Enhertu approved in EU in post-ET breast cancer

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Enhertu approved in the EU as first HER2-directed therapy for patients with HR-positive, HER2-low or HER2-ultralow metastatic breast cancer following at least one endocrine therapy

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 earlier in the treatment of HR-positive, HER2-low breast cancer and broadens the eligible patient population to those with HER2-ultralow disease

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been approved 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 approval by the European Commission follows the positive opinion of the Committee for Medicinal Products for Human Use and is based on results from the DESTINY-Breast06 Phase III trial, which were presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting and published in *The New England Journal of Medicine*.

HR-positive, HER2-negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.[1] Despite being classified as HER2-negative, many of these tumours still have some level of HER2 expression. Currently, regardless of HER2 expression, endocrine-based therapies are widely used in the early lines of treatment for HR-positive metastatic breast cancer. Following endocrine-based therapy, some patients discontinue treatment, and others are treated with conventional chemotherapy which is associated with poor response rates and outcomes.[2-5]

Giuseppe Curigliano, MD, PhD, Professor of Medical Oncology at the University of Milan and the Head of the Division of Early Drug Development at the European Institute of Oncology, IRCCS, Italy and principal investigator for the trial, said: "This approval introduces a new treatment option for HR-positive metastatic breast cancers that express HER2. In DESTINY-Breast06, *Enhertu* outperformed chemotherapy, providing progression-free survival of more than one year for patients with HR-positive, HER2-low or HER2-ultralow metastatic breast cancer, demonstrating the benefit of treating these patients with *Enhertu* instead of chemotherapy."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "*Enhertu* continues to open up new approaches to the diagnosis and treatment of patients with metastatic breast cancer. This approval underscores the importance of testing metastatic breast cancer tumours for any IHC staining to identify patients with HR-positive, HER2-low or HER2-ultralow disease who may be eligible for *Enhertu* once sustained responses are no longer achieved with endocrine-based therapy."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, said: "*Enhertu* continues to evolve what is possible with breast cancer treatment, becoming the first HER2-directed medicine approved in the EU for patients with HR-positive metastatic breast cancer with HER2-low or HER2-ultralow expression following endocrine therapy. Today's approval expands the use of *Enhertu* to now include an earlier treatment setting of HER2-low

metastatic breast cancer and broadens the patient population eligible for treatment to those with HER2-ultralow disease."

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 consistent between patients with HER2-low expression and HER2-ultralow expression.

HER2 testing in the trial was conducted by a central laboratory. Approximately 85-90% of patients with HR-positive, HER2-negative metastatic breast cancer screened were determined to be HER2-low or HER2-ultralow.[6]

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 approved in the US earlier this year based on the DESTINY-Breast06 results. Regulatory applications are under review in Japan and several other countries for this indication.

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.

Financial considerations

Following this approval for *Enhertu* in the EU, an amount of $125m is due from AstraZeneca to Daiichi 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 most EU territories are recognised by Daiichi Sankyo. AstraZeneca reports its share of gross profit margin from *Enhertu* sales in those territories as alliance revenue in the Company's financial statements. AstraZeneca will record product sales in respect of sales made in territories where AstraZeneca is the selling party.

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.[7] More than two million breast cancer cases were diagnosed in 2022 with more than 665,000 deaths globally.[7] In Europe, approximately 557,000 cases of breast cancer are diagnosed annually.[8] 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.[1]

HR-positive, HER2-negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.[1] HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours, including breast cancer.[9] 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.[10] Historically, tumours that were not classified as HER2-positive were classified as HER2-negative.[11]

Despite being classified as HER2-negative, many of these tumours may still have some level of HER2 expression detected by IHC.[11] In the DESTINY-Breast06 trial, approximately 85-90% of patients with HR-positive, HER2-negative metastatic breast cancer screened were determined to be HER2-low or HER2-ultralow.[6]

Prior to the approval of *Enhertu* in HER2-low and HER2-ultralow metastatic breast cancer based on the DESTINY-Breast04 and DESTINY-Breast06 trials, there were no HER2-targeted therapies approved specifically for patients with HER2-low or 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. 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.

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, 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 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 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 (5.4mg/kg) is approved in more than 30 countries for the treatment of 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 a locally or regionally approved 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 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 may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (5.4mg/kg) is approved in Brazil, Isreal, Russia and the US 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 TROP2-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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