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Daiichi-Sankyo

Press Release

ENHERTU® Recommended for Approval in the EU by CHMP for Patients with Previously Treated HER2 Positive Advanced Gastric Cancer

- Based on DESTINY-Gastric02, which showed Daiichi Sankyo and AstraZeneca's ENHERTU demonstrated clinically meaningful efficacy and DESTINY-Gastric01, which showed improved overall survival compared to chemotherapy

Tokyo and Munich – (November 14, 2022) – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) ENHERTU® (trastuzumab deruxtecan) has been recommended for approval in the European Union (EU) as a monotherapy for the treatment of adult patients with advanced HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

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

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on results from the DESTINY-Gastric02 and the DESTINY-Gastric01 phase 2 trials.

In DESTINY-Gastric02, conducted in patients from North America and Europe, updated results showed treatment with ENHERTU resulted in a confirmed objective response rate (ORR) of 41.8% (95% confidence interval [CI]: 30.8-53.4) as assessed by independent central review (ICR). Median duration of response (DoR) was 8.1 months (95% CI: 5.9-NE). Median overall survival (OS) was 12.1 months (95% CI: 9.4-15.4). Primary results from the DESTINY-Gastric02 phase 2 trial were presented at the 2021 European Society for Medical Oncology (ESMO) Congress with updated data presented at ESMO 2022.

In DESTINY-Gastric01, conducted in patients from Japan and South Korea, treatment with ENHERTU resulted in an ORR of 51.3% (95% CI: 41.9-60.5) versus 14.3% (95% CI: 6.4-26.2) with chemotherapy (irinotecan or paclitaxel) as assessed by ICR ($p<0.0001$). Confirmed ORR, a major efficacy outcome, was 42.0% (95% CI: 33.0-51.4) with ENHERTU versus 12.5% (95% CI: 5.2-24.1) with chemotherapy as assessed by ICR. Patients treated with ENHERTU also had a 40% reduction in the risk of death versus patients treated with chemotherapy (hazard ratio [HR] = 0.60; 95% CI: 0.42-0.86, $p=0.01$) with a median OS

of 12.5 months (95% CI: 10.3-15.2) versus 8.9 months (95% CI: 6.4-10.4). The primary analysis was published in *The New England Journal of Medicine,* with updated data presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting.

The recommendation will now be reviewed by the European Commission, which has the authority to grant marketing authorizations for medicines in the EU.

"ENHERTU is the first HER2 directed medicine to demonstrate a significant improvement in overall survival compared to chemotherapy in patients with gastric cancer following initial treatment with a HER2 directed medicine in the advanced or metastatic setting," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "The CHMP opinion recognizes the high unmet need in this patient population and brings us one step closer to bringing this medicine to patients with gastric cancer in Europe."

"Gastric cancer is usually diagnosed in the advanced stage in many European countries and patients face high mortality rates," said Susan Galbraith, MBBCh, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "If approved, ENHERTU would be the first HER2 directed medicine for patients with advanced gastric cancer in the European Union in more than a decade."

In DESTINY-Gastric02, the safety profile observed with patients treated with ENHERTU was consistent with that seen in other trials of ENHERTU with no new safety signals identified. Grade 3 or higher treatment-emergent adverse events (TEAEs) occurred in 55.7% of patients receiving ENHERTU 6.4 mg/kg. The most common grade 3 or higher treatment-related TEAEs occurring in ≥10% of patients receiving ENHERTU was anemia (13.9%). There were eight cases (10.1%) of treatment-related interstitial lung disease (ILD) or pneumonitis as determined by an independent adjudication committee. The majority (six) were low grade (grade 1 or 2), with two grade 5 ILD or pneumonitis events reported.

In DESTINY-Gastric01, the safety profile observed in patients treated with ENHERTU was consistent with that seen in other trials of ENHERTU with no new safety signals identified. Grade 3 or higher TEAEs occurred in 85.6% of patients receiving ENHERTU 6.4 mg/kg. The most common grade 3 or higher treatment-related TEAEs occurring in ≥20% of patients receiving ENHERTU were decreased neutrophil count (51.2%), anemia (38.4%) and decreased white blood cell count (20.8%). There were 16 cases (12.8%) of treatment-related ILD or pneumonitis as determined by an independent adjudication committee. The majority (13) were low grade (grade 1 or 2), with two grade 3 events and one grade 4 event reported. No grade 5 ILD or pneumonitis events occurred.

ENHERTU is not currently approved in the EU for the treatment of advanced gastric cancer and is subject to additional monitoring.

About DESTINY-Gastric02

DESTINY-Gastric02 is an open-label, single-arm phase 2 trial in Western patients evaluating the efficacy and safety of ENHERTU (6.4 mg/kg) in patients with HER2 positive metastatic and/or unresectable gastric or GEJ adenocarcinoma with disease progression on or after a trastuzumab-containing regimen.

The primary endpoint of DESTINY-Gastric02 is confirmed ORR based on ICR. Secondary endpoints include progression-free survival (PFS), OS, DoR and safety.

DESTINY-Gastric02 enrolled 79 patients at multiple sites in North America and Europe. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Gastric01

DESTINY-Gastric01 is a randomized, open-label phase 2 trial evaluating the efficacy and safety of ENHERTU (6.4 mg/kg) in patients from Japan and South Korea with primarily HER2 positive (defined as immunohistochemistry (IHC) 3+ or IHC 2+/*in-situ* hybridization (ISH)+) advanced gastric cancer or GEJ adenocarcinoma whose tumors have progressed on two or more prior treatment regimens including fluoropyrimidine (5-FU), platinum chemotherapy and trastuzumab. Patients were randomized 2:1 to receive ENHERTU or physician's choice of chemotherapy (paclitaxel or irinotecan monotherapy).

The primary endpoint of DESTINY-Gastric01 is ORR. Secondary endpoints include OS, PFS, DoR, disease control rate and time to treatment failure, as well as pharmacokinetic and safety endpoints.

DESTINY-Gastric01 enrolled 187 patients at multiple sites in Japan and South Korea. For more information about the trial, visit ClinicalTrials.gov.

About HER2 Positive Gastric Cancer

Gastric (stomach) cancer is the fifth most common cancer worldwide and the fourth highest leading cause of cancer mortality, with a five-year global survival rate of 5% to 10% for advanced or metastatic disease.[1,2,3] Approximately one million new patients were diagnosed with gastric cancer in 2020, with 768,000 deaths reported globally.[4] In Europe, approximately 136,000 cases of gastric cancer are diagnosed annually, and Eastern Europe has the second highest incidence of gastric cancer worldwide after Eastern Asia.[3,4] Gastric cancer is the sixth leading cause of cancer death in Europe and is typically diagnosed in the advanced stage. Even when diagnosed in earlier stages of the disease, the survival rate remains modest.[2,5,6]

Approximately one in five gastric cancers are HER2 positive.[7,8] 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 overexpression may be associated with a specific HER2 gene alteration known as HER2 amplification.[8]

Recommended first-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.[9,10] For patients with metastatic gastric cancer that progresses following initial treatment with a trastuzumab-based regimen, treatment options are limited, and in many regions of the world there are no additional HER2 directed medicines available.[1,11,12]

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 35 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 (5.4 mg/kg) is approved in Brazil and the U.S. 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 (5.4 mg/kg) is approved under accelerated approval in the U.S. for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating *HER2 (ERBB2*) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

based on the results of the DESTINY-Lung02 trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory 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 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.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU 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 ENHERTU 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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References
[1] Casamayor M, et al. *Ecancermedicalscience*. 2018;12:883.
[2] SEER Cancer Stat Facts: Stomach Cancer 2012-2018. Accessed November 2022.
[3] Sung H, et al. *Ca Cancer J Clin*. 2021;71:209–249.
[4] WHO. Stomach Cancer Fact Sheet. Accessed November 2022.
[5] WHO. Cancer Today Europe Mortality. Accessed November 2022
[6] Cancer Research UK. Stomach Cancer Survival Statistics. Accessed November 2022.
[7] Iqbal N, et al. *Mol Biol Int*. 2014;2014:852748.
[8] Abrahao-Machado LF, et al. *World J Gastroenterol.* 2016;22(19):4619-4625.
[9] Oditura M, et al. *World J Gastroenterol*. 2014 Feb 21;20(7):1635-49.
[10] Lordick F, et al. *Annals of Oncology*. 2022; 33(10):1012.
[11] Thuss-Patience PC, et al. *Lancet Oncol*. 2017;18(5):640-653.
[12] Satoh T, et al. *J Clin Oncol*. 2014;32(19):2039-2049.