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Daiichi-Sankyo

Press Release

Daiichi Sankyo Submits Supplemental New Drug Application for Trastuzumab Deruxtecan in Japan for Treatment of Patients with HER2 Positive Metastatic Gastric Cancer

- Submission based on pivotal phase 2 DESTINY-Gastric01 and phase 1 trial data
- Trastuzumab deruxtecan to receive expedited review by Japan MHLW based on SAKIGAKE-designation for second potential indication in Japan

Tokyo, Munich and Basking Ridge, NJ – (May 7, 2020) – 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 (DS-8201), a HER2 directed antibody drug conjugate (ADC), for the treatment of patients with HER2 positive metastatic gastric cancer.

Trastuzumab deruxtecan has previously received SAKIGAKE designation for this second potential indication and will receive an expedited review time of six months. Currently, there are no HER2 directed treatment options approved for patients with HER2 positive metastatic gastric cancer who have progressed after trastuzumab.

"Today's submission by Daiichi Sankyo brings us closer to bringing trastuzumab deruxtecan to a population of patients with unmet medical need in Japan," said Wataru Takasaki, PhD, Executive Officer, Head of R&D Division in Japan, Daiichi Sankyo. "If approved, trastuzumab deruxtecan has the potential to meaningfully advance the treatment of patients with HER2 positive metastatic gastric cancer as the first ever antibody drug conjugate approved to treat this type of cancer."

The Japan sNDA is based on data from the pivotal phase 2 DESTINY-Gastric01 trial and phase 1 trial published in *The Lancet Oncology*. In DESTINY-Gastric01, patients treated with trastuzumab deruxtecan demonstrated a statistically significant and clinically meaningful improvement in objective response rate (ORR) as assessed by an independent review committee as well as in overall survival (OS) compared to patients treated with investigator's choice of chemotherapy (irinotecan or paclitaxel monotherapy). The full results of DESTINY-Gastric01 will be presented at the 2020 American Society of Clinical Oncology Annual Meeting.

The overall safety and tolerability profile of trastuzumab deruxtecan in DESTINY-Gastric01 was consistent with that seen in the phase 1 trial in which the most common adverse events (≥30 percent, any grade) were hematologic and gastrointestinal including neutrophil count decrease, anemia, nausea and decreased appetite. There were cases of drug-related interstitial lung disease (ILD) and pneumonitis, the majority of

which were grade 1 and 2 with two grade 3 and one grade 4. No ILD-related deaths (grade 5) occurred in patients with gastric cancer in the phase 1 trial or in the DESTINY-Gastric01 trial.

Accelerated approval in the U.S. and approval in Japan under the conditional early approval system were recently received for trastuzumab deruxtecan 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.

About HER2

HER2 is a cell growth-promoting tyrosine kinase receptor protein expressed on the surface of many types of tumors including gastric, breast and lung cancers. HER2 overexpression is associated with a specific HER2 gene alteration known as HER2 amplification and is often associated aggressive disease and poorer prognosis.[1]

About Gastric Cancer

Gastric (stomach) cancer is the fifth most common cancer worldwide and the third leading cause of cancer mortality; there were approximately one million new cases reported in 2018 and 783,000 deaths.[2] Incidence rates for gastric cancer are markedly higher in eastern Asia, where approximately half of all cases occur.[8] South Korea and Japan have the first and third highest incidence rates of gastric cancer worldwide, respectively; in 2018, the age-standardized rate in Japan was 27.5 per 100,000 and in South Korea it was 39.6 per 100,000.[3]

Approximately one in five gastric cancers are HER2 positive.[4] Gastric cancer is usually diagnosed in the advanced stage, but even when diagnosed in earlier stages of the disease the survival rate remains modest.[5] Recommended first-line treatment for HER2 positive advanced or metastatic gastric cancer is combination chemotherapy plus trastuzumab, an anti-HER2 medicine, which has been shown to improve outcomes when added to chemotherapy.[6] For gastric cancer that progresses on first line treatment, trastuzumab has not shown any further benefit and there are no other approved HER2 targeting medicines.[6]

About DESTINY-Gastric01

DESTINY-Gastric01 is a pivotal phase 2, open-label, multi-center study assessing the safety and efficacy of trastuzumab deruxtecan in 189 patients from Japan and South Korea with HER2 expressing advanced gastric cancer or gastroesophageal junction adenocarcinoma (defined as IHC3+ or IHC2+/ISH+) who have progressed on two or more prior regimens including fluoropyrimidine (5-FU), platinum chemotherapy and trastuzumab. Patients were randomized 2:1 to receive trastuzumab deruxtecan or investigator's choice of chemotherapy (paclitaxel or irinotecan monotherapy). Patients were treated with trastuzumab deruxtecan 6.4 mg/kg once every three weeks or chemotherapy given on the same schedule. The primary endpoint of the study is ORR. Secondary endpoints include OS, progression-free survival, duration of response, disease control rate and time to treatment failure.

About Trastuzumab Deruxtecan

Trastuzumab deruxtecan (formerly known as DS-8201; trastuzumab deruxtecan outside the U.S.; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed ADC and is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced program in AstraZeneca's ADC Scientific platform.

ADCs are targeted cancer medicines that deliver cytotoxic chemotherapy ("payload") to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Designed using Daiichi Sankyo's proprietary DXd ADC technology, trastuzumab deruxtecan is comprised of a HER2 monoclonal antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide-based linker.

Trastuzumab deruxtecan has not been approved in the EU, or countries outside of Japan and the United States, for any indication. It is an investigational agent globally for various indications. Safety and effectiveness have not been established for the subject proposed use.

About the Trastuzumab Deruxtecan Clinical Development Program

A comprehensive development program for trastuzumab deruxtecan is underway globally with six pivotal trials evaluating the efficacy and safety of trastuzumab deruxtecan monotherapy across multiple HER2 driven cancers including breast, gastric, colorectal and lung cancers. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

About the Collaboration between Daiichi Sankyo and AstraZeneca

In March 2019, Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize trastuzumab deruxtecan worldwide, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is solely responsible for the manufacturing and supply.

U.S. FDA-Approved Indication for ENHERTU

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated 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 in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Contraindications

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. Median time to first onset was 1.4 months (range: 0.3 to 18.2). Febrile neutropenia was reported in 1.7% of patients.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L) interrupt ENHERTU until resolved to Grade 2 or less. Reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3ºC or a sustained temperature of ≥38ºC for more than 1 hour), interrupt ENHERTU until resolved. Reduce dose by one level.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of <40% or absolute decrease from baseline of >20% is confirmed. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for

at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

Adverse Reactions
The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common adverse reactions (frequency ≥20%) were nausea (79%), fatigue (59%), vomiting (47%), alopecia (46%), constipation (35%), decreased appetite (32%), anemia (31%), neutropenia (29%), diarrhea (29%), leukopenia (22%), cough (20%), and thrombocytopenia (20%).

Use in Specific Populations
- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (53%) as compared to younger patients (42%).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see accompanying full Prescribing Information, including Boxed WARNING, and Medication Guide.

About Daiichi Sankyo Cancer Enterprise

The mission of Daiichi Sankyo Cancer Enterprise is to leverage our world-class, innovative science and push beyond traditional thinking to create meaningful treatments for patients with cancer. We are dedicated to transforming science into value for patients, and this sense of obligation informs everything we do. Anchored by our DXd antibody drug conjugate (ADC) technology, our powerful 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 Berkeley, CA. For more information, please visit: www.DSCancerEnterprise.com.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 15,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for cardiovascular diseases, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo is primarily focused on providing novel therapies in oncology, as well as other research areas centered around rare diseases and immune disorders. For more information, please visit: www.daiichisankyo.com.

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References:
[1] Iqbal N, et al. *Mol Biol Int*. 2014; 2014: 852748.
[2] Bray F et al. *CA: Cancer J. Clin* 2018;68:394–424.
[3] World Cancer Research Fund International. Stomach Cancer Statistics. 2018.
[4] American Cancer Society. Tests for Stomach Cancer. 2017.
[5] Curea et al. *Cancer Biotherapy & Radiopharmaceuticals*. 2017;32 (10).
[6] NCCN Guidelines® Gastric Cancer. Version 4.2019. December 20, 2019: MS-22-36.