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Enhertu approved in the US for two new indications for patients with HER2-positive early breast cancer

Approved for use before surgery based on DESTINY-Breast11 Phase III trial

Approved for use following surgery based on DESTINY-Breast05 Phase III trial

Two new indications bring AstraZeneca and Daiichi Sankyo's Enhertu into curative-intent setting, reinforcing its role across stages of HER2-positive breast cancer

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been approved by the US Food and Drug Administration (FDA) for both the neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer based on results from the DESTINY-Breast11 and DESTINY-Breast05 Phase III trials, respectively.

In the neoadjuvant setting, *Enhertu* followed by a taxane, trastuzumab, and pertuzumab (THP) has been approved for the treatment of adult patients with HER2-positive Stage II or Stage III breast cancer. In the adjuvant setting, *Enhertu* has been approved for the treatment of adult patients with HER2-positive breast cancer who have residual invasive disease following trastuzumab (with or without pertuzumab) and taxane-based treatment.

Shanu Modi, MD, Medical Oncologist, Memorial Sloan Kettering Cancer Center, said: "HER2-positive breast cancer is an aggressive disease, and our goal is to reduce the risk of recurrence for patients as early as possible to achieve the best long-term outcomes. The neoadjuvant setting offers the earliest opportunity to improve outcomes, while the adjuvant setting provides another important chance to prevent recurrence for patients with residual disease after surgery. These two new indications in HER2-positive early breast cancer will evolve how we treat patients in these settings and support trastuzumab deruxtecan as a potential new standard of care in early-stage disease."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "HER2-positive early disease is considered highly curable, however up to one in four patients still experience disease recurrence, underscoring the need for new options in this setting. These approvals mark an important step forward, expanding the possibility of cure to more patients for the first time in many years and positioning *Enhertu* as a foundational treatment in early breast cancer."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. said: "*Enhertu* has redefined the treatment of HER2-expressing breast cancer with practice-changing data across six breast cancer indications in seven years. *Enhertu* is now approved in the US across both early and metastatic HER2-positive breast cancer, accomplishing what we set out to achieve a little over a decade ago for patients at the start of our comprehensive clinical development programme."

Victoria Smart, Senior Vice President, Mission, Susan G. Komen, said: "Providing patients with early breast cancer more options to help prevent progression to metastatic disease can lead to improved outcomes. Progression and recurrence remain among the most significant unmet needs for those diagnosed with early breast cancer, and continued advances in treatment bring new hope to patients and families facing this disease."

In DESTINY-Breast11, *Enhertu* followed by THP as a neoadjuvant treatment demonstrated a pathologic complete response (pCR) rate of 67.3% compared with 56.3% for dose-dense doxorubicin and cyclophosphamide followed by THP [ddAC-THP], an improvement of 11.2% (95% confidence interval [CI] 3.9-18.3; p=0.003). At the time of the pCR analysis, 29 patients (4.5%) had event-free survival (EFS) events, and 12 patients (1.9%) had overall survival (OS) events. The results were published in *Annals of Oncology*.[1]

In DESTINY-Breast05, *Enhertu* as an adjuvant treatment reduced the risk of invasive disease recurrence or death (invasive disease-free survival [IDFS]) by 53% compared to trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with residual invasive disease

following neoadjuvant therapy (hazard ratio [HR] 0.47; 95% CI 0.34-0.66; p<0.0001). At three years, 92.4% of patients in the *Enhertu* arm were alive and free of invasive disease, compared with 83.7% of those in the T-DM1 arm, with 51 (6%) events in the *Enhertu* arm and 102 (12%) in the T-DM1 arm. The results were published in *The New England Journal of Medicine*.[2]

Data from both trials were presented at the 2025 European Society for Medical Oncology (ESMO) Congress.

Based on the DESTINY-Breast05 results, trastuzumab deruxtecan (*Enhertu)* has been included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a Category 1 recommended treatment in the adjuvant setting for patients with HER2-positive early breast cancer with residual disease and a high risk of recurrence following preoperative therapy. See NCCN Guidelines® for detailed recommendations.

No new safety concerns were identified with *Enhertu* in the DESTINY-Breast11 or DESTINY-Breast05 trials.

In DESTINY-Breast11, *Enhertu* followed by THP showed similar rates of drug-related overall adverse events (AEs) and interstitial lung disease (ILD)/pneumonitis as ddAC-THP, and lower rates of Grade 3 or higher AEs, serious AEs, AEs leading to treatment interruptions, left ventricular dysfunction and haematological toxicities.

In DESTINY-Breast05, *Enhertu* and T-DM1 showed similar rates of overall drug-related AEs and Grade 3 or higher AEs. Adjudicated drug-related ILD/pneumonitis occurred in 9.6% of patients in the *Enhertu* arm and 1.6% of patients in the T-DM1 arm. The majority of ILD/pneumonitis events were low grade in both arms. There were seven Grade 3 events and two deaths (Grade 5) in the *Enhertu* arm.

The DESTINY-Breast11 and DESTINY-Breast05 US regulatory submissions were both reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. Separate regulatory applications for both trials are also under review in other countries. DESTINY-Breast05 previously received Priority Review and Breakthrough Therapy Designation by the FDA.

Enhertu is already approved in more than 95 countries, including the US, as a treatment for patients with HER2-positive metastatic breast cancer.

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.

Financial Considerations
Following these approvals in the US, an amount of $155 million is due from AstraZeneca to Daiichi Sankyo as milestone payments for both these indications. 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 early breast cancer
Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[3] More than two million breast cancer cases were diagnosed in 2022, with an estimated 665,000 deaths globally.[3] In the US, more than 320,000 cases of breast cancer are diagnosed annually with over 42,000 deaths.[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 and is often associated with aggressive disease and poor prognosis in breast cancer.[5] An estimated one in five cases of breast cancer is considered HER2-positive.[6] Approximately one in three patients with HER2-positive early-stage breast cancer is considered high-risk, meaning they are more likely to experience disease recurrence and have a poor prognosis, and up to one in four will experience disease recurrence.[7,8]

HER2-positive early breast cancer is generally treated across two phases: the neoadjuvant (pre-surgical) phase and the adjuvant or post-neoadjuvant (post-surgical) phase.

In the neoadjuvant setting, the current standard of care in many regions of the world involves combination chemotherapy regimens.[9] In the US, the current standard of care consists of a combination regimen of carboplatin, trastuzumab, pertuzumab and a taxane.[9,10] For patients with HER2-positive early breast cancer, achieving pCR, defined as no evidence of invasive cancer cells in the removed breast tissue or lymph nodes following treatment with neoadjuvant treatment, is an early indicator of improved long-term survival.[11] Approximately half of patients (39-66%) who receive neoadjuvant treatment do not reach pCR, putting them at increased risk of disease recurrence.[12-16]

In the adjuvant setting, despite receiving additional treatment with current standard of care for residual disease, some patients still experience invasive disease or death.[17] Once patients are diagnosed with metastatic disease, the five-year survival rate drops from nearly 90% to approximately 30%.[18]

DESTINY-Breast11
DESTINY-Breast11 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of neoadjuvant *Enhertu* (5.4mg/kg) monotherapy or *Enhertu* followed by THP compared to ddAC-THP in patients with high-risk HER2-positive early-stage breast cancer.

Patients were randomised 1:1:1 to receive either eight cycles of *Enhertu* monotherapy; four cycles of *Enhertu* followed by four cycles of THP; or four cycles of ddAC followed by four cycles of THP.

The *Enhertu* monotherapy arm was closed early following a recommendation from the Independent Data Monitoring Committee.

The primary endpoint of DESTINY-Breast11 is rate of pCR - defined as no evidence of invasive cancer cells in the removed breast cancer tissue or lymph nodes following treatment. Secondary endpoints include EFS, invasive disease-free survival, overall survival and safety.

DESTINY-Breast11 enrolled 927 patients across multiple sites in Asia, Europe, North America and South America. For more information about the trial, visit ClinicalTrials.gov.

DESTINY-Breast05
DESTINY-Breast05 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) versus 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.

Patients were randomised 1:1 to receive 14 cycles of *Enhertu* or T-DM1.

The primary endpoint of DESTINY-Breast05 is investigator-assessed IDFS, which is defined as the time from randomisation until first invasive local, axillary or distant recurrence or death from any cause. Secondary endpoints include investigator-assessed DFS, overall survival, distant recurrence-free interval, brain metastasis-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) is approved in the US as an adjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following trastuzumab (with or without pertuzumab) and taxane-based treatment based on the DESTINY-Breast05 trial.

Enhertu (5.4mg/kg) followed by THP is approved in the US and China as a neoadjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III 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 (5.4mg/kg) in combination with pertuzumab is approved in the US, Switzerland, United Arab Emirates and Saudi Arabia as a 1st-line treatment for adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer based on the results from the DESTINY-Breast09 trial.

Enhertu (5.4mg/kg) is approved in more than 95 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 95 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 70 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 authorised 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 75 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 85 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 (5.4mg/kg) is approved in more than 15 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, DESTINY-CRC02 and/or HERALD trials. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu **clinical 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 previously treated HER2-positive, HER2-low and HER2-ultralow metastatic breast cancer, and expanding 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 TROP-2-directed ADC, *Datroway*, 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/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Disease, 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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Disclosure: Dr. Modi provides consulting and advisory services to AstraZeneca (and Daiichi Sankyo).

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