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U.S. FDA Approves Pfizer's ADCETRIS® Combination Regimen for the treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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- *Approval is based on positive data from the Phase 3 ECHELON-3 trial, which demonstrated ADCETRIS regimen reduced the risk of death by 37%, a statistically significant, clinically meaningful improvement in overall survival (OS), compared to lenalidomide and rituximab plus placebo*
- *ECHELON-3 is the first Phase 3 trial to demonstrate OS advantage over lenalidomide and rituximab plus placebo for patients with at least 2 prior lines of therapy with R/R diffuse large B-cell lymphoma* (*DLBCL)*
- *Milestone represents the eighth FDA-approved indication for ADCETRIS, reinforcing its use as a standard of care for certain lymphomas*

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) announced today that the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application (sBLA) for ADCETRIS® (brentuximab vedotin) in combination with lenalidomide and a rituximab product for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for autologous hematopoietic stem cell transplantation (auto-HSCT) or chimeric antigen receptor (CAR) T-cell therapy.

"Each year, more than 3,500 patients in the U.S. with this aggressive form of non-Hodgkin lymphoma experience treatment failure or relapse after two prior lines of therapy," said Roger Dansey, M.D., Chief Oncology Officer, Pfizer. "Today's approval further reinforces the important role of ADCETRIS as an existing standard of care with overall survival improvement shown for certain types of lymphomas, and now allows physicians to have an option beyond chemotherapy or CAR-Ts for patients with relapsed/refractory large B-cell lymphoma."

The approval is based on efficacy and safety data from the Phase 3 ECHELON-3 study, which demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) in patients with relapsed/refractory DLBCL who received ADCETRIS in combination with lenalidomide and rituximab. The study included patients who were heavily pre-treated, some of whom had received prior CAR-T therapy, and survival benefit was observed irrespective of CD30 expression.

"Patients with large B-cell lymphoma can face a challenging journey, with too many patients enduring multiple rounds of chemotherapy and even CAR-T therapy with limited success," said principal investigator Dr. Craig Portell, Associate Professor, University of Virginia. "For patients who have previously faced setbacks with other therapies, ADCETRIS provides a new therapeutic option with outpatient administration and proven safety and

efficacy.”

LBCL is a type of non-Hodgkin lymphoma (NHL), that affects immune cells called B lymphocytes, a type of white blood cell crucial to the body's immune system. DLBCL is the most common, aggressive and difficult-to-treat form of the disease. More than 25,000 cases of DLBCL are diagnosed each year in the United States, accounting for more than 25% of all lymphoma cases. Up to 40% of patients relapse or have refractory disease after frontline treatment, and more than 3,500 patients a year fail two prior lines of therapy and require third-line therapy. Despite recent treatment advances including bispecifics and CAR-T therapy, there remains a high unmet need for patients who are not eligible for these treatments or whose disease returns following treatment with these therapies.

The ECHELON-3 study showed that the ADCETRIS combination reduced patients’ risk of death by 37% compared to placebo in combination with lenalidomide and rituximab (HR 0.63 [95% CI: 0.445-0.891] p=0.0085). The OS benefit was consistent across levels of CD30 expression. Positive outcomes were also observed in key secondary endpoints, including overall response rate (ORR)? and progression-free survival (PFS).

The safety profile of ADCETRIS in ECHELON-3 was consistent with its known safety profile as presented in the U.S. prescribing information. The most frequently reported treatment-emergent adverse events (TEAEs) Grade 3 or higher for the ADCETRIS versus placebo arms were: neutropenia (43% vs 28%), thrombocytopenia (25% vs 19%) and anemia (22% vs 21%). Peripheral sensory neuropathy was infrequent and low grade for each arm with Grade 3 events of 4% vs 0%.

Detailed data from ECHELON-3 were published in *JCO Oncology Practice* on January 7, 2025 and presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting.

About ECHELON-3

ECHELON-3 is an ongoing, randomized, double-blind, multicenter Phase 3 study evaluating ADCETRIS plus lenalidomide and rituximab versus lenalidomide and rituximab plus placebo in adult patients with relapsed/refractory or transformed DLBCL, regardless of CD30 expression, who have received two or more prior lines of therapy and are ineligible for stem cell transplant (HSCT) or CAR-T therapy. The study also includes patients with hard-to-treat subtypes with poorer outcomes including double hit/triple hit lymphoma and patients with transformed disease. Patients may be ineligible to receive either HSCT or CAR-T therapy due to co-morbidities or financial, geographic, insurance, manufacturing issues. In this global study, 230 patients were randomized across North America, Europe and Asia-Pacific. The primary endpoint is OS in the intent to treat population, with key secondary endpoints of PFS and ORR as assessed by investigator. Other secondary endpoints include complete response rate, duration of response, safety and tolerability.

About Large B-cell Lymphoma

LBCL accounts for about 1/3 of cases of NHL, a type of cancer that starts in the lymphocytes and affects immune cells called B lymphocytes. LBCL occurs most often in older people, with a median age of 67 at diagnosis. About 60-70% of people have advanced-stage disease when diagnosed, and up to 40% have disease that relapses or becomes refractory to initial therapy, and more than 3,500 patients a year fail two prior lines of therapy and require third-line therapy.

DLBCL is the most common and aggressive type of LBCL and is difficult to treat. More than 25,000 cases of DLBCL are diagnosed each year in the United States, accounting for more than 25% of all lymphoma cases. DLBCL can develop spontaneously or as a result of diseases such as chronic lymphocytic lymphoma/small

lymphocytic lymphoma, follicular lymphoma, or marginal zone lymphoma.

About ADCETRIS

More than 55,000 patients have been treated with ADCETRIS in the U.S. since its first U.S. approval in 2011, and more than 140,000 patients have been treated with ADCETRIS globally.

ADCETRIS is an antibody-drug conjugate (ADC) comprised of a CD30-directed monoclonal antibody attached by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E (MMAE), utilizing Pfizer's 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-positive tumor cells.

ADCETRIS is approved in eight indications in the U.S.:

- Adult patients with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) NOS, DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are not eligible for auto-HSCT or chimeric antigen receptor (CAR) T-cell therapy, in combination with lenalidomide and a rituximab product (2025)
- Adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine (2018)
- Pediatric patients 2 years and older with previously untreated high risk cHL in combination with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide (2022)
- Adult patients with cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation (2015)
- Adult patients with cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates (2011)
- Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone (2018)
- Adult patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen. (2011)
- Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) after prior systemic therapy (2017)

Pfizer and Takeda jointly develop ADCETRIS. Under the terms of the collaboration agreement, Pfizer has U.S. and Canadian commercialization rights, and Takeda has rights to commercialize ADCETRIS in the rest of the world. Pfizer 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.

ADCETRIS® (brentuximab vedotin) for injection U.S. Important Safety Information

BOXED WARNING

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML, and death can occur in ADCETRIS-treated patients.

CONTRAINDICATION

Contraindicated with concomitant 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. Patients experiencing new or worsening PN may require a delay, change in dose, or discontinuation of ADCETRIS.

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 (?1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS.

Administer G-CSF primary prophylaxis beginning with Cycle 1 for adult patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV cHL or previously untreated PTCL or relapsed or refractory LBCL and pediatric patients who receive ADCETRIS in combination with chemotherapy for previously untreated high risk cHL.

Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently 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 infections.

Tumor lysis syndrome: Patients with rapidly proliferating tumor and high tumor burden may be at increased risk. Monitor closely and take appropriate measures.

Increased toxicity in the presence of severe renal impairment: The frequency of ?Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment. Avoid use in patients with severe renal impairment.

Increased toxicity in the presence of moderate or severe hepatic impairment: The frequency of ?Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment. 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 have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors

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 pre-existing GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

Hyperglycemia: Serious cases, such as new-onset hyperglycemia, exacerbation of pre-existing diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported with ADCETRIS. Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.

Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of this potential risk, and to use effective contraception during ADCETRIS treatment and for 2 months after the last dose of ADCETRIS. Advise male patients with female partners of reproductive potential to use effective contraception during ADCETRIS treatment and for 4 months after the last dose of ADCETRIS.

ADVERSE REACTIONS

The most common adverse reactions (?20%) in adult patients are peripheral neuropathy, nausea, fatigue, musculoskeletal pain, constipation, diarrhea, vomiting, pyrexia, upper respiratory tract infection, mucositis, abdominal pain, and rash. The most common laboratory abnormalities (?20%) in adult patients are decreased neutrophils, increased creatinine, decreased hemoglobin, decreased lymphocytes, increased glucose, increased ALT, and increased AST.

The most common Grade ?3 adverse reactions (?5%) in combination with AVEPC in pediatric patients were neutropenia, anemia, thrombocytopenia, febrile neutropenia, stomatitis, and infection.

DRUG INTERACTIONS

Concomitant use of strong CYP3A4 inhibitors has the potential to affect the exposure to monomethyl auristatin E (MMAE). Closely monitor adverse reactions.

USE IN SPECIAL POPULATIONS

Lactation: Breastfeeding is not recommended during ADCETRIS treatment.

Please see the full Prescribing Information, including **BOXED WARNING**, for ADCETRIS here. There may be a delay as the document is updated with the latest information. It will be available as soon as possible. Please check back for the updated full information shortly.

About Pfizer Oncology

At Pfizer Oncology, we are at the forefront of a new era in cancer care. Our industry-leading portfolio and extensive pipeline includes three core mechanisms of action to attack cancer from multiple angles, including small molecules, antibody-drug conjugates (ADCs), and bispecific antibodies, including other immune-oncology biologics. We are focused on delivering transformative therapies in some of the world's most common cancers, including breast cancer, genitourinary cancer, hematology-oncology, and thoracic cancers, which includes lung cancer. Driven by science, we are committed to accelerating breakthroughs to help people with cancer live better and longer lives.

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety, and value in the discovery, development, and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments, and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments, and local communities to support and expand access to reliable, affordable health care around the world. For 175 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on X at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.

Disclosure Notice

The information contained in this release is as of February 12, 2025. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer Oncology and ADCETRIS (brentuximab vedotin), including its potential benefits, an approval in the U.S. for ADCETRIS in combination with lenalidomide and rituximab for adults with relapsed/refractory large B-cell lymphoma and the ongoing investigational trial for ADCETRIS in combination with lenalidomide and rituximab, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of ADCETRIS; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when drug applications may be filed in particular jurisdictions for ADCETRIS for any potential indications; whether and when any applications that may be pending or filed for ADCETRIS may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether ADCETRIS will be commercially successful;

decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of ADCETRIS; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2023 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

Media Contact:
+1 (212) 733-1226
PfizerMediaRelations@pfizer.com

Investor Contact:
+1 (212) 733-4848
IR@pfizer.com

Source: Pfizer Inc.