Enhertu recommended for breast cancer EU approval

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Enhertu recommended for approval in the EU by CHMP for patients with HER2-positive metastatic breast cancer treated with a prior anti-HER2-based regimen

Recommendation based on DESTINY-Breast03 trial results showing AstraZeneca and Daiichi Sankyo's Enhertu reduced the risk of disease progression or death by 72% vs. trastuzumab emtansine (T-DM1)

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been recommended for approval in the European Union (EU) as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

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

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on results from the DESTINY-Breast03 Phase III trial, which were published in *The New England Journal of Medicine*.[1] In the trial, *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.

In Europe, more than 530,000 cases of breast cancer are diagnosed annually.[2] Approximately one in five cases of breast cancer are considered HER2-positive.[3] Despite initial treatment with trastuzumab, pertuzumab and a taxane, patients with HER2-positive metastatic breast cancer will often experience disease progression.[4,5] More treatment options are needed to further delay progression and extend survival.[4,6,7]

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "This recommendation reflects the transformative progression-free survival benefit seen in the DESTINY-Breast03 trial compared to T-DM1, supporting *Enhertu* as a potential new standard of care and setting a new benchmark in the treatment of HER2-positive metastatic breast cancer. If approved by the European Commission, patients in Europe may be able to benefit from this important medicine earlier in the treatment of their disease, improving their chance for better outcomes."

Gilles Gallant, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo, said: "Today's CHMP opinion provides further validation of the significance of the DESTINY-Breast03 trial results, which for the first time showed superiority of *Enhertu* in prolonging progression-free survival in patients previously treated for HER2-positive metastatic breast cancer as compared to another HER2-directed ADC. This positive CHMP opinion is an important step forward in bringing this potentially practice-changing medicine to patients in Europe to use earlier in the treatment of HER2-positive metastatic breast cancer and builds on the recent approval of *Enhertu* in the US."

The recommendation will now be reviewed by the European Commission, which has the authority to grant marketing authorisations for medicines in the EU.

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

HER2-positive breast cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[8] More than two million cases of breast cancer were diagnosed in 2020, with nearly 685,000 deaths globally.[8] In Europe, more than 530,000 cases of breast cancer are diagnosed annually.[2] Approximately one in five cases of breast cancer are considered HER2-positive.[3]

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.[9] 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.[10]

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DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomised, open-label, registrational Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4 mg/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, duration of response, PFS based on investigator assessment and safety.

DESTINY-Breast03 enrolled 524 patients at multiple sites in Asia, Europe, North America, Oceania and South America. Results from DESTINY-Breast03 have been published in *The New England Journal of Medicine*.[1] 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 (5.4 mg/kg) is approved in Canada, Israel and 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 (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 China, 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 is under review in Europe for the treatment of adult patients with unresectable or metastatic HER2-low (immunohistochemistry (IHC) 1+ or IHC 2+/ in-situ hybridisation (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 from the DESTINY-Breast04 trial. Patients with hormone receptor (HR) positive breast cancer must 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 results of 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.

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 HR-positive breast cancer should additionally have received or be ineligible for endocrine therapy.

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 initial approvals 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

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References

1. Cortes J, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med* 2022; 386:1143-1154.

2. Globocan 2020. Europe Fact Sheets. Available at: https://gco.iarc.fr/today/data/factsheets/populations/908-europe-fact-sheets.pdf. Last accessed: June 2022.

3. Ahn S, et al. HER2 status in breast cancer: changes in guidelines and complicating factors for interpretation. *J Pathol Transl Med*. 2020; 54(1): 34-44.

4. Barok M, et al. Trastuzumab emtansine: mechanism of action and drug resistance. *Breast Cancer Res*. 2014; 16(2):209.

5. Nader-Marta G, et al. How we treat patients with metastatic HER2-positive breast cancer. *ESMO Open*. 2022; 7:1.

6. Mounsey L, et al. Changing Natural History of HER2-Positive Breast Cancer Metastatic to the Brain in the Era of New Targeted Therapies. *Clin Breast Cancer*. 2018; 18(1):29-37.

7. Martinez-S Sáez O, et al. Current and Future Management of HER2-Positive Metastatic Breast Cancer. *JCO Oncol Pract*. 2021. 10.1200/OP.21.00172.

8. Sung H, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021; 10.3322/caac.21660.

9. Iqbal N, et al. Human Epidermal Growth Factor Receptor 2 (HER2) in Cancers: Overexpression and Therapeutic Implications. *Mol Biol Int.* 2014;852748.

10. Pillai R, et al. HER2 mutations in lung adenocarcinomas: A report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;1;123(21):4099-4105.

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