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Daiichi-Sankyo

Press Release

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

- Approval based on DESTINY-Lung02 and DESTINY-Lung05 results which showed ENHERTU demonstrated clinically meaningful efficacy in previously treated patients
- Fourth approval in China for Daiichi Sankyo and AstraZeneca's ENHERTU across three different tumor types

Tokyo – (October 14, 2024) – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) ENHERTU® (trastuzumab deruxtecan) has received conditional approval in China as a monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating *HER2* (*ERBB2*) mutations and who have received a prior systemic therapy. This indication was granted as conditional approval based on the results of single-arm studies. Full approval of this indication will depend on the clinical benefit of the confirmatory trial.

ENHERTU is a specifically engineered HER2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca.

Approximately 2% to 4% of patients with NSCLC have tumors with *HER2* mutations.[1,2] More than 40% of the global cases of lung cancer occur in China, with approximately one million new cases and 733,000 deaths reported in 2022.[3,4] The prognosis is particularly poor for patients with NSCLC, the most common form of lung cancer, and the majority of patients are diagnosed with advanced disease.[5]

The conditional approval by China's National Medical Products Administration (NMPA) is based on results from the DESTINY-Lung02 and DESTINY-Lung05 phase 2 trials.

In DESTINY-Lung02, which included patients from Japan, Korea and Taiwan, ENHERTU (5.4 mg/kg) demonstrated strong and durable tumor responses in patients with *HER2* mutant metastatic NSCLC who had received at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy. In the trial, confirmed overall response rate (ORR) was 49.0% (95% confidence interval [CI]: 39.0-59.1) with one complete response (CR) and 49 partial responses (PRs), as assessed by blinded independent central review (BICR). Median duration of response (DOR) was 16.8 months (95% CI: 6.4-not

evaluable [NE]). Median progression-free survival (PFS) was 9.9 months (95% CI: 7.4-NE) and median overall survival (OS) was 19.5 months (95% CI: 13.6-NE).

In DESTINY-Lung05, ENHERTU (5.4 mg/kg) demonstrated a clinically meaningful response in patients in China with *HER2* mutant metastatic NSCLC with disease progression on or after at least one prior anticancer therapy. Treatment with ENHERTU resulted in a confirmed ORR of 58.3% (95% CI: 46.1-69.8), as assessed by independent central review (ICR) with one CR and 41 PRs. The results of DESTINY-Lung05 are consistent with the efficacy results of the global DESTINY-Lung02 phase 2 trial.

"While there have been many advancements in the treatment of non-small cell lung cancer in China in recent years, those with *HER2* mutant disease have had few treatment options and none directed towards this specific type of lung cancer," said Ying Cheng, MD, PhD, Director of Jilin Lung Cancer Centre, China and principal investigator of DESTINY-Lung05. "This approval of ENHERTU offers an important new targeted treatment for patients with this aggressive form of disease."

"Since our initial approval of ENHERTU for patients with HER2 positive metastatic breast cancer in China last year, we have remained committed to bringing this innovative antibody drug conjugate to more patients in China, especially those that have previously not been eligible for treatment with a HER2 directed therapy," said Kiminori Nagao, Head of the Asia, South and Central America Business Unit, Daiichi Sankyo. "Today's milestone marks the fourth approval of ENHERTU in China and follows the recent approval for HER2 positive metastatic gastric cancer, reinforcing its benefit across multiple HER2 targetable tumors."

"This approval of ENHERTU represents the first HER2 directed therapy approved in China for the treatment of *HER2* mutant metastatic non-small cell lung cancer, marking an important step forward in how the disease can be treated," said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. "It also reinforces the importance of testing for predictive biomarkers, including *HER2* mutations in lung cancer at the time of diagnosis to ensure patients can receive the most appropriate treatment for their specific disease."

The safety profiles of ENHERTU in DESTINY-Lung02 and DESTINY-Lung05 were similar and generally consistent with previous clinical trials of ENHERTU in lung cancer with no new safety concerns identified. Grade 3 or grade 4 treatment related adverse events from a pooled safety analysis of patients treated with ENHERTU (5.4 mg/kg) across multiple tumor types in clinical studies 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 (ILD) (1.0%). Discontinuation of treatment due to an

adverse event occurred in 13% of patients. The most frequent adverse event associated with permanent discontinuation was ILD (9.2%).

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 (DCR), DOR and PFS assessed by investigator and BICR, OS and safety. DESTINY-Lung02 enrolled 152 patients at multiple sites in Asia, Europe, North America and Oceania. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Lung05

DESTINY-Lung05 is an open-label, single-arm phase 2 trial in China evaluating the safety and efficacy of ENHERTU (5.4 mg/kg) in patients with *HER2* mutant metastatic NSCLC with disease progression on or after at least one prior anticancer therapy.

The primary endpoint of the trial is confirmed ORR as assessed by ICR. Secondary endpoints include investigator-assessed confirmed ORR, and ICR and investigator-assessed DOR, DCR, PFS and safety. DESTINY-Lung05 enrolled 72 patients at multiple sites in China. For more information about the trial, visit clinicaltrials.gov.

About *HER2* Mutant NSCLC

Lung cancer is the most common cancer globally and is the leading cause of cancer-related death in both men and women.[4] Nearly 2.5 million cases of lung cancer were diagnosed in 2022, with 1.8 million deaths reported globally.[4] Prognosis is particularly poor for patients with metastatic NSCLC as only approximately 9% will live beyond five years after diagnosis.[6]

Incidence rates for lung cancer are markedly higher in Asia, particularly in China, where more than 40% of all global cases occur.[3,4] Lung cancer is the most common cancer in China with more than one million new cases diagnosed in 2022.[3] Additionally, it is the leading cause of cancer-related death in China, with more than 733,000 deaths reported in 2022.[3] Approximately 68% of patients in China present with advanced disease at the time of diagnosis.[7]

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.[1,2] 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.[8] *HER2* gene mutations have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[9] Next-generation sequencing has been utilized in the identification of *HER2* (*ERBB2*) mutations.[10]

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 65 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (immunohistochemistry [IHC] 3+ or *in-situ* hybridization (ISH)+) breast cancer who have received a 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 65 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/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 45 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 and/or DESTINY-Lung05 trials. Continued approval in China and 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 45 countries worldwide for the treatment of adult patients with locally advanced or metastatic HER2 positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01, DESTINY-Gastric02 and/or DESTINY-Gastric06 trials. Continued approval

in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (5.4 mg/kg) is approved in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options based on efficacy results from the DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 trials. Continued approval for this indication in the U.S. may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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 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 ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where 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. The DXd ADC portfolio currently consists of ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which 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. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 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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