

## **Seattle Genetics Announces FDA Approval of ADCETRIS® (Brentuximab Vedotin) in Combination with Chemotherapy for Adults with Previously Untreated Stage III or IV Classical Hodgkin Lymphoma**

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*First FDA-Approved Regimen in Frontline Stage III or IV Classical Hodgkin Lymphoma in More Than 40 Years*

*FDA Approval Based on Clinical Trial Results from the Phase 3 ECHELON-1 Clinical Trial*

*Label Expansion Represents Fifth Indication for ADCETRIS in the U.S.; ECHELON-1 Trial Also Converts Prior Accelerated Approval to Regular Approval in Treatment of Relapsed Systemic Anaplastic Large Cell Lymphoma*

BOTHELL, Wash.--(BUSINESS WIRE)--Mar. 20, 2018-- [Seattle Genetics, Inc.](#) (Nasdaq: SGEN) announced today that the U.S. Food and Drug Administration (FDA) has approved ADCETRIS (brentuximab vedotin) in combination with chemotherapy in adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma. The approval is based on the successful outcome of the phase 3 ECHELON-1 clinical trial that compared ADCETRIS plus AVD (Adriamycin, vinblastine and dacarbazine) to ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine). In addition, data from the ECHELON-1 trial converted the U.S. accelerated approval of ADCETRIS for the treatment of adults with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one multi-agent chemotherapy regimen to regular approval. In October 2017, the FDA granted Breakthrough Therapy Designation (BTD) to ADCETRIS in combination with chemotherapy for the frontline treatment of patients with advanced classical Hodgkin lymphoma. The FDA also granted Priority Review for the supplemental Biologics License Application (BLA), and the Prescription Drug User Fee Act (PDUFA) target action date was May 1, 2018.

"The standard of care for treating newly diagnosed advanced Hodgkin lymphoma has not changed in more than four decades. For years, the physician community has been conducting clinical trials to identify improved regimens that are both less toxic and more effective to no avail," said Joseph M. Connors, M.D., FRCPC, Clinical Director, Center for Lymphoid Cancer at BC Cancer in Vancouver, Canada. "The ECHELON-1 study results demonstrated superior efficacy of the ADCETRIS plus chemotherapy regimen when compared to the standard of care while removing bleomycin, an agent that can cause unpredictable and sometimes

fatal lung toxicity, completely from the regimen. This represents a meaningful advance for this often younger patient population.”

This is the fifth FDA-approved indication for ADCETRIS, which also has regular approval for adult patients with: (1) classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation, (2) cHL after failure of auto-HSCT or failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, (3) sALCL after failure of at least one prior multi-agent chemotherapy regimen, and (4) primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.

“Currently, up to 30 percent of newly diagnosed advanced-stage classical Hodgkin lymphoma patients will experience disease progression after treatment with the current standard of care, representing a significant need for improved treatment options for these often younger patients,” said Clay Siegall, Ph.D., President and Chief Executive Officer of Seattle Genetics. “The ECHELON-1 trial was a bold, five-year effort to redefine the frontline treatment of Stage III/IV classical Hodgkin lymphoma and provide patients with a more effective treatment regimen. In the ECHELON-1 study, ADCETRIS plus AVD was shown to have superior efficacy to ABVD. With today’s FDA approval, the physician and patient community have a new treatment option for previously untreated Stage III or IV Hodgkin lymphoma patients. We want to thank all of the patients, physicians and their staff who participated in the ECHELON-1 trial which supported the FDA approval of this novel regimen.”

The FDA approval is based on positive results from a phase 3 trial called ECHELON-1 that were presented at the 59<sup>th</sup> American Society of Hematology (ASH) annual meeting in December 2017 with simultaneous publication in the *New England Journal of Medicine*. Results from the ECHELON-1 trial in 1,334 Stage III or IV classical Hodgkin lymphoma patients included:

- The trial achieved its primary endpoint with the combination of ADCETRIS plus AVD resulting in a statistically significant improvement in modified progression-free survival (PFS) versus the control arm of ABVD as assessed by an Independent Review Facility (IRF) (HR 0.77;

95% CI, 0.60-0.98; p-value=0.035). This corresponds to a 23 percent reduction in the risk of progression, death or need for additional anticancer therapy in patients not in complete response (CR) after frontline treatment.

- Overall survival (OS) was a key secondary endpoint and the rate of CR per IRF assessment at the end of the randomized regimen was a secondary endpoint. At the time of the modified PFS analysis, an interim OS analysis trended in favor of the ADCETRIS plus AVD arm, but did not demonstrate significant difference (HR 0.72; 95% CI, 0.44-1.17; p-value=0.19). The CR rate was 73 percent on the ADCETRIS plus AVD arm and 70 percent on the ABVD arm.
- The safety profile of ADCETRIS plus AVD in the ECHELON-1 trial was generally consistent with that known for the single-agent components of the regimen.
- The most common adverse events of any grade that occurred in at least 10 percent of patients in the ADCETRIS plus AVD arm were: anemia, neutropenia, peripheral sensory neuropathy, constipation, vomiting, diarrhea, pyrexia, decreased weight, stomatitis, abdominal pain, febrile neutropenia, bone pain, insomnia, decreased appetite, back pain, rashes/eruptions/exanthemas, dyspnea, peripheral motor neuropathy, and increased alanine aminotransferase. In both the ADCETRIS plus AVD and ABVD arms, the most common Grade 3 or 4 events were neutropenia, febrile neutropenia, and anemia.
- Based on ECHELON-1 clinical trial results, prophylactic growth factors (G-CSF) should be administered starting at cycle one for Stage III or IV classical Hodgkin lymphoma patients receiving ADCETRIS plus AVD.

### **About Classical Hodgkin Lymphoma**

Lymphoma is a general term for a group of cancers that originate in the lymphatic system. There are two major categories of lymphoma: Hodgkin lymphoma and non-Hodgkin lymphoma. Classical Hodgkin lymphoma is distinguished from other types of lymphoma by the presence of one characteristic type of cell, known as the Reed-Sternberg cell. The Reed-Sternberg cell expresses CD30.

According to the American Cancer Society, approximately 8,500 cases of Hodgkin lymphoma will be diagnosed in the United States during 2018 and more than 1,000 will die from the disease. Approximately half of all newly

diagnosed Hodgkin lymphoma patients have Stage III/IV disease. According to the Lymphoma Coalition, over 62,000 people worldwide are diagnosed with Hodgkin lymphoma each year and approximately 25,000 people die each year from this cancer.

### **About ADCETRIS**

ADCETRIS is being evaluated broadly in more than 70 clinical trials, including two ongoing phase 3 studies: the ECHELON-2 trial in frontline mature T-cell lymphomas and the CHECKMATE 812 trial of ADCETRIS in combination with Opdivo (nivolumab) for relapsed/refractory Hodgkin lymphoma.

ADCETRIS is an ADC comprising an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E (MMAE), utilizing Seattle Genetics' proprietary technology. The ADC employs a linker system that is designed to be stable in the bloodstream but to release MMAE upon internalization into CD30-expressing tumor cells.

ADCETRIS injection for intravenous infusion has received FDA regular approval for five indications in adult patients with: (1) previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy, (2) cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation, (3) cHL after failure of auto-HSCT or failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, (4) sALCL after failure of at least one prior multi-agent chemotherapy regimen, and (5) primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.

Health Canada granted ADCETRIS approval with conditions for relapsed or refractory Hodgkin lymphoma and sALCL in 2013, and non-conditional approval for post-autologous stem cell transplantation (ASCT) consolidation treatment of Hodgkin lymphoma patients at increased risk of relapse or progression.

ADCETRIS received conditional marketing authorization from the European Commission in October 2012. The approved indications in Europe are: (1) for the treatment of adult patients with relapsed or refractory CD30-positive Hodgkin lymphoma following ASCT, or following at least two prior

therapies when ASCT or multi-agent chemotherapy is not a treatment option, (2) the treatment of adult patients with relapsed or refractory sALCL, (3) for the treatment of adult patients with CD30-positive Hodgkin lymphoma at increased risk of relapse or progression following ASCT, and (4) for the treatment of adult patients with CD30-positive cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy.

ADCETRIS has received marketing authorization by regulatory authorities in 71 countries for relapsed or refractory Hodgkin lymphoma and sALCL. See select important safety information, including Boxed Warning, below.

Seattle Genetics and Takeda are jointly developing ADCETRIS. Under the terms of the collaboration agreement, Seattle Genetics has U.S. and Canadian commercialization rights and Takeda has rights to commercialize ADCETRIS in the rest of the world. Seattle Genetics and Takeda are funding joint development costs for ADCETRIS on a 50:50 basis, except in Japan where Takeda is solely responsible for development costs.

### **About Seattle Genetics**

Seattle Genetics is an innovative biotechnology company dedicated to improving the lives of people with cancer through targeted therapies. The company's industry-leading antibody-drug conjugate (ADC) technology harnesses the targeting ability of antibodies to deliver cell-killing agents directly to cancer cells. Seattle Genetics commercializes ADCETRIS® (brentuximab vedotin) for the treatment of several types of CD30-expressing lymphomas. The company is also advancing a robust pipeline of novel therapies for solid tumors and blood-related cancers designed to address significant unmet medical needs and improve treatment outcomes for patients. More information can be found at [www.seattlegenetics.com](http://www.seattlegenetics.com) and follow @SeattleGenetics on Twitter.

### **ADCETRIS (brentuximab vedotin) U.S. Select Important Safety Information BOXED WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**

**JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.**

### **Contraindication**

ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

### **Warnings and Precautions**

- **Peripheral neuropathy (PN):** ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
- **Anaphylaxis and infusion reactions:** Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.
- **Hematologic toxicities:** Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged ( $\geq 1$  week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis starting with Cycle 1 for previously untreated patients who receive ADCETRIS in combination with chemotherapy for Stage III or IV HL. Monitor complete blood counts prior to each ADCETRIS dose. Consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.
- **Serious infections and opportunistic infections:** Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.
- **Tumor lysis syndrome:** Closely monitor patients with rapidly proliferating tumor and high tumor burden.
- **Increased toxicity in the presence of severe renal impairment:** The frequency of  $\geq$ Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.
- **Increased toxicity in the presence of moderate or severe hepatic impairment:** The frequency of  $\geq$ Grade 3 adverse reactions and deaths



was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.

- **Hepatotoxicity:** Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.
- **PML:** Fatal cases of JC virus infection resulting in PML and death have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. Other possible contributory factors other than ADCETRIS include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- **Pulmonary toxicity:** Fatal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.
- **Serious dermatologic reactions:** Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- **Gastrointestinal (GI) complications:** Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

- **Embryo-fetal toxicity:** Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

**Most Common (≥20%) Adverse Reactions:** neutropenia, anemia, peripheral sensory neuropathy, nausea, fatigue, constipation, diarrhea, vomiting, and pyrexia.

#### **Drug Interactions**

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE).

#### **Use in Specific Populations**

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

**For additional Important Safety Information, including BOXED WARNING, please see the full Prescribing Information for ADCETRIS at [www.seattlegenetics.com](http://www.seattlegenetics.com) or [www.ADCETRIS.com](http://www.ADCETRIS.com).**

#### **Forward-Looking Statements**

Certain of the statements made in this press release are forward looking, such as those, among others, relating to the potential utilization of ADCETRIS (brentuximab vedotin) for patients with previously untreated Stage III or IV classical Hodgkin lymphoma. Actual results or developments may differ materially from those projected or implied in these forward-looking statements due to factors such as utilization and adoption of the approved treatment regimen by prescribing physicians, competitive conditions including the availability of alternative treatment regimens, the availability and extent of reimbursement, the risk of adverse events, and adverse regulatory action. More information about the risks and uncertainties faced by Seattle Genetics is contained under the caption "Risk Factors" included in the company's Annual Report on Form 10-K for the year ended December 31, 2017 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.

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