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Enhertu granted Breakthrough Therapy Designation in the US as post-neoadjuvant therapy for patients with HER2-positive early breast cancer

Tenth Breakthrough Therapy Designation for AstraZeneca and Daiichi Sankyo's Enhertu with the latest based on DESTINY-Breast05 Phase III trial results

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been granted Breakthrough Therapy Designation (BTD) in the US for adult patients with HER2-positive early breast cancer with residual invasive disease in the breast and/or axillary lymph nodes after neoadjuvant treatment and high risk of disease recurrence.

The Food and Drug Administration (FDA) BTD accelerates the development and regulatory review of potential new medicines intended to treat a serious condition and address a significant unmet medical need.

The FDA granted this BTD based on results from the DESTINY-Breast05 Phase III trial presented in a Presidential Symposium at the 2025 European Society for Medical Oncology (ESMO) Congress and subsequently published in *The New England Journal of Medicine*.

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "For patients with residual disease after neoadjuvant treatment, the post-neoadjuvant setting represents a critical opportunity to reduce the risk of recurrence and prevent progression to metastatic disease. This Breakthrough Therapy Designation highlights the impressive clinical benefit of *Enhertu* over the current standard of care and underscores its potential to become an important treatment option in the post-neoadjuvant setting."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo, said: "This tenth Breakthrough Therapy Designation reinforces how *Enhertu* continues to deliver transformational results that advance the treatment of breast cancer. We look forward to working with the FDA with the goal of bringing *Enhertu* to the post-neoadjuvant setting of HER2-positive early breast cancer, as DESTINY-Breast05 clearly demonstrated that *Enhertu* may help halt invasive disease recurrence over the current standard of care, resulting in potentially more patients achieving a cure."

DESTINY-Breast05 is the second positive trial of *Enhertu* in early breast cancer in 2025. The first trial, DESTINY-Breast11, evaluating patients with high-risk HER2-positive disease in the neoadjuvant setting, is currently under review by the FDA.

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.

Notes

Post-neoadjuvant Treatment for HER2-Positive Early Breast Cancer
Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[1] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[1]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours including breast cancer.[2] HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease and poor prognosis in breast cancer.[2] Approximately one in five cases of breast cancer are considered HER2 positive.[3]

For patients with HER2-positive early breast cancer, achieving pathologic complete response (pCR) with neoadjuvant treatment is the earliest indicator of improved long-term survival.[4] However, approximately half of patients who receive neoadjuvant treatment do not experience pCR, putting them at increased risk of disease recurrence.[5-9]

Despite receiving additional treatment with T-DM1 for residual disease in the post-neoadjuvant setting, approximately 20% of patients still experience invasive disease or death, with no reduction in the risk of central nervous system recurrence.[10-11] Once patients are diagnosed with metastatic disease, the five-year survival rate drops from nearly 90% to approximately 30%.[12]

Post-neoadjuvant therapy represents a key opportunity to minimise the risk of recurrence and prevent progression to metastatic disease for patients with residual disease. New treatment options are needed in the early breast cancer setting to help reduce the likelihood of disease progression and improve long-term outcomes for more patients.[13,14]

DESTINY-Breast05
DESTINY-Breast05 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4 mg/kg) versus trastuzumab emtansine (T-DM1) in patients with HER2-positive early breast cancer with residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy and a high risk of recurrence. High risk of recurrence was defined as presentation with inoperable cancer (prior to neoadjuvant therapy) or pathologically positive axillary lymph nodes following neoadjuvant therapy.

The primary endpoint of DESTINY-Breast05 is investigator-assessed invasive disease-free survival (IDFS). IDFS is defined as the time from randomisation until first invasive local, axillary or distant recurrence or death from any cause. The key secondary endpoint is investigator-assessed disease-free survival. Other secondary endpoints include overall survival, distant recurrence-free interval, brain metastases-free interval and safety.

DESTINY-Breast05 enrolled 1,635 patients in Asia, Europe, North America, Oceania 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
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