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Press Release

Trastuzumab Deruxtecan Supplemental New Drug Application Submitted in Japan for Treatment of Patients with HER2 Positive Metastatic Breast Cancer

- Submission based on groundbreaking DESTINY-Breast03 phase 3 trial, in which trastuzumab deruxtecan demonstrated a 72% reduction in the risk of disease progression or death versus trastuzumab emtansine (T-DM1)

Tokyo – (December 14, 2021) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that it has submitted a supplemental New Drug Application (sNDA) to Japan's Ministry of Health, Labour and Welfare (MHLW) for trastuzumab deruxtecan, a HER2 directed antibody drug conjugate (ADC), for the treatment of adult patients with HER2 positive unresectable or recurrent breast cancer previously treated with trastuzumab and a taxane.

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide, resulting in nearly 685,000 deaths globally.[1] In Japan, breast cancer is the most common cancer in women, with approximately 92,000 cases of breast cancer diagnosed in 2020.[2] Approximately one in five cases of breast cancer are considered HER2 positive.[3,4] Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[5] More treatment options are needed to further delay progression and extend survival.[5,6,7]

"There is a continued need in Japan for new therapeutic options for patients with HER2 positive metastatic breast cancer who often experience disease progression after initial treatment with available standards of care," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "We look forward to working with the Japan MHLW on this submission, as it marks a significant step towards bringing this important medicine to an earlier use in the metastatic setting for patients with HER2 positive breast cancer."

The sNDA is based on data from the pivotal DESTINY-Breast03 phase 3 trial that were presented at the 2021 European Society for Medical Oncology (ESMO) Congress. In the trial, trastuzumab deruxtecan 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; $p=7.8 \times 10^{-22}$) 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 trastuzumab deruxtecan 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 the secondary endpoint analysis of PFS assessed by investigators, patients treated with trastuzumab deruxtecan experienced a three-fold improvement in PFS of 25.1 months (95% CI: 22.1-NE) compared to 7.2 months (95% CI: 6.8-8.3) for T-DM1 (HR=0.26; 95% CI: 0.20-0.35; $p=6.5x10^{-24}$). There was a strong trend towards improved overall survival (OS) with trastuzumab deruxtecan (HR=0.56; 95% CI: 0.36-0.86; p=0.007172), however, this analysis is not yet mature and is not statistically significant. Nearly all patients treated with trastuzumab deruxtecan were alive at one year (94.1%; 95% CI: 90.3-96.4) compared to 85.9% of patients treated with T-DM1 (95% CI: 80.9-89.7). Confirmed objective response rate (ORR) was more than doubled in the trastuzumab deruxtecan 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; p<0.0001]).

The safety profile of the most common adverse events with trastuzumab deruxtecan in DESTINY-Breast03 was consistent with previous clinical trials with no new safety concerns identified. The most common grade 3 or higher drug-related treatment emergent adverse events in the trastuzumab deruxtecan arm were neutropenia (19.1%), thrombocytopenia (7.0%), leukopenia (6.6%), nausea (6.6%), anemia (5.8%), fatigue (5.1%), vomiting (1.6%), increase in ALT (1.6%), decreased appetite (1.2%), increase in AST (0.8%), diarrhea (0.4%) and alopecia (0.4%). Overall, 10.5% of patients had interstitial lung disease (ILD) or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD events (9.7%) were low grade (grade 1 (2.7%) or grade 2 (7.0%)) with two grade 3 (0.8%) events reported. No grade 4 or grade 5 ILD or pneumonitis events occurred.

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 cases of breast cancer were diagnosed in 2020, resulting in nearly 685,000 deaths globally.[1] In Japan, breast cancer is the most common cancer in women, with approximately 92,000 cases of breast cancer diagnosed in 2020.[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.[8] 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.[9] Approximately one in five cases of breast cancer are considered HER2 positive.[3,4]

Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[5] More effective options are needed to further delay progression and extend survival.[5,6,7]

About DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety of trastuzumab deruxtecan (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. Secondary efficacy endpoints include OS, ORR, 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. For more information about the trial, visit ClinicalTrials.gov.

About Trastuzumab Deruxtecan

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, trastuzumab deruxtecan is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced program in AstraZeneca's ADC scientific platform. Trastuzumab deruxtecan consists of a HER2 monoclonal antibody attached to a topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

Trastuzumab deruxtecan (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 two or more prior anti-HER2 based regimens based on the results from the DESTINY-Breast01 trial.

Trastuzumab deruxtecan (6.4 mg/kg) is also 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.

A Type II Variation is currently under review by the European Medicines Agency 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.

About the Trastuzumab Deruxtecan Clinical Development Program

A comprehensive global development program is underway evaluating the efficacy and safety of trastuzumab deruxtecan 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.

Trastuzumab deruxtecan was highlighted in the Clinical Cancer Advances 2021 report as one of two significant advancements in the "ASCO Clinical Advance of the Year: Molecular Profiling Driving Progress

in GI Cancers," based on data from both the DESTINY-Gastric01 and DESTINY-CRC01 trials, as well as one of the targeted therapy advances of the year in NSCLC based on the interim results of the *HER2* mutated cohort of the DESTINY-Lung01 trial.

In September 2021, trastuzumab deruxtecan received its fourth Breakthrough Therapy Designation in the U.S. 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.

About the Daiichi Sankyo and AstraZeneca Collaboration

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 in Oncology

The oncology portfolio of Daiichi Sankyo is powered by our team of world-class scientists that push beyond traditional thinking to create transformative medicines for people with cancer. Anchored by our DXd antibody drug conjugate (ADC) technology, our research engines include biologics, medicinal chemistry, modality and other research laboratories in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in the U.S. We also work alongside leading academic and business collaborators to further advance the understanding of cancer as Daiichi Sankyo builds towards our ambitious goal of becoming a global leader in oncology by 2025.

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] Sung H, et al. *CA Cancer J Clin*. 2021; 10.3322/caac.21660.
[2] GLOBOCAN. *Cancer Fact Sheets, Japan*. 2021.
[3] Ahn S, et al. *J Pathol Transl Med*. 2020; 54(1): 34-44.
[4] Shibuta K, et al. *Breast Cancer*. 2011; 18, 292–298.
[5] Barok M, et al. *Breast Cancer Res*. 2014; 16(2):209.
[6] Mounsey L, et al. *Clin Breast Cancer*. 2018; 18(1):29-37.
[7] Martínez-Sáez O, Prat A. *JCO Oncol Pract*. 2021. 10.1200/OP.21.00172.
[8] Iqbal N, et al. *Mol Biol Int*. 2014;852748.
[9] Pillai R, et al. *Cancer*. 2017;1;123(21):4099-4105.