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Press Release

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Daiichi Sankyo Announces Two *Lancet Oncology* Publications of Phase 1 Dose Expansion Results of [Fam-] Trastuzumab Deruxtecan in HER2 Positive Metastatic Breast and Gastric Cancer

- 20.7 months median duration of response achieved in patients with HER2 positive metastatic breast cancer previously treated with T-DM1
- 7.0 months median duration of response achieved in patients with HER2 positive metastatic gastric cancer previously treated with trastuzumab

Basking Ridge, NJ and Munich – (April 29, 2019) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca today announced the publication of two manuscripts in *The Lancet Oncology* reporting long-term phase 1 safety and efficacy results of [fam-] trastuzumab deruxtecan (DS-8201). The investigational HER2 targeting antibody drug conjugate (ADC) was evaluated in heavily pretreated patients with HER2 positive metastatic breast cancer and gastric cancer.

HER2 Positive Breast Cancer Results

The first manuscript reports efficacy results for 115 patients who received at least one dose of [fam-] trastuzumab deruxtecan, of which 111 were evaluable for confirmed response. These patients with HER2 positive metastatic breast cancer previously treated with ado-trastuzumab emtansine (T-DM1) received [fam-] trastuzumab deruxtecan at a recommended expansion dose of 5.4 or 6.4 mg/kg in the dose escalation or dose expansion parts of the phase 1 study. Patients enrolled in this part of the study had a median of seven prior anticancer regimens, including T-DM1 and trastuzumab, and in 86 percent of cases, pertuzumab.

A confirmed objective response rate of 59.5 percent [95 percent CI: 49.7-68.7] and a disease control rate of 93.7 percent [95 percent CI: 87.4-97.4] was observed with [fam-] trastuzumab deruxtecan. Median duration of response was 20.7 months (range 0.0-21.8), median progression-free survival was 22.1 months (range 0.8-27.9), and median overall survival has not yet been reached in the study. Fifty-five (48 percent) patients remain on treatment with [fam-] trastuzumab deruxtecan, as of data cut-off on August 10, 2018.

“For patients with HER2 positive metastatic breast cancer that progresses after trastuzumab, pertuzumab, and T-DM1, optimal treatment is not clearly defined and choices may be limited,” said Kenji Tamura, MD, PhD, Department of Breast and Medical Oncology National Cancer Center Hospital, Tokyo, Japan,

and lead author on the study. “These results demonstrate preliminary clinically meaningful response rates with an impressive duration of response, supporting further development and suggesting a potential role for [fam-] trastuzumab deruxtecan as a HER2 targeted therapy option in this setting.”

Safety results for 115 patients with HER2 positive metastatic breast cancer, who received at least one dose of [fam-] trastuzumab deruxtecan 5.4 or 6.4 mg/kg in part one or part two of the study also were reported. The most common adverse events (≥30 percent, any grade) included nausea, decreased appetite, vomiting, alopecia, fatigue, anemia, diarrhea, and constipation. Fifty (50.0) percent of patients experienced an adverse event grade ≥3, and 19.0 percent had a serious adverse event, including two previously reported cases of grade 5 drug-related pneumonitis. Any reported cases of interstitial lung disease (ILD)/pneumonitis in the [fam-] trastuzumab deruxtecan clinical development program are evaluated by an independent adjudication committee, and a formal monitoring and management program is in place with ongoing analyses to help optimally characterize the risk. A presentation of ILD risk characterization at the San Antonio Breast Cancer Symposium in December 2018 in patients with metastatic breast cancer treated at the recommended dose of 5.4 mg/kg showed an overall incidence of 5.6 percent, with the majority of cases being grades 1 and 2, and 1.1 percent grade 3 and above, including one (1) case of grade 5 (Poster # P6-17-06).[1]

Summary of Results

	Total evaluable[i] **(n=114)**
Confirmed Objective Response Rate (ORR)[ii, iii] (95% CI)	59.5% (49.7-68.7)
Disease Control Rate (DCR)[ii, iv] (95% CI)	93.7% (87.4-97.4)
Duration of Response (DOR)[v] Median in months (95% CI)[vi]	20.7 (0.0-21.8)[vi]
Progression Free Survival (PFS) Median in months (95% CI)[vi]	22.1 (0.8 - 27.9)[vi]

[i] *The activity evaluable set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg and for whom both baseline and post-treatment activity data were available.*
[ii] *There were 111 patients who had two or more post baseline scans, had progressive disease, or discontinued treatment for any reason before second postbaseline scan and were considered evaluable for confirmed response.*
[iii] *Objective response was calculated as the proportion of patients showing complete response or partial response for a minimum of 5 weeks from the first dosing date.*
[iv] *Disease control was calculated as the proportion of patients demonstrating complete response, partial response, or stable disease for a minimum of 5 weeks from the first dosing date.*
[v] *Duration of response was measured from the time at which complete response or partial response criteria are first met until the first date of objectively documented progressive disease.*
[vi] *Censored observation indicated with plus (+).*

HER2 Positive Gastric Cancer Results

The second manuscript reports results for 44 patients with HER2 positive advanced gastric or gastro-esophageal junction cancer previously treated with trastuzumab who received [fam-] trastuzumab deruxtecan at a recommended expansion dose of 5.4 or 6.4 mg/kg in the dose escalation or dose expansion parts of the study. These patients had a median of three prior anticancer regimens including trastuzumab.

A confirmed objective response rate of 43.2 percent [95 percent CI: 28.3, 59.0] and a disease control rate of 79.5 percent [95 percent CI: 64.7-90.2] were seen with [fam-] trastuzumab deruxtecan. The median duration of response was 7.0 months (range 4.4-16.6), median progression free survival was 5.6 months [95 percent CI: 3.0-8.3], and median overall survival was 12.8 months (range 1.4-25.4). Three (3) patients remain on treatment with [fam-] trastuzumab deruxtecan as of data cut-off on August 10, 2018.

"These results are encouraging given the limited options for patients with advanced HER2 positive gastric cancer that progresses after initial treatment regimens including trastuzumab," said lead study author Kohei Shitara, MD, National Cancer Center Hospital East, Chiba, Japan. "There are no other anti-HER2 therapies approved for gastric cancer beyond trastuzumab, and these data support further study of [fam-] trastuzumab deruxtecan in these patients."

Safety results for the 44 patients with HER2 positive gastric or gastro-esophageal junction cancer who received at least one dose of [fam-] trastuzumab deruxtecan 5.4 or 6.4 mg/kg in part one or part two of the study also were presented. The most common adverse events (≥30 percent, any grade) included nausea, decreased appetite, white blood cell count decrease, anemia, platelet count decrease, and constipation. Sixty-four (64.0) percent of patients experienced an adverse event grade ≥3, and 25.0 percent had a serious adverse event. There were two deaths due to TEAEs, (one due to pneumonia and one due to progression of disease), and neither were considered drug-related.

Summary of Results

	Total evaluable[vii] **(n=44)**
Confirmed Objective Response Rate (ORR)[viii] (95% CI)	43.2% (28.3-59.0)
Disease Control Rate (DCR)[ix] (95% CI)	79.5% (64.7-90.2)
Duration of Response (DOR)[x] Median in months (95% CI)[xi]	7.0 (4.4-16.6)[xi]
Progression Free Survival (PFS) Median in months (95% CI)[xi]	5.6 (3.0-8.3)[xi]
Overall Survival (OS) Median in months (95% CI)[xi]	12.8 (1.4-25.4)[xi]

[vii] The activity evaluable set included all patients who received at least one dose of trastuzumab deruxtecan at 5·4 mg/kg or 6·4 mg/kg and for whom both baseline and post-treatment activity data were available.
[viii] Objective response is calculated as the proportion of patients showing complete response or partial response for a minimum of 5 weeks from the first dosing date.
[ix] Disease control was calculated as the proportion of patients showing complete response, partial response, or stable disease for a minimum of 5 weeks from the first dosing date.
[x] Duration of response was measured from the time at which complete response or partial response criteria are first met until the first date of objectively documented progressive disease.
[xi] Censored observation indicated with plus (+).

"These long-term phase 1 results support our ongoing pivotal development program with [fam-] trastuzumab deruxtecan in HER2 positive metastatic breast and gastric cancers, where significant unmet

treatment needs remain," said Gilles Gallant, BPharm, PhD, FOPQ, Vice President, DS-8201 Global Team Leader, Oncology Research and Development, Daiichi Sankyo. "Our pivotal phase 2 DESTINY-Breast01 study has completed enrollment and our phase 3 DESTINY-Breast02 and DESTINY-Breast03 trials are underway to further evaluate [fam-] trastuzumab deruxtecan in HER2 positive metastatic breast cancer. We also are enrolling patients with advanced HER2 positive gastric cancer previously treated with trastuzumab in the pivotal phase 2 DESTINY-Gastric01 study."

"These results reinforce our belief that [fam-] trastuzumab deruxtecan could become a transformative new medicine for the treatment of HER2 positive breast and gastric cancers," said Hesham Abdullah, Vice President, Head of Late-Stage Immuno-Oncology Development, Research and Development, Oncology, AstraZeneca. "The encouraging response rates and quality of the duration of response in this heavily pretreated and difficult-to-treat setting demonstrate the value this potential treatment can bring to patients with unmet medical needs."

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.[2,3] 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+. A finding of IHC 3+ is considered HER2 positive, and a finding of IHC 2+ is borderline and typically is confirmed by a positive FISH test.[5,]**Error! Bookmark not defined.**

Unmet Need in HER2 Positive Breast and Gastric Cancer

Approximately one in five breast and gastric cancers (20 percent) are HER2 positive.[4,5] Several unmet treatment needs remain today in HER2 positive metastatic breast cancer. Many HER2 positive breast cancers eventually advance to the point where no currently approved HER2 targeting therapy continues to control the disease;[6] after treatment with trastuzumab, pertuzumab, and T-DM1, optimal treatment is less clearly defined and choices may be limited.[7]

HER2 expressing gastric cancer also is an area of unmet medical need, where treatment advances have been limited, largely due to the genetic complexity and heterogeneity of the disease.[8] Currently, there are no approved HER2 targeting therapies for patients with HER2-positive advanced gastric cancer that progresses after treatment with a trastuzumab regimen.

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 objectives of the dose escalation

part of the study were to assess the safety, tolerability, and activity of [fam-] trastuzumab deruxtecan and determine the recommended dose for expansion. These data were published in *The Lancet Oncology*.[9]

In the dose expansion part of the study, [fam-] trastuzumab deruxtecan is being evaluated at two recommended doses (5.4 mg/kg and 6.4 mg/kg) in five patient cohorts, including HER2 positive advanced or metastatic breast cancer and gastric cancer, HER2 low expressing breast cancer, and other HER2 expressing solid tumors. Enrollment for patients with HER2 positive breast cancer and HER2 positive gastric/gastro-esophageal cancer has completed. 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 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 studies. [Fam-] trastuzumab deruxtecan is in pivotal phase 3 development in previously treated HER2 low expressing metastatic breast cancer versus investigator's choice (DESTINY-Breast04); phase 3 development in HER2 positive metastatic breast cancer versus ado-trastuzumab emtansine (T-DM1) (DESTINY-Breast03); and phase 3 development in HER2 positive metastatic breast cancer versus investigator's choice post T-DM1 (DESTINY-Breast02). [Fam-] trastuzumab deruxtecan also is in pivotal phase 2 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 non-squamous HER2 overexpressing or HER2 mutated metastatic 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 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. 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.

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