AstraZeneca

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Enhertu approved in the EU for the treatment of HER2-positive metastatic breast cancer

Approval based on DESTINY-Breast01 Phase II trial which showed clinically meaningful and durable responses in patients with previously treated disease

AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo)'s *Enhertu* (trastuzumab deruxtecan) has been granted conditional 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 two or more prior anti-HER2-based regimens.

In Europe, approximately 531,000 cases of breast cancer in women are diagnosed annually, with an estimated one in five cases being HER2-positive.[1-3] The impact of the disease is significant, with breast cancer responsible for more than 141,000 deaths per year in Europe.[1]

The approval by the European Commission was based on positive results from the single-arm DESTINY-Breast01 Phase II trial, in which *Enhertu* showed clinically meaningful and durable antitumour activity in patients with HER2-positive metastatic breast cancer who had received two or more prior anti-HER2-based regimens.[4] Itfollows the December 2020 recommendation for approval by the Committee for Medicinal Products for Human Use of the European Medicines Agency, which reviewed the application under its accelerated assessment procedure.

Professor Fabrice André, Head of Research, Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France, said: "One in five women with breast cancer have HER2-positive disease and those with previously treated metastatic disease often progress quickly. One of the biggest challenges in this setting has been identifying treatments that produce a durable response. The DESTINY-Breast01 trial showed a breadth, depth and durability of response not previously seen in this patient population."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "*Enhertu* is already transforming outcomes for patients with HER2-positive metastatic breast cancer in the US and Japan, and this approval enables us to bring the benefits of this medicine to patients in the EU. We will continue to explore the potential of *Enhertu* in this setting, as well as in earlier lines of treatment and stages of disease, with the ambition of improving the lives of patients with HER2-targetable breast cancer."

Gilles Gallant, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo, said: "This expedited review underscores the practice-changing potential of *Enhertu* for patients in the metastatic setting. *Enhertu* is the first-ever new medicine to be approved in breast cancer in Europe on the basis of Phase II single-arm data, and one of the fastest accelerated assessment procedures for an application in oncology."

In the DESTINY-Breast01 Phase II trial, after a median follow-up of 20.5 months, *Enhertu* showed a confirmed objective response rate (ORR) of 61.4%, including a 6.5% complete response rate and a 54.9% partial response rate,

and an estimated median duration of response (DoR) of 20.8 months for patients with HER2-positive metastatic breast cancer who had received at least two previous lines of therapy.[4]

The analysis was presented during the 2020 San Antonio Breast Cancer Symposium. An earlier analysis with a median follow-up of 11.1 months was published in The New England Journal of Medicine in February 2020.[5]

The safety of *Enhertu* has been evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of *Enhertu* 5.4mg/kg in clinical trials. The most common adverse reactions were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anaemia, neutropenia, diarrhoea, thrombocytopenia, cough, leukopenia and headache. Cases of interstitial lung disease (ILD) or pneumonitis, were reported in 15.0% of patients, and in 2.6% of patients, ILD led to death.

Enhertu(5.4mg/kg) is approved in the US under accelerated approval, and in Japan under the conditional early approval system 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 in the metastatic setting based on the DESTINY-Breast01 Phase II trial. It is also approved in the US and Japan for the treatment of patients with HER2-positive unresectable advanced or recurrent gastric cancer that has progressed after a trastuzumab-containing regimen based on the DESTINY-Gastric01 Phase II trial.

Enhertu is being further assessed in several ongoing Phase III breast cancer trials as part of a broad development programme, including DESTINY-Breast02, a confirmatory trial in 3rd-line HER2-positive metastatic breast cancer, and DESTINY-Breast03, as a 2nd-line treatment. DESTINY-Breast04 is testing *Enhertu* in patients with metastatic breast cancer and low expression of HER2; and DESTINY-Breast05 is evaluating *Enhertu* as an adjuvant treatment of patients with high-risk HER2-positive early breast cancer. Additional ongoing trials are testing *Enhertu* in combination with other anti-cancer medicines in HER2-positive and HER2-low metastatic breast cancer.

Financial considerations

Following EU approval, an amount of $75m is due from AstraZeneca to

Daiichi Sankyo as a milestone payment for HER2-positive 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 most EU territories are recognised by Daiichi Sankyo. AstraZeneca reports its share of gross profit margin from *Enhertu*sales in those territories as collaboration revenue in the Company's financial statements. AstraZeneca will record product sales in respect of sales made in territories where AstraZeneca is the selling party.

For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

HER2-positive breast cancer

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours, including breast cancer. HER2 overexpression may be associated with a specific HER2 gene alteration known as HER2 amplification and is often associated with aggressive disease and a poor prognosis in breast cancer.[6]

There remain significant unmet clinical needs for patients with HER2-positive metastatic breast cancer. The disease remains incurable with patients eventually progressing after currently available treatment options.[7,8]

DESTINY-Breast01

DESTINY-Breast01 was a single-arm, open-label, global, multicentre, two-part Phase II trial testing the safety and efficacy of *Enhertu* in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine. The primary endpoint of the trial was ORR, as determined by independent central review. Secondary objectives included DoR, disease control rate, clinical benefit rate, progression-free survival and overall survival.

Enhertu

Enhertu (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the

US*)* is a HER2-directed antibody drug conjugate (ADC). It is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced programme in AstraZeneca's ADC scientific platform.

ADCs are targeted cancer medicines that deliver cytotoxic chemotherapy ('payload') to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. *Enhertu* is comprised of a humanised anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab attached to a topoisomerase I inhibitor payload, an exatecan derivative, via by a tetrapeptide-based cleavable linker.

Development programme

A comprehensive development programme is underway globally, with nine registrational trials evaluating the efficacy and safety of *Enhertu* monotherapy across multiple HER2 cancers, including breast, gastric and lung cancers. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

In May 2020, *Enhertu* also received a Breakthrough Therapy Designation for the treatment of patients with metastatic non-small cell lung cancer whose tumours have a HER2 mutation and with disease progression on or after platinum-based therapy.

Daiichi Sankyo collaboration

Daiichi Sankyo and AstraZeneca entered 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 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 SERD and potential new medicine AZD9833. PARP inhibitor, *Lynparza* (olaparib) is a targeted treatment option for 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 state.

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 durvalumab in combination with other oncology medicines, including *Lynparza* and *Enhertu*, assessing 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 has a deep-rooted heritage in oncology and offers a quickly growing portfolio of new medicines that has the potential to transform patients' lives and the Company's future. With seven new medicines launched between 2014 and 2020, and a broad pipeline of small molecules and biologics in development, the Company is committed to advance oncology as a key growth driver for AstraZeneca focused on lung, ovarian, breast and blood cancers.

By harnessing the power of six scientific platforms – Immuno-Oncology, Tumour Drivers and Resistance, DNA Damage Response, Antibody Drug Conjugates, Epigenetics, and Cell Therapies – and by championing the development of personalised combinations, AstraZeneca has the vision to

redefine cancer treatment 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, primarily for the treatment of diseases in three therapy areas - Oncology, 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 är ett globalt, innovationsdrivet bioläkemedelsföretag med fokus på forskning, utveckling och marknadsföring av receptbelagda läkemedel, primärt för behandling av sjukdomar inom tre huvudsakliga terapiområden: cancer, kardiovaskulära sjukdomar, njursjukdomar och metabola sjukdomar och sjukdomar i andningsvägarna. AstraZeneca bedriver verksamhet i över 100 länder och 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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