# Enhertu granted Priority Review for breast cancer

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## *Enhertu* granted Priority Review in the US for patients with HER2-positive metastatic breast cancer treated with a prior anti-HER2-based regimen

***Based on ground-breaking DESTINY-Breast03 results showing AstraZeneca and Daiichi Sankyo's Enhertu reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1)***

***Application being evaluated under FDA Real-Time Oncology Review and Project Orbis***

AstraZeneca and Daiichi Sankyo have received notification of acceptance of the supplemental Biologics License Application (sBLA) of *Enhertu* (trastuzumab deruxtecan) for the treatment of adult patients in the US with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen. The application has also been granted Priority Review.

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

The Food and Drug Administration (FDA) grants Priority Review to applications for medicines that, if approved, would offer significant improvements over available options by demonstrating safety or efficacy improvements, preventing serious conditions, or enhancing patient compliance.[1] The Prescription Drug User Fee Act (PDUFA) date, the FDA action date for their regulatory decision, is during the second quarter of 2022.

The sBLA is being reviewed under the Real-Time Oncology Review (RTOR) programme and Project Orbis, two initiatives of the FDA which are designed to bring effective cancer treatments to patients as early as possible. RTOR allows the FDA to review components of an application before submission of the complete application. Project Orbis provides a framework for concurrent submission and review of oncology medicines among participating international partners.

Breast cancer is the most common cancer worldwide, with more than two million cases diagnosed in 2020, resulting in nearly 685,000 deaths globally.[2] Approximately one in five cases of breast cancer are considered HER2-positive.[3] Despite initial treatment with trastuzumab and a taxane, patients with HER2-positive metastatic breast cancer will often experience disease progression.[4] More treatment options are needed to further delay progression and extend survival.[4-6]

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca said: "This review across geographies and the Priority Review in the US as part of Project Orbis is so important because it speaks to the transformative potential of *Enhertu* based on the unprecedented progression-free survival benefit in this setting. The news reinforces the importance of bringing this potential new option to patients as quickly as possible."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo, said: "This regulatory review of *Enhertu* in the US marks the first time this medicine is participating in both the Real-Time Oncology Review and Project Orbis programmes. The FDA's prioritisation of our application underscores the potential of this medicine and the continued need to expedite the availability of new treatment options, while making it possible to potentially receive approvals in several countries concurrently."

The sBLA is based on data from the DESTINY-Breast03 trial presented during the European Society for Medical Oncology (ESMO) Congress 2021.

In the trial, *Enhertu* demonstrated a 72% reduction in the risk of disease progression or death compared to T-DM1 (hazard ratio [HR] 0.28; 95% confidence interval [CI]: 0.22-0.37; $p=7.8x10^{-22}$) in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane.

DESTINY-Breast03 also recorded that nearly all patients treated with *Enhertu* during the trial were alive at one year (94.1%) compared to 85.9% of patients treated with T-DM1. Confirmed objective response rate (ORR) more than doubled in the *Enhertu* arm versus the T-DM1 arm (79.7% vs. 34.2%). The safety profile of *Enhertu* was consistent with previous clinical trials, with no new safety concerns identified and no Grade 4 or 5 treatment-related interstitial lung disease events.

In September 2021, *Enhertu* received its fourth Breakthrough Therapy Designation (BTD) in the US for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

*Enhertu* is approved 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 in more than 30 countries based on the results from the DESTINY-Breast01 trial.

*Enhertu* is being further assessed in a comprehensive clinical development programme evaluating efficacy and safety across multiple HER2-targetable cancers, including breast, gastric, lung and colorectal cancers.

## Notes

### HER2-positive breast cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths in women worldwide.[2] More than two million patients with breast cancer were diagnosed in 2020, resulting in nearly 685,000 deaths globally.[2] Approximately one in five cases of breast cancer are considered HER2-positive.[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.[7] 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.[8]

Despite initial treatment with trastuzumab and a taxane, people with HER2-positive metastatic breast cancer will often experience disease progression.[4] More treatment options are needed to further delay progression and extend survival.[4-6]

### DESTINY-Breast03

DESTINY-Breast03 is a global head-to-head, randomised, open-label, registrational Phase III trial evaluating the safety and efficacy of *Enhertu* (5.4mg/kg) versus T-DM1 in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane.

The primary efficacy endpoint of DESTINY-Breast03 is progression-free survival (PFS) based on blinded independent central review. Secondary efficacy endpoints include overall survival, ORR, duration of response, PFS based on investigator assessment and safety.

DESTINY-Breast03 enrolled approximately 500 patients at multiple sites 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 topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

*Enhertu* (5.4mg/kg) is approved in more than 30 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. A Type II Variation is currently under review by the European Medicines Agency (EMA) for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast03 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 trial. A Type II Variation is currently under review by the EMA for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior anti-HER2-based regimen.

***Enhertu* development programme**
A comprehensive development programme is underway globally, 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.

*Enhertu* was highlighted in the Clinical Cancer Advances 2021 report as one of two significant advancements in the "ASCO Clinical Advance of the Year: Molecular Profiling Driving Progress in GI Cancers," based on data from both the DESTINY-CRC01 and DESTINY-Gastric01 trials, as well as one of the targeted therapy advances of the year in non-small cell lung cancer (NSCLC), based on the interim results of the HER2-mutated cohort of the DESTINY-Lung01 trial.

**Daiichi Sankyo collaboration**
Daiichi Sankyo Company, Limited (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 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. AstraZeneca aims to continue to transform outcomes for HR-positive breast cancer with foundational medicines *Faslodex* (fulvestrant) and *Zoladex* (goserelin) and the next-generation oral selective oestrogen receptor degrader (SERD) and potential new medicine camizestrant.

PARP inhibitor *Lynparza* (olaparib) is a targeted treatment option for 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 metastatic breast cancer patients with an inherited BRCA mutation and are exploring new opportunities to treat these patients earlier in

their disease.

Building on the first approval of *Enhertu*, a HER2-directed ADC, in previously treated HER2-positive metastatic breast cancer, AstraZeneca and Daiichi Sankyo are exploring its potential in earlier lines of treatment and in new breast cancer settings.

To bring much needed treatment options to patients with triple-negative breast cancer, an aggressive form of breast cancer, AstraZeneca is testing immunotherapy *Imfinzi* (durvalumab) in combination with other oncology medicines, including *Lynparza* and *Enhertu*, evaluating the potential of AKT kinase inhibitor, capivasertib, in combination with chemotherapy, and collaborating with Daiichi Sankyo to explore the potential of TROP2-directed ADC, datopotamab deruxtecan.

**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.

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