

Press Release

Daiichi Sankyo Advances [Fam-] Trastuzumab Deruxtecan (DS-8201) in Japan with Regulatory Submission in HER2 Positive Metastatic Breast Cancer

- Global regulatory submission for the antibody drug conjugate is based on the pivotal phase 2 DESTINY-Breast01 and phase 1 trials

Tokyo, Munich and Basking Ridge, NJ – (September 9, 2019) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced the submission of a New Drug Application (NDA) to Japan’s Ministry of Health, Labour and Welfare (MHLW) for the use of [fam-] trastuzumab deruxtecan (DS-8201), an investigational HER2 targeting antibody drug conjugate (ADC), for the treatment of patients with HER2 positive metastatic breast cancer.

The Japan NDA is primarily based on the positive results from the pivotal phase 2 DESTINY-Breast01 trial of [fam-] trastuzumab deruxtecan, an open-label, global, multicenter trial, which evaluated dosing, efficacy and safety in patients with HER2 positive metastatic breast cancer. The submission also includes data from the phase 1 trial published in [*The Lancet Oncology*](#).¹ The response rate observed in DESTINY-Breast01, as assessed by an independent review committee, confirmed the clinical activity observed in the phase 1 trial. Data from DESTINY-Breast01 will be presented at an upcoming medical meeting.

“We are proud to initiate this critical next step in the regulatory process in Japan and look forward to the presentation of the phase 2 DESTINY-Breast01 study of [fam-] trastuzumab deruxtecan to the scientific community,” said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. “We look forward to working closely with the Japan Health Authority on our application for [fam-] trastuzumab deruxtecan in order to bring this important potential new treatment to patients in Japan.”

[Fam-] trastuzumab deruxtecan is currently in development for the treatment of patients with a variety of HER2 expressing or HER2 mutant cancers, including gastric, colorectal and lung cancer, as well as in breast cancer with HER2 low expression.

The safety and tolerability profile of [fam-] trastuzumab deruxtecan in DESTINY-Breast01 was consistent with the phase 1 trial data published in [*The Lancet Oncology*](#), in which the most common adverse events (≥30 percent, any grade) included nausea, decreased appetite, vomiting, alopecia, fatigue, anemia, diarrhea and constipation. Cases of drug-related pneumonitis, including grade 5 events, have also been reported in the clinical development program.

About HER2

HER2 is a tyrosine kinase receptor growth-promoting protein found on the surface of some cancer cells that is associated with aggressive disease and poorer prognosis in breast cancer patients.² To be considered HER2 positive, tumor cancer cells are usually tested by one of two methods: immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH). IHC test results are reported as: 0, IHC 1+, IHC 2+, or IHC 3+.² A finding of IHC 3+ and/or FISH amplification is considered positive.² There are currently no approved HER2 targeted therapies for HER2 FISH negative, IHC 2+ or IHC 1+ tumors.

Unmet Need in HER2 Positive Breast Cancer

Approximately one in five breast cancers are HER2 positive.^{3,4} Despite recent improvements and approvals of new therapies, there remains significant unmet clinical needs for patients with advanced HER2 positive metastatic breast cancer.^{5,6} This disease remains incurable with these patients eventually progressing after available therapies.^{5,6}

About DESTINY-Breast01

DESTINY-Breast01 is a pivotal phase 2, open-label, global, multicenter, two-part trial evaluating the safety and efficacy of [fam-] trastuzumab deruxtecan in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine (T-DM1). The primary endpoint of the trial is objective response rate. Secondary objectives include duration of response, disease control rate, clinical benefit rate, progression-free survival and overall survival.

The first part of the trial includes a pharmacokinetic stage and a dose-finding stage to identify the recommended dose of [fam-] trastuzumab deruxtecan to be evaluated in the second part of the trial. The second part enrolled patients into one of two cohorts: patients resistant or refractory to T-DM1 (part 2a) and patients who discontinued treatment with T-DM1 for reasons other than resistant or refractory disease (part 2b). Enrollment into DESTINY-Breast01 was completed in September 2018 with 253 patients at more than 100 sites across North America, Europe, Japan and other countries in Asia.

About [Fam-] Trastuzumab Deruxtecan

[Fam-] trastuzumab deruxtecan (DS-8201; fam-trastuzumab deruxtecan in U.S. only; trastuzumab deruxtecan in other regions of world) is the lead product in the investigational ADC Franchise of the Daiichi Sankyo Cancer Enterprise 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, [fam-] trastuzumab deruxtecan is comprised of a humanized HER2 antibody attached to a novel topoisomerase I inhibitor payload by a

tetrapeptide-based linker. It is designed to target and deliver chemotherapy inside cancer cells and reduce systemic exposure to the cytotoxic payload (or chemotherapy) compared to the way chemotherapy is commonly delivered.

A broad and comprehensive development program with [fam-] trastuzumab deruxtecan is underway in North America, Europe and Asia, including five pivotal trials in HER2 expressing breast and gastric cancers, including in breast cancer patients with HER2 low expression. [Fam-] trastuzumab deruxtecan is also in phase 2 development for HER2 expressing advanced colorectal cancer and metastatic non-squamous HER2 overexpressing or HER2 mutated NSCLC, and phase 1 development in combination with nivolumab for HER2 expressing metastatic breast and bladder cancers.

[Fam-] trastuzumab deruxtecan was granted Breakthrough Therapy Designation in 2017 by the U.S. FDA for the treatment of patients with HER2 positive, locally-advanced or metastatic breast cancer who have been treated with trastuzumab and pertuzumab and have disease progression after T-DM1. Fast Track Designation was also granted in the U.S. for the treatment of HER2 positive unresectable and/or metastatic breast cancer in patients who have progressed after prior treatment with HER2 targeted medicines, including T-DM1. Trastuzumab deruxtecan has received SAKIGAKE designation for the treatment of advanced HER2 positive advanced gastric or gastroesophageal junction cancer by the Japan Ministry of Health, Labour and Welfare.

[Fam-] trastuzumab deruxtecan is an investigational agent that has not been approved for any indication in any country. Safety and efficacy have not been established.

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 [fam-] trastuzumab deruxtecan as a medicine worldwide, except in Japan where Daiichi Sankyo will maintain exclusive rights. Daiichi Sankyo will be solely responsible for manufacturing and supply.

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 three pillars including our investigational Antibody Drug Conjugate Franchise, Acute Myeloid Leukemia Franchise and Breakthrough Science, we aim to deliver seven distinct new molecular entities over eight years during 2018 to 2025. Our powerful research engines include two laboratories for biologic/immuno-oncology and small molecules 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 Tamura, K, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol.* 2019;20(6):816-826.

² American Cancer Society. Breast Cancer HER2 Status. Available at <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html>. Accessed August 2019.

³ Tandon A, et al. HER-2/neu Oncogene Protein and Prognosis in Breast Cancer. *J Clin Oncol.* 1989;7(8):1120-8.

⁴ Sledge G, et al. Past, Present, and Future Challenges in Breast Cancer Treatment. *J Clin Oncol.* 2014;32(19):1979-1986.

⁵ de Melo Gagliato D, et al. Mechanisms of Resistance and Sensitivity to Anti-HER2 Therapies in HER2+ Breast Cancer. *Oncotarget.* 2016;7(39):64431-46.

⁶ National Comprehensive Cancer Network (NCCN). NCCN Guidelines. Breast Cancer. Available at <https://nccn.org>. Accessed August 2019.