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Daiichi-Sankyo

Press Release

ENHERTU® Approved in the EU for Patients with HER2 Positive Metastatic Breast Cancer Treated with One or More Prior Anti-HER2-Based Regimens

- Approval broadens indication for Daiichi Sankyo and AstraZeneca's ENHERTU across Europe to earlier use in HER2 positive metastatic breast cancer
- Based on groundbreaking DESTINY-Breast03 results in which ENHERTU demonstrated a 72% reduction in the risk of disease progression or death vs. trastuzumab emtansine (T-DM1)

Tokyo and Munich – (July 19, 2022) – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) 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 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 commercialized by Daiichi Sankyo and AstraZeneca.

The approval by the European Commission (EC) follows the positive opinion of the Committee for Medicinal Products for Human Use and is based on results from the DESTINY-Breast03 phase 3 trial, which were published in *The New England Journal of Medicine.* In the DESTINY-Breast03 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; $p<0.000001$) in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. The median progression-free survival (PFS) for patients treated with ENHERTU was not reached (95% CI: 18.5-NE) compared to 6.8 months for T-DM1 (95% CI: 5.6-8.2), as assessed by blinded independent central review (BICR).

In Europe, more than 530,000 patients are diagnosed with breast cancer each year.[1] Approximately one in five patients with breast cancer are considered HER2 positive.[2] Despite initial treatment with trastuzumab, pertuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[3,4]

“This approval is an important milestone for patients and clinicians in Europe, since previously treated patients with HER2 positive metastatic breast cancer typically experience disease progression in less than a year with historical standard of care treatment,” said Javier Cortés, MD, PhD, Head, International Breast Cancer Center (IBCC), Barcelona, Spain. “In the DESTINY-Breast03 trial, the time to progression was extended well beyond a year for patients receiving ENHERTU, illustrating the potential for this medicine to set a new benchmark in the treatment of HER2 positive metastatic breast cancer.”

Additional results from the DESTINY-Breast03 phase 3 trial showed that in the secondary endpoint of overall survival (OS), there was a strong trend towards improved OS with ENHERTU (HR=0.55; 95% CI: 0.36-0.86), however this analysis is not yet mature and further follow-up is ongoing. Nearly all patients treated with ENHERTU were alive at nine months (96.1%; 95% CI: 92.8-97.9) compared to 91.3% of patients treated with T-DM1 (95% CI: 87.1-94.2). Confirmed objective response rate (ORR) was more than doubled in the ENHERTU arm versus the T-DM1 arm (79.7% [n=208; 95% CI: 74.3-84.4] versus 34.2% [n=90; 95% CI: 28.5-40.3]).

The safety of ENHERTU has been evaluated in a pooled analysis of 573 patients across multiple tumor types who had received at least one dose of ENHERTU (5.4 mg/kg) in clinical studies. The median duration of treatment with ENHERTU was 11.3 months (range 0.7-37.9 months). The most common adverse reactions were nausea (77.0%), fatigue (57.2%), vomiting (46.8%), alopecia (38.0%), neutropenia (34.6%), constipation (33.9%), decreased appetite (33.7%), anemia (32.3%), diarrhea (30.7%), musculoskeletal pain (27.4%), transaminases increased (24.4%), leukopenia (24.1%), thrombocytopenia (23.0%), and upper respiratory tract infection (22.7%).

Cases of interstitial lung disease (ILD) or pneumonitis were reported in 12.0% of patients. Most ILD cases were grade 1 (2.6%) and grade 2 (7.3%). Grade 3 cases occurred in 0.7% of patients, no grade 4 cases occurred and grade 5 cases occurred in 1.4% of patients. Patients should be advised to immediately report cough, dyspnea (shortness of breath), fever and/or any new worsening respiratory symptoms. Patients should be monitored for signs and symptoms of ILD or pneumonitis and those with suspected ILD or pneumonitis should be evaluated by radiographic imaging, preferably a computed tomography (CT) scan. Patients with a history of ILD or pneumonitis may be at increased risk.

“We believe there is a significant need to transform outcomes for patients with HER2 positive metastatic breast cancer in Europe,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “In DESTINY-Breast03, treatment with ENHERTU demonstrated superior progression-free survival and a doubling of the response rate compared to another HER2 directed ADC. With this approval we are now able to offer patients with HER2 positive metastatic breast cancer another option earlier in their treatment.”

"With this approval, patients across Europe with HER2 positive metastatic breast cancer will have the opportunity to be treated with ENHERTU even earlier in the treatment of their disease, improving their chance for better outcomes beyond what we can already offer patients treated in later line settings," said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. "Today's news is a further step in achieving our vision to continuously bring the transformative potential of ENHERTU to patients as early as possible in their treatment to improve cancer outcomes."

Based on the results of DESTINY-Breast03, the European Society for Medical Oncology Clinical Practice Guidelines were updated in October 2021 to recommend ENHERTU for use as the preferred second-line therapy for patients with HER2 positive metastatic breast cancer following progression with a taxane and trastuzumab.[5]

As part of this approval, the EC has also extended the market protection period for ENHERTU in this setting by one extra year based on the significant clinical benefit compared to existing approved therapies.

Financial Considerations

Following approval in the EU, an amount of $75 million is due from AstraZeneca to Daiichi Sankyo as a second-line milestone payment in HER2 positive metastatic breast cancer. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

About DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomized, open-label, pivotal phase 3 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 PFS based on blinded independent central review. Overall survival (OS) was a key secondary efficacy outcome measure. Secondary endpoints included ORR, duration of response and PFS based on investigator assessment. 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*. For more information about the trial, visit ClinicalTrials.gov.

About HER2 Positive Breast Cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[6] More than two million patients were diagnosed with breast cancer in 2020, with nearly 685,000 deaths globally.[6] In Europe, more than 530,000 patients are diagnosed with breast cancer each year.[1] Approximately one in five patients with breast cancer are considered HER2 positive.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast, gastric, lung and colorectal cancers.[7] 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.[8]

Despite initial treatment with trastuzumab, pertuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[3,4]

About ENHERTU

ENHERTU (trastuzumab deruxtecan, fam-trastuzumab deruxtecan-nxki in the U.S. only) 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 program 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 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 also 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 (6.4 mg/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.

About the ENHERTU Clinical Development Program

A comprehensive global development program is underway 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, Japan and several other countries for the treatment of adult patients with HER2 positive unresectable or metastatic 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 and Japan for the treatment of adult patients with unresectable or metastatic HER2 low (immunohistochemistry (IHC) 1+ or IHC 2+/*in-situ* hybridization (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 also is currently under review in the U.S. for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have a *HER2 (ERBB2)* mutation and who have received a prior systemic therapy based on the results from the DESTINY-Lung01 and DESTINY-Lung02 trials, 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 recently was granted Breakthrough Therapy Designation in the U.S. 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.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo Company, Limited (referred to as Daiichi Sankyo) and AstraZeneca entered into a global collaboration to jointly develop and commercialize trastuzumab deruxtecan in March 2019 and datopotamab deruxtecan (Dato-DXd) 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 trastuzumab deruxtecan and datopotamab deruxtecan.

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose “to contribute to the enrichment of quality of life around the world.” In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi

Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com.

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