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Daiichi-Sankyo

Press Release

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

- Approval based on DESTINY-Breast04 results showing ENHERTU reduced the risk of disease progression or death by 50% versus chemotherapy
- Third indication approved for ENHERTU in Japan in three years

Tokyo – (March 27, 2023) – Daiichi Sankyo (TSE: 4568) today announced that ENHERTU® (trastuzumab deruxtecan) has been approved in Japan for the treatment of adult patients with HER2 low (IHC 1+ or IHC 2+/ISH-) unresectable or recurrent breast cancer after prior chemotherapy.

In Japan, breast cancer is the most common cancer in women.[1] Approximately 92,000 cases of breast cancer were diagnosed in Japan in 2020, with approximately 17,000 deaths.[1]

The approval by Japan's Ministry of Health, Labour and Welfare (MHLW) is based on results of the DESTINY-Breast04 phase 3 trial first presented at the American Society of Clinical Oncology 2022 Annual Meeting and published in *The New England Journal of Medicine*.

In DESTINY-Breast04, ENHERTU significantly 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 patients with HER2 low metastatic breast cancer with 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. ENHERTU was granted priority review in 2022 by the Japan MHLW for this tumor type based on these data.

"For the first time, certain patients in Japan whose tumors have a low HER2 expression have a treatment option available targeted specifically for them," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "This is the third indication approved within three years in Japan for ENHERTU for patients with breast cancer and this medicine has the potential to become standard of care for patients with low HER2 expression."

In DESTINY-Breast04, the safety profile of ENHERTU was consistent with previous clinical trials with no new safety concerns identified. Adverse events (AEs) occurred in 357 patients (96.2%) treated with ENHERTU (5.4 mg/kg). The most common AEs were nausea (73.0%), fatigue (47.7%), alopecia (37.7%), vomiting (34.0%), anemia (33.2%) and decreased neutrophil count (33.2%). In Japanese patients, interstitial lung disease (ILD) occurred in 26.8% of patients.

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. Closely observe patients during therapy by monitoring for early signs or symptoms of ILD (such as dyspnea, cough or fever) and regularly perform 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, perform a chest CT scan and interview 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 or adjuvant therapy for the treatment of HER2 low unresectable or recurrent breast cancer has not been established. ENHERTU should be administered only to patients who have been confirmed to have low HER2 expression based on approved in vitro diagnostics or medical devices performed at testing facilities or by pathologists with sufficient experience.

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), overall survival (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.[2] More than two million cases of breast cancer were diagnosed in 2020 with nearly 685,000 deaths globally.[2] In Japan, breast cancer is the most common cancer in women.[1] Approximately 92,000 cases of breast cancer were diagnosed in Japan in 2020, with approximately 17,000 deaths.[1]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including breast, gastric, lung and colorectal cancers, and is one of many biomarkers expressed in breast cancer tumors.[3]

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.[3,4] 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. 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-.[3] However, approximately half of all breast cancers are HER2 low, defined as a HER2 score of IHC 1+ or IHC 2+ /ISH-.[5,6,7] 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 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 (5.4 mg/kg) is approved in more than 30 countries 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 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 an 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 more than 30 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 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 including breast, gastric, lung and colorectal 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 (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.

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 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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