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Press Release

Daiichi Sankyo Presents Updated Phase 1 Results of [Fam-] Trastuzumab Deruxtecan (DS-8201) in Patients with HER2 Low Expressing Metastatic Breast Cancer at 2018 San Antonio Breast Cancer Symposium (SABCS)

- Updated analysis from ongoing phase 1 study of [fam-] trastuzumab deruxtecan (DS-8201) demonstrated a confirmed overall response rate of 44.2 percent and a disease control rate of 79.1 percent in 43 evaluable patients with heavily pretreated HER2 low metastatic breast cancer
- A further subgroup analysis of 38 patients whose disease was also hormone receptor (HR) positive showed a 47.4 percent confirmed overall response rate and 81.6 percent disease control rate
- No anti-HER2 therapies are currently approved for HER2 low expressing breast cancer, and plans for a phase 3 study are underway

Tokyo, Munich, and Basking Ridge, NJ – (December 8, 2018) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced that updated safety and efficacy data from the ongoing phase 1 study with [fam-] trastuzumab deruxtecan, an investigational HER2 targeting antibody drug conjugate (ADC), were presented for a subgroup of patients with heavily pretreated HER2 low expressing metastatic breast cancer during a Poster Session at the 2018 San Antonio Breast Cancer Symposium (SABCS) (#P6-17-02).

The updated analysis of 43 evaluable patients with HER2 low expressing metastatic breast cancer (IHC 2+/ISH- or IHC 1+), who received [fam-] trastuzumab deruxtecan at a recommended expansion dose of 5.4 or 6.4 mg/kg, demonstrated a confirmed overall response rate of 44.2 percent (19/43 patients) and a disease control rate of 79.1 percent (34/43 patients). Preliminary estimate of median duration of response was 9.4 months (range: 1.5+, 23.6+), and median progression-free survival was 7.6 months (95 percent CI: 4.9, 13.7). A total of 54 patients with heavily pretreated (median 7.5 prior anticancer regimens) HER2 low breast cancer have received ≥1 dose [fam-] trastuzumab deruxtecan 5.4 or 6.4 mg/kg in the study and 23 patients remain on treatment as of data cut-off on October 12, 2018.

“While anti-HER2 therapies play an important role in the treatment of HER2 positive breast cancer, they historically have not demonstrated effectiveness against tumors that express lower levels of HER2,” said Shanu Modi, MD, Breast Medical Oncologist, Memorial Sloan Kettering Cancer Center and study investigator. “These data offer preliminary evidence of [fam-] trastuzumab deruxtecan activity in HER2 low expressing breast cancers, and based on further study, we are beginning to consider the implications for how we classify and treat these patients.”

A further subgroup analysis of 38 evaluable patients whose disease was also hormone receptor (HR) positive demonstrated a confirmed overall response rate of 47.4 percent (18/38 patients) and a disease control rate of 81.6 percent (31/38 patients) with [fam-] trastuzumab deruxtecan. Preliminary estimate of

median duration of response was 11.0 months (range: 1.5+, 23.6+), and median progression-free survival was 7.9 months (95 percent CI: 4.4, 13.7) in this patient subgroup. A total of 45 patients with HR positive, HER2 low breast cancer have received ≥1 dose [fam-] trastuzumab deruxtecan 5.4 or 6.4 mg/kg in the study and 21 of these patients remain on treatment as of data cut-off.

"There are no anti-HER2 therapies currently approved for HER2 low expressing breast cancer, which represents about half of all breast cancers," said Gilles Gallant, BPharm, PhD, Vice President, DS-8201 Global Team Leader, Oncology Research and Development, Daiichi Sankyo. "Based on these data, plans for a phase 3 trial in patients with HER2 low metastatic breast cancer are underway, adding to our broad development program evaluating [fam-] trastuzumab deruxtecan in HER2 expressing breast cancers and other tumor types."

Updated overall safety data as of October 12, 2018 for all breast cancer patients in the ongoing phase 1 study were also reported at SABCS. Among 170 patients who received at least one dose of [fam-] trastuzumab deruxtecan 5.4 or 6.4 mg/kg for advanced breast cancer in the dose expansion or dose escalation part of the study (regardless of HER2 status), the most common adverse events (≥30 percent, any Grade) included nausea (79.4 percent), decreased appetite (54.1 percent), alopecia (46.5 percent), vomiting (45.9 percent), fatigue (42.4 percent), anemia (40.0 percent), constipation (38.2 percent) and diarrhea (38.2 percent). A total of 50.0 percent of the breast cancer patients experienced a Grade ≥3 adverse event and 22.9 percent had a serious adverse event, including 2.9 percent of patients who experienced an adverse event that lead to death.

ILD Data in Metastatic Breast Cancer Presented

An independent committee evaluates any reported cases of interstitial lung disease (ILD)/pneumonitis in the [fam-] trastuzumab deruxtecan clinical development program.The first analysis of ILD data, including adjudicated case results, in patients who received [fam-] trastuzumab deruxtecan for metastatic breast cancer across trials was presented at SABCS 2018 (Poster #P6-17-06).

Among 510 trial patients who received [fam-] trastuzumab deruxtecan for metastatic breast cancer at one of seven dose levels, there were fifty-four (54) investigator-reported ILD cases of any grade (10.6 percent) including four (4) Grade 5. Thirty-three (33) cases were adjudicated and twenty-eight (28) were considered to be drug-related ILD, including four (4) Grade 5 events.

Among 269 trial patients who received [fam-] trastuzumab deruxtecan for metastatic breast cancer at a 5.4 mg/kg dose, which is the recommended dose for continued development in HER2 positive breast cancer, there were fifteen (15) investigator-reported ILD cases any grade (5.6 percent) including one (1) Grade 5. Seven (7) cases were adjudicated and five (5) were considered to be drug-related ILD, including one (1) Grade 5 event.

A third data set was also presented for all patients with advanced solid tumors who received at least one dose of [fam-] trastuzumab deruxtecan across seven ongoing global studies. Among the 665 patients, there were sixty-six (66) investigator-reported ILD cases any grade (9.9 percent) including five (5) Grade 5. Thirty-eight (38) cases were adjudicated and thirty (30) were considered drug-related ILD, including four (4) Grade 5. Of the reported potential ILD cases from all studies, most were mild to moderate in severity, with 80.3 percent (53 of 66) ≤ Grade 2. The median time to onset of ILD was 149 (16–596) days. The study reflects all cases that occurred as of October 15, 2018.

Dose Justification in HER2 Positive Breast Cancer Presented

Research establishing 5.4 mg/kg as the recommended dose for continued development of [fam-] trastuzumab deruxtecan in advanced HER2 positive breast cancer was presented at SABCS (Poster #P6-17-10). A comprehensive analysis of observed data and exposure-response parameters from the phase 2 DESTINY-Breast01 trial in HER2 positive breast cancer and the ongoing phase 1 trial in multiple types of HER2 expressing tumors was conducted. Efficacy results for a total of 140 patients with HER2 positive breast cancer were included in the exposure-efficacy analysis, and safety results for a total of 276 patients with any tumor type were included in the exposure-safety analysis. Based on the benefit/risk profile, 5.4 mg/kg was chosen as the recommended dose for continued development in HER2 positive breast cancer for DESTINY-Breast01 and in phase 3 trials DESTINY-Breast02 and DESTINY-Breast03.

About HER2 Low Expressing Breast Cancer

Breast cancer is the most common cancer and the most common cause of cancer mortality among women worldwide.[1] There were approximately 1.67 million new cases of breast cancer diagnosed in 2012.[1]

About one in five breast cancers (20 percent) are HER2 positive (IHC3+ or IHC2+/ISH+).[2] 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.[3,4] A number of HER2 targeting therapies are approved to treat HER2 positive metastatic breast cancer and have improved survival rates.[5] The remaining 80 percent of breast cancers are classified as HER2 negative; however, about half still express some level of HER2 as a cell surface antigen.[6] No anti-HER2 agents are indicated for these low expressing tumors, which may be defined as IHC 2+/ISH- or IHC 1+, and there is no targeted treatment paradigm for HER2 low expressing breast cancer.[7] HER2 low expression has not been evaluated in clinical practice or in other clinical trials.

About the [Fam-] Trastuzumab Deruxtecan Phase 1 Study

An open-label, two-part phase 1 study is currently evaluating [fam-] trastuzumab deruxtecan in patients with advanced/unresectable or metastatic solid tumors that are refractory or intolerant to standard treatment, or for whom no standard treatment is available. The primary objective of the dose escalation part of this study was to assess the safety and tolerability of [fam-] trastuzumab deruxtecan and determine the maximum tolerated dose. Data from this part of the study were published in the *Lancet Oncology*.[8]

In the dose expansion part of the phase 1 study, [fam-] trastuzumab deruxtecan is given in one of two doses (5.4 mg/kg and 6.4 mg/kg) to patients with HER2 positive advanced or metastatic breast cancer and gastric cancer, HER2 low expressing breast cancer and other HER2 expressing solid tumors. Overall, 292 patients have been enrolled into this phase 1 study of [fam-] trastuzumab deruxtecan. For more information about the study, visit ClinicalTrials.gov.

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. 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 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. [Fam-] trastuzumab deruxtecan is in phase 3 development versus ado-trastuzumab emtansine (T-DM1) (DESTINY-Breast03) and versus investigator's choice post T-DM1 (DESTINY-Breast02) for HER2 positive metastatic breast cancer; pivotal phase 2 clinical development for HER2 positive metastatic breast cancer resistant or refractory to T-DM1 (DESTINY-Breast01); pivotal phase 2 development for HER2 positive advanced gastric cancer resistant or refractory to trastuzumab (DESTINY-Gastric01); phase 2 development for HER2 expressing advanced colorectal cancer; phase 2 development for metastatic non-squamous HER2 overexpressing or HER2 mutated NSCLC; and, phase 1 development in combination with nivolumab for HER2 expressing metastatic breast and bladder cancer.

[Fam-] trastuzumab deruxtecan has been granted Breakthrough Therapy designation 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, and Fast Track designation for the treatment of HER2 positive unresectable and/or metastatic breast cancer in patients who have progressed after prior treatment with HER2 targeted therapies including T-DM1 by the U.S. Food and Drug Administration (FDA). [Fam-] trastuzumab deruxtecan has received SAKIGAKE Designation for the treatment of HER2 positive advanced gastric or gastroesophageal junction cancer by the Japan Ministry of Health, Labour and Welfare (MHLW).

[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 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. Compounds in pivotal stage development include: [fam-] trastuzumab deruxtecan, an antibody drug conjugate (ADC) for HER2 expressing breast, gastric and other cancers; quizartinib, an oral selective FLT3 inhibitor, for newly-diagnosed and relapsed/refractory *FLT3*-ITD acute myeloid leukemia (AML); and pexidartinib, an oral CSF1R inhibitor, for tenosynovial giant cell tumor (TGCT). For more information, please visit: www.DSCancerEnterprise.com.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 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 hypertension and thrombotic disorders, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo research and development is primarily focused on bringing forth novel therapies in oncology, including immuno-oncology, with additional focus on new horizon areas, such as pain management, neurodegenerative diseases, heart and kidney diseases, and other rare diseases. For more information, please visit: www.daiichisankyo.com.

Contact

Jennifer Brennan
Daiichi Sankyo, Inc.
jbrennan2@dsi.com
+1 908 992 6631 (office)
+1 201 709 9309 (mobile)

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