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Daiichi-Sankyo

Press Release

ENHERTU® Approved in China as the First HER2 Directed Therapy for Patients with HER2 Low Metastatic Breast Cancer

- Approval based on DESTINY-Breast04 results which showed Daiichi Sankyo and AstraZeneca's ENHERTU reduced the risk of disease progression or death by 50% and increased median overall survival by more than six months versus chemotherapy

Tokyo – (July 12, 2023) – Daiichi Sankyo (TSE:4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) ENHERTU® (trastuzumab deruxtecan) has been approved in China as a monotherapy indicated 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.

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

In China, breast cancer is the most common cancer in women with more than 415,000 cases diagnosed in 2020.[1] Additionally, there were nearly 120,000 deaths, representing around 18% of global breast cancer deaths.[1] Approximately half of all breast cancers are considered HER2 low.[2,3,4]

The approval by China's National Medical Products Administration (NMPA) is based on the results of the DESTINY-Breast04 phase 3 trial first presented at the American Society of Clinical Oncology (ASCO) 2022 Annual Meeting and published in *The New England Journal of Medicine*. It follows the approval granted by China's NMPA in Feburary 2023 for ENHERTU in patients with previously treated unresectable or metastatic HER2 positive breast cancer.

In DESTINY-Breast04, ENHERTU reduced the risk of disease progression or death by 50% versus physician's choice of chemotherapy (hazard ratio [HR] = 0.50; 95% confidence interval [CI]: 0.40-0.63; p<0.0001) in all randomized patients with HER2 low metastatic breast cancer with either hormone receptor (HR) positive or HR negative disease. A median progression-free survival (PFS) of 9.9 months (95% CI: 9.0-11.3) was seen with ENHERTU versus 5.1 months (95% CI: 4.2-6.8) in those treated with chemotherapy as assessed by blinded independent central review (BICR). A 36% reduction in the risk of death (HR = 0.64; 95% CI: 0.49-0.84; p=0.001) also was seen with ENHERTU compared to chemotherapy with a median

overall survival (OS) of 23.4 months (95% CI: 20.0-24.8) in patients treated with ENHERTU versus 16.8 months (95% CI: 14.5-20.0) in those treated with chemotherapy.

“Historically breast cancer tumors with low levels of HER2 expression have been classified as HER2 negative and have not been eligible for treatment with HER2 directed therapies,” said Binghe Xu, MD, Director of the National Clinical Research Center for New Anticancer Drugs, Tenured Professor and Former Director, the Department of Medical Oncology, Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College. “With this approval in China based on the results of the DESTINY-Breast04 trial, clinicians will now be able to identify and potentially treat a distinct patient population based on HER2 low status.”

“This approval of ENHERTU for patients with HER2 low metastatic breast cancer, which comes shortly after the approval of ENHERTU in patients with HER2 positive disease, marks the first time patients with HER2 low tumors will have the opportunity to be treated with a HER2 directed therapy,” said Kiminori Nagao, Head of the Asia, South & Central America (ASCA) Business Unit, Daiichi Sankyo. “ENHERTU now has the potential to become a new standard of care treatment option in China for a broad range of patients with HER2 expressing metastatic breast cancer.”

“Patients with HR positive or HR negative, HER2 low metastatic breast cancer previously had few effective treatment options beyond chemotherapy,” said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. “The results from the DESTINY-Breast04 trial show ENHERTU provides a significant improvement in outcomes compared to chemotherapy for patients whose tumors are determined to be HER2 low via routine testing. This approval is an important advance in the way breast cancer is classified and treated in China and supports our vision to bring ENHERTU to more patients worldwide.”

The safety profile of ENHERTU in DESTINY-Breast04 was consistent with previous clinical trials 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 (16.3%), anemia (9.2%), fatigue (7.5%), leukopenia (6.3%), thrombocytopenia (5.9%), nausea (5.6%), lymphopenia (4.8%), transaminases increased (3.9%), hypokalemia (3.5%), vomiting (2.2%), pneumonia (1.9%), diarrhea (1.8%), decreased appetite (1.7%), febrile neutropenia (1.2%), dyspnea (1.2%), blood bilirubin increased (1.1%), ejection fraction decreased (1.1%), and musculoskeletal pain (1.1%). Grade 5 adverse reactions occurred in 1.5% of patients, including interstitial lung disease (ILD) (1.2%). Discontinuation of therapy due to an adverse event occurred in 12.1% of patients treated with ENHERTU. The most frequent adverse event associated with permanent discontinuation was ILD (8.5%).

About DESTINY-Breast04

DESTINY-Breast04 is a global, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) in patients with HR positive or HR negative, HER2 low unresectable and/or metastatic breast cancer previously treated with one or two prior lines of chemotherapy. Patients were randomized 2:1 to receive either ENHERTU or chemotherapy.

The primary endpoint of DESTINY-Breast04 is PFS in patients with HR positive disease based on BICR. Key secondary endpoints include PFS based on BICR in all randomized patients (HR positive and HR negative disease), OS in patients with HR positive disease and OS in all randomized patients (HR positive and HR negative disease). Other secondary endpoints include PFS based on investigator assessment, objective response rate based on BICR and on investigator assessment, duration of response based on BICR and safety. DESTINY-Breast04 enrolled 557 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About Breast Cancer and HER2 Expression

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[5] More than two million cases of breast cancer were diagnosed in 2020 with nearly 685,000 deaths globally.[5] In China, breast cancer is the most common cancer in women with more than 415,000 cases diagnosed in 2020.[1] Additionally, there were nearly 120,000 deaths, representing approximately 18% of global breast cancer deaths.[1]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors and is one of many biomarkers expressed in breast cancer tumors.[6]

HER2 expression is determined by an immunohistochemistry (IHC) test, which estimates the amount of HER2 protein on a cancer cell, and/or an *in-situ* hybridization (ISH) test, which counts the copies of the *HER2* gene in cancer cells.[6,7] HER2 tests provide IHC and ISH scores across the full HER2 spectrum and are routinely used to determine appropriate treatment options for patients with metastatic breast cancer.[6] HER2 positive cancers are currently defined as HER2 expression measured as IHC 3+ or IHC 2+/ISH+, and HER2 negative cancers are defined as HER2 expression measured as IHC 0, IHC 1+ or IHC 2+/ISH-.[6] However, approximately half of all breast cancers are HER2 low, defined as a HER2 score of IHC 1+ or IHC 2+/ISH-.[2,3,4] HER2 low occurs in both HR positive and HR negative disease.[8]

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 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+/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 of the DESTINY-Breast04 trial.

ENHERTU (5.4 mg/kg) is approved in Israel and 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 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 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. The company's clinical trial stage DXd ADCs include ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan, 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 raludotag deruxtecan (R-DXd; DS-6000), a CDH6 directed ADC, are being developed through a strategic early-stage research collaboration with Sarah Cannon Research Institute.

Designed using Daiichi Sankyo's proprietary DXd ADC technology, each ADC targets and delivers 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 raludotag 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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