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Daiichi-Sankyo

Press Release

ENHERTU® Type II Variation Application Validated by EMA for the Treatment of *HER2* Mutant Metastatic Non-Small Cell Lung Cancer

- Submission based on DESTINY-Lung02 and DESTINY-Lung01 phase 2 trial results which showed Daiichi Sankyo and AstraZeneca's ENHERTU demonstrated a clinically meaningful tumor response

Tokyo and Munich – (January 4, 2023) – Daiichi Sankyo (TSE: 4568) today announced that the European Medicines Agency (EMA) has validated the Type II Variation application for ENHERTU® (trastuzumab deruxtecan) as a monotherapy for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating *HER2* (*ERBB2*) mutations and who have received a prior systemic therapy.

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

Validation confirms that the application is complete and commences the scientific review process by the EMA's Committee for Medicinal Products for Human Use. This application is based on data from the DESTINY-Lung02 phase 2 trial presented at the European Society for Medical Oncology (ESMO) 2022 Congress and the DESTINY-Lung01 phase 2 trial published in *The New England Journal of Medicine* with updated data also presented at ESMO 2022.

"ENHERTU is the first HER2 directed medicine shown to have a clinically meaningful tumor response in patients with previously treated *HER2* mutant metastatic non-small cell lung cancer based on the results of the DESTINY-Lung02 and DESTINY-Lung01 trials," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "As there are no approved therapies targeting *HER2* mutant non-small cell lung cancer in Europe, we look forward to working closely with the European Medicines Agency to potentially bring a new treatment option to these patients."

About DESTINY-Lung02

DESTINY-Lung02 is a global, randomized phase 2 trial evaluating the safety and efficacy 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 (Cohort 1; n=102) or ENHERTU 6.4 mg/kg (Cohort 2; n=50).

The primary endpoint of the trial is confirmed objective response rate (ORR) as assessed by blinded independent central review (BICR). Secondary endpoints include confirmed disease control rate (DCR), duration of response (DoR) and progression free survival (PFS) assessed by investigator and BICR, investigator-assessed overall survival (OS) 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 DESTINY-Lung01

DESTINY-Lung01 is a global phase 2, open-label, two-cohort trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg or 6.4 mg/kg) in patients with *HER2* mutant (cohort 2, n=91) or HER2 overexpressing (cohort 1 and 1a, n=90) (defined as immunohistochemistry (IHC) 3+ or IHC 2+) unresectable or metastatic non-squamous NSCLC relapsed from or refractory to standard treatment or for which no standard treatment is available.

The primary endpoint of the trial is confirmed ORR by independent central review (ICR). Key secondary endpoints include DoR, DCR, PFS, OS and safety. DESTINY-Lung01 enrolled 181 patients at multiple sites, including Asia, Europe 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 8% will live beyond five years after diagnosis.[3]

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 has been utilized in the identification of *HER2* (*ERBB2*) mutations.[8,9]

Although the role of anti-HER2 treatment is well established in breast and gastric cancers, there were no approved HER2 directed therapies in NSCLC prior to the accelerated U.S. Food and Drug Administration (FDA) approval of ENHERTU in unresectable or metastatic *HER2* mutant NSCLC.[10,11]

About ENHERTU

ENHERTU® (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed antibody drug conjugate (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 40 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 also is approved in several countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast01 trial.

ENHERTU (5.4 mg/kg) is approved in Brazil and the U.S. for the treatment of adult patients with unresectable or metastatic HER2 low (immunohistochemistry (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 under accelerated approval in the U.S. for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating *HER2 (ERBB2*) mutations, as detected by a FDA-approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 trial. Continued approval 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 several countries 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 trial.

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 including breast, gastric, lung and colorectal cancers. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

Regulatory applications for ENHERTU in breast, non-small cell lung and gastric cancers are currently under review in several countries.

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. The company's clinical trial stage DXd ADCs include ENHERTU, a HER2 directed ADC and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca; and, patritumab deruxtecan (HER3-DXd), a HER3 directed ADC. Two additional ADCs including ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, and DS-6000, a CDH6 directed ADC, are being developed through a strategic early-stage research collaboration with Sarah Cannon Research Institute.

Each ADC is 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 DS-6000 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 dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi

Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com.

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