Enhertu approved in US for HER2-mutant NSCLC

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Enhertu approved in the US as the first HER2-directed therapy for patients with previously treated HER2-mutant metastatic non-small cell lung cancer

Based on DESTINY-Lung02 results which showed AstraZeneca and Daiichi Sankyo's Enhertu reported a confirmed objective response rate of 57.7% in patients with HER2-mutant disease

AstraZeneca and Daiichi Sankyo's *Enhertu* (trastuzumab deruxtecan) has been approved in the US 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 Food and Drug Administration (FDA)-approved test, and who have received a prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DoR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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

The accelerated approval by the FDA was based on the results from the DESTINY-Lung02 Phase II trial. An interim efficacy analysis in a pre-specified patient cohort showed *Enhertu* (5.4mg/kg) demonstrated a confirmed ORR of 57.7% (n=52; 95% confidence interval [CI] 43.2-71.3), as assessed by blinded independent central review (BICR), in patients with previously treated unresectable or metastatic non-squamous HER2-mutant (HER2m) NSCLC. Complete responses (CR) were seen in 1.9% of patients and partial responses (PR) in 55.8% of patients with a median DoR of 8.7 months (95% CI 7.1-NE). Results from the DESTINY-Lung02 trial will be presented at an upcoming medical meeting.

Bob T. Li, MD, PhD, MPH, Medical Oncologist and Physician-Scientist, Memorial Sloan Kettering Cancer Center, US, said: "The approval of trastuzumab deruxtecan in non-small cell lung cancer is an important milestone for patients and the oncology community. After two decades of research into the role of targeting HER2 in lung cancer, the approval of the first HER2-directed treatment option validates HER2 as an actionable target in lung cancer and marks an important step forward for treating this patient population with unmet medical needs."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca, said: "HER2-mutant non-small cell lung cancer is an aggressive form of disease which commonly affects young patients who have faced limited treatment options and a poor prognosis to date. Today's news provides these patients with the opportunity to benefit from a targeted therapy and highlights the importance of testing for predictive markers, including HER2 in lung cancer, at the time of diagnosis to ensure patients receive the most appropriate treatment for their specific disease."

Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc, said: "We are excited that the FDA has granted accelerated approval for *Enhertu* for patients with HER2-mutant metastatic non-small cell lung cancer. *Enhertu* has now been approved in three different tumour types, underscoring its significant potential across several HER2-targetable tumours. We are continuing to evaluate the efficacy and safety of *Enhertu* versus standard chemotherapy in our DESTINY clinical trials in lung cancer."

The safety of *Enhertu* was evaluated in an analysis of 101 patients with unresectable or metastatic HER2m NSCLC who received at least one dose of *Enhertu* (5.4mg/kg) in the DESTINY-Lung02 trial. In the analysis, the safety profile of *Enhertu* was consistent with previous clinical trials with no new safety concerns identified.

Concurrently with this approval, the FDA also approved companion diagnostic tests to detect HER2 mutations in lung tumour tissue and plasma. This is the third tumour type approved by the FDA for *Enhertu* in three years, following approval in breast and gastric cancers. The approval follows the recently received Priority Review in the US as well as the Breakthrough Therapy Designation granted in 2020 by the FDA for this specific type of lung cancer based on the results of the DESTINY-Lung01 trial.

Notes

Financial considerations

Following US approval, an amount of $125m is due from AstraZeneca to Daiichi Sankyo as a milestone payment for the HER2-mutant metastatic NSCLC indication. The milestone will be capitalised as an addition to the upfront payment made by AstraZeneca to Daiichi Sankyo in 2019 and subsequent capitalised milestones, and will be amortised through the profit and loss statement.

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.

Further details on the financial arrangements were set out in the March 2019 announcement of the collaboration.

HER2m NSCLC

Lung cancer is the second most common form of cancer globally, with more than two million patients diagnosed in 2020.[1] In the US, lung cancer is the second most commonly diagnosed cancer, with more than 236,000 patients expected to be diagnosed in 2022.[2] For patients with metastatic NSCLC, prognosis is particularly poor, as only approximately 8% will live beyond five years after diagnosis.[3]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours, including lung, breast, gastric and colorectal cancers. Certain HER2 gene alterations (called HER2 mutations) have been identified in patients with non-squamous NSCLC as a distinct molecular target, and occur in approximately 2-4% of patients with this type of lung cancer.[4,5] Next-generation sequencing is used to identify HER2 (ERBB2) mutations.[6]

While HER2 gene mutations can occur in a range of patients, they are more commonly found in patients with NSCLC who are younger, female and have never smoked.[7] HER2 gene mutations have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[8] Although the role of anti-HER2 treatment is well established in breast and gastric cancers, there were no approved HER2-directed therapies in NSCLC prior to the accelerated approval of *Enhertu* in unresectable or metastatic NSCLC.[8,9]

DESTINY-Lung02

DESTINY-Lung02 is a global Phase II trial evaluating the safety and efficacy of two doses (5.4mg/kg or 6.4mg/kg) of *Enhertu* in patients with HER2m metastatic NSCLC with disease recurrence or progression during or after at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy.

The primary endpoint of the trial is ORR as assessed by BICR. Secondary endpoints include disease control rate (DCR), DoR, progression-free survival (PFS), investigator-assessed ORR, overall survival (OS) and safety.

DESTINY-Lung02 enrolled 152 patients at multiple sites, including Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

DESTINY-Lung01

DESTINY-Lung01 is a global Phase II, open-label, two-cohort trial evaluating the safety and efficacy of *Enhertu* in patients with HER2m (6.4mg/kg) or HER2-overexpressing (defined as IHC 3+ or IHC 2+) [6.4mg/kg and 5.4mg/kg] unresectable and/or metastatic non-squamous NSCLC who had progressed after one or more systemic therapies. The primary endpoint is confirmed ORR by independent central review (ICR). Key secondary endpoints include DoR, DCR, PFS, OS and safety. DESTINY-Lung01 enrolled 181 patients at multiple sites, including Asia, Europe and North America.

Data from the DESTINY-Lung01 Phase II trial was published in *The New England Journal of Medicine*.[10] Primary results from previously-treated patients with HER2-mutations (cohort 2) of DESTINY-Lung01 demonstrated an ORR of 54.9% (95% CI 44.2-65.4) in patients treated with *Enhertu* (6.4mg/kg) as assessed by ICR. One (1.1%) CR and 49 (53.8%) PRs were observed. A confirmed DCR of 92.3% was seen with a reduction in tumour size observed in most patients. After a median follow-up of 13.1 months, the median DoR for *Enhertu* was 9.3 months. The median PFS was 8.2 months and the median OS was 17.8 months.

The safety profile of the most common adverse events with *Enhertu* in DESTINY-Lung01 was consistent with previous clinical trials with no new safety concerns identified. 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 30 countries for the treatment of adult patients with unresectable or metastatic HER2-positive 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 several 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 (5.4mg/kg) is approved in the US 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 chemotherapy 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 the US for the treatment of adult patients with unresectable or metastatic NSCLC whose tumours have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 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* in breast and gastric cancer are currently under review in several countries based on the DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Gastric01 and DESTINY-Gastric02 trials, respectively.

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 (a TROP2-directed ADC) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for the manufacturing and supply of *Enhertu* and datopotamab deruxtecan.

AstraZeneca in lung cancer

AstraZeneca is working to bring patients with lung cancer closer to cure through the detection and treatment of early-stage disease, while also pushing the boundaries of science to improve outcomes in the resistant and advanced settings. By defining new therapeutic targets and investigating innovative approaches, the Company aims to match medicines to the patients who can benefit most.

The Company's comprehensive portfolio includes leading lung cancer medicines and the next wave of innovations, including *Tagrisso* (osimertinib) and *Iressa* (gefitinib); *Imfinzi* (durvalumab) and tremelimumab; *Enhertu* (trastuzumab deruxtecan) and datopotamab deruxtecan in collaboration with Daiichi

Sankyo; *Orpathys* (savolitinib) in collaboration with HUTCHMED; as well as a pipeline of potential new medicines and combinations across diverse mechanisms of action.

AstraZeneca is a founding member of the Lung Ambition Alliance, a global coalition working to accelerate innovation and deliver meaningful improvements for people with lung cancer, including and beyond treatment.

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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Dr. Li has provided uncompensated advisory services to AstraZeneca and Daiichi Sankyo.

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