Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

ENHERTU® Approved in Japan for Patients with Previously Treated HER2 Positive Metastatic Breast Cancer

- Approval broadens indication for ENHERTU to earlier use in metastatic breast cancer and requirement for confirmatory phase 3 trial as part of conditional early approval system is complete
- Based on groundbreaking DESTINY-Breast03 results where ENHERTU demonstrated a 72% reduction in the risk of disease progression or death versus trastuzumab emtansine (T-DM1)

Tokyo – (November 24, 2022) – Daiichi Sankyo (TSE:5468) today announced that ENHERTU® (trastuzumab deruxtecan) has been approved in Japan for the treatment of adult patients with HER2 positive unresectable or recurrent breast cancer after prior chemotherapy, which includes trastuzumab and a taxane.

The approval by Japan's Ministry of Health, Labour and Welfare (MHLW) was based on the results of the DESTINY-Breast03 trial where ENHERTU demonstrated a 72% reduction in the risk of disease progression or death compared to 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).

Data from DESTINY-Breast03 has met the requirement for a confirmatory phase 3 trial as part of the conditional early approval received in Japan in March 2020.

"We are proud of the quality and speed in which we were able to deliver a confirmatory phase 3 trial that demonstrated the superiority of ENHERTU in prolonging progression-free survival compared to T-DM1 in patients with previously treated HER2 positive metastatic breast cancer," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "This approval by the MHLW highlights the importance of the conditional approval system in Japan that allows for early approval of medicines to treat serious conditions such as breast cancer."

Efficacy and safety of ENHERTU in patients without prior trastuzumab and a taxane, or as a neoadjuvant or adjuvant therapy, has not been established. ENHERTU is approved in Japan with a Warning for Interstitial Lung Disease (ILD). As cases of ILD, including fatal cases, have occurred in ENHERTU-treated patients,

ENHERTU is to be used in close collaboration with a respiratory disease expert. Closely observe patients during therapy by monitoring for early signs or symptoms of ILD (such as dyspnea, cough or fever) and regularly perform peripheral artery oxygen saturation (SpO2) tests, chest X-ray scans and chest CT scans. If abnormalities are observed, discontinue administration of ENHERTU, and take appropriate measures such as corticosteroid administration. Prior to initiation of ENHERTU therapy, perform a chest CT scan and interview to confirm the absence of any comorbidity or history of ILD with the patient and carefully consider the eligibility of the patient for ENHERTU therapy.

The safety profile of ENHERTU in DESTINY-Breast03 was consistent with previous clinical trials with no new safety concerns identified. The most common adverse reactions included nausea (72.8%), fatigue (44.7%), vomiting (44.0%), decreased neutrophil count (42.8%), alopecia (36.2%), anemia (30.4%) and decreased leucocyte count (30.0%). Interstitial lung disease occurred in 22.2% of Japanese patients.

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 BICR. Overall survival was a key secondary efficacy outcome measure. Other secondary endpoints include objective response rate, duration of response, PFS based on investigator assessment and safety.

DESTINY-Breast03 enrolled 524 patients at multiple sites in Asia, Europe, North America, Oceania and South America, including 68 patients from Japan. Results from DESTINY-Breast03 were 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.[1] More than two million patients were diagnosed with breast cancer in 2020, with nearly 685,000 deaths globally.[1] In Japan, breast cancer is the most common cancer in women.[2] Approximately 92,000 patients were diagnosed with breast cancer in Japan in 2020, with approximately 17,000 deaths.[2] Approximately one in five cases of breast cancer are considered HER2 positive.[3]

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.[4] 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.[5]

Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[6,7]

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 (immunohistochemistry (IHC) 1+ or IHC 2+/*in-situ* hybridization (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 a FDA-approved test, and who have received a prior systemic therapy based on the results from 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.

Media Contacts:

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

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] Sung H, et al. *CA Cancer J Clin*. 2021;10.3322/caac.21660.
[2] GLOBOCAN 2020. Cancer Fact Sheets, Japan. Accessed November 2022.
[3] Ahn S, et al. *J Pathol Transl Med*. 2019;54(1):34-44.
[4] Iqbal N, et al. *Mol Biol Int*. 2014;852748.
[5] Pillai R, et al. *Cancer*. 2017;1;123(21):4099-4105.
[6] Barok M, et al. *Breast Cancer Res*. 2014;16(2):209.
[7] Nader-Marta G, et al. *ESMO Open*. 2022;7:1.