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Enhertu recommended for approval in the EU by CHMP for patients with HER2-low or HER2-ultralow metastatic breast cancer following at least one endocrine therapy

Recommendation 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

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been recommended for approval in the European Union (EU) as a monotherapy for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on the 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*.

In the trial, *Enhertu* showed a 38% reduction in the risk of disease progression or death versus chemotherapy (hazard ratio [HR] 0.62; confidence interval [CI] 0.52-0.75; p<0.0001) in patients with chemotherapy-naïve HR-positive, HER2-low metastatic breast cancer with a median progression-free survival (PFS) of 13.2 months versus 8.1 months.

In the overall trial population (patients with HER2-low or HER2-ultralow metastatic breast cancer), the median PFS was 13.2 months in patients randomised to *Enhertu* compared to 8.1 months in those randomised to chemotherapy (HR 0.64; 95% CI 0.54-0.76; p<0.0001). In an exploratory analysis, results were seen to be consistent between patients with HER2-low expression and HER2-ultralow expression.

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "Endocrine therapy is typically used in the initial treatment of HR-positive metastatic breast cancer but as the disease progresses the benefit of continued endocrine therapy is limited, and subsequent standard-of-care chemotherapy is associated with poor outcomes. *Enhertu* has the potential to be the first HER2-directed treatment for patients in the EU with HR-positive, HER2-low or HER2-ultralow metastatic breast cancer directly following endocrine therapy, which would mark an important shift in how patients in this setting are treated."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo, said: "*Enhertu* is the first HER2-directed treatment and antibody drug conjugate to show a progression-free survival of more than one year in patients with HER2-low or HER2-ultralow metastatic breast cancer following endocrine therapy. The CHMP recommendation is encouraging and supports our goal of further developing and advancing the way breast cancer is classified and treated."

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 be HER2-low or HER2-ultralow.[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 was recently approved in the US for patients with HR-positive, HER2-low or HER2-ultralow metastatic breast cancer that has progressed on one or more endocrine therapies in the metastatic setting. In addition to the EU, regulatory applications are under review in Japan and several other countries based on the DESTINY-Breast06 results.

Enhertu is already approved in more than 75 countries, including the EU, for patients with HER2-low metastatic breast cancer who have received prior chemotherapy 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.

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 Europe, approximately 557,000 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] In the DESTINY-Breast06 trial, approximately 85-90% of patients with HR-positive, HER2-negative metastatic breast cancer were determined to be HER2-low or HER2-ultralow.[1]

Prior to the approval of *Enhertu* in HER2-low metastatic breast cancer based on the DESTINY-Breast04 trial, there were no targeted therapies specifically approved for patients with HER2-low expression. There are no targeted therapies specifically approved in the EU for patients with HER2-ultralow expression.[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 objective response rate, 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 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 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 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 TROP-2-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 and to explore its potential in earlier disease. 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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