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Enhertu approved in the EU as first tumour agnostic HER2-directed therapy and antibody drug conjugate for patients with previously treated HER2-positive metastatic solid tumours

Based on three Phase II trials of AstraZeneca and Daiichi Sankyo's Enhertu which demonstrated clinically meaningful responses across a broad range of tumours

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been approved in the European Union (EU) as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) solid tumours who have received prior treatment and who have no satisfactory treatment options.

The approval by the European Commission follows the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and is based on results from a subgroup of patients with HER2-positive (IHC 3+) tumours across three Phase II trials, DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02.

Benedikt Westphalen, MD, Head of the Precision Oncology Program, Comprehensive Cancer Center of the University of Munich, Germany, said: "HER2 overexpression occurs across multiple tumour types and is associated with aggressive disease and a poor prognosis. Until now, HER2-directed therapies were only available for specific tumour types. The approval of trastuzumab deruxtecan as a tumour-agnostic therapy opens a new treatment option for patients with HER2-positive cancers regardless of where the tumour originated."

Dave Fredrickson, Executive Vice President, Oncology Haematology Business Unit, AstraZeneca, said: "Precision medicine is reshaping cancer care by helping inform treatment decisions based on the molecular and biological characteristics of a patient's disease. *Enhertu* is already approved in breast, gastric, and lung cancers, and with this approval, clinicians may now consider *Enhertu* for patients with HER2-positive status across multiple additional tumour types. This highlights the importance of biomarker testing to identify eligible patients and ensure that those with HER2-positive disease are considered for targeted treatment."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc., said: "This approval of *Enhertu* marks a significant milestone in the EU for patients with HER2-positive metastatic solid tumours and establishes the first tumour-agnostic indication for a HER2-directed therapy and antibody drug conjugate in the region. *Enhertu* is now approved for six indications in the EU, which demonstrates our commitment to advancing innovative medicines in areas of high unmet need to patients with cancer."

In the DESTINY-PanTumor02 Phase II trial, *Enhertu* demonstrated a confirmed objective response rate (ORR) of 52.3% (95% confidence interval [CI] 42.6-61.8) and median duration of response (DOR) of 21.1 months (95% CI 10.6-25.0) in patients with previously treated centrally or locally assessed IHC 3+ solid tumours (n=111) including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic or other tumours. In DESTINY-Lung01, *Enhertu* demonstrated a confirmed ORR of 52.9% (95% CI 27.8-77.0) and median DOR of 6.9 months (95% CI 4.0-9.8) in patients with previously treated centrally confirmed IHC 3+ non-small cell lung cancer (NSCLC) (n=17). In DESTINY-CRC02, *Enhertu* demonstrated a confirmed ORR of 46.9% (95% CI 34.3-59.8) and median DOR of 5.5 months (95% CI 4.2-8.1) in patients with previously treated centrally confirmed IHC 3+ colorectal cancer (n=64).

The safety profile of *Enhertu* was based on a pooled analysis of patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours enrolled in DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-CRC02 and DESTINY-Breast01, and was consistent with previous clinical trials, with no new safety concerns identified.

Enhertu has received a tumour agnostic indication in the US and other countries based on the DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 trials.

Additional regulatory submissions for *Enhertu* are under review in the EU, including in combination with pertuzumab for the 1st-line treatment of patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer based on data from the DESTINY-Breast09 Phase III trial and for patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease after neoadjuvant HER2-targeted treatment based on data from the DESTINY-Breast05 Phase III trial.

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.

Financial considerations
Following this approval in the EU, an amount of $25 million is due from AstraZeneca to Daiichi Sankyo as a milestone payment for the tumour-agnostic indication. Sales of *Enhertu* in most EU territories are recognised by Daiichi Sankyo. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

Notes

HER2 expression in solid tumours
HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of various tissue cells throughout the body and is involved in normal cell growth.[1] HER2 protein overexpression may occur as a result of *HER2* gene amplification and is often associated with aggressive disease and poor prognosis in some cancers.[2] HER2 overexpression occurs in a range of solid tumours with the prevalence varying by tumour type.[3]

HER2-directed therapies have been used to treat HER2 overexpression in breast, gastric and biliary tract cancers in the EU.[1,4-6] Although HER2 is overexpressed in additional solid tumour types including lung, bladder, cervical, colorectal, endometrial, ovarian, salivary gland and pancreatic cancers, HER2 testing is not routinely performed for these additional tumour types and prior to this approval there were no HER2-directed treatments approved in the EU to treat a broad range of solid tumours.[2,3,7,]

DESTINY-PanTumor02
DESTINY-PanTumor02 is a global, multicentre, multi-cohort, open-label, Phase II trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) for the treatment of previously treated HER2-expressing tumours, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic cancer or other tumours.

The primary endpoint of DESTINY-PanTumor02 is confirmed ORR as assessed by investigator. Secondary endpoints include DOR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, tolerability and pharmacokinetics. Results from DESTINY-PanTumor02 were published in the *Journal of Clinical Oncology*.[8]

DESTINY-PanTumor02 enrolled 267 HER2-positive (IHC 3+ [n=111] and IHC 2+ [n=156]) adult patients at multiple sites in Asia, Europe, North America, South America and Oceania. For more information about the trial, visit ClinicalTrials.gov.

DESTINY-Lung01
DESTINY-Lung01 is a global, open-label, two-cohort, Phase II trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg or 6.4mg/kg) in patients with *HER2*-mutant or HER2-overexpressing unresectable or metastatic NSCLC who had progressed after one or more systemic therapies.

The primary endpoint of DESTINY-Lung01 is confirmed ORR by independent central review. Key secondary endpoints include DOR, DCR, PFS, OS and safety. Results from the *HER2*-mutant cohort were published in *The New England Journal of Medicine* and results from the HER2-overexpressing cohort were published in *The Lancet Oncology*.[9,10]

DESTINY-Lung01 enrolled 181 adult patients (HER2-mutant [n=91] and HER2-overexpressing [n=90; IHC 3+, n=17 and IHC 2+, n=73]) at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

DESTINY-CRC02

DESTINY-CRC02 is a global, randomised, two-arm, parallel, multicentre, Phase II trial evaluating the efficacy and safety of two doses (5.4mg/kg or 6.4mg/kg) of *Enhertu* in patients with locally advanced, unresectable or metastatic HER2-positive (IHC 3+ or IHC 2+) colorectal cancer of BRAF wild-type, RAS wild-type or RAS mutant tumour types previously treated with standard therapy. The trial was conducted in two stages. In the first stage, patients (n=80) were randomised 1:1 to receive either 5.4mg/kg or 6.4mg/kg of *Enhertu*. In the second stage, additional patients (n=42) were enrolled in the 5.4mg/kg arm.

The primary endpoint in DESTINY-CRC02 is confirmed ORR as assessed by blinded independent central review. Secondary endpoints include DOR, DCR, investigator-assessed confirmed ORR, clinical benefit ratio, PFS, OS and safety. Results from DESTINY-CRC02 were published in *The Lancet Oncology*.[11]

DESTINY-CRC02 enrolled 122 adult patients (including 64 patients with IHC 3+ receiving 5.4mg/kg) at multiple sites in Asia, Europe, North America and Oceania. 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 the US as an adjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following trastuzumab (with or without pertuzumab) and taxane-based treatment based on the DESTINY-Breast05 trial.

Enhertu (5.4mg/kg) followed by THP is approved in China and the US as a neoadjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or Stage III breast cancer based on the results from the DESTINY-Breast11 trial. Continued approval in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (5.4mg/kg) in combination with pertuzumab is approved in the US, Switzerland, United Arab Emirates, Saudi Arabia, Israel, Brazil and India as a 1st-line treatment for adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test, based on the results from the DESTINY-Breast09 trial.

Enhertu (5.4mg/kg) is approved in more than 95 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) 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 the results from the DESTINY-Breast03 trial.

Enhertu (5.4mg/kg) is approved in more than 95 countries/regions 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 70 countries/regions worldwide 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 75 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic 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 90 countries/regions worldwide for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 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-Gastric04 trials.

Enhertu (5.4mg/kg) is approved in more than 40 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who have received prior systemic treatment and/or have no satisfactory alternative treatment options based on efficacy results from the DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-CRC02 and/or HERALD trials. trials. Continued approval in the US for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu clinical development programme
A comprehensive global clinical development programme is underway evaluating the efficacy and safety of *Enhertu* as a monotherapy, in combination or sequentially with other cancer medicines 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 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/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Disease, 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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