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Daiichi-Sankyo

Press Release

ENHERTU® Approved in China as First HER2 Directed Medicine for Patients with HER2 Low or HER2 Ultralow Metastatic Breast Cancer Following Disease Progression After One or More Endocrine Therapies

- Based on DESTINY-Breast06 phase 3 trial results demonstrating that Daiichi Sankyo and AstraZeneca's ENHERTU significantly extended progression-free survival versus chemotherapy
- Approval brings ENHERTU earlier in the treatment of HR positive, HER2 low breast cancer and broadens the eligible patient population to those with HER2 ultralow disease
- Fifth approval for ENHERTU in China across three tumor types in less than three years

Tokyo – (December 25, 2025) – ENHERTU® (trastuzumab deruxtecan) has been approved in China for the treatment of adult patients with unresectable or metastatic hormone receptor (HR) positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining) breast cancer that has progressed on one or more endocrine therapies in the metastatic setting.

ENHERTU is a specifically engineered HER2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca (LSE/STO/Nasdaq: AZN).

Breast cancer is the second most common cancer in women in China.[1] Approximately 357,000 cases of breast cancer were diagnosed in China in 2022, with nearly 75,000 deaths.[1] HR positive, HER2 negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.[2] Despite being classified as HER2 negative, many of these tumors still carry some level of HER2 expression.[3]

The approval of ENHERTU by China's National Medical Products Administration (NMPA) is based on results from the DESTINY-Breast06 phase 3 trial presented at the 2024 American Society of Clinical Oncology (#ASCO24) Annual Meeting and published in *The New England Journal of Medicine*.

In DESTINY-Breast06, ENHERTU demonstrated a 38% reduction in the risk of disease progression or death versus chemotherapy in patients with chemotherapy-naïve HR positive, HER2 low metastatic breast cancer (n=713; hazard ratio [HR] 0.62; 95% confidence interval [CI]: 0.52-0.75; p<0.0001) as assessed by blinded independent central review (BICR). Median progression-free survival (PFS) was 13.2 months (95% CI: 11.4-15.2) in the ENHERTU arm compared to 8.1 months (95% CI: 7.0-9.0) in the chemotherapy arm. Confirmed

objective response rate (ORR) in the HER2 low population was 56.5% (95% CI: 51.2-61.7) with ENHERTU compared to 32.2% (95% CI: 27.4, 37.3) with chemotherapy. Median duration of response (DOR) was 14.1 months (95% CI: 11.8-15.9) with ENHERTU compared to 8.6 months (95% CI: 6.7-11.3) with chemotherapy.

In the HER2 ultralow population (n=153; HR 0.78; 95% CI: 0.50-1.21), median PFS was 13.2 months (95% CI: 9.8-17.3) in patients treated with ENHERTU compared to 8.3 months (95% CI: 5.8-15.2) in those treated with chemotherapy. Confirmed ORR was 61.8% (95% CI: 50.0, 72.8) with ENHERTU compared to 26.3% (95% CI: 16.9, 37.7) with chemotherapy. Median DOR was 14.3 months (95% CI: 9.2, 20.7) with ENHERTU compared to 14.1 months (95% CI: 5.9-not estimable) with chemotherapy.

“For many years, tumors with low levels of HER2 expression were grouped under the broader category of HER2 negative, leaving patients with HER2 low and HER2 ultralow breast cancer without targeted treatment options after progressing on endocrine therapy,” said Xichun Hu, MD, PhD, Chair Professor of the Department of Medical Oncology, Fudan University Shanghai Cancer Center and lead investigator of the DESTINY-Breast06 trial in China. “The DESTINY-Breast06 results demonstrate for the first time that a precision-targeted therapy can benefit this underserved population, marking an important scientific advance. With this approval, more patients can benefit from antibody drug conjugate therapy, including those with HER2 expressing, HR positive metastatic breast cancer.”

“As the first HER2 directed medicine approved in China for patients with HER2 low or ultralow disease, ENHERTU continues to redefine the diagnosis and treatment of metastatic breast cancer with this new use,” said Michio Hayashi, China President, Daiichi Sankyo. “This fifth approval for ENHERTU in China in less than three years underscores our commitment to bringing this innovative therapy to more patients that may benefit from treatment.”

“DESTINY-Breast06 marks a meaningful shift in the treatment of patients with HR positive breast cancer, enabling more patients to benefit from a HER2 directed treatment option,” said Dave Fredrickson, Executive Vice President, Oncology Hematology Business Unit, AstraZeneca. “This new approval in China underscores the critical need to test metastatic breast cancer tumors for any level of HER2 staining to identify those with HER2 low or ultralow disease that could potentially be treated with ENHERTU following disease progression on endocrine therapy.”

The safety profile of ENHERTU in DESTINY-Breast06 was consistent with previous clinical trials with no new safety concerns identified. The most common grade 3 or grade 4 adverse reactions from a pooled safety population receiving at least one dose of ENHERTU (n=2,225) were neutropenia (18.0%), anemia (10.5%), fatigue (7.8%), leukopenia (6.0%), thrombocytopenia (5.4%), nausea (4.9%), lymphopenia (3.9%),

hypokalemia (3.8%), increased transaminases (3.5%), diarrhea (2.5%), vomiting (2.4%), decreased appetite (1.8%), pneumonia (1.3%) and decreased ejection fraction (1.0%). Grade 5 adverse reactions occurred in 1.4% of patients, including interstitial lung disease (ILD; 1.0%). Discontinuation of treatment due to an adverse reaction occurred in 11.2% of patients. The most frequent adverse reaction associated with permanent discontinuation was ILD (8.1%).

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 (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.

HER2 IHC status was confirmed by a central laboratory and determined based on the most recent evaluable metastatic sample prior to randomization. In tumor samples from patients screened for trial eligibility, nearly two-thirds of tumors previously assessed as IHC 0 at a local laboratory were re-classified as HER2 low or HER2 ultralow upon central analysis of the archival tumor sample. It was also observed that approximately 85% to 90% of patients with HR positive, HER2 negative metastatic breast cancer may have actionable levels of HER2 expression**.**

The primary endpoint of DESTINY-Breast06 is PFS in the HR positive, HER2 low patient population as measured by 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 ORR, DOR, 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) 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.[4] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[4] In China, breast cancer is the second most common cancer in women.[5] Approximately 357,000 cases of breast cancer were diagnosed in China in 2022, with nearly 75,000 deaths.[5] 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.[2]

HR positive, HER2 negative breast cancer is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.[2] 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 IHC 2+/ISH+) are classified as HER2 positive and treated with HER2 targeted therapies, representing approximately 15% to 20% of all breast cancers.[7,8] Historically, tumors that were not classified as HER2 positive were classified as HER2 negative, despite the fact that many of these tumors still have some level of HER2 expression.[3]

Endocrine therapy is widely given consecutively in the early lines of treatment for HR positive metastatic breast cancer. However, after initial therapy, further efficacy with additional endocrine treatment is often limited.[9] Prior to the approval of ENHERTU in HER2 low and HER2 ultralow metastatic breast cancer based on the DESTINY-Breast04 and DESTINY-Breast06 trials, there were no HER2 targeted therapies approved specifically for these patient populations.[10,11,12]

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) in combination with pertuzumab is approved in the U.S. as a first-line treatment for adult patients with unresectable or metastatic HER2 positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test, based on the results from the DESTINY-Breast09 trial.

ENHERTU (5.4 mg/kg) is approved in more than 90 countries/regions 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 85 countries/regions 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 55 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic hormone receptor (HR) positive, HER2 low (IHC 1+ or IHC 2+/ ISH-) or HER2 ultralow (IHC 0 with membrane staining) breast cancer, as determined by a locally or regionally approved test, that have progressed on one or more endocrine therapies in the metastatic setting based on the results from the DESTINY-Breast06 trial.

ENHERTU (5.4 mg/kg) is approved in more than 60 countries/regions 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 and/or DESTINY-Lung05 trials. Continued approval in China and 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 70 countries/regions 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. Continued approval in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (5.4 mg/kg) is approved in more than 10 countries/regions worldwide 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 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 as a monotherapy or in combination or sequentially with other cancer medicines across multiple HER2 targetable cancers.

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 DATROWAY® 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 DATROWAY.

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of eight ADCs in clinical development crafted from ADC technology discovered in-house by Daiichi Sankyo.

The DXd ADC Technology platform of Daiichi Sankyo consists of six ADCs in clinical development where each ADC is comprised of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADCs include ENHERTU and DATROWAY, which are being jointly developed and commercialized globally with AstraZeneca, and ifinatamab deruxtecan (I-DXd), raludotatug deruxtecan (R-DXd) and patritumab deruxtecan (HER3-DXd), which are being jointly developed and commercialized globally with Merck & Co., Inc, Rahway, NJ, USA. DS-3939 is being developed by Daiichi Sankyo.

Additional ADCs being developed by Daiichi Sankyo include DS-9606, which consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload and DS3610, which consists of an antibody attached to a novel immunomodulatory payload that acts as an agonist of STING.

Ifinatamab deruxtecan, raludotatug deruxtecan, patritumab deruxtecan, DS-3939, DS-9606 and DS3610 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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