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Daiichi-Sankyo

Press Release

ENHERTU® Type II Variation Application Validated by EMA for Patients with HER2 Low or HER2 Ultralow Metastatic Breast Cancer Following At Least One Endocrine Therapy

- Submission based on DESTINY-Breast06 phase 3 trial results that showed Daiichi Sankyo and AstraZeneca's ENHERTU demonstrated a statistically significant and clinically meaningful improvement in progression-free survival compared to standard of care chemotherapy

Tokyo and Munich – (August 19, 2024) – 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 HER2 low (defined as IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (defined as IHC 0 with membrane staining) breast cancer who have received at least one endocrine therapy in the metastatic setting.

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 (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-Breast06 phase 3 trial presented as a late-breaking oral session at the 2024 American Society of Clinical Oncology (#ASCO24) Annual Meeting.

"This submission builds on our existing indication for ENHERTU in patients with HER2 low metastatic breast cancer and an expanded approval would enable the potential for use in an earlier disease setting as well as in a broader patient population that now includes HER2 ultralow," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "We look forward to working closely with the EMA to potentially bring this medicine to more patients in the EU."

Additional regulatory submissions for ENHERTU in this indication are underway globally.

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 (defined as IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (defined as 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 Europe, approximately 557,000 cases of breast cancer are diagnosed annually.[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.[4] 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% percent of all breast cancers.[5] 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.[6] 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.[7,8]

Endocrine therapies are widely given consecutively in the early lines of treatment for HR positive metastatic breast cancer.[9] 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 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 (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 35 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 DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, 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 & Co., Inc., Rahway, N.J. USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

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, raludotatug deruxtecan and DS-3939 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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