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Daiichi-Sankyo

Press Release

DESTINY-Breast05 Head-to-Head Phase 3 Trial of ENHERTU® Versus T-DM1 Initiated in Patients with HER2 Positive Early Breast Cancer at High Risk After Neo-adjuvant Therapy

Tokyo, Munich, and Basking Ridge, NJ – (November 2, 2020) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca today announced the initiation of DESTINY-Breast05, a global phase 3, head-to-head trial of ENHERTU® (fam-trastuzumab deruxtecan-nxki) versus ado-trastuzumab emtansine (T-DM1) as adjuvant therapy in patients with HER2 positive early breast cancer with high risk of disease recurrence who have residual invasive disease in the breast or axillary lymph nodes after receiving neo-adjuvant therapy. DESTINY-Breast05 will be conducted in collaboration with the National Surgical Adjuvant Breast and Bowel Project Foundation (NSABP), the German Breast Group (GBG), Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-B) and the SOLTI Breast Cancer Research Group.

Neo-adjuvant treatment is given before surgery to help shrink the tumor and make it easier to remove. Patients with residual invasive disease in the breast or lymph nodes at surgery following neo-adjuvant treatment are at greater risk for disease recurrence or death than patients who achieve a pathological complete response, meaning there is no detectable disease in the tissue removed during surgery.[1] Adjuvant treatment, given after surgery, aims to eradicate any remaining cancer cells in the breast or the rest of the body, to help lower the risk of the cancer returning.

“Despite recent improvements and approvals of new medicines, there remain significant clinical needs for patients with HER2 positive early breast cancer with residual invasive disease after completing neo-adjuvant treatment. We recognize the important opportunity that exists post-surgery to slow disease progression with further adjuvant treatment,” said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. “This research builds on the data from DESTINY-Breast01 which showed durability of response in previously treated HER2 positive metastatic breast cancer. DESTINY-Breast05 will evaluate ENHERTU in patients with early HER2 positive breast cancer, versus T-DM1, the current standard of care, which marks the first time we will evaluate the clinical benefit of ENHERTU in early breast cancer, reflecting our commitment to transforming treatment for even more patients with HER2 targetable disease.”

"NSABP and our academic collaborators are committed to designing and conducting trials that have potential for further improving the way breast cancer is treated by evaluating promising new therapies that may provide patients and physicians with additional treatment options," said Charles E. Geyer, Jr, MD, chair of the NSABP Foundation Breast Cancer Committee and Deputy Director of the Houston Methodist Cancer Center. "We are excited to collaborate with Daiichi Sankyo and AstraZeneca on this important study, with the goal of comparing the safety and clinical benefit of the two currently available HER2 directed antibody drug conjugates in early stage breast cancer."

ENHERTU is approved in the U.S. with Boxed WARNINGS for Interstitial Lung Disease and Embryo-Fetal Toxicity. For more information, please see accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

About DESTINY-Breast05

DESTINY-Breast05 is a phase 3, multicenter, randomized, open-label, active-controlled study of ENHERTU versus T-DM1 in patients with high-risk HER2 positive primary breast cancer who have residual invasive disease in breast or axillary lymph nodes following neo-adjuvant therapy. Patients will be defined as high risk based on inoperable cancer at disease presentation (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) or operable at presentation (clinical stages T1-3, N0-1, M0) with positive pathological node status (ypN1-3) after neo-adjuvant therapy.

Patients will be randomized in a 1:1 ratio to either the ENHERTU or T-DM1 treatment group. Randomization will be stratified by the following factors:

- Operative status at disease presentation, prior to neo-adjuvant therapy (operable [clinical stages T1-3, N0-1, M0] versus inoperable [clinical stages T4, N0-3, M0 or T1-3, N2-3, M0])
- Tumor hormone receptor status (positive versus negative)
- Post-neo-adjuvant therapy pathologic nodal status (positive [ypN1-3] versus negative [ypN0])
- HER2 targeted neo-adjuvant therapy approach (single versus dual)

The primary efficacy endpoint is invasive disease-free survival (IDFS) based on investigator assessment. Secondary efficacy endpoints include overall survival and disease-free survival based on disease recurrence per investigator assessment. Safety endpoints include serious adverse events, treatment-emergent adverse events and adverse events of special interest. Health economics and outcomes research endpoints as well as pharmacokinetic and biomarker endpoints will also be measured.

DESTINY-Breast05 will enroll up to 1,600 patients at approximately 400 sites in North America, Europe, and Asia. For more information about the study, visit ClinicalTrials.gov.

About HER2 Positive 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.[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 may be associated with a specific HER2 gene alteration known as HER2 amplification and is often associated with aggressive disease and poor prognosis in breast cancer.[3]

About ENHERTU

ENHERTU 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, 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 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 (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 eight registrational trials evaluating the efficacy and safety of ENHERTU monotherapy across multiple HER2 targetable cancers including breast, gastric 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 non-small cell lung cancer (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 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 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 DS-1062.

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 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 (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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