Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

ENHERTU® Approved in Japan as First HER2 Directed Medicine for Patients with HER2 Low or HER2 Ultralow Metastatic Breast Cancer Following at Least One Endocrine Therapy

- Based on DESTINY-Breast06 phase 3 trial results that showed ENHERTU demonstrated superiority versus chemotherapy with a median progression-free survival of more than one year
- 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

Tokyo – (August 25, 2025) – ENHERTU® (trastuzumab deruxtecan) has been approved in Japan for the treatment of adult patients with hormone receptor (HR) positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining) unresectable or recurrent breast cancer.

ENHERTU is a specifically engineered HER2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being developed and commercialized by Daiichi Sankyo in Japan.

Breast cancer is the most common cancer in women in Japan.[1] Approximately 92,000 cases of breast cancer were diagnosed in Japan in 2022, with approximately 17,600 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 have some level of HER2 expression.[3]

The approval of ENHERTU by Japan's Ministry of Health, Labour and Welfare 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. In the HER2 ultralow population (n=152; HR 0.78; 95% CI: 0.50-1.21) the 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.

“ENHERTU continues to transform the way breast cancer is treated, becoming the first HER2 directed medicine approved in Japan for patients with HR positive, HER2 low or HER2 ultralow metastatic breast cancer,” said Yuki Abe, PhD, Head of R&D Division in Japan and Head of Research, Daiichi Sankyo. “This approval, which is the fifth indication for ENHERTU in Japan in five years, brings this important medicine to an earlier treatment setting and a broader patient population with lower levels of HER2 expression.”

In DESTINY-Breast06, the safety profile of ENHERTU was consistent with previous clinical trials with no new safety concerns identified. Treatment-emergent adverse events (TEAEs) occurred in 417 patients (96.1%) treated with ENHERTU (5.4 mg/kg), including 35 Japanese patients. The most common TEAEs were nausea (65.9%), fatigue (46.8%), alopecia (45.4%), decreased neutrophil count (37.6%), increased transaminase (29.5%), anemia (28.1%) and vomiting (27.2%). Interstitial lung disease (ILD) occurred in 20.0% of Japanese patients treated with ENHERTU as determined by an independent ILD adjudication committee.

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. Patients should be closely observed during therapy by monitoring for early signs or symptoms of ILD (such as dyspnea, cough or fever) and performing regular 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, a chest CT scan should be performed and medical history taken 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 HR positive, HER2 low or HER2 ultralow unresectable or recurrent breast cancer has not been established. ENHERTU should be administered only to patients who have been confirmed to have low or ultralow HER2 expression based on approved in vitro diagnostics or medical devices performed at testing facilities or by pathologists with sufficient experience.

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 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=152 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 Japan, breast cancer is the most common cancer in women.[1] Approximately 92,000 cases of breast cancer were diagnosed in Japan in 2022, with approximately 17,600 deaths.[1] 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 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.[5] 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.[6] 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.[7] 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.[8,9]

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 85 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 85 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 40 countries 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 has 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 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 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 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 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 DATROWAY, 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 & Co., Inc, Rahway, NJ, USA. 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.

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.

Media Contacts:

Global/US:
Jennifer Brennan
Daiichi Sankyo
jennifer.brennan@daiichisankyo.com
+1 908 900 3183 (mobile)

Japan:
Daiichi Sankyo Co., Ltd.
DS-PR_jp@daiichisankyo.com

Investor Relations Contact:
DaiichiSankyoIR_jp@daiichisankyo.com

References:

[1] Globocan 2022. Japan. Accessed August 2025.
[2] National Cancer Institute. SEER Cancer Stat Facts: Female Breast Cancer Subtypes. Accessed August 2025.
[3] Sajjadi E, et al. *Cancer Drug Resist.* 2022;5(4):882-888.
[4] Bray F, et al. *CA Cancer J. Clin.* 2024; 10.3322/caac.21834.
[5] Iqbal N, et al. *Mol Biol Int.* 2014;852748.
[6] Ahn S, et al. *J Pathol Transl Med.* 2020;54(1):34-44.
[7] Manohar P, et al. *Cancer Biol Med*. 2022 Feb 15; 19(2):202–212.
[8] Modi S, et al. *N Engl J Med.* 2022;387:9-20.
[9] Eiger D, et al. *Cancers.* 2021 Mar; 13(5): 1015.