Pfizer Logo

Takeda and Pfizer Announce Four-Year Results from Positive Phase 3 HD21 Trial of Additional ADCETRIS® (brentuximab vedotin) Combination in Frontline Hodgkin Lymphoma

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- Four-year Analysis Conducted by GHSG Reported ADCETRIS + ECADD Combination Improved Progression-Free Survival, Showing Superior Efficacy and Tolerable Safety Profile in Patients with Newly Diagnosed Stage IIb/III/IV classical Hodgkin Lymphoma vs eBEACOPP, a Current Standard of Care in This Setting in Europe
- The HD21 Study Adds to the Body of Evidence Supporting ADCETRIS as a Backbone Agent in the Treatment of Specific Lymphomas
- Results To Be Featured as Oral Presentations at ASCO and EHA 2024

OSAKA, Japan, CAMBRIDGE, Mass., and NEW YORK, June 1, 2024 – Takeda (TSE:4502/NYSE:TAK) and Pfizer (NYSE: PFE) today announced that the German Hodgkin Study Group (GHSG) will present positive results from the Phase 3 HD21 trial evaluating ADCETRIS® (brentuximab vedotin) in combination with chemotherapy as a late-breaking oral presentation at the 60th American Society of Clinical Oncology (ASCO) Annual Meeting (LBA7000) and at the 29th European Hematology Association (EHA) Annual Meeting (S225). The four-year analysis presented by the GHSG showed superior progression-free survival (PFS) and improved tolerability for patients compared to a current standard of care regimen used in Europe in this setting.

The HD21 study is a Phase 3, randomized, multi-country, prospective, open-label study, sponsored by the GHSG and supported by Takeda, designed to evaluate ADCETRIS in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone (BrECADD) in comparison to a standard of care treatment – escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (eBEACOPP) – in patients with newly diagnosed Stage IIb/III/IV classical Hodgkin lymphoma. At a preplanned three-year analysis, the study met its co-primary endpoints, with the ADCETRIS combination regimen demonstrating significantly improved safety as assessed by treatment-related morbidity (TRMB) and non-inferior PFS.

The study found that the addition of ADCETRIS to this chemotherapy regimen improved the risk-to-benefit profile of the combination treatment, maintaining efficacy with significantly fewer acute and long-lasting treatment-related toxicities than the comparator arm.

“We initiated the HD21 trial with the hope of improving outcomes currently being achieved by a standard of care, as many patients with newly diagnosed disease often experience a high treatment burden,” said Peter

Borchmann, MD, PhD, University Hospital of Cologne, Germany, and trial chairman of the HD21 study. “The presented analysis, in which the ADCETRIS regimen demonstrates superior progression-free survival, as well as a tolerable safety profile, reveals the meaningful potential this ADCETRIS + ECADD regimen has to offer these patients.”

The ASCO presentation provides details of a four-year PFS analysis of the HD21 study conducted by GHSG. After 48 months, BrECADD showed superior efficacy to BEACOPP (94.3% PFS for BrECADD and 90.9% PFS for eBEACOPP; hazard ratio [HR]: 0.66 [95% CI:88.7-93.1]; $p<0.035$). As previously reported in the three-year analysis, treatment with BrECADD was also associated with a significant reduction in the incidence of TRMB compared with BEACOPP (n=738; 42% vs 59%; $p<0.001$), as well as clinically meaningful reductions in adverse events (AEs). The safety profile of ADCETRIS in patients receiving BrECADD remained consistent with other approved ADCETRIS combination regimens, and no new safety signals were identified.

“In our ongoing effort to improve outcomes for patients with lymphoma, we’ve partnered with the GHSG on the HD21 study to deepen our understanding of how ADCETRIS could further benefit patients in need of new options,” said Awny Farajallah, chief medical officer, global oncology at Takeda. “We are excited about the impact these results could have on patients with newly diagnosed Hodgkin lymphoma, potentially bringing them an additional ADCETRIS-based combination regimen that may significantly reduce side effects without compromising on efficacy.”

Takeda will be responsible for submission of potential regulatory filings based on the HD21 study outside of the U.S. and Canada. 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.

About the HD21 Trial
The HD21 study is a Phase 3, multi-country, prospective, open-label, randomized, multicenter trial sponsored by the German Hodgkin Study Group (GHSG) with a PET-response adapted designed to assess the feasibility, efficacy, safety and tolerability of BrECADD, a novel, rationally designed, CD30-intensified frontline regimen for patients with advanced classical Hodgkin lymphoma.

Enrolled patients with newly diagnosed, Stage IIb with large mediastinal mass and/or extranodal lesions, Stage III or IV Hodgkin lymphoma were randomized to receive two cycles of either escalated BEACOPP or BrECADD, respectively, followed by interim PET staging. A decision is then made if patients received a further two or four cycles of escalated BEACOPP or BrECADD.

The HD21 trial aims to evaluate a modified treatment regimen to minimize side effects, while maintaining similar responses to treatment. The study has co-primary endpoints: safety is assessed by treatment-related morbidity (TRMB) (superiority), a novel endpoint focused on clinically relevant, acute toxicities of primary chemotherapy, and efficacy is assessed by PFS (non-inferiority). Secondary endpoints are tumor response (complete response [CR] rate), overall survival (OS), infertility rate at one year, second malignancies, frequency of adverse events, therapy adherence and quality of life.

About Hodgkin Lymphoma
Lymphoma is a general term for a group of cancers that originate in the lymphatic system affecting a type of white blood cell called lymphocytes. There are two major categories of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma. Hodgkin lymphoma is distinguished from other types of lymphoma by the presence of one characteristic type of cell, known as the Reed-Sternberg cell, present in lymph nodes. Reed-Sternberg cells usually have a special protein on their surface called CD30, which is a key marker of HL. CD30 is present in approximately 95 percent of all cases of Hodgkin lymphoma.

According to the International Agency for Research on Cancer, in 2020, over 83,000 people worldwide were diagnosed with Hodgkin lymphoma and approximately 23,000 people died from this cancer.

About ADCETRIS® (brentuximab vedotin)
ADCETRIS is an antibody-drug conjugate (ADC) comprising an anti-CD30 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 injection for intravenous infusion has received FDA approval for seven indications:
  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)

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 in 2017, adults with pcALCL or CD30-expressing MF who have had prior systemic therapy in 2018, for previously untreated Stage IV Hodgkin lymphoma in combination with doxorubicin, vinblastine, and dacarbazine in 2019, and for previously untreated adult patients with sALCL, peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) or angioimmunoblastic T-cell lymphoma (AITL), whose tumors express CD30, in combination with cyclophosphamide, doxorubicin, prednisone in 2019.

ADCETRIS received conditional marketing authorization from the European Commission in October 2012, and the specific obligations of the conditional marketing authorization were fulfilled in May 2022. The approved indications in the European Union are: (1) for the treatment of adult patients with previously untreated CD30-positive Stage III & IV Hodgkin lymphoma in combination with doxorubicin, vinblastine and dacarbazine (AVD), (2) for the treatment of adult patients with CD30-positive Hodgkin lymphoma at increased risk of relapse or progression following ASCT, (3) 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, (4) for the treatment of adult patients with relapsed or refractory sALCL, (5) for the treatment of adult patients with previously untreated sALCL in combination with CHP and (6) 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 more than 70 countries for relapsed or refractory Hodgkin lymphoma and sALCL. See Important Safety Information below.

ADCETRIS is being evaluated broadly in more than 70 clinical trials, including a Phase 3 study in first-line Hodgkin lymphoma (ECHELON-1) and another Phase 3 study in first-line CD30-positive peripheral T-cell lymphomas (ECHELON-2), as well as trials in many additional types of CD30-positive malignancies.

Pfizer and Takeda fund joint development costs for ADCETRIS on a 50:50 basis, except in Japan where Takeda is solely responsible for development costs.

ADCETRIS (brentuximab vedotin) Important Safety Information (European Union)
Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Contraindications
ADCETRIS is contraindicated for patients with hypersensitivity to brentuximab vedotin and its excipients. In addition, combined use of ADCETRIS with bleomycin causes pulmonary toxicity.

Special Warnings and Precautions
Progressive multifocal leukoencephalopathy (PML): John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in patients treated with ADCETRIS. PML has been reported in patients who received ADCETRIS after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.

Closely monitor patients for new or worsening neurological, cognitive, or behavioral signs or symptoms, which may be suggestive of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established. Hold dosing for any suspected case of PML and permanently discontinue ADCETRIS if a diagnosis of PML is confirmed.

Be alert to PML symptoms that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

Pancreatitis: Acute pancreatitis has been observed in patients treated with ADCETRIS. Fatal outcomes have been reported. Closely monitor patients for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Hold ADCETRIS for any suspected case of acute pancreatitis. ADCETRIS should be discontinued if a diagnosis of acute pancreatitis is confirmed.

Pulmonary Toxicity: Cases of pulmonary toxicity, some with fatal outcomes, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), have been reported in patients receiving ADCETRIS. Although a causal association with ADCETRIS has not been established, the risk of pulmonary toxicity cannot be ruled out. Promptly evaluate and treat new or worsening pulmonary symptoms (e.g., cough, dyspnea) appropriately. Consider holding dosing during evaluation and until symptomatic improvement.

Serious infections and opportunistic infections: Serious infections such as pneumonia, staphylococcal bacteremia, sepsis/septic shock (including fatal outcomes), and herpes zoster, cytomegalovirus (CMV) (reactivation) and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with ADCETRIS. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

Infusion-related reactions (IRR): Immediate and delayed IRR, as well as anaphylaxis, have been reported with ADCETRIS. Carefully monitor patients during and after an infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an IRR occurs, interrupt the infusion and institute appropriate medical management. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. IRRs are more frequent and more severe in patients with antibodies to ADCETRIS.

Tumor lysis syndrome (TLS): TLS has been reported with ADCETRIS. Patients with rapidly proliferating tumor and high tumor burden are at risk of TLS. Monitor these patients closely and manage according to best medical practice.

Peripheral neuropathy (PN): ADCETRIS treatment may cause PN, both sensory and motor. ADCETRIS-induced PN is typically an effect of cumulative exposure to ADCETRIS and is reversible in most cases. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening PN may require a delay and a dose reduction or discontinuation of ADCETRIS.

Hematological toxicities: Grade 3 or Grade 4 anemia, thrombocytopenia, and prolonged (equal to or greater than one week) Grade 3 or Grade 4 neutropenia can occur with ADCETRIS. Monitor complete blood counts prior to administration of each dose.

Febrile neutropenia: Febrile neutropenia has been reported with ADCETRIS. Complete blood counts should be monitored prior to administration of each dose of treatment. Closely monitor patients for fever and manage according to best medical practice if febrile neutropenia develops.

When ADCETRIS is administered in combination with AVD or CHP, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose.

Severe cutaneous adverse reactions (SCARs): Cases of SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with ADCETRIS. Fatal outcomes have been reported for SJS and TEN. If SJS, TEN or DRESS occur, ADCETRIS should be discontinued and appropriate medical therapy should be administered.

Gastrointestinal (GI) Complications: GI complications, some with fatal outcomes, including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, have been reported with ADCETRIS. Promptly evaluate and treat patients if new or worsening GI symptoms occur.

Hepatotoxicity: Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported with ADCETRIS. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk. Test liver function prior to treatment initiation and routinely monitor during treatment. Patients experiencing hepatotoxicity may require a delay, dose modification, or discontinuation of ADCETRIS.

Hyperglycemia: Hyperglycemia has been reported during trials in patients with an elevated body mass index (BMI) with or without a history of diabetes mellitus. Closely monitor serum glucose for patients who experience an event of hyperglycemia. Administer anti-diabetic treatment as appropriate.

Infusion site extravasation: Extravasation during intravenous infusion has occurred. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

Renal and Hepatic Impairment: There is limited experience in patients with renal and hepatic impairment. Available data indicate that MMAE clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations.

CD30+ CTCL: The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. In two single arm phase II studies of ADCETRIS, disease activity has been shown in the subtypes Sézary syndrome (SS), lymphomatoid papulosis (LyP) and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Carefully consider the benefit-risk per patient and use with caution in other CD30+ CTCL patient types.

Sodium content in excipients: This medicinal product contains 13.2 mg sodium per vial, equivalent to 0.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

INTERACTIONS

Patients who are receiving a strong CYP3A4 and P-gp inhibitor, concomitantly with ADCETRIS may have an increased risk of neutropenia. If neutropenia develops, refer to dosing recommendations for neutropenia (see SmPC section 4.2). Co-administration of ADCETRIS with a CYP3A4 inducer did not alter the plasma exposure of ADCETRIS, but it appeared to reduce plasma concentrations of MMAE metabolites that could be assayed. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

PREGNANCY: Advise women of childbearing potential to use two methods of effective contraception during treatment with ADCETRIS and until 6 months after treatment. There are no data from the use of ADCETRIS in pregnant women, although studies in animals have shown reproductive toxicity. Do not use ADCETRIS during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus.

LACTATION (breast-feeding): There are no data as to whether ADCETRIS or its metabolites are excreted in human milk, therefore a risk to the newborn/infant cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy, taking into account a potential risk of breast-feeding for the child and the benefit of therapy for the woman.

FERTILITY: In non-clinical studies, brentuximab vedotin treatment has resulted in testicular toxicity, and may alter
male fertility. MMAE has been shown to have anagenic properties. Therefore, men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men being treated with this medicine are advised not to father a child during treatment and for up to 6 months following the last dose.

Effects on ability to drive and use machines: ADCETRIS may have a moderate influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Monotherapy: The most frequent adverse reactions (?10%) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnea, weight decreased, myalgia and abdominal pain. Serious adverse drug reactions occurred in 12% of patients. The frequency of unique serious adverse drug reactions was ?1%. Adverse events led to treatment discontinuation in 24% of patients.

Combination Therapy: In the studies of ADCETRIS as combination therapy in 662 patients with previously untreated advanced HL (C25003) and 223 patients with previously untreated CD30+ PTCL, the most common adverse reactions (? 10%) were: infections, neutropenia, peripheral sensory neuropathy, nausea, constipation, vomiting, diarrhea, fatigue, pyrexia, alopecia, anemia, weight decreased, stomatitis, febrile neutropenia, abdominal pain, decreased appetite, insomnia, bone pain, rash, cough, dyspnea, arthralgia, myalgia, back pain, peripheral motor neuropathy, upper respiratory tract infection, and dizziness. In patients receiving ADCETRIS combination therapy, serious adverse reactions occurred in 34% of patients. Serious adverse reactions occurring in ? 3% of patients included febrile neutropenia (15%), pyrexia (5%), and neutropenia (3%). Adverse events led to treatment discontinuation in 10% of patients.

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, 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 any study) are peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, mucositis, thrombocytopenia, and febrile neutropenia.

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.

About Takeda
Takeda is focused on creating better health for people and a brighter future for the world. We aim to discover and deliver life-transforming treatments in our core therapeutic and business areas, including gastrointestinal and inflammation, rare diseases, plasma-derived therapies, oncology, neuroscience and vaccines. Together with our partners, we aim to improve the patient experience and advance a new frontier of treatment options through our dynamic and diverse pipeline. As a leading values-based, R&D-driven biopharmaceutical company headquartered in Japan, we are guided by our commitment to patients, our people and the planet. Our employees in approximately 80 countries and regions are driven by our purpose and are grounded in the values that have defined us for more than two centuries. For more information, visit www.takeda.com.

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.

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This press release and any materials distributed in connection with this press release may contain forward-looking statements, beliefs or opinions regarding Takeda’s future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as “targets”, “plans”, “believes”, “hopes”, “continues”, “expects”, “aims”, “intends”, “ensures”, “will”, “may”, “should”, “would”, “could” “anticipates”, “estimates”, “projects” or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-looking statements: the economic circumstances surrounding Takeda’s global business, including general economic conditions in Japan and the United States; competitive pressures and developments; changes to applicable laws and regulations, including global health care reforms; challenges inherent in new product development, including uncertainty of clinical success and decisions of regulatory authorities and the timing thereof; uncertainty of commercial success for new and existing products; manufacturing difficulties or delays; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic, on Takeda and its customers and suppliers, including foreign governments in countries in which Takeda operates, or on other facets of its business; the timing and impact of post-merger integration efforts with acquired companies; the ability to divest assets that are not core to Takeda’s operations and the timing of any such divestment(s); and other factors identified in Takeda’s most recent Annual Report on Form 20-F and Takeda’s other reports filed with the U.S. Securities and Exchange Commission, available on Takeda’s website at: https://www.takeda.com/investors/sec-filings-and-security-reports/ or at www.sec.gov. Takeda does not undertake to update any of the forward-looking statements contained in this press release or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this press release may

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Pfizer Disclosure Notice:

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This release contains forward-looking information about ADCETRIS (brentuximab vedotin), including its potential benefits, its potential in newly diagnosed Stage IIb/III/IV classical Hodgkin lymphoma, and potential regulatory filings, 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 with eCADD or as a single agent for any potential indication; 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 with eCADD or as a single agent 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.

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