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Press Release

Trastuzumab Deruxtecan Type II Variation Application Validated by EMA for Patients with HER2 Low Metastatic Breast Cancer with HR Positive and HR Negative Disease

- Application based on DESTINY-Breast04 results that showed Daiichi Sankyo and AstraZeneca's trastuzumab deruxtecan demonstrated superior progression-free and overall survival versus chemotherapy

Tokyo and Munich – (June 22, 2022) – Daiichi Sankyo (TSE: 4568) today announced that the European Medicines Agency (EMA) has validated the Type II Variation application for trastuzumab deruxtecan as monotherapy 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. Patients with hormone receptor (HR) positive breast cancer must additionally have received or be ineligible for endocrine therapy.

Trastuzumab deruxtecan is a specifically engineered HER2 directed antibody drug conjugate (ADC) being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca (LSE/STO/Nasdaq: AZN).

Validation confirms that the application is complete and commences the scientific review process by the EMA's Committee for Medicinal Products for Human Use (CHMP). This application is based on data from the DESTINY-Breast04 phase 3 trial recently presented at the plenary session of the American Society of Clinical Oncology (#ASCO22) Annual Meeting and simultaneously published in *The New England Journal of Medicine*.

"Trastuzumab deruxtecan is the first HER2 directed therapy to demonstrate a survival benefit in patients with HER2 low metastatic breast cancer. We now have the potential to redefine how we classify and treat approximately half of all metastatic breast cancers," said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Clinical Development, Oncology R&D, Daiichi Sankyo. "In addition to the ongoing review of two other applications for the treatment of patients with HER2 positive metastatic breast cancer or gastric cancer in Europe, we are pleased to have received this third validation for HER2 low metastatic breast cancer with the goal of bringing trastuzumab deruxtecan to as many eligible patients with HER2 targetable cancers as possible."

In DESTINY-Breast04, trastuzumab deruxtecan demonstrated superior and clinically meaningful efficacy in progression-free survival (PFS) and overall survival (OS) in previously treated patients with HER2 low unresectable and/or metastatic breast cancer with HR positive or HR negative disease versus standard of care physician's choice of chemotherapy. The safety profile of trastuzumab deruxtecan was consistent with previous clinical trials with no new safety concerns identified. Interstitial lung disease (ILD) or pneumonitis rates were consistent with that observed in late-line HER2 positive breast cancer trials of trastuzumab deruxtecan with a lower rate of grade 5 ILD observed, as determined by an independent adjudication committee.

About DESTINY-Breast04

DESTINY-Breast04 is a global, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety of trastuzumab deruxtecan (5.4 mg/kg) versus physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) in patients with HR positive or HR negative, unresectable and/or metastatic breast cancer with low HER2 expression previously treated with one or two prior lines of chemotherapy. Patients were randomized 2:1 to receive either trastuzumab deruxtecan or chemotherapy.

The primary endpoint of DESTINY-Breast04 is PFS in patients with HR positive disease based on blinded independent central review (BICR). Key secondary endpoints include PFS based on BICR in all randomized patients (HR positive and HR negative disease), OS in patients with HR positive disease and OS in all randomized patients (HR positive and HR negative disease). Other secondary endpoints include PFS based on investigator assessment, objective response rate based on BICR and on investigator assessment, duration of response based on BICR and safety. DESTINY-Breast04 enrolled 557 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About Breast Cancer and HER2 Expression

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 Europe, approximately 531,000 cases of breast cancer are diagnosed annually.[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, and is one of many biomarkers expressed in breast cancer tumors.[3]

HER2 expression is currently defined as either positive or negative, and is determined by an IHC test which estimates the amount of HER2 protein on a cancer cell, and/or an ISH test, which counts the copies of the HER2 gene in cancer cells.[3,4] HER2 positive cancers are defined as IHC 3+, IHC 2+/ISH+.[3] HER2 negative cancers are currently defined as IHC 0, IHC 1+ or IHC 2+/ISH-.[3] Approximately half of all patients with

breast cancer have tumors with a HER2 IHC score of 1+, or a HER2 IHC score of 2+ in combination with a negative ISH test, an expression level not currently eligible for HER2 targeted therapy.[5,6,7,8] Low HER2 expression occurs in both HR positive and HR negative disease.[9]

HER2 testing is routinely used to determine appropriate treatment options for patients with metastatic breast cancer. Targeting the lower range of expression in the HER2 spectrum may offer another approach to delay disease progression and extend survival in patients with metastatic breast cancer.[10] Currently, patients with low HER2 expression with HR positive tumors have limited treatment options following progression on endocrine (hormone) therapy.[11] Few targeted options are available for those who are HR negative.[12]

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 Canada, Israel and the U.S. for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a 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 results from the DESTINY-Breast03 trial. Trastuzumab deruxtecan also is approved in approximately 40 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 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 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, also are underway.

Regulatory applications for trastuzumab deruxtecan are currently under review in China, Europe, 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.

Trastuzumab deruxtecan 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 trial, 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.

Trastuzumab deruxtecan 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.

Media Contacts:

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

Japan:
Masashi Kawase
Daiichi Sankyo Co., Ltd.
kawase.masashi.a2@daiichisankyo.co.jp
+81 3 6225 1126 (office)

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

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

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