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Press Release

ENHERTU® Continues to Demonstrate Durable Responses with New Data from DESTINY-Breast01 in HER2 Positive Metastatic Breast Cancer

- Median duration of response exceeded 20 months
- Updates show encouraging landmark survival in exploratory analysis with an estimated three out of four patients alive at 18 months

Tokyo, Munich and Basking Ridge, NJ – (December 10, 2020) – Updated results from the positive phase 2 DESTINY-Breast01 trial show Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca's ENHERTU® (fam-trastuzumab deruxtecan-nxki) continued to demonstrate impressive efficacy and durable responses in patients with HER2 positive metastatic breast cancer following two or more prior HER2 based regimens. These data were presented in a Spotlight Poster Discussion at the virtual 2020 San Antonio Breast Cancer Symposium (#SABCS20).

Approximately one in five patients with breast cancer are considered HER2 positive, which is associated with aggressive disease, high recurrence rate and increased mortality.[1,2]

With median duration of follow-up of 20.5 months, patients with HER2 positive metastatic breast cancer treated with ENHERTU (5.4 mg/kg) achieved an objective response rate (ORR) of 61.4% and a median duration of response (DoR) of 20.8 months. The median progression-free survival (PFS) was 19.4 months. In an exploratory landmark analysis of overall survival (OS), evaluated at 35% maturity, an estimated 74% of patients remained alive at 18 months. In the previous analysis at 11.1 months of follow-up, an ORR of 60.9% was seen with a median DoR of 14.8 months and median PFS of 16.4 months. Additional follow-up is required for more mature OS data, and additional trials are ongoing to confirm the results seen in DESTINY-Breast01.

“These longer-term data from the DESTINY-Breast01 trial further highlight the role that this treatment option may have in changing clinical outcomes for patients with previously treated HER2 positive metastatic breast cancer,” said Shanu Modi, MD, Breast Medical Oncologist, Memorial Sloan Kettering Cancer Center. “It is important that we are able to offer patients therapy like this which provides a meaningful clinical benefit, as historically there have been few therapies that were able to do that in this patient population.”

The overall safety and tolerability profile of ENHERTU was consistent with what has been previously observed with few additional treatment discontinuations due to adverse events with longer treatment duration. Overall, 52.7% of patients experienced a drug-related grade ≥3 treatment-emergent adverse event. In the updated analysis with an additional median 9 months of follow-up, 18.5% of patients discontinued treatment due to adverse events, compared to 15.2% in the previous analysis. Most cases of interstitial lung disease (ILD) or pneumonitis occurred during the first 12 months of treatment and the study findings suggest that the risk of developing ILD or pneumonitis toxicity is not related to cumulative treatment with ENHERTU. There were three new cases of treatment-related ILD reported, as determined by an independent adjudication committee (one grade 1, one grade 2, and one death [grade 5]). Two cases were pending adjudication at data cut-off. Continued attention to careful monitoring to identify pulmonary symptoms and to intervene early is warranted.

"These updated findings illustrate the practice-changing potential for ENHERTU to become a long-term treatment option for patients with previously treated HER2 positive metastatic breast cancer," said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. "The duration of response and long-term safety profile further validate that our DXd antibody drug conjugate technology delivers effective and durable treatment."

"These results reinforce the transformational potential of ENHERTU in patients with previously treated HER2 positive metastatic breast cancer," said José Baselga, MD, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "With a median duration of response greater than twenty months, the updated results of DESTINY-Breast01 are unprecedented. We look forward to further confirming the DESTINY-Breast01 findings with results from our phase 3 development program of ENHERTU."

The majority of patients in the study received multiple lines of previous therapy, including trastuzumab, trastuzumab emtansine (T-DM1) and pertuzumab. Median duration of follow-up was 20.5 months. As of data cut-off on June 8, 2020, 20.1% of patients remained on treatment with ENHERTU.

Summary of Results

DESTINY-Breast01 Efficacy Measure	**As of August 1, 2019 (n=184)[i]**	**As of June 8, 2020 (n=184)[ii]**
Median duration of follow-up	11.1 months (0.7-19.9 months)	20.5 months (0.7-31.4 months)
Patients remaining on treatment, n/N (%)	42.9% (n=79)	20.1% (n=37)
ORR (%) (95% CI)	60.9% [53.4-68.0] (n=112)	61.4% [54.0-68.5] (n=113)

CR (%)	6.0% (n=11)	6.5% (n=12)
PR (%)	54.9% (n=101)	54.9% (n=101)
SD (%)	36.4% (n=67)	35.9% (n=66)
PD (%)	1.6% (n=3)	1.6% (n=3)
Median DoR (months) (95% CI)	14.8 months (13.8-16.9)	20.8 months (15.0-NE)
Median PFS (months) (95% CI)[iii]	16.4 months (12.7 months-NE)	19.4 months (14.1 months-NE)
Median OS (months) (95% CI)[iv]	NE (NE-NE)	24.6 months (23.1 months-NE)
Estimated OS at 12 months (95% CI)	86.2% (79.8-90.7)	85% (79-90)
Estimated OS at 18 months (95% CI)	--	74% (67-80)

CI, confidence interval; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; NE, not estimable.

[i] Data from the August 1 2019 cut-off were presented at the 2019 SABCS and published in *The New England Journal of Medicine*

[ii] As of data cut-off, 20.1% of patients remained on treatment with ENHERTU

[iii] 114 patients (62.0%) were censored at time of analysis

[iv] OS was estimated at 35% maturity, with 119 patients (64.7%) censored and only 17 patients at risk at 24 months; additional follow-up is required for more mature OS data

About DESTINY-Breast01

DESTINY-Breast01 is a pivotal phase 2, single-arm, open-label, global, multicenter, two-part trial evaluating the safety and efficacy of ENHERTU in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with T-DM1. The primary endpoint of the trial is ORR, as determined by independent central review. Secondary objectives include DoR, disease control rate, clinical benefit rate, PFS and OS.

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.[3,4] Breast cancer occurs mainly in women, but in rare cases it can also occur in men. [5]

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 poorer prognosis.[6]

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 (5.4mg/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 have received two or more prior anti-HER2-based regimens in the metastatic setting 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 non-small cell lung cancer whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy.

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 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 (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.

Dr. Modi has provided consulting/advisory services for Daiichi Sankyo.

Media Contacts:

Global:
Victoria Amari
Daiichi Sankyo, Inc.
vamari@dsi.com
+1 908 900 3010 (mobile)

Japan:
Masashi Kawase
Daiichi Sankyo Co., Ltd.
kawase.masashi.a2@daiichisankyo.co.jp
+81 3 6225 1126 (office)

U.S.:
Don Murphy
Daiichi Sankyo, Inc.
domurphy@dsi.com
+1 917 817 2649 (mobile)

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

EU:
Lydia Worms
Daiichi Sankyo Europe GmbH
lydia.worms@daiichi-sankyo.eu
+49 (89) 7808751 (office)
+49 176 11780861 (mobile)

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