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Enhertu approved in the US as first HER2-directed therapy for patients with HER2-low or HER2-ultralow metastatic breast cancer following disease progression after one or more endocrine therapies

Based on DESTINY-Breast06 Phase III trial results which showed Enhertu demonstrated superiority vs. chemotherapy with a median progression-free survival of more than one year

Approval brings AstraZeneca and Daiichi Sankyo's Enhertu to an earlier HR-positive treatment setting and broadens the patient population eligible for treatment with a HER2-directed therapy to those with HER2-ultralow disease

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been approved in the US 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 Food and Drug Administration (FDA)-approved test, that has progressed on one or more endocrine therapies in the metastatic setting.

The approval was granted by the FDA after securing Priority Review and Breakthrough Therapy Designation and was based on results from the DESTINY-Breast06 Phase III trial, which were presented at the 2024 American Society of Clinical Oncology (ASCO) Meeting and published in [The New England Journal of Medicine](#).

Aditya Bardia, MD, MPH, Program Director of Breast Oncology and Director of Translational Research Integration, UCLA Health Jonsson Comprehensive Cancer Center, US, and investigator in the DESTINY-Breast06 trial, said: "Endocrine therapy is typically used in the initial treatment of HR-positive metastatic breast cancer and following progression, subsequent chemotherapy is associated with poor outcomes. With a median progression-free survival exceeding one year and a response rate of more than 60 per cent, trastuzumab deruxtecan offers a potential new standard of care for patients with HR-positive, HER2-low or HER2-ultralow metastatic breast cancer following endocrine therapy."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "Building on the practice-changing previous approvals for *Enhertu*, this new approval brings this important medicine to an earlier treatment setting and a broader patient population with HER2-expressing metastatic breast cancer. The approval also highlights the importance of testing metastatic breast cancer tumours for detectable staining with a standard IHC test to identify those who may be eligible for treatment with *Enhertu* following endocrine therapy."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, said: "*Enhertu* continues to redefine the classification and treatment of HR-positive metastatic breast cancer with important new data across the spectrum of HER2 expression. Today's approval underscores our ongoing commitment to realising the full potential of this innovative antibody drug conjugate and represents another paradigm shift in how certain breast cancers can be treated."

Krissa Smith, Vice President, Education, Susan G. Komen, said: "We are excited to see more treatment options for these patients which enable more personalised care. It is critical for patients to understand the HER2 status of their metastatic breast cancer to help them make informed treatment decisions. Patients with tumours that are HER2-low or HER2-ultralow now have more options to consider with their healthcare team."

In the trial, *Enhertu* showed a 36% reduction in the risk of disease progression or death versus chemotherapy (hazard ratio [HR] 0.64; 95% confidence interval [CI]: 0.54-0.76; $p < 0.0001$) in the overall trial population of patients with chemotherapy-naïve HER2-low or HER2-ultralow metastatic breast cancer. A median progression-free survival (PFS) of 13.2 months was seen in patients randomised to *Enhertu* compared to 8.1 months in those randomised to chemotherapy. The confirmed objective response rate (ORR) in the overall trial population was 62.6% for *Enhertu* versus 34.4% for chemotherapy.

In an exploratory analysis of patients with HER2-ultralow expression, results were seen to be consistent between patients with HER2-low expression and HER2-ultralow expression.

HER2 status in the trial was confirmed by a central laboratory and was performed on a tumour sample obtained at the time of initial metastatic diagnosis or later. Approximately 85-90% of patients with HR-positive, HER2-negative metastatic breast cancer were determined to have actionable levels of HER2-expression.¹ Further, nearly two-thirds of patients previously assessed as IHC 0 at a local laboratory were classified as HER2-low or HER2-ultralow upon central analysis of the tumour sample.¹

The safety profile of *Enhertu* in DESTINY-Breast06 was consistent with previous clinical trials of *Enhertu* in breast cancer 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.

Enhertu is already approved in more than 70 countries, including the US, for patients with HER2-low metastatic 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. Regulatory applications are under review in the EU, Japan and several other countries based on the DESTINY-Breast06 results.

Financial considerations

Following this approval for *Enhertu* in the US, an amount of 175m is due from AstraZeneca to Daiichi Sankyo as a milestone payment for the HER2-low and HER2-ultralow chemotherapy-naïve breast

Sankyo as a milestone payment for the HER2-low and HER2-ultralow chemotherapy-naïve breast cancer indication. The milestone will be capitalised as an addition to the upfront payment made by AstraZeneca to Daiichi Sankyo in 2019 and subsequent capitalised milestones and will be amortised through the profit and loss statement.

Sales of *Enhertu* in the US are recognised by Daiichi Sankyo. AstraZeneca reports its share of gross profit margin from *Enhertu* sales in the US as Alliance Revenue in the Company's financial statements.

Further details on the financial arrangements were set out in the [March 2019 announcement](#) of the collaboration.

Notes

Breast cancer and HER2 expression

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.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 Patients with high levels of HER2 expression (IHC 3+ or 2+/ISH+) are classified as HER2-positive and treated with HER2-directed therapies, representing approximately 15-20% of all breast cancers.⁶ Historically, tumours that were not classified as HER2-positive were classified as HER2-negative.⁷

HR-positive, HER2-negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.⁴ Endocrine therapies are widely given consecutively in the early lines of treatment for HR-positive metastatic breast cancer. However, after initial treatment, further efficacy from endocrine therapy is often limited.⁸ The current standard of care following endocrine therapy is chemotherapy, which is associated with poor response rates and outcomes.⁸⁻¹¹

Despite being classified as HER2-negative, many of these tumours may still carry some level of HER2 expression.⁷ Prior to the approvals of *Enhertu* in HER2-low or HER2-ultralow metastatic breast cancer based on the DESTINY-Breast04 and DESTINY-Breast06 trials, there were no targeted therapies specifically approved for these patient populations.^{12,13}

DESTINY-Breast06

DESTINY-Breast06 is a global, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) versus investigator's choice of chemotherapy (capecitabine, paclitaxel or nab-paclitaxel) in patients with HR-positive, HER2-low (IHC 1+ or 2+/ISH-) or HER2-ultralow (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 were also 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 1st-line treatment or received endocrine therapy as an adjuvant treatment and experienced disease recurrence within 24 months.

The primary endpoint is PFS in the HR-positive, HER2-low patient population as measured by blinded independent central review (BICR). Key secondary endpoints include PFS by BICR in the overall trial population (HER2-low and HER2-ultralow), overall survival (OS) in the HER2-low patient population and OS in the overall trial population. Other secondary endpoints include ORR, duration of response, time to first subsequent treatment or death, time to second subsequent treatment or death and safety.

DESTINY-Breast06 enrolled 866 patients (n=713 for HER2-low and n=153 for HER2-ultralow) in Asia, Europe, Australia, 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) is approved in more than 75 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC 3+ or in-situ hybridisation [ISH] +) breast cancer who have received a (or one or more) 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 75 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 the US for adult patients with unresectable or metastatic HR-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting based on the results

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 (5.4mg/kg) is approved in more than 50 countries 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 65 countries worldwide for the treatment of adult patients with locally advanced or metastatic *HER2*-positive (IHC 3+ or 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 will depend on whether a randomised controlled confirmatory clinical trial can demonstrate clinical benefit in this population.

Enhertu (5.4mg/kg) is approved in the US, Russia, Israel and Brazil 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 the results from the [DESTINY-PanTumor02](#), [DESTINY-Lung01](#) and [DESTINY-CRC02](#) trials. Continued approval for this indication in the US 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* monotherapy across multiple *HER2*-targetable cancers. Trials in combination with other anti-cancer treatments, such as immunotherapy, also are underway.

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 starting to challenge, and redefine, 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*, a *HER2*-directed ADC, AstraZeneca and Daiichi Sankyo are aiming to improve outcomes in previously treated *HER2*-positive and *HER2*-low 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), and next-generation SERD and potential new medicine camizestrant. AstraZeneca is also collaborating with Daiichi Sankyo to explore the potential of TROP2-directed ADC, *Datroway*, in this setting.

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 and to explore its potential in earlier disease.

To bring much-needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is evaluating the potential of *Datroway* alone and in combination with immunotherapy *Imfinzi* (durvalumab), *Truqap* in combination with chemotherapy, and *Imfinzi* in combination with other oncology medicines, including *Lynparza* and *Enhertu*.

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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