Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

ENHERTU® Approved in the EU for Patients with Previously Treated HER2 Positive Advanced Gastric Cancer

- First HER2 directed medicine to be approved for gastric cancer in the EU in more than a decade
- Based on DESTINY-Gastric02 and DESTINY-Gastric01 where Daiichi Sankyo and AstraZeneca's ENHERTU demonstrated clinically meaningful efficacy

Tokyo and Munich – (December 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 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.

Approximately 136,000 cases of gastric cancer are diagnosed annually in Europe, where it represents the sixth leading cause of cancer death.[1,2] Gastric cancer is typically diagnosed in the advanced stage, and even when the disease is diagnosed at earlier stages, the survival rate remains modest.[3,4] Approximately one in five gastric cancers are HER2 positive.[5,6]

The approval by the European Commission follows the positive opinion of the Committee for Medicinal Products for Human Use in November 2022 and is based on results from the DESTINY-Gastric02 and DESTINY-Gastric01 phase 2 trials.

"Today's news is a welcome advance for patients with HER2 positive advanced gastric cancer," said Eric Van Cutsem, MD, PhD, Head of Department of Oncology, University of Leuven, Belgium and Founding Chair of the ESMO-GI/World Congress of Gastrointestinal Cancers. "Patients with this disease face poor outcomes following progression on initial treatment with a HER2 directed medicine as many do not respond to further treatment, and even those that do respond often do not have durable responses. Data from the DESTINY-Gastric02 and DESTINY-Gastric01 trials support ENHERTU becoming a new standard of care for patients in this setting."

In DESTINY-Gastric02, which enrolled patients from Europe and North America, treatment with ENHERTU (6.4 mg/kg) 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).

In DESTINY-Gastric01, which enrolled patients from Japan and South Korea, treatment with ENHERTU resulted in a confirmed ORR of 40.5% versus 11.3% with chemotherapy (irinotecan or paclitaxel) as assessed by ICR. The median DoR was 11.3 months with ENHERTU versus 3.9 months with chemotherapy. Patients treated with ENHERTU had a 41% reduction in the risk of death versus patients treated with chemotherapy (hazard ratio [HR] = 0.59; 95% CI: 0.39-0.88, p=0.0097) with a median OS of 12.5 months (95% CI: 9.6-14.3) versus 8.4 months (95% CI: 6.9-10.7).

“ENHERTU is the first antibody drug conjugate to be approved in Europe for advanced gastric cancer, representing a major advance in treating this difficult-to-treat cancer,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “With this approval, we can now offer patients with previously treated HER2 positive gastric cancer a treatment with clinically meaningful efficacy.”

“Today’s important approval makes ENHERTU the first HER2 directed medicine to be approved for gastric cancer in the European Union in more than a decade,” said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. “Patients across the EU with advanced HER2 positive disease who have progressed following treatment in the first-line setting may now have the potential opportunity to benefit from treatment with ENHERTU.”

In both trials, the safety profiles observed in patients treated with ENHERTU were consistent with those seen in other trials of ENHERTU with no new safety signals identified. Grade 3 or grade 4 treatment-related adverse events from a pooled safety analysis of patients treated with ENHERTU (6.4 mg/kg) across multiple tumor types in clinical studies included neutropenia (27.9%), anemia (23.1%), leukopenia (12.9%), thrombocytopenia (9.0%), fatigue (8.2%), decreased appetite (8.1%), lymphopenia (7.4%), nausea (5.8%), increased transaminases (4.7%), hypokalemia (4.2%), pneumonia (2.9%), febrile neutropenia (2.9%), vomiting (2.4%), diarrhea (2.1%), decreased weight (2.1%), increased blood alkaline phosphate (1.8%), interstitial lung disease (ILD) (1.6%), dyspnea (1.3%) and decrease ejection fraction (1.1%). Grade 5 treatment-related events occurred in 2.6% of patients including ILD (1.9%).

Financial Considerations

Following approval in the EU, an amount of $35 million is due from AstraZeneca to Daiichi Sankyo as a second-line milestone payment in HER2 positive metastatic gastric cancer. Sales of ENHERTU in most EU territories are recognized by Daiichi Sankyo. For further details on the financial arrangements, please consult the collaboration agreement from March 2019.

About DESTINY-Gastric02

DESTINY-Gastric02 is an open-label, single-arm phase 2 trial in 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. Primary results from the DESTINY-Gastric02 phase 2 trial were presented at the European Society for Medical Oncology (ESMO) Congress 2021 with updated data presented at 2022 ESMO.

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 with primarily HER2 positive (defined as immunohistochemistry (IHC) 3+ or IHC 2+/*in-situ* hybridization (ISH)+) advanced gastric cancer or GEJ adenocarcinoma with disease progression following 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. The primary analysis was published in *The New England Journal of Medicine* with updated data presented at the 2021 American Society of Clinical Oncology Annual Meeting.

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.[3,7,8] Approximately one million new patients were diagnosed with gastric cancer in 2020, with 768,000 deaths reported globally.[2] 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.[2,8] Gastric cancer is the sixth leading cause of cancer death in Europe and is typically diagnosed in the advanced stage, and even when diagnosed in earlier stages of the disease, the survival rate remains modest.[1,3,4]

Approximately one in five gastric cancers are HER2 positive.[5,6] 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.[5] HER2 overexpression may be associated with a specific HER2 gene alteration known as HER2 amplification.[6]

Recommended first-line treatment in the EU 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, there were previously no other approved HER2 directed medicines in the EU prior to the approval of ENHERTU.[7,11,12]

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 40 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 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.

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 and/or DESTINY-Gastric02 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, also are underway.

Regulatory applications for ENHERTU in breast, non-small cell lung and gastric cancers are currently under review in several countries.

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 the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of five ADCs in clinical development across multiple types of cancer. The company's clinical trial stage DXd ADCs include ENHERTU, a HER2 directed ADC and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca; and, patritumab deruxtecan (HER3-DXd), a HER3 directed ADC. Two additional ADCs including ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3

directed ADC, and DS-6000, a CDH6 directed ADC, are being developed through a strategic early-stage research collaboration with Sarah Cannon Research Institute.

Each ADC is designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen. Each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan and DS-6000 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

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.

Media Contacts:

Global:
Victoria Amari
Daiichi Sankyo, Inc.
vamari@dsi.com
+1 908 900 3010 (mobile)

EU:
Simone Jendsch-Dowé
Daiichi Sankyo Europe GmbH
simone.dowe@daiichi-sankyo.eu
+49 (89) 78080 (office)

Japan:
Koji Ogiwara
Daiichi Sankyo Co., Ltd.
ogiwara.koji.ay@daiichisankyo.co.jp
+81 3 6225 1126 (office)

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

References:

[1] WHO. Cancer Today Europe Mortality. Accessed December 2022.
[2] WHO. Stomach Cancer Fact Sheet. Accessed December 2022.
[3] SEER Cancer Stat Facts: Stomach Cancer 2012-2018. Accessed December 2022.
[4] Cancer Research UK. Stomach Cancer Survival Statistics. Accessed December 2022.
[5] Iqbal N, et al. *Mol Biol Int.* 2014; 2014:852748.
[6] Abrahao-Machado LF, et al. *World J Gastroenterol*. 2016;22(19):4619-4625.
[7] Casamayor M, et al. *Ecancermedicalscience*. 2018;12:883.
[8] Sung H, et al. *Ca Cancer J Clin*. 2021;71:209–249.
[9] Oditura M, et al. *World J Gastroenterol*. 2014 Feb 21;20(7):1635-49.
[10] Lordick F, et al. *Ann Oncol*. 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.