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Press Release

Results from First Combination Trial of ENHERTU® and Immune Checkpoint Inhibitor in Patients with HER2 Expressing Metastatic Breast Cancer Presented at the 2020 San Antonio Breast Cancer Symposium

- Initial results demonstrate ENHERTU may be safely combined with nivolumab, an immune checkpoint inhibitor in patients with HER2 positive or HER2 low metastatic breast cancer
- Additional immunotherapy combination trials underway with ENHERTU to determine optimal combination strategies in these settings

Tokyo, Basking Ridge, NJ and Munich – (December 10, 2020) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today presented the first immunotherapy combination study results for ENHERTU® (fam-trastuzumab deruxtecan-nxki), reporting preliminary results from two cohorts of a four cohort phase 1b trial evaluating the efficacy and safety of ENHERTU in combination with nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, in patients with previously treated HER2 positive or HER2 low metastatic breast cancer. Results were presented in a Spotlight Poster Discussion at the virtual 2020 San Antonio Breast Cancer Symposium (#SABCS20).

This interim analysis found that the combination of ENHERTU (5.4 mg/kg) and nivolumab (360 mg), administered every three weeks, was well tolerated in patients with HER2 positive or HER2 low metastatic breast cancer, providing the first data showing that ENHERTU may be safely combined with an immunotherapy agent, at therapeutic doses of both agents and for a meaningful treatment duration.

The overall safety and tolerability of ENHERTU and nivolumab combination therapy was similar to that seen with ENHERTU monotherapy in patients with HER2 positive metastatic breast cancer and nivolumab monotherapy across tumors. No new safety signals were observed; however, the rate of treatment-emergent adverse events leading to treatment discontinuation (18.8%) was numerically higher with the combination than previous reports from either monotherapy alone. There were no dose limiting toxicities observed in part 1 of the trial. Overall, 43.8% of patients experienced a grade 3 or higher treatment-emergent adverse event, with 18.8% identified as events related to ENHERTU and 18.8% related to nivolumab. The most common any-grade treatment-emergent adverse events were nausea (54.2%), fatigue (45.8%), and alopecia (41.7%). There were five cases (10.4%, all HER2 positive) of

treatment-related interstitial lung disease (ILD) or pneumonitis, determined by an independent adjudication committee, including one death (grade 5). The remaining four cases were grade 2.

Preliminary efficacy results for 48 evaluable patients found that patients in the HER2 positive cohort (n=32) and the HER2 low cohort (n=16) showed a confirmed objective response rate of 59% and 38%, respectively. Disease control rates of 91% and 75% were observed in the HER2 positive and HER2 low cohorts, respectively. Median duration of response has not yet been reached in either cohort.

"As HER2 positive metastatic breast cancer continues to progress, and multiple lines of HER2 directed therapy have been exhausted, consideration needs to be given to evaluating a combination of medicines with different mechanisms of action," said Erika Hamilton, MD, Director, Breast Cancer and Gynecologic Cancer Research Program, Sarah Cannon Research Institute at Tennessee Oncology. "These preliminary data provide a promising signal that ENHERTU, a HER2 directed antibody drug conjugate, may be combined with nivolumab, an immune checkpoint inhibitor. Longer follow-up and more research is needed to determine whether adding immunotherapy to ENHERTU to treat HER2 positive or HER2 low metastatic breast cancer may provide further clinical benefit than receiving ENHERTU alone."

"Additional treatment strategies are needed for patients with HER2 positive metastatic breast cancer as the disease still remains incurable," said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. "These initial findings indicate treatment with ENHERTU and nivolumab, an immune checkpoint inhibitor, may be combined and administered for longer periods of time. These findings also support our broader research effort to better understand whether the directed delivery of potent chemotherapy with ENHERTU along with immunotherapy may benefit patients with HER2 expressing metastatic breast cancer regardless of the levels of HER2 expression."

In the phase 1b study, the majority of patients in the HER2 positive (88%) and HER2 low (75%) cohorts had received four or more prior therapies. Median duration of treatment with ENHERTU was 6.5 months (range, 1.4-14.0 months) in the HER2 positive cohort and 6.3 months (range, 0.7-10.4 months) in the HER2 low cohort. The median duration of treatment with nivolumab was 5.2 months (range, 1.3-11.3 months) and 4.9 months (range, 0.7-10.4 months) in the HER2 positive and HER2 low cohorts, respectively. Median duration of follow-up was 7.0 months for HER2 positive patients and 6.9 months for HER2 low patients. As of data cut-off on June 8, 2020, 56.3% of HER2 positive and 50.0% of HER2 low

patients remained on treatment with ENHERTU. Fifty percent of HER2 positive and 43.8% of HER2 low patients remained on treatment with nivolumab.

About the Trial

The trial is a two-part, phase 1b, multicenter, open-label trial evaluating ENHERTU in combination with nivolumab in patients with HER2 expressing breast and urothelial cancer that experience disease progression during or after prior therapies, did not respond to standard therapies, or for whom no standard therapy is currently available.

The trial was performed in two parts: Part 1 evaluated different doses of ENHERTU when given along with a fixed dose of nivolumab (360 mg), administered every three weeks, to determine the recommended dose for expansion (RDE); Part 2 assessed the efficacy and safety of this dose combination at the RDE. Part 2 of the trial enrolled patients into four cohorts: cohort 1 was comprised of patients with HER2 positive breast cancer who had received prior treatment with trastuzumab emtansine (T-DM1); cohort 2 was comprised of patients with HER2 low triple negative breast cancer who had previously received standard treatment; cohorts 3 and 4 are comprised of patients with HER2 high or HER2 low expressing urothelial cancer, respectively, who had received prior platinum-based therapy with documented progression and had not received prior immunotherapy.

The primary efficacy endpoint in Part 2 of the trial is objective response rate confirmed by independent central review. Additional efficacy endpoints include duration of response, disease control rate, progression-free survival, overall survival, safety, and pharmacokinetics.

About HER2 Expressing Breast Cancer

In women, breast cancer is the most common cancer and one of the most common causes of cancer mortality worldwide; there were an estimated 2.1 million new cases of female breast cancer diagnosed in 2018.[1] Breast cancer occurs mainly in women but in rare cases, it can also occur in men.[2]

HER2 is a tyrosine kinase receptor growth-promoting 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 with aggressive disease and poor prognosis.[3]

Approximately one in five breast cancers are HER2 positive, and an additional 40% of all breast cancers may have low levels of HER2 expression.[4,5,6] Despite recent improvements and approvals of new medicines, metastatic breast cancer remains incurable and additional treatment strategies are needed for patients with HER2 positive metastatic breast cancer.[7,8] Currently, no anti-HER2 agents are indicated for HER2 low expressing tumors.

About ENHERTU

ENHERTU is a HER2 directed antibody drug conjugate (ADC). Designed using Daiichi Sankyo's proprietary DXd ADC technology, ENHERTU 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. ENHERTU is comprised of a HER2 monoclonal antibody attached to a topoisomerase I inhibitor payload by a tetrapeptide-based linker.

ENHERTU (5.4 mg/kg) is approved in the U.S. under Accelerated Approval, and in Japan for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who received two or more prior anti-HER2 based regimens based on the DESTINY-Breast01 trial. ENHERTU is approved in the U.S. with Boxed WARNINGS for Interstitial Lung Disease and Embryo-Fetal Toxicity.

ENHERTU (6.4 mg/kg) is also approved in Japan for the treatment of patients with HER2 positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy based on the DESTINY-Gastric01 trial.

About the ENHERTU Clinical Development Program

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

In October 2020, ENHERTU was granted Priority Review from the U.S. Food and Drug Administration (FDA) for the treatment of patients with HER2 positive metastatic gastric or gastroesophageal junction

(GEJ) adenocarcinoma. In May 2020, ENHERTU received a Breakthrough Therapy Designation (BTD) and Orphan Drug Designation (ODD) for gastric cancer, including GEJ adenocarcinoma.

In May 2020, ENHERTU also received a BTD for the treatment of patients with metastatic NSCLC whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy. ENHERTU is not approved in the U.S. in either NSCLC or gastric cancer.

In July 2020, the European Medicines Agency's Committee for Medicinal Products for Human Use granted accelerated assessment of ENHERTU for the treatment of adults with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2 based regimens.

About the Collaboration Between Daiichi Sankyo and AstraZeneca

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU (a HER2 directed ADC) in March 2019, and datopotamab deruxtecan (DS-1062; a TROP2 directed ADC) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for manufacturing and supply of ENHERTU and datopotamab deruxtecan.

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 click for full Prescribing Information, including Boxed WARNINGS, 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 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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