FDA Grants Accelerated Approval to Astellas' and Seattle Genetics' PADCEV™ (enfortumab vedotin-ejfv) for People with Locally Advanced or Metastatic Urothelial Cancer, the Most Common Type of Bladder Cancer

- First-in-Class Antibody-Drug Conjugate Directed Against Nectin-4, a Protein Highly Expressed in Urothelial Tumors[1,2] -

- PADCEV is the First Treatment Approved for Locally Advanced or Metastatic Urothelial Cancer Following Treatment with Platinum-based Chemotherapy and a PD-1 or PD-L1 Inhibitor -

TOKYO and BOTHELL, Wash., December 18, 2019 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") and Seattle Genetics, Inc. (Nasdaq:SGEN) today announced that the U.S. Food and Drug Administration (FDA) granted accelerated approval to PADCEV™ for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy before (neoadjuvant) or after (adjuvant) surgery or in a locally advanced or metastatic setting. PADCEV is approved under the FDA's Accelerated Approval Program based on tumor response rate. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. PADCEV is the first FDA approved treatment in the U.S. for these patients. It 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.[1,3]

"Metastatic urothelial cancer is an aggressive and devastating disease with limited treatment options, and the approval of PADCEV is a significant advance for these patients who previously had limited options after initial therapies failed," said Jonathan E. Rosenberg, M.D., Medical Oncologist, Chief, Genitourinary Medical Oncology Service, Memorial Sloan Kettering Cancer Center in New York. "The PADCEV clinical trial enrolled a range of patients whose cancer was difficult to treat, including those whose disease had spread to the liver."

"The FDA approval of PADCEV is welcome news for patients with bladder cancer," said Andrea Maddox-Smith, Chief Executive Officer, Bladder Cancer Advocacy Network. "Though new medicines for bladder cancer have been approved in recent years, most people living with advanced stages of this disease face a difficult journey with few treatment options."

"This approval underscores our commitment to develop novel medicines that address unmet patient needs, and we're grateful to the patients and physicians whose participation led to this outcome," said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head, Astellas.

"PADCEV is the first antibody-drug conjugate approved for patients facing this aggressive disease, and it is the culmination of years of innovative work on this technology," said Roger Dansey, M.D., Chief Medical Officer, Seattle Genetics.

PADCEV was evaluated in the pivotal trial EV-201, a single-arm phase 2 multi-center trial that enrolled 125 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy.[1] In the study, the primary endpoint of confirmed objective response rate (ORR) was 44 percent per blinded independent central review (55/125; 95% Confidence Interval [CI]: 35.1, 53.2). Among patients treated with the single agent PADCEV, 12 percent (15/125) experienced a complete response, meaning no cancer could be detected at the time of assessment, and 32 percent (40/125) experienced a partial response, meaning a decrease in tumor size or extent of cancer in the body. The median duration of response (DoR), a secondary endpoint, was 7.6 months (95% CI: 6.3, not estimable [NE]). 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%). The most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). 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%).

The FDA's Accelerated Approval Program allows approval of a medicine based on a surrogate endpoint if the medicine fills an unmet medical need for a serious condition. A global, randomized phase 3 confirmatory clinical trial (EV-301) is underway and is also intended to support global registrations.

About PADCEV
PADCEV 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.[1,2] 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). PADCEV is co-developed by Astellas and Seattle Genetics.

PADCEV Support Solutions offers access and reimbursement support to help patients access PADCEV. For more information go to PADCEV Support Solutions at PADCEVSupportSolutions.com.

About Bladder and Urothelial Cancer
Approximately 80,000 people in the U.S. will be diagnosed with bladder cancer this year.[4] Urothelial cancer accounts for 90 percent of all bladder cancers and can also be found in the renal pelvis, ureter and urethra.[5]

Important Safety Information

Warnings and Precautions

- **Hyperglycemia** occurred in patients treated with PADCEV, including death and diabetic ketoacidosis (DKA), 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.

- **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), bullous dermatitis, exfoliative dermatitis, 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 for skin reactions. Consider appropriate treatment, such as topical corticosteroids and antihistamines for skin reactions, as clinically indicated. For severe (Grade 3) skin reactions, withhold PADCEV until improvement or resolution and administer appropriate medical treatment. Permanently discontinue PADCEV in patients that develop Grade 4 or recurrent Grade 3 skin reactions.

- **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, hemoglobin decreased, phosphate decreased, lipase increased, sodium decreased, glucose increased, urate increased, neutrophils decreased.

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 Astellas
Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. For more information, please visit our website at https://www.astellas.com/en.

About Seattle Genetics
Seattle Genetics, Inc. is an emerging multi-product, global biotechnology company that develops and commercializes transformative therapies targeting cancer to make a meaningful difference in people's lives. The company is headquartered in Bothell, Washington, and has a European office in Switzerland. For more information on our robust pipeline, visit www.seattlegenetics.com and follow @SeattleGenetics on Twitter.

About the Astellas and Seattle Genetics Collaboration
Seattle Genetics and Astellas are co-developing PADCEV (enfortumab vedotin) under a collaboration that was entered into in 2007 and expanded in 2009. Under the collaboration, the companies are sharing costs and profits on a 50:50 basis worldwide.

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.

Seattle Genetics Forward Looking Statements
Certain statements made in this press release are forward looking, such as those, among others, relating to the continued FDA approval of PADCEV™ (enfortumab vedotin-ejfv) for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1/L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting; the conduct of an ongoing randomized phase 3 confirmatory clinical trial (EV-301) intended to verify the clinical benefit of PADCEV and support global registrations; and the therapeutic potential of PADCEV including its efficacy, safety and therapeutic uses. 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 the possibility that EV-301 and subsequent clinical trials may fail to establish sufficient efficacy; that adverse events or safety signals may occur; that utilization and adoption of PADCEV by prescribing physicians may be limited by the availability and extent of reimbursement or other factors; and that adverse regulatory actions may occur. More information about the risks and uncertainties faced by Seattle Genetics is contained under the caption "Risk Factors" included in the company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 filed with the Securities and Exchange Commission. Seattle Genetics 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] Padcev [package insert]. Northbrook, IL: Astellas, Inc.
[2] Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. J Clin Oncol 2019;37(29):2592-600.
[3] 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.
[4] American Society of Clinical Oncology. Bladder cancer: introduction (10-2017). https://www.cancer.net/cance r-types/bladdercancer/introduction. Accessed 05-09-2019.
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