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Enhertu demonstrated highly statistically significant and clinically meaningful improvement in invasive disease-free survival vs. T-DM1 in DESTINY-Breast05 Phase III trial in patients with high-risk early breast cancer following neoadjuvant therapy

Second positive Phase III trial of AstraZeneca and Daiichi Sankyo's Enhertu in HER2-positive early breast cancer reinforces its potential to become a foundational treatment option in curative-intent setting

Results from the DESTINY-Breast05 and DESTINY-Breast11 trials will be presented at ESMO 2025 in a Presidential Symposium

Positive high-level results from a planned interim analysis of the DESTINY-Breast05 Phase III trial showed *Enhertu* (trastuzumab deruxtecan) demonstrated a highly statistically significant and clinically meaningful improvement in invasive disease-free survival (IDFS) versus trastuzumab emtansine (T-DM1) in patients with HER2-positive early breast cancer with residual invasive disease in the breast or axillary lymph nodes after neoadjuvant treatment and a high risk of disease recurrence. This is the second positive Phase III trial of *Enhertu* in the HER2-positive early breast cancer setting following positive results from the DESTINY-Breast11 Phase III neoadjuvant trial earlier this year.

Overall survival (OS) was not mature at the time of this planned interim analysis and will be assessed at a subsequent analysis.

Currently, approximately half of patients with HER2-positive early breast cancer have residual disease following neoadjuvant treatment, putting them at an increased risk of disease recurrence.[1-7] Despite receiving additional treatment in the post-neoadjuvant setting with current standards of care, some patients still ultimately experience tumour progression to metastatic disease.[8-10] New treatment options are needed in the early breast cancer setting to help reduce the likelihood of disease progression and improve long-term outcomes for more patients.[10-11]

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "This landmark trial is the first to directly compare *Enhertu* and T-DM1 in early breast cancer, and the results clearly show that *Enhertu* delivers superior outcomes, indicating that it may be a better option for patients with high-risk HER2-positive disease in the post-neoadjuvant setting. These results from DESTINY-Breast05, coupled with DESTINY-Breast11, underscore our commitment to moving *Enhertu* into early-stage HER2-positive breast cancer where patients can achieve sustained long-term outcomes, increasing the opportunity for cure."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo, said: "In patients with early breast cancer with residual disease following neoadjuvant treatment, it is critical to optimise treatment as this represents the last opportunity to prevent progression to metastatic disease. The results of DESTINY-Breast05 demonstrate that treatment with *Enhertu* following surgery increases the length of time patients are able to live free of invasive disease compared to the existing standard of care, potentially offering patients with HER2-positive early breast cancer a new treatment approach in this curative-intent setting."

The safety profile of *Enhertu* observed in DESTINY-Breast05 was consistent with its known profile 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.

Data from DESTINY-Breast05 (Abstract #LBA1) and DESTINY-Breast11 (Abstract #291O) will be presented during Presidential Symposium 1 on 18 October at the upcoming European Society for Medical Oncology (ESMO) Congress 2025. The DESTINY-Breast05 data will also be shared with global regulatory authorities.

DESTINY-Breast05 was conducted in collaboration with the National Surgical Adjuvant Breast and Bowel Project Foundation (NSABP), the German Breast Group (GBG), Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-B) and SOLTI Breast Cancer Research Group.

Notes

HER2-positive early breast cancer
Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[12] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[12]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours including breast cancer.[13] 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.[14] Approximately one in five cases of breast cancer are considered HER2-positive.[15]

Currently, approximately half of patients with HER2-positive early breast cancer have residual disease following neoadjuvant treatment, putting them at an increased risk of disease recurrence.[1-7] Despite receiving additional treatment in the post-neoadjuvant setting, some patients still ultimately experience tumour progression to metastatic disease.[8-10] Once patients are diagnosed with metastatic disease, the five-year survival rate drops from nearly 90 percent to approximately 30 percent.[16] New treatment options are needed in the early breast cancer setting to help reduce the likelihood of disease progression in order to improve long-term outcomes for more patients.[10-11]

DESTINY-Breast05
DESTINY-Breast05 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy

DESTINY-Breast05 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4 mg/kg) versus trastuzumab ematansine (T-DM1) in patients with HER2-positive primary breast cancer that are at high risk of recurrence and have residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy. High risk of recurrence was defined as presentation with inoperable cancer (prior to neoadjuvant therapy) or pathologically positive axillary lymph nodes following neoadjuvant therapy.

The primary endpoint of DESTINY-Breast05 is investigator-assessed IDFS. IDFS is defined as the time from randomisation until first occurrence of invasive breast cancer recurrence, distant recurrence, or death from any cause. The key secondary endpoint is investigator-assessed disease-free survival. Other secondary endpoints include OS, distant recurrence-free interval, brain metastases-free interval and safety.

DESTINY-Breast05 enrolled 1,635 patients in Asia, Europe, Oceania, 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 85 countries/regions 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 85 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 45 countries/regions for the treatment of adult patients with unresectable or metastatic hormone receptor (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 60 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 70 countries/regions 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 by contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (5.4mg/kg) is approved in more than 10 countries/regions 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 and DESTINY-CRC02 trials. Continued approval for this indication 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. 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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