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Daiichi-Sankyo

Press Release

ENHERTU® Supplemental New Drug Application Submitted in Japan for Patients with HER2 Low or HER2 Ultralow Metastatic Breast Cancer

- Submission based on DESTINY-Breast06 phase 3 trial results that showed ENHERTU demonstrated a statistically significant and clinically meaningful improvement in progression-free survival compared to standard of care chemotherapy
- ENHERTU has the potential to become the first HER2 directed therapy and antibody drug conjugate approved in Japan in this setting

Tokyo – (October 4, 2024) – Daiichi Sankyo (TSE: 4568) today announced that it has submitted a supplemental New Drug Application (sNDA) to Japan's Ministry of Health, Labour and Welfare (MHLW) for ENHERTU® (trastuzumab deruxtecan) for the treatment of adult patients with HER2 low (IHC 1+ or IHC 2+/ISH-) or ultralow (IHC 0 with membrane staining) unresectable or recurrent breast cancer.

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide, with more than 665,000 deaths globally.[1] In Japan, breast cancer is the most common cancer in women, with approximately 92,000 cases of breast cancer diagnosed in 2022.[2] Hormone receptor (HR) positive, HER2 negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.[3] It is estimated that approximately 60% to 65% of HR positive, HER2 negative breast cancers are HER2 low and potentially an additional 25% may be HER2 ultralow.[4,5]

The sNDA is based on data from the DESTINY-Breast06 phase 3 trial presented as a late-breaking oral presentation at the 2024 American Society of Clinical Oncology (#ASCO24) Annual Meeting and recently published in *The New England Journal of Medicine*.

"This submission builds on the current HER2 low indication and if approved will provide the opportunity for the earlier use of ENHERTU for patients with HER2 low expression as well as expanding into the HER2 ultralow patient population," said Toshinori Agatsuma, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "The DESTINY-Breast06 results represent the first time a HER2 directed therapy has shown a clinically meaningful benefit in these patient populations and we look forward to working with regulatory authorities in Japan to bring ENHERTU to these patients."

Additional regulatory submissions for ENHERTU based on data from DESTINY-Breast06 are under review in the EU and U.S.

About DESTINY-Breast06

DESTINY-Breast06 is a global, randomized, open-label, phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus investigator's choice of chemotherapy (capecitabine, paclitaxel or nab paclitaxel) in patients with HR positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining) advanced or metastatic breast cancer. Patients in the trial had no prior chemotherapy for advanced or metastatic disease and received at least two lines of prior endocrine therapy in the metastatic setting. Patients also were eligible if they had received one prior line of endocrine therapy combined with a CDK4/6 inhibitor in the metastatic setting and experienced disease progression within six months of starting first-line treatment or received endocrine therapy as an adjuvant treatment and experienced disease recurrence within 24 months.

The primary endpoint is progression-free survival (PFS) in the HR positive, HER2 low patient population as measured by blinded independent central review (BICR). Key secondary endpoints include PFS by BICR in the overall trial population (HER2 low and HER2 ultralow), overall survival (OS) in patients in the HER2 low patient population and OS in the overall trial population. Other secondary endpoints include objective response rate, duration of response, time to first subsequent treatment or death, time to second subsequent treatment or death and safety. Analysis of the HER2 ultralow subgroup was not powered to demonstrate statistical significance.

DESTINY-Breast06 enrolled 866 patients (n=713 for HER2 low and n=153 for HER2 ultralow) at multiple sites in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit ClinicalTrials.gov.

About Breast Cancer and HER2 Expression

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[1] More than two million breast cancer cases were diagnosed in 2022 with more than 665,000 deaths globally.[1] In Japan, breast cancer is the most common cancer in women, with approximately 92,000 cases of breast cancer diagnosed in 2022.[2] While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or who progress to metastatic disease are expected to live five years following diagnosis.[3]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including breast cancer.[6] Patients with high levels of HER2 expression (IHC 3+ or IHC2+/ISH+) are classified as HER2 positive and treated with HER2 targeted therapies, representing approximately 15 to 20%

of all breast cancers.[7] Historically, tumors that were not classified as HER2 positive were classified as HER2 negative, despite the fact that many of these tumors still carry some level of HER2 expression.[8] It is estimated that approximately 60% to 65% of HR positive, HER2 negative breast cancers are HER2 low and potentially an additional 25% may be HER2 ultralow.[4,5]

Endocrine therapies are widely given consecutively in the early lines of treatment for HR positive metastatic breast cancer. However, following two lines of endocrine therapy, further efficacy with additional endocrine treatment is often limited.[9] The current standard of care following endocrine therapy is chemotherapy, which is associated with poor response rates and outcomes.[9,10,11,12]

Prior to the approval of ENHERTU following chemotherapy in HER2 low metastatic breast cancer based on the DESTINY-Breast04 trial, there were no targeted therapies approved specifically for patients with HER2 low expression.[13] There are no targeted therapies specifically approved for patients with HER2 ultralow expression.[14]

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 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 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 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. Full approval in China for this indication will depend on whether a randomized controlled confirmatory clinical trial can demonstrate clinical benefit in this population.

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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