



Astellas and Seagen Announce Initial Results of PADCEV[®] (enfortumab vedotin-ejfv) in Patients with Muscle-Invasive Bladder Cancer Not Eligible for Cisplatin Chemotherapy

– Late-breaking data from Cohort H of EV-103 trial to be presented at the 2022 ASCO Genitourinary Cancers Symposium –

– Activity, tolerability of enfortumab vedotin support ongoing investigation in Phase 3 trials–

TOKYO and BOTHELL, Wash. – February 14, 2022 -- Astellas Pharma Inc. (TSE:4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) and Seagen Inc. (Nasdaq:SGEN) today announced the initial results from Cohort H of the EV-103 trial investigating PADCEV[®] (enfortumab vedotin-ejfv) as a monotherapy in patients with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin-based chemotherapy. Data from this late-breaking abstract will be included in an oral presentation (Abstract 435) at the 2022 ASCO Genitourinary Cancers Symposium (ASCO GU) on February 18.

MIBC is a stage of bladder cancer signified by the tumor spreading into the muscle of the bladder wall. Treatment for MIBC typically combines cisplatin-based chemotherapy with radical cystectomy, or removal of the bladder, as well as pelvic lymph node dissection. Cohort H of the Phase 1b/2 EV-103 trial enrolled patients with MIBC who were eligible for surgical treatment, but ineligible for cisplatin-based chemotherapy. Patients received three cycles of neoadjuvant (prior to surgery) enfortumab vedotin on days one and eight of every three-week cycle.

Results from the preliminary analysis of 22 patients showed 36.4% had a pathologic complete response, the primary endpoint, displaying no signs of cancer upon microscopic examination of tissue cells removed during surgery. Half (50%) of all patients had a pathological downstaging, or reduction in tumor size, a secondary endpoint of the trial. All patients underwent surgery, and no surgeries were delayed following treatment with enfortumab vedotin. The most common ($\geq 20\%$) adverse events (AEs) related to treatment with enfortumab vedotin were fatigue (45.5%), alopecia (36.4%), dysgeusia (36.4%), diarrhea (27.3%), nausea (27.3%), peripheral sensory neuropathy (27.3%), dry eye (22.7%) and rash maculopapular (22.7%), consistent with the known safety profile of enfortumab vedotin.

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

“Neoadjuvant cisplatin-based chemotherapy, which is intended to shrink tumors prior to surgery, prolongs survival in patients with MIBC. However, up to half of these patients with MIBC are ineligible for cisplatin treatment and typically must undergo surgery without that treatment,” said Ahsan Arozullah, M.D., M.P.H., Vice President, Medical Sciences-Oncology, Astellas.

“Results from EV-103 Cohort H showed that, when patients received enfortumab vedotin prior to surgery, more than one-third displayed no evidence of cancer when their bladder was removed and examined microscopically for residual tumors,” said Daniel Petrylak, M.D., Yale School of Medicine Professor of

Medicine (Medical Oncology) and of Urology, Co-Leader, Cancer Signaling Networks, Yale Cancer Center, and principal investigator for EV-103 Cohort H. “After treatment with enfortumab vedotin, all patients proceeded to surgery. Given there is no standard of care for neoadjuvant treatment in cisplatin-ineligible patients, these results are important and support further research.”

“The initial findings from EV-103 Cohort H are encouraging, and we look forward to learning more from the Phase 3 studies evaluating enfortumab vedotin in muscle-invasive bladder cancer in combination with the anti-PD-1 therapy pembrolizumab,” said Marjorie Green, M.D., Senior Vice President and Head of Late-Stage Development at Seagen.

In addition to this trial, enfortumab vedotin is being investigated as a monotherapy and in combination with other therapies in clinical trials across lines of treatment and stages of bladder cancer.

Astellas and Seagen will also present updates from the broader enfortumab vedotin program in four posters at ASCO GU 2022, including:

- EV-302: A 2-arm, open-label, randomized controlled phase 3 trial of enfortumab vedotin in combination with pembrolizumab vs chemotherapy in previously untreated advanced urothelial carcinoma (aUC) (Trial in Progress) (Abstract TPS589)
- EV-103 Cohort L: Evaluating perioperative enfortumab vedotin monotherapy in cis-ineligible muscle invasive bladder cancer (MIBC) (Trial in Progress) (Abstract TPS587)
- Clinical pharmacology of the antibody-drug conjugate enfortumab vedotin in advanced urothelial carcinoma and other malignant solid tumors (Abstract 568)
- Systematic literature review (SLR) and network meta-analysis (NMA) of first-line therapies (1L) for locally advanced/metastatic urothelial carcinoma (la/mUC) (Abstract 570)

The abstract titles published in advance of the meeting can be found [here](#).

About Muscle-Invasive Bladder Cancer

Muscle-invasive bladder cancer, which makes up about 25% of bladder cancers, is a cancer that has spread into the muscle of the bladder wall and is more likely to spread to other parts of the body.^{1,2} Each year in the U.S., there are more than 83,000 new cases of bladder cancer diagnosed in men and women.² Survival rates are poor for muscle-invasive bladder cancer, with around 45% of patients surviving for 5 years regardless of the type of treatment.³

About the EV-103 Trial

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.

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.^{4,5} 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).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 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 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 EV-103 clinical trial and other ongoing or planned clinical trials for enfortumab vedotin; clinical development plans relating to enfortumab vedotin; and the therapeutic potential of enfortumab vedotin, including its possible efficacy, safety and therapeutic uses, including in MIBC. 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 ongoing and subsequent clinical trials of enfortumab vedotin may fail to establish sufficient efficacy; that adverse events or safety signals may occur; that adverse regulatory actions or other setbacks could occur as enfortumab vedotin advances in clinical trials even after promising results in earlier clinical trials; that setbacks in the development and commercialization of enfortumab vedotin could occur as a result of the difficulty and uncertainty of pharmaceutical product development; and 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, 2021 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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References

¹ Robertson AG, et.al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. *Cell* 2017; 171(3): 540-556. <https://doi.org/10.1016/j.cell.2017.09.007>.

² Urology Care Foundation. What is Muscle Invasive Bladder Cancer (MIBC). <https://www.urologyhealth.org/urology-a-z/m/muscle-invasive-bladder-cancer>. Accessed January 10, 2022.

³ James ND, et.al. Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer. *N Engl J Med* 2012; 366:1477-1488. DOI: 10.1056/NEJMoa1106106

⁴ PADCEV [package insert]. Northbrook, Ill.: Astellas Pharma US, Inc.

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.