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

Based on DESTINY-Breast09 Phase III trial which showed AstraZeneca and Daiichi Sankyo's Enhertu plus pertuzumab reduced the risk of disease progression or death by 44% vs. THP with median progression-free survival exceeding three years

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) in combination with pertuzumab has been approved in the European Union (EU) for the 1st-line treatment of adult patients with unresectable or metastatic HER2-positive breast cancer.

The approval by the European Commission follows the positive opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency and is based on results from the DESTINY-Breast09 Phase III trial presented at the 2025 American Society of Clinical Oncology Annual Meeting and subsequently published in *The New England Journal of Medicine*.[1]

Cristina Saura, MD, PhD, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, steering committee member and investigator for the DESTINY-Breast09 trial, said: "For patients diagnosed with HER2-positive metastatic breast cancer, maintaining disease control for as long as possible in the first-line setting is a critical treatment goal. The combination of trastuzumab deruxtecan and pertuzumab represents a significant therapeutic advance, with progression-free survival exceeding three years compared to approximately two years with the current standard of care, and has the potential to become the new first-line standard of care."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "This approval brings *Enhertu* to patients in the EU earlier in the course of their metastatic disease and sets a new benchmark for progression-free survival in the first-line setting. HER2-positive metastatic breast cancer is an aggressive disease, so to give patients the best chance of improving long-term outcomes, it is critical to initiate effective HER2-directed therapy early and continue treatment for as long as patients benefit."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc., said: "This milestone marks the second new indication for *Enhertu* in the EU in just two months following the recent tumour agnostic approval, underscoring our goal to bring this medicine to more eligible patients as quickly as possible. This approval of *Enhertu* in combination with pertuzumab has the potential to reshape clinical practice in the first-line treatment setting for patients with HER2-positive metastatic breast cancer."

In DESTINY-Breast09, *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<0.00001) in patients with HER2-positive metastatic breast cancer who had not received prior chemotherapy or HER2-targeted therapy or had received neoadjuvant or adjuvant HER2-targeted therapy more than six months before the diagnosis of advanced or metastatic disease. Median progression-free survival (PFS) was 40.7 months with *Enhertu* in combination with pertuzumab compared to 26.9 months with THP as assessed by blinded independent central review (BICR).

The safety profile of *Enhertu* plus pertuzumab was consistent with the known profiles of each individual treatment with no new safety concerns identified.

Based on the results of DESTINY-Breast09, *Enhertu* in combination with pertuzumab has been included in the ESMO Clinical Practice Guidelines as a Category IA 1st-line treatment option for patients with metastatic HER2-positive breast cancer, regardless of hormone receptor (HR) status.[2]

Enhertu is also under review in the EU for patients with HER2-positive breast cancer who have residual invasive disease after neoadjuvant HER2-targeted treatment based on data from the DESTINY-Breast05 trial.

Enhertu is a specifically engineered HER2-directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being jointly developed and commercialised by AstraZeneca and Daiichi Sankyo.

Financial considerations
Following this approval in the EU, an amount of $100 million 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 most EU territories 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 most common cancer in women worldwide and the leading cause of cancer-related death among women.[3] Approximately, 2.4 million breast cancer cases were diagnosed in 2024, with more than 690,000 deaths globally.[3] In Europe, approximately 540,000 cases of breast cancer were diagnosed in 2024, with more than 140,000 deaths.[4] While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or whose disease has progressed to metastatic disease are expected to live five years following diagnosis.[5]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours including breast cancer.[6] HER2 protein overexpression may occur as a result of *HER2* gene amplification.[6] Approximately one in five cases of breast cancer is considered HER2-positive.[7]

HER2-positive metastatic breast cancer is an aggressive disease driven by overexpression or amplification of HER2 that affects 15% to 20% of patients with metastatic breast cancer.[7] 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.[8,9,10] Further, approximately one in three patients do not receive any treatment following 1st-line therapy due to disease progression or death.[11,12]

DESTINY-Breast09
DESTINY-Breast09 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) either alone or in combination with pertuzumab versus standard of care THP as 1st-line treatment in patients with HER2-positive metastatic breast cancer who had not received prior chemotherapy or HER2-targeted therapy or had received neoadjuvant or adjuvant HER2-targeted therapy more than six months before the diagnosis of advanced or metastatic disease.

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), HR status and *PIK3CA* mutation status.

The primary endpoint of DESTINY-Breast09 is PFS as assessed by BICR in both the *Enhertu* monotherapy and *Enhertu* combination arms. Secondary endpoints include investigator-assessed PFS, overall survival, overall 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 the proprietary DXd ADC Technology of Daiichi Sankyo, *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) followed by THP is approved in China, India, Singapore, Brazil and the US as a neoadjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or Stage 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) is approved in Brazil, India and the US for the adjuvant treatment for adult patients with HER2-positive breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment based on the DESTINY-Breast05 trial.

Enhertu (5.4mg/kg) in combination with pertuzumab is approved in more than 40 countries/regions worldwide as a 1st-line treatment for adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by a locally or regionally approved test, based on the results from the DESTINY-Breast09 trial.

Enhertu (5.4mg/kg) is approved in more than 100 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 75 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic hormone receptor 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, who 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 100 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 80 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 90 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 45 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 in the US 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, *Etcamah* (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 *Etcamah* 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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