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Daiichi-Sankyo

Press Release

ENHERTU® Plus Pertuzumab Supplemental New Drug Application Submitted in Japan as First-Line Therapy for Patients with HER2 Positive Metastatic Breast Cancer

- Submission based on DESTINY-Breast09 phase 3 trial results that showed ENHERTU plus pertuzumab reduced the risk of disease progression or death by 44% versus THP with a median progression-free survival of greater than three years
- If approved, this ENHERTU-based treatment approach would move into the first-line HER2 positive metastatic setting with potential to become a new standard of care

Tokyo – (October 7, 2025) – Daiichi Sankyo (TSE: 4568) has submitted a supplemental New Drug Application (sNDA) to Japan's Ministry of Health, Labour and Welfare (MHLW) for ENHERTU® (trastuzumab deruxtecan) in combination with pertuzumab for the treatment of patients with HER2 positive unresectable or recurrent breast cancer.

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

HER2 targeted therapies have improved outcomes in HER2 positive metastatic breast cancer; however, prognosis remains poor with most patients experiencing disease progression within two years of first-line treatment with taxane, trastuzumab and pertuzumab (THP), which has been the standard of care for more than a decade.[1,2,3,4]

The sNDA is based on data from the DESTINY-Breast09 phase 3 trial presented during a special late-breaking oral session at the 2025 American Society of Clinical Oncology (#ASCO25) Annual Meeting.

"In DESTINY-Breast09, ENHERTU plus pertuzumab demonstrated a median progression-free survival of more than three years, which represents an impressive improvement over the current standard of care," said Yuki Abe, PhD, Head of R&D Division in Japan and Head of Research, Daiichi Sankyo. "Following the recent approval of ENHERTU in Japan for the treatment of HER2 low or HER2 ultralow metastatic breast cancer, this new submission of ENHERTU plus pertuzumab for the first-line treatment of patients with HER2 positive disease underscores the commitment of Daiichi Sankyo to bring ENHERTU to as many patients as possible in this region across certain subtypes of metastatic breast cancer."

A supplemental Biologics License Application for ENHERTU plus pertuzumab based on data from DESTINY-Breast09 was granted Priority Review in the U.S. under the Real-Time Oncology Review program. The Priority Review follows receipt of Breakthrough Therapy Designation granted by the FDA in July 2025.

About DESTINY-Breast09

DESTINY-Breast09 is a global, multicenter, randomized, open-label, phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) either alone or in combination with pertuzumab versus standard of care THP (a taxane [docetaxel or paclitaxel], trastuzumab and pertuzumab) as a first-line treatment in patients with HER2 positive metastatic breast cancer.

Patients were randomized 1:1:1 to receive either ENHERTU monotherapy with a pertuzumab matching placebo; ENHERTU in combination with pertuzumab; or THP. Randomization was stratified by prior treatment (*de novo* metastatic disease versus progression from early-stage disease), hormone receptor (HR) status and *PIK3CA* mutation status.

The primary endpoint of DESTINY-Breast09 is progression-free survival (PFS) as assessed by blinded independent central review in both the ENHERTU monotherapy and ENHERTU combination arms. Secondary endpoints include investigator-assessed PFS, overall survival, objective response rate, duration of response, pharmacokinetics and safety. The investigational arm assessing ENHERTU monotherapy versus THP remains blinded to patients and investigators and will continue to the final PFS analysis.

DESTINY-Breast09 enrolled 1,157 patients across multiple sites in Africa, Asia, Europe, North America, and South America. For more information about the trial, visit ClinicalTrials.gov.

About HER2 Positive Metastatic Breast Cancer

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[5] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[5] In Japan, breast cancer is the most common cancer in women, with approximately 92,000 cases of breast cancer diagnosed and 17,600 deaths in 2022.[6] While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or progress to metastatic disease are expected to live five years following diagnosis.[7]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast cancer.[8] HER2 protein overexpression may occur as a result of *HER2* gene amplification.[1] Approximately one in five cases of breast cancer are considered HER2 positive.[9]

HER2 positive metastatic breast cancer is an aggressive disease driven by overexpression or amplification of HER2 that affects 15% to 20% of patients with metastatic breast cancer.[10] While HER2 targeted therapies have improved outcomes, prognosis remains poor with most patients experiencing disease progression within two years of first-line treatment with THP, which has been the standard of care for more than a decade.[1,2,3,4] Further, approximately 25% to 30% of patients do not receive any treatment following first-line therapy due to discontinuation or death.[11,12,13]

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/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 45 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 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.

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References:

[1] Pillai R, et al. *Cancer*. 2017;1;123(21):4099-4105.
[2] Swain SM, et al. *Lancet Oncol.* 2020;21(4):519-530.
[3] Blumenthal G, et al. *Clinical Cancer Research*. 2013;19(18).
[4] Tripathy D, et al. *The Oncologist*. 2020;25(2):e214-e222.
[5] Bray F, et al. *CA Cancer J Clin*. 2024;10.3322/caac.21834.
[6] Globocan 2022. Japan. Accessed October 2025.
[7] National Cancer Institute. SEER Cancer Stat Facts: Female Breast Cancer Subtypes. Accessed October 2025.
[8] Iqbal N, et al. *Mol Biol Int*. 2014;852748.
[9] Ahn S, et al. *J Pathol Transl Med.* 2019;54(1):34–44.
[10] Tarantino P, et al. *J An Onc*. 2023;34(8):645-659.
[11] Hartkopf AD, et al. *Geburtshilfe Frauenheilkd*. 2024;84(5):459–469.
[12] Cottu P, et al. *Breast Cancer Research Treatment*. 2025;209:419-430.
[13] Lam C, et al. *The Oncologist.* 2025 Apr 4;30(4).