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Enhertu plus pertuzumab approved in the US as first new treatment in a decade for the 1st-line treatment of patients with HER2-positive metastatic breast cancer

Based on DESTINY-Breast09 Phase III trial results that showed AstraZeneca and Daiichi Sankyo's Enhertu in combination with pertuzumab reduced the risk of disease progression or death by 44% vs. THP with a median progression-free survival of more than three years

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) in combination with pertuzumab has been approved in the US for the 1st-line treatment of adult patients with unresectable or metastatic HER2-positive breast cancer, as determined by a Food and Drug Administration (FDA)-approved test.

The approval follows Priority Review and Breakthrough Therapy Designation by the FDA and is based on the results of the DESTINY-Breast09 Phase III trial. The data were presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting and published in *The New England Journal of Medicine*.[1]

Sara Tolaney, MD, MPH, Chief of the Division of Breast Oncology, Dana-Farber Cancer Institute and principal investigator for the trial, said: "Trastuzumab deruxtecan plus pertuzumab is the only 1st-line treatment approved in more than a decade to demonstrate a statistically significant improvement in progression-free survival over the current standard regimen for patients with HER2-positive metastatic breast cancer. With a median progression-free survival exceeding three years, versus approximately two years with THP, trastuzumab deruxtecan combined with pertuzumab should become a new 1st-line standard of care in this setting."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "With this approval, we are bringing *Enhertu* to the earliest setting for HER2-positive metastatic breast cancer, where optimising efficacy has an important impact on long term outcomes. The treatment approach with *Enhertu* plus pertuzumab in DESTINY-Breast09 sets a new benchmark of more than three years without disease progression or death for patients in this setting."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, said: "Since its initial approval six years ago, *Enhertu* has transformed the treatment of HER2-positive metastatic breast cancer. With this approval of *Enhertu* in the 1st-line HER2-positive metastatic setting, *Enhertu* once again offers significant improvements in progression-free survival and has practice-changing potential when used in combination with pertuzumab."

In the trial, *Enhertu* in combination with pertuzumab reduced the risk of disease progression or death by 44% versus a taxane, trastuzumab and pertuzumab (THP) (based on a hazard ratio of 0.56; 95% confidence interval [CI] 0.44-0.71; p<0.0001) as a 1st-line treatment for patients with HER2-positive metastatic breast cancer. Median progression-free survival (PFS) was 40.7 months with *Enhertu* plus pertuzumab compared to 26.9 months for THP. The PFS benefit for *Enhertu* plus pertuzumab versus THP was consistent across subgroups.[1]

The safety profile of *Enhertu* plus pertuzumab in DESTINY-Breast09 was consistent with the known profiles of each individual therapy with no new safety concerns identified.

Enhertu is a specifically engineered HER2-directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed and commercialised by AstraZeneca and Daiichi Sankyo.

This application was approved under the FDA's Real-Time Oncology Review (RTOR), an initiative by the FDA to ensure safe and effective treatments are available to patients as early as possible.

This US regulatory submission was also reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. As part of Project Orbis, the *Enhertu* plus pertuzumab 1st-line regimen is under review by Switzerland's Swissmedic (SMC) and Singapore's Health Sciences Authority (HSA). Separate regulatory applications are also under review in other countries.

Financial considerations

Following this approval in the US, an amount of 150m is due from AstraZeneca to Daiichi Sankyo as a milestone payment for the 1st-line unresectable or metastatic HER2-positive breast cancer indication. Sales of *Enhertu* in the US are recognised by Daiichi Sankyo. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

Notes

HER2-positive metastatic breast cancer

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[2] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[2] In the US, more than 300,000 cases of breast cancer are diagnosed annually with more than 42,000 deaths.[3] 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.[4]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours including breast cancer.[5] HER2 protein overexpression may occur as a result of HER2 gene amplification.[6]

Approximately one in five cases of breast cancer are considered HER2-positive.[7]

HER2-positive metastatic breast cancer is an aggressive disease driven by overexpression or amplification of HER2.[8] Approximately 10,000 patients are treated each year in the 1st-line HER2-positive metastatic setting in the US.[9] While HER2-targeted therapies have improved outcomes, prognosis remains poor with most patients experiencing disease progression within two years of 1st-line treatment with THP, which has been the standard of care for more than a decade.[6,10-12] Approximately 25% to 30% of patients do not receive any treatment following 1st-line therapy due to discontinuation or death.[13-15]

DESTINY-Breast09
DESTINY-Breast09 is a global, multicentre, randomised, open-label, Phase III 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 a 1st-line treatment in patients with HER2-positive metastatic breast cancer.

Patients were randomised 1:1:1 to receive either *Enhertu* monotherapy with a pertuzumab matching placebo; *Enhertu* in combination with pertuzumab; or THP. Randomisation 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 PFS as assessed by blinded-independent central review in 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.

Enhertu
Enhertu 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 programme 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 (5.4mg/kg) in combination with pertuzumab is approved in the US as a 1st-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 (5.4mg/kg) is approved in more than 90 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 (5.4mg/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 (5.4mg/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 (5.4mg/kg) is approved in more than 60 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumours 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 US for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (6.4mg/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 (5.4mg/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 tumours 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.

***Enhertu* development programme**
A comprehensive global clinical development programme is underway evaluating the efficacy and safety of *Enhertu* as a monotherapy, in combination or sequentially with other cancer medicines across multiple HER2-targetable cancers.

Daiichi Sankyo collaboration
AstraZeneca and Daiichi Sankyo entered into a global collaboration to jointly develop and commercialise *Enhertu* in March 2019 and *Datroway* (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 *Datroway*.

AstraZeneca in breast cancer
Driven by a growing understanding of breast cancer biology, AstraZeneca is challenging, and redefining, the current clinical paradigm for how breast cancer is classified and treated to deliver even more effective treatments to patients in need - with the bold ambition to one day eliminate breast cancer as a cause of death.

AstraZeneca has a comprehensive portfolio of approved and promising compounds in development that leverage different mechanisms of action to address the biologically diverse breast cancer tumour environment.

With *Enhertu*, AstraZeneca and Daiichi Sankyo are aiming to improve outcomes in patients with HER2-positive, HER2-low and HER2-ultralow metastatic breast cancer and are exploring its potential in earlier lines of treatment and in new breast cancer settings.

In HR-positive breast cancer, AstraZeneca continues to improve outcomes with foundational medicines *Faslodex* (fulvestrant) and *Zoladex* (goserelin) and aims to reshape the HR-positive space with first-in-class AKT inhibitor, *Truqap* (capivasertib), the TROP2-directed ADC, *Datroway* (datopotamab deruxtecan), and next-generation oral SERD and potential new medicine camizestrant.

PARP inhibitor *Lynparza* (olaparib) is a targeted treatment option that has been studied in early and metastatic breast cancer patients with an inherited *BRCA* mutation. AstraZeneca with MSD (Merck & Co., Inc. in the US and Canada) continue to research *Lynparza* in these settings. AstraZeneca is also exploring the potential of saruparib, a potent and selective inhibitor of PARP1, in combination with camizestrant in *BRCA*-mutated, HR-positive, HER2-negative advanced breast cancer.

To bring much-needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is collaborating with Daiichi Sankyo to evaluate the potential of *Datroway* alone and in combination with immunotherapy *Imfinzi* (durvalumab).

AstraZeneca in oncology
AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca
AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Social Media @AstraZeneca.

Contacts
For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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