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Press Release

Trastuzumab Deruxtecan Recommended for Approval in the EU by CHMP for Patients with HER2 Positive Metastatic Breast Cancer Treated with a Prior Anti-HER2-Based Regimen

- Recommendation based on DESTINY-Breast03 trial results showing Daiichi Sankyo and AstraZeneca's trastuzumab deruxtecan reduced the risk of disease progression or death by 72% vs. trastuzumab emtansine (T-DM1)

Tokyo and Munich – (June 27, 2022) – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) trastuzumab deruxtecan has been recommended for approval in the European Union (EU) as a monotherapy 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.

Trastuzumab deruxtecan 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-Breast03 phase 3 trial, which were published in *The New England Journal of Medicine*. In the DESTINY-Breast03 trial, trastuzumab deruxtecan reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1) (hazard ratio [HR] = 0.28; 95% confidence interval [CI]: 0.22-0.37; p<0.0001) 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).

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

In Europe, more than 530,000 cases of breast cancer are diagnosed annually.[1] Approximately one in five cases of breast cancer are considered HER2 positive.[2] Despite initial treatment with trastuzumab, pertuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[3,4] More treatment options are needed to further delay progression and extend survival.[3,5,6]

“Today’s CHMP opinion provides further validation of the significance of the DESTINY-Breast03 trial results, which for the first time showed superiority of trastuzumab deruxtecan in prolonging progression-free survival in patients previously treated for HER2 positive metastatic breast cancer as compared to another HER2 directed ADC,” said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. “This positive CHMP opinion is an important step forward in bringing this potentially practice-changing medicine to patients in Europe to use earlier in the treatment of HER2 positive metastatic breast cancer and builds on the recent approval of trastuzumab deruxtecan in the U.S.”

“This recommendation reflects the transformative progression-free survival benefit seen in the DESTINY-Breast03 trial compared to T-DM1, supporting trastuzumab deruxtecan as a potential new standard of care and setting a new benchmark in the treatment of HER2 positive metastatic breast cancer,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “If approved by the European Commission, patients in Europe may be able to benefit from this important medicine earlier in the treatment of their disease, improving their chance for better outcomes.”

Additional results from the DESTINY-Breast03 phase 3 trial showed that in the secondary endpoint analysis of PFS assessed by investigators, patients treated with trastuzumab deruxtecan experienced an 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). 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]).

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%), increased alanine aminotransferase (1.6%), decreased appetite (1.2%), increased aspartate aminotransferase (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 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 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. Results from DESTINY-Breast03 have been 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.[7] More than two million cases of breast cancer were diagnosed in 2020, with nearly 685,000 deaths globally.[7] In Europe, more than 530,000 cases of breast cancer are diagnosed annually.[1] Approximately one in five cases of breast cancer are considered HER2 positive.[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]

Despite initial treatment with trastuzumab, pertuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.3,4 More treatment options are needed to further delay progression and extend survival.[3,5,6]

About Trastuzumab Deruxtecan

Trastuzumab deruxtecan 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 is also 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, are also 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 is under review in Europe 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, based on the results from the DESTINY-Breast04 trial. Patients with hormone receptor (HR) positive breast cancer must additionally have received or be ineligible for endocrine therapy.

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 recently 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 hormone receptor (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.

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