Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

Press Release

ENHERTU® Achieved a Tumor Response Rate of 45.3% in Patients with HER2 Positive Metastatic Colorectal Cancer in Phase 2 DESTINY-CRC01 Trial

Tokyo, Basking Ridge, NJ and Munich - (May 29, 2020) – Results from the phase 2 DESTINY-CRC01 trial of Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca's ENHERTU® (fam-trastuzumab deruxtecan-nxki) demonstrated clinically meaningful activity in patients with HER2 positive unresectable and/or metastatic colorectal cancer who received at least two prior lines of standard treatment. These results were presented today at the 2020 American Society of Clinical Oncology Virtual Scientific Program (#ASCO20).

Colorectal cancer is the third most common cancer and second most common cause of cancer death worldwide.[1] There are currently no medicines approved to specifically treat HER2 positive colorectal cancer, which affects approximately two to five percent of patients with colorectal cancer.[2]

The primary endpoint of confirmed objective response rate (ORR), also called a tumor response rate, which was assessed by independent central review, showed 45.3% of patients with HER2 positive advanced colorectal cancer (defined as IHC 3+ or IHC 2+/ISH+) treated with ENHERTU monotherapy (6.4mg/kg) achieved a tumor response. A disease control rate (DCR) of 83.0% was observed with a median progression-free survival (PFS) of 6.9 months. Median duration of response (DoR) and overall survival (OS) have not yet been reached at the time of data cut-off.

The overall safety and tolerability profile of ENHERTU in DESTINY-CRC01 was consistent with that seen in previously reported ENHERTU trials. The most common grade 3 or higher treatment-emergent adverse events were decreased neutrophil count (25.6%) and anemia (14.1%). There were five cases (6.4%) of treatment-related interstitial lung disease (ILD) and pneumonitis determined by an independent adjudication committee. Two were grade 2 and one was grade 3. Two deaths (grade 5) were determined to be due to ILD.

"Understanding new ways we can treat patients with colorectal cancer, such as targeting HER2, is critical as patients have few remaining treatment options once progression occurs in the advanced disease setting," said Salvatore Siena, MD, Professor of Medical Oncology, Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, and Niguarda Cancer Center Milan, Italy and principal investigator of the DESTINY-CRC01 trial. "The results from DESTINY-CRC01 in patients with HER2 positive advanced

colorectal cancer are striking and warrant further research, especially considering many of these patients have had numerous prior therapies."

Prespecified exploratory analysis evaluated ORR in subgroups, including patients previously treated with a prior anti-HER2 regimen (n=16). In these patients an ORR of 43.8% was seen.

Patients were treated with a median of four prior lines of therapy (range, 2-11) with all patients having received prior chemotherapy treatment with irinotecan and oxaliplatin. The median treatment duration was 4.8 months (range, 1-11). As of data cut-off on August 9, 2019, 38.5% (30 out of 78) remained on treatment across all cohorts.

"Metastatic colorectal cancer has a devastating prognosis and there have been limited treatment advances following progression on first-line treatment and there are no therapies approved that specifically target HER2," said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. "We are encouraged by the tumor response rates seen in patients with previously-treated advanced colorectal cancer and we will continue to explore the potential of ENHERTU to address this unmet medical need."

"These clinically meaningful and durable responses in patients with advanced HER2 positive colorectal cancer support our belief that HER2 is an important target in this disease," said José Baselga, MD, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "ENHERTU has now demonstrated impressive clinical activity in four different cancer settings, reinforcing the potential of this remarkable medicine to transform patient outcomes across a range of HER2 targetable tumors."

Summary of Results

Efficacy Measure	**Total Evaluable in Primary Cohort (n=53)[i,ii]**
ORR (%) (95% CI)[iii,iv]	45.3% (31.6 - 59.6)
ORR (previously HER2 treated) (%)	43.8% (19.8 -70.1)
CR (%)	1.9%
PR (%)	43.4%
SD (%)	37.7%
DCR (%) (95% CI)[v]	83.0% (70.2 - 91.9)
Median DoR (months) (95% CI)	Not reached (4.2 months - NE)
Median PFS (months) (95% CI)	6.9 months (4.1 months - NE)
Median OS (months) (95% CI)	Not reached (0.74 months - NE)

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

[i] ENHERTU 6.4 mg/kg

[ii] Primary cohort included patients with HER2-positive disease (defined as IHC3+ or IHC2+/ISH+).

[iii] As assessed by independent central review.
[iv] ORR is (CR + PR)
[v] DCR is (CR + PR + SD)

Two exploratory cohorts enrolled patients with tumors with lower levels of HER2 expression (HER2 IHC 2+/ISH- and HER2 IHC 1+, respectively). There were no responses seen in these two exploratory cohorts.

About HER2

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast, gastric, lung and colorectal cancers. In some tumors, HER2 overexpression is associated with a specific HER2 gene alteration known as amplification and is often associated with aggressive disease and poorer prognosis.[3]

HER2 overexpression and amplification occurs in approximately two to five percent of all patients with colorectal cancer.[2] Research indicates that HER2 amplification may be associated with resistance to anti-epidermal growth factor receptor (EGFR)-targeted therapy and shorter survival.[4,5]

About Colorectal Cancer

Colorectal cancer is the second most common cancer in women and the third most common cancer in men worldwide.[1] In 2018, more than 1.8 million people worldwide received colorectal cancer diagnoses and approximately 880,800 died from the disease.[1] Approximately 25% of patients have metastatic disease at diagnosis, meaning the disease has spread to distant organs, and about 50% of patients with colorectal cancer will eventually develop metastases.[5]

About DESTINY-CRC01

DESTINY-CRC01 is a global, phase 2, open-label, multicenter, trial evaluating the safety and efficacy of ENHERTU in patients (n=78) with HER2 expressing, unresectable and/or metastatic colorectal cancer. DESTINY-CRC01 excluded patients with a mutation in the RAS or BRAF gene. The primary cohort of the trial enrolled patients (n=53) with HER2 positive (defined as IHC 3+ or IHC2+/ISH+) disease. The primary endpoint of the trial is confirmed ORR, assessed by independent central review, in the primary cohort. ORR, or tumor response rate, represents the percentage of patients whose disease decreased and/or disappeared. Secondary endpoints include DCR, DoR, PFS, and OS. Two additional exploratory cohorts enrolled patients whose tumor had lower levels of HER2 expression (HER2 IHC 2+/ISH, n=7, and HER2 IHC 1+, n=18, respectively).

About ENHERTU

ENHERTU (fam-trastuzumab deruxtecan-nxki in the U.S. only; trastuzumab deruxtecan outside the U.S.) is a HER2 directed antibody drug conjugate (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 novel topoisomerase I inhibitor payload by a tetrapeptide-based linker.

ENHERTU is approved in the U.S. 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 has not been approved in the EU, or countries outside of Japan and the United States, for any indication. It is an investigational agent globally for various indications. Safety and effectiveness have not been established for the subject proposed use.

About the ENHERTU Clinical Development Program

A comprehensive development program for ENHERTU is underway globally with six pivotal 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, also are underway.

In May 2020, ENHERTU received Breakthrough Therapy Designation (BTD) from the U.S. Food and Drug Administration (FDA) for the treatment of patients with HER2 positive unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma who have received two or more prior regimens including trastuzumab, and Orphan Drug Designation for gastric cancer, including gastroesophageal junction cancer. In March 2018, ENHERTU received a SAKIGAKE designation for potential use in the same HER2 positive patient population and a supplemental New Drug Application (NDA) was submitted to the Japan Ministry of Health, Labour and Welfare (MHLW) for approval in April 2020.

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.

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 ENHERTU worldwide, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is solely responsible for the manufacturing and supply.

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 WARNING, 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

Media Contacts:

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

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

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

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

References:
[1] Bray F, et al. *CA: Cancer J Clin*. 2018;68:394-424
[2] Siena S, et al. *Annals of Oncology.* 2018;29:1108–1119.
[3] Iqbal N, et al. *Mol Biol Int.* 2014;2014:852748.
[4] Martin, et al. *Br J Cancer*. 2013;108(3):668-75
[5] Jeong JH, et al. *Clinical Colorectal Cancer*. Vol 16. No3, e147-52.