Press Release

Daiichi-Sankyo

Enhertu® Plus Pertuzumab Approved in the EU as First New Regimen in More than a Decade for First-Line Treatment of Patients with HER2 Positive Metastatic Breast Cancer

- Approval based on DESTINY-Breast09 phase 3 trial results that showed Daiichi Sankyo and AstraZeneca's Enhertu plus pertuzumab reduced the risk of disease progression or death by 44% versus THP with a median progression-free survival exceeding three years
- Second approval for Enhertu in the EU in two months

Tokyo – (September 1, 2026) – Enhertu® (trastuzumab deruxtecan) in combination with pertuzumab has been approved in the European Union (EU) for the first-line treatment of adult patients with unresectable or metastatic HER2 positive (immunohistochemistry [IHC] 3+ or *in-situ* hybridization [ISH]+) breast cancer.

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/NYSE: AZN).

The approval by the European Commission follows the positive opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency and is based on results from the DESTINY-Breast09 phase 3 trial presented at the 2025 American Society of Clinical Oncology Annual Meeting and subsequently published in *The New England Journal of Medicine*.

In DESTINY-Breast09, Enhertu in combination with pertuzumab reduced the risk of disease progression or death by 44% versus a taxane, trastuzumab and pertuzumab (THP) (hazard ratio: 0.56; 95% confidence interval [CI]: 0.44-0.71; p<0.00001) in patients (n=383) with HER2 positive metastatic breast cancer who had not received prior chemotherapy or HER2 targeted therapy or had received neoadjuvant or adjuvant HER2 targeted therapy more than six months before the diagnosis of advanced or metastatic disease. Median progression-free survival (PFS) was 40.7 months (95% CI: 36.5-not estimable [NE]) with Enhertu in combination with pertuzumab compared to 26.9 months (95% CI: 21.8-NE) with THP as assessed by blinded independent central review (BICR). Confirmed objective response rate (ORR) was 85.1% (95% CI: 81.2-88.5) for Enhertu in combination with pertuzumab compared to 78.6% (95% CI: 74.1-82.5) with THP.

"For patients diagnosed with HER2 positive metastatic breast cancer, maintaining disease control for as long as possible in the first-line setting is a critical treatment goal," said Cristina Saura, MD, PhD, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Steering Committee Member and Investigator for the DESTINY-Breast09 trial. "The combination of trastuzumab deruxtecan and pertuzumab represents a significant therapeutic advance, with progression-free survival exceeding three years compared to approximately two years with the current standard of care, and has the potential to become the new first-line standard of care."

In DESTINY-Breast09, the safety profile of Enhertu in combination with pertuzumab was consistent with the known profiles of each individual treatment with no new safety concerns identified. Grade 3 or grade 4 adverse reactions from a pooled safety analysis of 431 patients with unresectable or metastatic breast cancer treated with Enhertu (5.4 mg/kg) in combination with pertuzumab across two clinical trials included neutropenia (24.8%), hypokalemia (13.2%), anemia (10.7%), diarrhea (7.4%), fatigue (7.2%), thrombocytopenia (7.0%), increased transaminases (5.3%), leukopenia (5.1%), nausea (4.9%), lymphopenia (3.9%), decreased ejection fraction (3.2%), decreased weight (2.8%), febrile neutropenia (2.3%), decreased appetite (2.1%), vomiting (2.1%), upper respiratory tract infection (1.6%), pneumonia (1.2%) and stomatitis (1.2%). Grade 5 adverse reactions occurred in 1.6% of patients,

including pneumonia (0.9%), interstitial lung disease (ILD)/pneumonitis (0.5%), dyspnea (0.2%) and febrile neutropenia (0.2%).

“This milestone marks the second new indication for Enhertu in the EU in just two months, following the recent tumor agnostic approval, underscoring our goal to bring this medicine to more eligible patients as quickly as possible,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “This approval of Enhertu in combination with pertuzumab has the potential to reshape clinical practice in the first-line treatment setting for patients with HER2 positive metastatic breast cancer.”

“This approval brings Enhertu to patients in the EU earlier in the course of their metastatic disease and sets a new benchmark for progression-free survival in the first-line setting,” said Dave Fredrickson, Executive Vice President, Oncology Hematology Business Unit, AstraZeneca. “HER2 positive metastatic breast cancer is an aggressive disease, so to give patients the best chance of improving long-term outcomes, it is critical to initiate effective HER2 directed therapy early and continue treatment for as long as patients benefit.”

Based on the results of DESTINY-Breast09, Enhertu in combination with pertuzumab has been included in the ESMO Clinical Practice Guidelines as a Category IA first-line treatment option for patients with metastatic HER2 positive breast cancer, regardless of hormone receptor (HR) status.[1]

Enhertu (5.4 mg/kg) in combination with pertuzumab is approved in more than 40 countries/regions worldwide as a first-line treatment for adult patients with unresectable or metastatic HER2 positive (IHC 3+ or ISH+) breast cancer, as determined by a locally or regionally approved test, based on the results from the DESTINY-Breast09 trial.

Enhertu also is under review in the EU for patients with HER2 positive breast cancer who have residual invasive disease after neoadjuvant HER2 targeted treatment based on data from the DESTINY-Breast05 trial.

Financial Considerations

Following this approval in the EU, an amount of $100 million is due from AstraZeneca to Daiichi Sankyo as a milestone payment for the first-line unresectable or metastatic HER2 positive breast cancer indication. Sales of Enhertu in most EU territories are recognized by Daiichi Sankyo. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

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 as 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 status and *PIK3CA* mutation status.

The primary endpoint of DESTINY-Breast09 is PFS as assessed by BICR in both the Enhertu monotherapy and Enhertu combination arms. Secondary endpoints include investigator-assessed PFS, overall survival, ORR, 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 most common cancer in women worldwide and the leading cause of cancer-related deaths among women.[2] Approximately 2.4 million breast cancer cases were diagnosed in 2024, with more than 690,000 deaths globally.[2] In Europe, approximately 540,000 cases of breast cancer were diagnosed in 2024, with more than 140,000 deaths.[3] While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or whose disease has progressed to metastatic disease are expected to live five years following diagnosis.[4]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast cancer.[5] HER2 protein overexpression may occur as a result of *HER2* gene amplification.[5] Approximately one in five cases of breast cancer is considered HER2 positive.[6]

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.[6] 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.[7,8,9] Further, approximately one in three patients do not receive any treatment following first-line therapy due to disease progression or death.[10,11]

About Enhertu

Enhertu (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed ADC. Designed using the proprietary DXd ADC Technology of Daiichi Sankyo, 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) followed by THP is approved in Brazil, China, India, Singapore and the U.S. as a neoadjuvant treatment for adult patients with HER2 positive (IHC 3+ or ISH+) stage 2 or stage 3 breast cancer based on the results from the DESTINY-Breast11 trial. 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 Brazil, India and the U.S. for the adjuvant treatment of adult patients with HER2 positive breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment based on the DESTINY-Breast05 trial.

Enhertu (5.4 mg/kg) in combination with pertuzumab is approved in more than 40 countries/regions worldwide as a first-line treatment for adult patients with unresectable or metastatic HER2 positive (IHC 3+ or ISH+) breast cancer, as determined by a locally or regionally approved test, based on the results from the DESTINY-Breast09 trial.

Enhertu (5.4 mg/kg) is approved in more than 100 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+ or 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 75 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic hormone receptor 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 100 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 80 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 90 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-Gastric04 trials.

Enhertu (5.4 mg/kg) is approved in more than 45 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, DESTINY-CRC02 and/or HERALD trials. Continued approval in the U.S. 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 nine ADCs in clinical development crafted from ADC technology discovered in-house by Daiichi Sankyo.

The DXd ADC Technology platform of Daiichi Sankyo consists of seven 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 and DS3790 are being developed by Daiichi Sankyo.

Additional ADCs being developed by Daiichi Sankyo include DS3610, which consists of an antibody attached to a novel payload that acts as an agonist of STING, and DS1025, which consists of a CD25 directed antibody attached to an immuno-oncology optimized cytotoxic payload.

Ifinatamab deruxtecan, raludotatug deruxtecan, patritumab deruxtecan, DS-3939, DS3610, DS3790 and DS1025 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 (TSE: 4568) is a global healthcare company committed to becoming a trusted healthcare innovator, transforming the lives of people through its strength in science and technology. The company discovers and develops new standards of care to address diverse medical needs to fulfill its purpose of contributing to the enrichment of quality of life around the world. With a strategic focus on oncology, Daiichi Sankyo is advancing an industry-leading antibody drug conjugate portfolio along with identifying new breakthrough generating technologies to deliver practice-changing medicines to patients, healthcare professionals and society. For more information, please visit www.daiichisankyo.com.

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