AstraZeneca

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Enhertu approved in the US for patients with HER2-positive metastatic breast cancer treated with a prior anti-HER2-based regimen

Approval broadens indication for AstraZeneca and Daiichi Sankyo's Enhertu to earlier use in metastatic breast cancer. Based on ground-breaking DESTINY-Breast03 results showing Enhertu reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1).

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been approved in the US for the treatment of adult patients with unresectable or

metastatic HER2-positive 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.

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

The approval by the Food and Drug Administration (FDA) was based on positive results from the DESTINY-Breast03 Phase III trial that showed *Enhertu* reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1) (hazard ratio [HR] 0.28; 95% confidence interval [CI]: 0.22-0.37; p<0.0001) in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane.

The approval was granted under the FDA's Real-Time Oncology Review (RTOR) programme and converts the accelerated approval of *Enhertu* in later line HER2-positive metastatic breast cancer to standard approval, broadening *Enhertu*'s breast cancer indication in the US to earlier lines of use in patients with HER2-positive metastatic breast cancer.

Erika Hamilton, MD, Director of the Breast Cancer and Gynecological Cancer Research Program for Sarah Cannon Research Institute, Nashville, Tennessee, US, said: "*Enhertu*has demonstrated significant progression-free survival in the earlier metastatic setting, potentially establishing it as a new standard of care in previously treated patients with HER2-positive metastatic breast cancer. Today's approval is an important milestone for the clinical community as we will now be able to offer *Enhertu* to these patients earlier in their treatment."

Catherine Ormerod, Executive Vice President, Strategy and Mission, Living Beyond Breast Cancer, said: "This is an important day for the breast cancer community. With this approval, Enhertu now provides a new treatment option for patients with HER2-positive metastatic breast cancer which can be used earlier in treatment to potentially delay progression of disease."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca, said: "*Enhertu* is already established in the later-line treatment

of patients with HER2-positive metastatic breast cancer, and we are thrilled that with this approval, patients in the US will now be able to access the transformative potential of *Enhertu*earlier in their treatment. We look forward to bringing this important, potentially paradigm-shifting medicine to even more patients across the globe in an earlier setting as quickly as possible."

Ken Keller, Global Head, Oncology Business and President and CEO, Daiichi Sankyo, Inc, said: "Today's FDA approval, which converts the accelerated approval of *Enhertu* to regular approval, highlights the importance of the FDA's accelerated pathway that allows for earlier approval of medicines to treat serious medical conditions such as breast cancer. Data from DESTINY-Breast03 not only confirmed the results of DESTINY-Breast01, but also demonstrated the superiority of *Enhertu* in prolonging progression-free survival compared to T-DM1 in an earlier setting of HER2-positive metastatic breast cancer."

The DESTINY-Breast03 Phase III trial results were recently published online in The New England Journal of Medicine.[1] In the trial, 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.

Based on the DESTINY-Breast03 data**,** *fam-trastuzumab deruxtecan-nxki (Enhertu) r*ecently was added to the NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines®) as the Category 1 preferred regimen as second-line therapy for recurrent unresectable (local or regional) or Stage IV HER2-positive disease.[2]

The US regulatory submission was reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. Five national health authorities collaborated with the FDA on this review, including the Australian Therapeutic Goods Administration, the Brazilian Health Regulatory Agency (ANVISA), Health Canada, Israel's Ministry of Health Pharmaceutical Administration and Switzerland's Swissmedic.

This approval follows the recent Priority Review and Breakthrough Therapy Designation of *Enhertu* in the US in this earlier setting.

Regulatory applications for *Enhertu* are currently under review in Europe,

Japan 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.

Notes

Financial considerations

Following this approval for *Enhertu* in the US, an amount of $100m is due from AstraZeneca to Daiichi Sankyo as a 2nd-line milestone payment in HER2-positive metastatic breast cancer. In AstraZeneca, the milestones paid will be capitalised as an addition to the upfront payment made in 2019 and subsequent capitalised milestones and amortised through the profit and loss.

Sales of *Enhertu* in the US are recognised by Daiichi Sankyo. AstraZeneca reports its share of gross profit margin from *Enhertu* sales in the US as collaboration revenue in the Company's financial statements. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

HER2-positive breast cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide and in the US.[3,4]More than two million patients with breast cancer were diagnosed in 2020, with nearly 685,000 deaths globally.[3] More than 290,000 new cases are expected in the US in 2022, with more than 43,000 deaths.[5] Approximately one in five cases of breast cancer are considered HER2-positive.[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.[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, patients with HER2-positive metastatic breast cancer will often experience disease progression.[9] More treatment options are needed to further delay progression and extend

survival.[9-11]

DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomised, open-label, registrational Phase III trial evaluating the efficacy and safety 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, objective response rate (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 the US for the treatment of adult patients with unresectable or metastatic HER2-positive 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 results from the DESTINY-Breast03 trial.

Enhertu (5.4mg/kg) is also approved in approximately 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 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 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 was granted Breakthrough Therapy Designation in the US for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-negative) 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 of the DESTINY-Breast04 trial. Patients with hormone receptor (HR) positive breast cancer should additionally have received or be ineligible for endocrine therapy.

Enhertu is also currently under review in the US for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumours have a HER2 (ERBB2) mutation and who have received a prior systemic therapy, based on the DESTINY-Lung01 trial, and 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 (TSE:4568) [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 that has been studied in HER2-negative 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 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.

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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