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This announcement contains inside information

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Enhertu plus pertuzumab demonstrated highly statistically significant and clinically meaningful improvement in progression-free survival vs. THP as 1st-line therapy for patients with HER2-positive metastatic breast cancer

DESTINY-Breast09 Phase III trial of AstraZeneca and Daiichi Sankyo's Enhertu is the first trial in more than a decade to demonstrate superior efficacy across a broad HER2-positive metastatic patient population versus current 1st-line standard of care

Positive high-level results from a planned interim analysis of the DESTINY-Breast09 Phase III trial showed *Enhertu* (trastuzumab deruxtecan) in combination with pertuzumab demonstrated a highly statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to a taxane, trastuzumab and pertuzumab (THP) as a 1st-line treatment for patients with HER2-positive metastatic breast cancer.

The PFS improvement was seen across all pre-specified patient subgroups with *Enhertu* in combination with pertuzumab. The key secondary endpoint of overall survival (OS) was not mature at the time of this planned interim analysis; however, interim OS data showed an early trend favouring the *Enhertu* combination compared with THP.

The second arm assessing *Enhertu* monotherapy versus THP remains blinded to patients and investigators and will continue to the final PFS analysis.

HER2-positive metastatic breast cancer is an aggressive disease driven by overexpression or amplification of HER2 affecting 15-20% of patients with metastatic breast cancer.[1] While HER2-targeted therapies have improved outcomes, prognosis remains poor, with most patients experiencing disease progression within two years of 1st-line treatment with THP, which has been the standard of care for more than a decade.[2-4] Further, approximately one in three patients never go on to receive treatment following 1st-line therapy due to disease progression or death.[5,6]

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "This is the first trial in more than a decade to demonstrate superior efficacy across a broad HER2-positive metastatic breast cancer patient population compared to the current 1st-line standard of care. This is a significant milestone for patients and sets the foundation for *Enhertu* in combination with pertuzumab as an important treatment option in the first-line HER2-positive setting."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo, said: "The results from DESTINY-Breast09 reinforce the importance of effectively targeting HER2 to achieve durable disease control early in the treatment of HER2-positive metastatic breast cancer. Building on the positive results seen with *Enhertu* in the second-line setting, these new findings suggest that starting treatment with *Enhertu* in combination with pertuzumab at the time of metastatic diagnosis delays disease progression, postponing the time until additional treatment may be needed."

The safety profile of *Enhertu* in combination with pertuzumab was consistent with the known profiles of each individual therapy.

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 the combination arm of DESTINY-Breast09 will be presented at an upcoming medical meeting and shared with regulatory authorities.

Enhertu is already approved in more than 75 countries as 2nd-line treatment for patients with HER2-positive breast cancer based on the results from the DESTINY-Breast03 trial.

Notes

HER2-positive metastatic breast cancer
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] 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.[8]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours, including breast cancer.[9] HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease in breast cancer.[1] Approximately one in five cases of breast cancer are considered HER2-positive.[10]

While HER2-targeted therapies have improved outcomes, prognosis remains poor, with most patients experiencing disease progression within two years of 1st-line treatment with THP, which has been the standard of care for more than a decade.[2-4] Further, approximately one in three patients never go on to receive treatment following 1st-line therapy due to disease progression or death.[5,6]

DESTINY-Breast09
DESTINY-Breast09 is a global, multicentre, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) either alone or in combination with pertuzumab versus standard of care THP (a taxane

of *Enhertu* (5.4mg/kg) either alone or in combination with pertuzumab versus standard of care THP (a taxane [docetaxel or paclitaxel], trastuzumab and pertuzumab) as a 1st-line treatment in patients with HER2-positive metastatic breast cancer.

Patients were randomised 1:1:1 to receive either *Enhertu* monotherapy with a pertuzumab matching placebo; *Enhertu* in combination with pertuzumab; or THP. Randomisation was stratified by prior treatment (*de novo* metastatic disease versus progression from early-stage disease), hormone receptor (HR) status and PIK3CA mutation status.

The primary endpoint of DESTINY-Breast09 is PFS as assessed by blinded independent central review in both the *Enhertu* monotherapy and *Enhertu* combination arms. Secondary endpoints include investigator-assessed PFS, overall survival, objective response rate, duration of response, investigator-assessed time to second progression or death, patient-reported tolerability, pharmacokinetics and safety.

DESTINY-Breast09 enrolled 1,157 patients across multiple sites in Africa, 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 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 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 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 TROP-2-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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