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Daiichi-Sankyo

Press Release

ENHERTU® Approved in the EU as the First HER2 Directed Therapy for Patients with *HER2* Mutant Advanced Non-Small Cell Lung Cancer

- Approval based on DESTINY-Lung02 trial results where Daiichi Sankyo and AstraZeneca's ENHERTU demonstrated a confirmed objective response rate of 49.0% and median duration of response of 16.8 months in previously treated patients

Tokyo and Munich – (October 23, 2023) – ENHERTU® (trastuzumab deruxtecan) has been approved in the European Union (EU) as a monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have an activating *HER2* (*ERBB2*) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

ENHERTU is a specifically engineered HER2 directed antibody drug conjugate (ADC) being jointly developed and commercialized by Daiichi Sankyo (TSE: 4568) and AstraZeneca (LSE/STO/Nasdaq: AZN).

The approval by the European Commission (EC) follows the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) and is based on results from the DESTINY-Lung02 phase 2 trial presented at the IASLC 2023 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer and simultaneously published in the *Journal of Clinical Oncology*.

In DESTINY-Lung02, ENHERTU (5.4 mg/kg) demonstrated a confirmed objective response rate (ORR) of 49.0% (95% confidence interval [CI]: 39.0-59.1) in patients with previously treated advanced or metastatic *HER2* mutant NSCLC as assessed by blinded independent central review (BICR). One (1.0%) complete response (CR) and 49 (48.0%) partial responses (PR) were observed. The median duration of response (DOR) was 16.8 months (95% CI: 6.4-not estimable [NE]).

"*HER2* mutant non-small cell lung cancer is more commonly diagnosed in patients who are younger and female, and there are limited treatment options, which often results in a poor prognosis," said Professor Martin Reck, MD, Head of Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Germany. "ENHERTU is the first HER2 directed therapy to demonstrate strong and durable results for these patients, and this approval in the EU marks an important step forward in how the disease can be treated."

"Since our initial approval of ENHERTU for metastatic breast cancer in the EU more than two years ago, we have remained committed to bringing this innovative antibody drug conjugate to more patients with HER2 targetable tumors, especially those that have previously not been eligible for treatment with a HER2 directed therapy," said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. "With today's news, ENHERTU is the first antibody drug conjugate approved for lung cancer in the EU and is now approved in three different tumor types."

"Understanding the molecular drivers behind a lung cancer diagnosis is critical, and while there are now targeted options for many patients, those with *HER2* mutant non-small cell lung cancer have had few treatment options, none of which have been approved to treat their specific type of lung cancer," said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. "ENHERTU is the first HER2 directed option approved for *HER2* mutant disease and confirms the relevance of HER2 as a target in lung cancer."

In DESTINY-Lung02, the safety profile of ENHERTU was consistent with other trials of ENHERTU with no new safety signals observed. Grade 3 or grade 4 treatment-related adverse events from a pooled safety analysis of patients treated with at least one dose of ENHERTU 5.4 mg/kg across multiple tumor types in clinical studies (n=1,449) included neutropenia (17.0%), anemia (9.5%), fatigue (8.4%), leukopenia (6.4%), nausea (5.9%), thrombocytopenia (5.0%), lymphopenia (4.8%), hypokalemia (3.8%), transaminases increased (3.6%), vomiting (2.7%), diarrhea (2.0%), decreased appetite (1.7%), pneumonia (1.4%) and ejection fraction decreased (1.1%). Grade 5 adverse reactions occurred in 1.4% of patients, including interstitial lung disease (1.0%).

Financial Considerations

Following approval in the EU, an amount of $75 million is due from AstraZeneca to Daiichi Sankyo as a milestone payment in *HER2* mutant non-small cell lung cancer. Sales of ENHERTU in most EU territories are recognized by Daiichi Sankyo. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

About DESTINY-Lung02

DESTINY-Lung02 is a global, randomized phase 2 trial evaluating the safety and efficacy of ENHERTU in patients with *HER2* mutant unresectable and/or metastatic NSCLC with disease recurrence or progression during or after at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy. Patients were randomized 2:1 to receive ENHERTU 5.4 mg/kg (n=102) or ENHERTU 6.4 mg/kg (n=50).

The primary endpoint of the trial is confirmed ORR as assessed by BICR. Secondary endpoints include disease control rate, DOR and progression-free survival assessed by investigator and BICR, overall survival and safety. DESTINY-Lung02 enrolled 152 patients at multiple sites, including Asia, Europe, Oceania and North America. For more information about the trial, visit ClinicalTrials.gov.

About *HER2* Mutant NSCLC

Lung cancer is the second most common form of cancer globally with more than two million cases diagnosed in 2020.[1] In Europe, lung cancer is the third most commonly diagnosed cancer with more than 477,000 cases diagnosed in 2020.[2] Lung cancer is also the leading cause of cancer-related deaths in Europe, with nearly 400,000 deaths reported in 2020.[2] Prognosis is particularly poor for patients with metastatic NSCLC as only approximately 9% will live beyond five years after diagnosis.[3]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of multiple tumor types. Certain *HER2* (*ERBB2*) gene alterations (called *HER2* mutations) have been identified in patients with non-squamous NSCLC as a distinct molecular target, and occur in approximately 2% to 4% of patients with this type of lung cancer.[4,5] While *HER2* gene mutations can occur in a range of patients, they are more commonly found in patients with NSCLC who are younger, female and have never smoked.[6] *HER2* gene mutations have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[7] Next-generation sequencing has been utilized in the identification of *HER2* (*ERBB2*) mutations.[8,9]

About ENHERTU

ENHERTU (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC technology, ENHERTU is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced program in AstraZeneca's ADC scientific platform. ENHERTU consists of a HER2 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

ENHERTU (5.4 mg/kg) is approved in more than 55 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a (or one or more) prior anti-HER2-based regimen, either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within six months of completing therapy based on the results from the DESTINY-Breast03 trial.

ENHERTU (5.4 mg/kg) is approved in more than 40 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/*in-situ* hybridization (ISH)-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during

or within six months of completing adjuvant chemotherapy based on the results from the DESTINY-Breast04 trial.

ENHERTU (5.4 mg/kg) is approved in more than 30 countries worldwide for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 trial. Continued approval for this indication in the U.S. may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in more than 30 countries worldwide for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 and/or DESTINY-Gastric02 trials.

About the ENHERTU Clinical Development Program

A comprehensive global clinical development program is underway evaluating the efficacy and safety of ENHERTU monotherapy across multiple HER2 targetable cancers. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in March 2019 and datopotamab deruxtecan (Dato-DXd) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and datopotamab deruxtecan.

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc., Rahway, N.J. USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

Designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan and DS-3939 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical need. For more information, please visit www.daiichisankyo.com.

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