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First HER2-directed medicine approved for patients with gastric cancer in a decade

AstraZeneca and Daiichi Sankyo Company, Limited (Daiichi Sankyo)'s *Enhertu* (trastuzumab deruxtecan) has been approved in the US 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.

In the US, gastric cancer is most frequently diagnosed in the advanced stage, with only approximately 5% of patients surviving beyond five years.[1,2] Approximately one in five gastric cancers are HER2 positive.[3]

The approval by the Food and Drug Administration (FDA) was based on the positive results from the randomised DESTINY-Gastric01 Phase II trial conducted in Japan and South Korea. In the trial, *Enhertu* demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) and objective response rate (ORR) versus chemotherapy (irinotecan or paclitaxel) in patients with advanced gastric cancer or GEJ adenocarcinoma who had progressed on at least two or more prior regimens including trastuzumab plus a fluoropyrimidine- and platinum-based chemotherapy combination.[4]

Ronan Kelly, MD, MBA, Director of the Charles A. Sammons Cancer Center and the W.W. Caruth, Jr. Chair of Immunology at Baylor University Medical Center, Dallas, Texas, US, said: "Patients with metastatic HER2-positive gastric cancer with progression following 1st-line treatment have historically faced poor outcomes, including low response to treatment and rapid disease progression. This approval represents the first time a HER2-directed medicine has demonstrated a significant improvement in survival compared to chemotherapy following initial treatment in the metastatic setting, and it has the potential to become the new standard of care for this patient population."

Dave Fredrickson, Executive Vice President, Oncology Business Unit, said: "Today's approval of *Enhertu* represents the first HER2-directed medicine approved in a decade for patients with HER2-positive metastatic gastric cancer. The results from the DESTINY-Gastric01 trial highlight the potential to change clinical practice, showing a 41 per cent improvement in survival and a response rate more than three times higher with *Enhertu* compared to chemotherapy. We are thrilled to bring this important medicine to more patients and physicians in the US."

Antoine Yver, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo, said: "*Enhertu* is the first antibody drug conjugate to receive approval in the US for the treatment of patients with metastatic gastric cancer, and represents a major advance in managing this difficult-to-treat disease. This second indication in the US represents an important step forward in our ambitious plan to accelerate the development of *Enhertu* across a broad range of HER2-targetable cancers."

In a pre-specified interim analysis from the DESTINY-Gastric01 trial, patients treated with *Enhertu* had a 41% reduction in the risk of death versus patients treated with chemotherapy (based on a hazard ratio [HR] of 0.59; 95% confidence interval [CI] 0.39-0.88; p=0.0097) with a median OS of 12.5 months versus 8.4 months.[3]

Confirmed ORR, assessed by independent central review was a major efficacy outcome. Results showed a confirmed ORR of 40.5% in patients treated with *Enhertu* (n=126) compared to 11.3% in patients treated with chemotherapy (n=62). Patients treated with *Enhertu* had a 7.9% complete response rate and a 32.5% partial response rate compared to a complete response rate of 0% and a partial response rate of 11.3% for patients treated with chemotherapy.[4]

Enhertu demonstrated a median progression-free survival (PFS) of 5.6 months compared to 3.5 months with chemotherapy (HR=0.47; 95% CI 0.31-0.71). Additionally, *Enhertu* showed a median duration of response (DoR) of 11.3 months versus 3.9 months with chemotherapy.[4]

Results from the DESTINY-Gastric01 trial were published in *The New England Journal of Medicine* in June 2020.[5]

The most common adverse reactions, including laboratory abnormalities, of any grade (greater than or equal to 20%) for patients treated with *Enhertu* (n=125) in the DESTINY-Gastric01 trial were anaemia, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, nausea, decreased appetite, increased aspartate aminotransferase, fatigue, increased blood alkaline phosphatase, increased alanine aminotransferase, diarrhoea, hypokalaemia, vomiting, constipation, increased blood bilirubin, pyrexia and alopecia. Interstitial lung disease or pneumonitis occurred in 10% of patients.[4]

This is the second indication approved for *Enhertu* in the US following the accelerated approval for 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 trial.

Enhertu was previously granted Priority Review, Breakthrough Therapy Designation (BTD) in HER2-positive metastatic gastric cancer and Orphan Drug Designation for gastric cancer by the FDA. Two additional Phase II trials, DESTINY-Gastric02 and DESTINY-Gastric03, are underway, further evaluating treatment with *Enhertu* in patients with HER2-positive metastatic gastric cancer.

Financial considerations

Following US approval, an amount of $115m is due from AstraZeneca to Daiichi Sankyo as a combined 2nd-line and 3rd-line milestone payment in HER2-positive gastric 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.

Gastric cancer

Gastric (stomach) cancer is the fifth most common cancer worldwide and the third leading cause of cancer mortality with a five-year survival rate of 5% for metastatic disease; there were approximately one million new cases reported in 2020 and more than 768,000 deaths.[6] In the US, it is estimated that 27,600 new cases of gastric cancer were diagnosed in 2020 and more than 11,000 people died from the disease.[7]

Approximately one in five gastric cancers are HER2 positive.[1] 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. Gastric cancer is usually diagnosed in the advanced stage, but even when diagnosed in earlier stages of the disease the survival rate remains modest.[2] Recommended 1st-line treatment for HER2-positive advanced or metastatic gastric cancer is combination chemotherapy plus trastuzumab, an anti-HER2 medicine, which has been shown to improve survival outcomes when added to chemotherapy. For patients with metastatic gastric cancer that progresses following initial treatment with a trastuzumab-based regimen, there were previously no other approved HER2-targeted medicines prior to the approval of *Enhertu*.[8]

DESTINY-Gastric01

DESTINY-Gastric01 is a Phase II, open-label, multi-centre, randomised controlled trial testing the safety and efficacy of *Enhertu* (6.4 mg/kg) versus investigator's choice of chemotherapy in a primary cohort of patients from Japan and South Korea with HER2-positive (defined as IHC3+ or IHC2+/ISH+), locally advanced or metastatic gastric cancer or GEJ adenocarcinoma who have progressed on at least two or more prior regimens including trastuzumab plus a fluoropyrimidine- and platinum-based chemotherapy combination. Patients (n=188) were randomised 2:1 to receive *Enhertu* or physician's choice of chemotherapy (paclitaxel or irinotecan monotherapy). Patients were treated with *Enhertu* 6.4mg/kg once every three weeks or chemotherapy.

The main efficacy outcome measures were ORR, assessed by independent central review, and OS. Additional efficacy outcome measures were PFS and DoR.[4]

Enhertu

Enhertu (trastuzumab deruxtecan; fam-trastuzuab 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 a tetrapeptide-based cleavable linker.

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 trial. In addition to the US, *Enhertu* (6.4mg/kg) is also approved in Japan for patients with HER2-positive unresectable advanced or recurrent gastric cancer that progressed after chemotherapy based on the DESTINY-Gastric01 trial.

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* received a BTD 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 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 manufacturing and supply of *Enhertu* and datopotamab deruxtecan.

AstraZeneca in gastrointestinal cancers

AstraZeneca has a broad development programme for the treatment of gastrointestinal (GI) cancers across several medicines spanning a variety of tumour types and stages of disease. In 2020, GI cancers collectively represented over five million new cancer cases leading to more than 3.5 million deaths.[6] Within this programme, the Company is committed to improving outcomes in gastric, liver, oesophageal, pancreatic, and colorectal cancers.

The Company aims to understand the potential of *Enhertu* in the two most common GI cancers, colorectal and gastric cancers. *Imfinzi* (durvalumab) is being assessed as both as monotherapy and in combinations including with tremelimumab across the two main types of liver cancer, hepatocellular carcinoma and biliary tract cancer, and in oesophageal and gastric

cancers. *Lynparza* (olaparib) is a first-in-class PARP inhibitor with a broad and advanced clinical trial programme across multiple GI tumour types including pancreatic and colorectal cancers. *Lynparza* is developed and commercialised in collaboration with MSD (Merck & Co., Inc. inside the US and Canada).

AstraZeneca in oncology

AstraZeneca has a deep-rooted heritage in oncology and offers a quickly growing portfolio ofnew 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 pipelineof 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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