AstraZeneca

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Enhertu significantly improved both progression-free and overall survival in DESTINY-Breast04 trial in patients with HER2-low metastatic breast cancer

First HER2-low metastatic breast cancer Phase III results for AstraZeneca and Daiichi Sankyo's Enhertu offer potential to redefine how the disease is classified and treated.

Positive high-level results from the pivotal DESTINY-Breast04 Phase III trial showed *Enhertu*(trastuzumab deruxtecan) demonstrated a statistically significant and clinically meaningful improvement in both progression-free

survival (PFS) and overall survival (OS) in patients with HER2-low unresectable and/or metastatic breast cancer regardless of hormone receptor (HR) status versus physician's choice of chemotherapy.

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

All patients in the trial received a HER2 test, and the results were centrally confirmed. HER2-low status was defined as an immunohistochemistry (IHC) score of 1+ or IHC 2+ with a negative in-situ hybridisation (ISH) score.

Up to 55% of all patients with breast cancer have tumours with a HER2 IHC score of 1+, or 2+ in combination with a negative ISH test, a level of HER2 expression not currently eligible for HER2-targeted therapy.[1,2] HER2-low expression occurs in both HR-positive and HR-negative disease.[3]

HER2 testing is well established to determine an appropriate treatment strategy in metastatic breast cancer. Targeting the lower range of HER2 expression may offer another approach to delay disease progression and extend survival in patients with metastatic breast cancer.[4] Currently, chemotherapy remains the only treatment option both for patients with HR-positive tumours following progression on endocrine (hormone) therapy, and for those who are HR-negative.[5]

DESTINY-Breast04 met its primary endpoint, where *Enhertu* demonstrated superior PFS in previously treated patients with HR-positive HER2-low metastatic breast cancer compared to the standard-of-care chemotherapy. The trial met the key secondary endpoint of PFS in patients with HER2-low metastatic breast cancer regardless of HR status (HR-positive or HR-negative). The trial also met the key secondary endpoints of OS in patients with HR-positive disease and in patients regardless of HR status at interim analysis.

The safety profile of *Enhertu*was consistent with previous clinical trials, with no new safety concerns identified. Overall interstitial lung disease (ILD) rates were consistent with that observed in late-line HER2-positive breast cancer trials of *Enhertu*, with a lower rate of Grade 5 ILD observed as determined by an independent adjudication committee.

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca said: "Today's historic news from DESTINY-Breast04 could reshape how breast cancer is classified and treated. A HER2-directed therapy has never-before shown a benefit in patients with HER2-low metastatic breast cancer. These results for *Enhertu* are a huge step forward and could potentially expand our ability to target the full spectrum of HER2 expression, validating the need to change the way we categorise and treat breast cancer."

Ken Takeshita, Global Head, R&D, Daiichi Sankyo said: "*Enhertu* continues to redefine the treatment of HER2-targetable cancers. DESTINY-Breast04 is the first ever Phase III trial of a HER2-directed therapy in patients with HER2-low metastatic breast cancer to show statistically significant and clinically meaningful benefit in progression-free and overall survival compared to standard treatment. We look forward to sharing the detailed findings of DESTINY-Breast04 with the medical community and initiating discussions with regulatory agencies globally with the goal of bringing *Enhertu* to patients with metastatic breast cancer previously considered to be HER2-negative."

The data will be presented at a forthcoming medical meeting and shared with global health authorities.

Enhertu (5.4mg/kg) is approved in more than 40 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.

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

Breast cancer and HER2 expression

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[6] More than two million cases of breast cancer were diagnosed in 2020 resulting in nearly 685,000 deaths globally.[6]

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, and is one of many biomarkers expressed in breast cancer tumours.[7] HER2 expression is currently defined as either positive or negative, and is determined by an IHC test which measures the amount of HER2 protein in a cancer cell, and/or an ISH test which counts the copies of the HER2 gene in cancer cells.[7,8] HER2-positive cancers are defined as IHC 3+ or IHC 2+/ISH+, and HER2-negative cancers are currently defined as IHC 0, IHC 1+ or IHC 2+/ISH-.[7]

DESTINY-Breast04

DESTINY-Breast04 is a global, randomised, open-label, registrational Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4 mg/kg) versus physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) in patients with HR-positive (n=480) or HR-negative (n=60) HER2-low unresectable and/or metastatic breast cancer previously treated with one or two prior lines of chemotherapy. Patients were randomised 2:1 to receive either *Enhertu*or chemotherapy.

The primary endpoint of DESTINY-Breast04 is PFS in patients with HR-positive disease based on blinded independent central review (BICR). Key secondary endpoints include PFS based on BICR in all randomised patients (regardless of HR status), OS in patients with HR-positive disease and OS in all randomised patients (regardless of HR status). Other secondary endpoints include PFS based on BICR and investigator assessment, duration of response based on BICR and safety.

DESTINY-Breast04 enrolled approximately 540 patients at multiple sites in Asia, Europe and North 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 40 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.

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 (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 trial.

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.

Regulatory applications for *Enhertu* are currently under review in Europe, Japan, the US and several other countries for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen based on the results from the DESTINY-Breast03 trial.

Enhertu also is currently under review in Europe for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior anti-HER2 based regimen based on the DESTINY-Gastric01 and DESTINY-Gastric02 trials.

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. *Lynparza*has also demonstrated a statistically significant and clinically meaningful improvement in invasive disease-free survival versus placebo in the adjuvant treatment of patients with germline BRCA-mutated HER2-negative early breast cancer. 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*, 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.

Contacts

For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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Om AstraZeneca

AstraZeneca (LSE/STO/Nasdaq: AZN) är ett globalt, innovationsdrivet bioläkemedelsföretag med fokus på forskning, utveckling och marknadsföring av receptbelagda läkemedel för sjukdomar inom terapiområdena Onkologi, Sällsynta sjukdomar och Bioläkemedel, inklusive kardiovaskulära sjukdomar, njursjukdomar och metabola sjukdomar (CVRM) samt Andningsvägar och Immunologi. AstraZeneca är baserat i Cambridge i Storbritannien och bedriver verksamhet i över 100 länder. Dess innovativa läkemedel används av miljontals patienter över hela världen.

Mer information finns på: www.astrazeneca.com och www.astrazeneca.se. Du kan även följa oss på twitter https://twitter.com/AstraZenecaSE

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