Enhertu recommended for EU approval in HER2-low BC

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Enhertu recommended for approval in the EU by CHMP for patients with HER2-low metastatic breast cancer

AstraZeneca and Daiichi Sankyo's Enhertu is the first HER2-directed therapy to demonstrate a significant survival benefit vs. chemotherapy in this patient population

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been recommended for approval in the European Union (EU) as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

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

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency based its positive opinion on results from the DESTINY-Breast04 Phase III trial, which were presented at the American Society of Clinical Oncology 2022 Annual Meeting and simultaneously published in *The New England Journal of Medicine*.[1]

In the trial, *Enhertu* reduced the risk of disease progression or death by 50% versus physician's choice of chemotherapy (based on a hazard ratio [HR] of 0.50; 95% confidence interval [CI]: 0.40-0.63; p<0.001) in patients with HER2-low metastatic breast cancer with HR-positive or HR-negative disease. A median progression-free survival (PFS) of 9.9 months was seen with *Enhertu* versus 5.1 months in those treated with chemotherapy, as assessed by blinded independent central review (BICR). A 36% reduction in the risk of death (HR 0.64; 95% CI: 0.49-0.84; p=0.001) was seen with *Enhertu* compared to chemotherapy with a median overall survival (OS) of 23.4 months versus 16.8 months.

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "*Enhertu* is the first-ever HER2-directed medicine to show a survival benefit in patients with HER2-low metastatic breast cancer, confirming the importance of targeting lower levels of HER2 expression in patients previously classified as HER2-negative. The CHMP's recommendation is encouraging and supports our ambition to evolve the way breast cancer is classified and treated to ultimately improve patient outcomes."

Ken Takeshita, Global Head, R&D Daiichi Sankyo, said: "This positive CHMP opinion recognises the unmet need in the European Union for patients with HER2-low metastatic breast cancer. Currently, once patients with HR-positive disease progress on hormone therapy there are limited effective treatments, and few targeted options are available for patients with HR-negative disease. We look forward to the European Commission decision and aim to bring *Enhertu* to eligible patients as soon as possible."

The safety profile observed in patients treated with *Enhertu* in the DESTINY-Breast04 trial was consistent with that seen in other trials of *Enhertu* in breast cancer with no new safety signals identified.

Notes

Breast cancer and HER2 expression

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[2] More than two million patients with breast cancer were diagnosed in 2020 with nearly 685,000 deaths globally.[2] In Europe, approximately 531,000 breast cancer patients are diagnosed annually with nearly 141,000 deaths.[3]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours including breast, gastric, lung and colorectal cancers, and is one of many biomarkers expressed in breast cancer tumours.[4]

HER2 expression is currently determined by an immunohistochemistry (IHC) test which estimates the amount of HER2 protein on a cancer cell, and/or an in situ hybridisation (ISH) test, which counts the copies of the HER2 gene in cancer cells.[4,5] HER2 tests provide IHC and ISH scores across the full HER2 spectrum and are routinely used to determine appropriate treatment options for patients with metastatic breast cancer.

HER2-positive cancers are currently defined as HER2 expression measured as IHC 3+ or IHC 2+/ISH+, and HER2-negative cancers are defined as HER2 expression measured as IHC 0, IHC 1+ or IHC 2+/ISH-.[4] However, approximately half of all breast cancers are HER2-low, defined as a HER2 score of IHC1+ or IHC 2+/ISH-.[6-8] HER2-low occurs in both HR-positive and HR-negative disease.[9]

Currently, patients with HR-positive metastatic breast cancer and HER2-low disease have limited effective treatment options following progression on endocrine (hormone) therapy.[10] Additionally, few targeted options are available for those with HR-negative disease.[11]

DESTINY-Breast04

DESTINY-Breast04 is a global, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) versus physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) in patients with HR-positive or HR-negative, HER2-low unresectable and/or metastatic breast cancer previously treated with one or two prior lines of chemotherapy. Patients were randomised 2:1 to receive either *Enhertu* or chemotherapy.

The primary endpoint of DESTINY-Breast04 is PFS in patients with HR-positive disease based on BICR. Key secondary endpoints include PFS based on BICR in all randomised patients (HR-positive and HR-negative disease), OS in patients with HR-positive disease and OS in all randomised patients (HR-positive and HR-negative disease). Other secondary endpoints include PFS based on investigator assessment, objective response rate based on BICR and on investigator assessment, duration of response based on BICR and safety.

DESTINY-Breast04 enrolled 557 patients at multiple sites in Asia, Europe and North 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 topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

Enhertu (5.4mg/kg) is approved in more than 40 countries for the treatment of adult patients with unresectable or metastatic HER2-positive 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* also is approved in several countries for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast01 trial.

Enhertu (5.4mg/kg) is approved in Brazil and the US 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 of the DESTINY-Breast04 trial.

Enhertu (5.4mg/kg) is approved under accelerated approval in the US for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer whose tumours have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (6.4mg/kg) is approved in several countries for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 and/or the DESTINY-Gastric02 trial.

Enhertu development programme

A comprehensive global development programme is underway evaluating the efficacy and safety of *Enhertu* monotherapy across multiple HER2-targetable cancers including breast, gastric, lung and colorectal cancers. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

Regulatory applications for *Enhertu* in breast, non-small cell lung and gastric cancer are currently under review in several countries.

Daiichi Sankyo collaboration

Daiichi Sankyo Company, Limited (TSE: 4568) [referred to as Daiichi Sankyo] and AstraZeneca entered into a global collaboration to jointly develop and commercialise *Enhertu* (a HER2-directed ADC) in March 2019, and datopotamab deruxtecan (DS-1062; a TROP2-directed ADC) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for the manufacturing and supply of *Enhertu* and datopotamab deruxtecan.

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* (trastuzumab deruxtecan), 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 ngSERD and potential new medicine camizestrant as well as a potential first-in-class

AKT kinase inhibitor, capivasertib. AstraZeneca is also collaborating with Daiichi Sankyo to explore the potential of TROP2-directed ADC, datopotamab deruxtecan, in this setting.

PARP inhibitor *Lynparza* (olaparib) is a targeted treatment option that has been studied in early and metastatic breast cancer 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 datopotamab deruxtecan alone and in combination with immunotherapy *Imfinzi* (durvalumab), capivasertib 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 operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

Contacts
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