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Enhertu followed by THP before surgery showed statistically significant and clinically meaningful improvement in pathologic complete response in patients with high-risk HER2-positive early-stage breast cancer in DESTINY-Breast11 Phase III trial

AstraZeneca and Daiichi Sankyo's Enhertu followed by THP showed an improved safety profile vs. standard of care

First Phase III trial to demonstrate benefit of Enhertu in early breast cancer

Positive high-level results from the DESTINY-Breast11 Phase III trial showed *Enhertu* (trastuzumab deruxtecan) followed by paclitaxel, trastuzumab and pertuzumab (THP) demonstrated a statistically significant and clinically meaningful improvement in pathologic complete response (pCR) rate versus standard of care (dose-dense doxorubicin and cyclophosphamide followed by THP [ddAC-THP]) when used in the neoadjuvant setting (before surgery) in patients with high-risk, locally advanced HER2-positive early-stage breast cancer. Pathologic complete response is defined as no evidence of invasive cancer cells in the removed breast tissue and lymph nodes following treatment.

The secondary endpoint of event-free survival (EFS) was not mature at the time of analysis; however, EFS data showed an early positive trend favouring *Enhertu* followed by THP compared to standard of care. The trial will continue to follow EFS.

Approximately one in three patients with early-stage breast cancer are considered high risk, as they are more likely to experience disease recurrence and have a poor prognosis.[1,2] Achieving pCR in early-stage HER2-positive breast cancer is associated with improved long-term outcomes.[2,3] The current standard of care in many regions of the world in this neoadjuvant setting involves combination chemotherapy regimens.[2] These regimens often include anthracyclines, which can be challenging for patients to tolerate and may result in long-term cardiovascular side effects.[4] Further, nearly half of patients who receive neoadjuvant treatment do not achieve pCR, reinforcing the need for new treatment options.[2,3]

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "The clinically meaningful improvement in pathologic complete response and the safety data seen in DESTINY-Breast11 highlight the potential of *Enhertu* to challenge the current standard of care in early-stage HER2-positive breast cancer. *Enhertu* is already an important treatment option in the metastatic setting, and these data have the potential to allow this medicine to move into early stages of disease where cure is possible."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo, said: "There are still many patients with early-stage breast cancer who do not achieve a pathologic complete response with treatment in the neoadjuvant setting, increasing the risk of disease recurrence. These topline results from DESTINY-Breast11 demonstrate that *Enhertu* followed by THP could offer patients with HER2-positive breast cancer a promising new treatment approach prior to surgery, setting more patients on a path towards a potential cure."

Enhertu followed by THP showed an improved safety profile compared to ddAC-THP. The safety profiles of *Enhertu* and THP were consistent with the known profiles of each individual medicine with no new safety concerns identified. Rates of interstitial lung disease were similar across the *Enhertu* followed by THP and the ddAC-THP arms as determined by an independent adjudication committee.

Following a recommendation by the Independent Data Monitoring Committee, patient enrolment in a third arm of the trial evaluating *Enhertu* alone was closed after a previous interim efficacy assessment of the trial arms.

Data from DESTINY-Breast11 will be presented at an upcoming medical meeting and shared with regulatory authorities.

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 has demonstrated improved outcomes in six Phase III breast cancer trials across different subtypes and stages of disease, including the recently announced DESTINY-Breast09 Phase III trial in the 1st-line HER2-positive metastatic setting. *Enhertu* is also being studied in several ongoing breast cancer trials including the DESTINY-Breast05 Phase III trial which is evaluating *Enhertu* in the high-risk adjuvant early HER2-positive setting.

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.[5] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[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 and is often associated with aggressive disease and poor prognosis in breast cancer.[7] Approximately one in five cases of breast cancer are considered HER2-positive.[8]

DESTINY-Breast11

DESTINY-Breast11 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of neoadjuvant *Enhertu* (5.4mg/kg) monotherapy or *Enhertu* followed by THP vs. the standard of care regimen in patients with high-risk (lymph node positive [N1-2] or primary tumour stage T2-4), locally advanced or inflammatory

patients with high-risk (lymph node positive [N1-3] or primary tumour stage T3-4), locally advanced or inflammatory HER2-positive early-stage breast cancer.

Patients were randomised 1:1:1 to receive either eight cycles of *Enhertu* monotherapy; four cycles of *Enhertu* followed by four cycles of THP; or four cycles of ddAC (dose-dense doxorubicin and cyclophosphamide) followed by four cycles of THP.

The primary endpoint of DESTINY-Breast11 is pCR (absence of invasive disease in the breast and lymph nodes). Secondary endpoints include EFS, invasive disease-free survival, overall survival and safety.

DESTINY-Breast11 enrolled 927 patients across multiple sites in 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 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 (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 (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 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 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 is 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 will depend on whether a randomised controlled confirmatory clinical trial can demonstrate clinical benefit in this population.

Enhertu (5.4mg/kg) is approved in the US and other countries 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 is 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* as monotherapy or in combination or sequentially with other anti-cancer therapies 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 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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