology* 30 (Supplement 5): v356–v402, 2019.

² American Cancer Society. Cancer Facts & Figures 2021. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf>. Accessed July 25, 2022.

³ American Society of Clinical Oncology. Bladder cancer: introduction (9-20). <https://www.cancer.net/cancer-types/bladder-cancer/introduction>. Accessed July 25, 2022.

⁴ International Agency for Research on Cancer. Cancer Tomorrow: Bladder. <http://gco.iarc.fr/tomorrow>. Accessed July 25, 2022.

⁵ Challita-Eid P, 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.

⁶ PADCEV [package insert]. Northbrook, IL: Astellas Pharma US, Inc.