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Daiichi-Sankyo

Press Release

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

- Approval based on DESTINY-Lung02 results showing ENHERTU demonstrated a clinically meaningful tumor response of 53.8% in patients with *HER2* mutant non-small cell lung cancer
- ENHERTU now approved for four indications in Japan

Tokyo – (August 23, 2023) – Daiichi Sankyo (TSE:4568) today announced that ENHERTU® (trastuzumab deruxtecan) has been approved in Japan for the treatment of adult patients with unresectable advanced or recurrent non-small cell lung cancer (NSCLC) with *HER2* (*ERBB2*) mutations that has progressed after chemotherapy.

Lung cancer is the second most diagnosed cancer in Japan, with more than 138,000 cases diagnosed in 2020.[1] Only 18.2% of patients with metastatic NSCLC in Japan live more than three years following diagnosis, making prognosis particularly poor for these patients.[2]

The approval of ENHERTU by Japan's Ministry of Health, Labour and Welfare (MHLW) is based on results from the DESTINY-Lung02 phase 2 trial presented at the European Society for Medical Oncology (ESMO) 2022 Congress. ENHERTU previously received an Orphan Drug Designation by the Japan MHLW for this tumor type, a designation that provided priority review of the application.

In DESTINY-Lung02, a pre-specified interim analysis of patients with previously-treated *HER2* mutant NSCLC showed that ENHERTU (5.4 mg/kg) demonstrated a confirmed objective response rate (ORR) of 53.8% (n=52; 95% confidence interval [CI]: 39.5-67.8) in patients with unresectable advanced or recurrent NSCLC with activating *HER2* (*ERBB2*) mutations after prior chemotherapy as assessed by blinded independent central review (BICR).

"*HER2* mutant non-small cell lung cancer is a rare but serious disease and now patients and physicians in Japan have the potential to benefit from the first HER2 directed treatment option approved specifically for this type of lung cancer," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "This is the fourth indication secured for ENHERTU in Japan in just over three years and the second approval this year alone, underscoring the benefit of this medicine across a range of HER2 targetable cancers."

In DESTINY-Lung02, the safety profile of ENHERTU was consistent with previous clinical trials with no new safety concerns identified. Treatment related adverse events (AEs) occurred in 93 patients (92.1%) treated with ENHERTU (5.4 mg/kg). The most common treatment related AEs were nausea (59.4%), decreased neutrophil count (33.7%), anemia (28.7%), decreased appetite (28.7%), fatigue (25.7%), constipation (24.8%), decreased leukocyte count (23.8%) and vomiting (22.8%). In Japanese patients, interstitial lung disease (ILD) occurred in 2.7% of patients treated with 5.4 mg/kg of ENHERTU at interim analysis.

ENHERTU is approved in Japan with a Warning for ILD. As cases of ILD, including fatal cases, have occurred in ENHERTU-treated patients, ENHERTU is to be used in close collaboration with a respiratory disease expert. Patients should be closely observed during therapy by monitoring for early signs or symptoms of ILD (such as dyspnea, cough or fever) and performing regular peripheral artery oxygen saturation (SpO_2) tests, chest X-ray scans and chest CT scans. If abnormalities are observed, discontinue administration of ENHERTU and take appropriate measures, such as corticosteroid administration. Prior to initiation of ENHERTU therapy, a chest CT scan should be performed and medical history taken to confirm the absence of any comorbidity or history of ILD with the patient and carefully consider the eligibility of the patient for ENHERTU therapy.

The efficacy and safety of ENHERTU as a neoadjuvant, adjuvant or first-line metastatic therapy for the treatment of patients with *HER2* (*ERBB2*) mutant unresectable advanced or recurrent NSCLC has not been established. ENHERTU should be administered only to patients with NSCLC with confirmed *HER2* (*ERBB2*) mutations as detected by an approved test.

About DESTINY-Lung02

DESTINY-Lung02 is a global phase 2 trial evaluating the safety and efficacy of two doses (5.4 mg/kg or 6.4 mg/kg) of ENHERTU in patients with *HER2* mutant 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=101) or ENHERTU 6.4 mg/kg (n=50) every three weeks.

The primary endpoint of the study is confirmed ORR as assessed by BICR. Secondary endpoints include confirmed disease control rate, duration of response and progression free survival assessed by investigator and BICR, overall survival and safety. DESTINY-Lung02 enrolled 151 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 Japan, lung cancer is the second most diagnosed cancer, with more than 138,000 cases diagnosed in 2020.[1] Prognosis is particularly poor for patients with metastatic NSCLC, as only approximately 9% will live beyond five years after diagnosis.[3] In Japan, only 18.2% of patients with metastatic NSCLC will live more than three years following diagnosis.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including lung, breast, gastric and colorectal cancers. 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 is being utilized in the identification of *HER2* (*ERBB2*) mutations.[8]

Although the role of anti-HER2 treatment is well established in breast and gastric cancers, there were no approved HER2 directed therapies for NSCLC in Japan prior to this approval of ENHERTU in unresectable or metastatic *HER2* mutant NSCLC.

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 topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

ENHERTU (5.4 mg/kg) is approved in more than 50 countries 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 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 Israel, Japan and under accelerated approval in the U.S. 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 in the U.S. for this indication 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 for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction 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 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 five 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. Three additional Daiichi Sankyo DXd ADCs include patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd; DS-6000), a CDH6 directed ADC.

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 and raludotatug deruxtecan 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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