

Press Release

ENHERTU® Significantly Improved Tumor Response Rate and Overall Survival in HER2 Positive Metastatic Gastric Cancer in Pivotal Phase 2 DESTINY-Gastric01 Trial

- First HER2 directed therapy to show an improvement in overall survival for previously-treated metastatic gastric cancer with a 41% reduction in the risk of death versus chemotherapy
- Breakthrough Therapy Designation recently granted in the U.S. for ENHERTU in this setting

Tokyo, Basking Ridge, NJ and Munich - (May 29, 2020) – Detailed results from the positive pivotal randomized, controlled phase 2 [DESTINY-Gastric01](#) trial showed Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca’s ENHERTU® (fam-trastuzumab deruxtecan-nxki) demonstrated a statistically significant and clinically meaningful improvement in objective response rate (ORR) and overall survival (OS), a key secondary endpoint, versus chemotherapy.

The trial evaluated patients with HER2 positive unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma that had progressed following two or more treatment regimens including trastuzumab and chemotherapy. These results were presented today during the American Society of Clinical Oncology Virtual Scientific Program (#ASCO20) and simultaneously published online in *The New England Journal of Medicine*.

Gastric cancer is the third leading cause of cancer mortality worldwide with a five-year survival rate of five percent for metastatic disease.¹ Approximately one in five gastric cancers are considered HER2 positive.²

The confirmed ORR, also called a tumor response rate, which was assessed by independent central review, was 42.9% with ENHERTU monotherapy (6.4 mg/kg) (p<0.0001; CI: 33.8-52.3) compared to 12.5% with investigator’s choice of chemotherapy (paclitaxel or irinotecan). Ten complete responses and 41 partial responses were seen in patients treated with ENHERTU versus no complete responses and seven partial responses seen in patients treated with chemotherapy.

Patients treated with ENHERTU had a 41% reduction in the risk of death compared to patients treated with chemotherapy (based on a hazard ratio [HR] of 0.59; 95% confidence interval [CI]: 0.39-0.88; p=0.0097) at a pre-specified interim analysis. The median OS was 12.5 months versus 8.4 months with chemotherapy. The estimated OS rate at one year with ENHERTU was 52.1% and 28.9% with the chemotherapy arm.

The safety and tolerability profile of ENHERTU in DESTINY-Gastric01 was consistent with that observed in the phase 1 gastric trial and previously reported ENHERTU trials. The most common grade 3 or higher treatment-emergent adverse events were decreased neutrophil count (51.2%), anemia (37.6%), decreased white blood cell count (20.8%) and decreased appetite (16.8%). There were 12 cases (9.6%) of confirmed treatment-related interstitial lung disease (ILD) and pneumonitis as determined by an independent review. The majority were grade 1 or 2 with two grade 3, one grade 4 and no grade 5 (ILD-related deaths).

“Once patients with HER2 positive metastatic gastric cancer progress following initial treatment with an anti-HER2 regimen, there are limited treatment options and no approved HER2 targeted therapies,” said Kohei Shitara, MD, Chief of Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan and principal investigator in the phase 2 DESTINY-Gastric01 trial. “Based on the compelling results of the DESTINY-Gastric01 trial, ENHERTU has the potential to become a new standard of care for these patients.”

ENHERTU showed a confirmed disease control rate (DCR) of 85.7% (CI: 78.1-91.5) versus 62.5% (CI: 48.5-75.1) and a median confirmed duration of response (DoR) of 11.3 months (CI: 5.6-NE) versus 3.9 months (CI: 3.9-4.9) as compared to chemotherapy.

“ENHERTU is the first HER2 directed therapy to show an improvement in overall survival for patients with previously-treated HER2 positive metastatic gastric cancer,” said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. “These data are encouraging and meaningful since patients with advanced gastric cancer have limited therapeutic options once they progress and face markedly high mortality rates. We are working with regulatory authorities to bring ENHERTU to patients with metastatic gastric cancer as quickly as possible.”

“In DESTINY-Gastric01, the response rate was more than three times higher with ENHERTU versus chemotherapy. Additionally, more than half of patients treated with ENHERTU were alive at one year compared to less than a third with chemotherapy,” said José Baselga, MD, PhD, Executive Vice President, R&D Oncology, AstraZeneca. “In addition to the impressive results we saw in HER2 positive metastatic breast cancer in DESTINY-Breast01, these results in gastric cancer help further define the role of ENHERTU in transforming patient outcomes across multiple HER2 targetable cancers.”

Summary of Results:ⁱ

Efficacy Measure	ENHERTU Monotherapy ⁱⁱ	Investigator's Choice of Chemotherapy (Irinotecan or Paclitaxel)
	<i>n=119</i>	<i>n=56</i>
Confirmed ORR (%) (95% CI %) ^{iii, iv, v}	42.9% (33.8-52.3; p<0.0001)	12.5% (5.2-24.1)
CR (%)	8.4%	0%
PR (%)	34.5%	12.5%
SD (%)	42.9%	50.0%
Confirmed DCR (%)^{vi} (95% CI, %)	85.7% (78.1-91.5)	62.5% (48.5-75.1)
Confirmed Median DoR (months) (95% CI)	11.3 months (5.6- NE)	3.9 months (3.0-4.9)

PR, partial response; SD, stable disease

ⁱ Data cutoff was November 8, 2019.

ⁱⁱ ENHERTU 6.4mg/kg

ⁱⁱⁱ As assessed by independent central review.

^{iv} ORR is (CR + PR)

^v Confirmed ORR represents responses confirmed by a follow-up scan ≥ 4 weeks after initial CR/PR; unconfirmed ORR is the primary endpoint of the trial [51.3% (95% CI 41.9–60.5) versus 14.3% (95% CI 6.4–26.2); p<0.0001]. Both confirmed and unconfirmed ORR were assessed by independent central review.

^{vi} DCR is (CR + PR + SD)

ENHERTU was recently granted a [Breakthrough Therapy Designation](#) (BTD) in the U.S. 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. A [supplemental new drug application](#) (sNDA) was submitted to Japan's Ministry of Health, Labour and Welfare (MHLW) based on these data and will undergo expedited review as a SAKIGAKE-designated medicine for this potential indication.

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

About Gastric Cancer

Gastric (stomach) cancer is the fifth most common cancer worldwide and the third leading cause of cancer mortality with a five-year survival rate of five percent for metastatic disease; there were approximately one million new cases reported in 2018 and 783,000 deaths.¹

Approximately one in five gastric cancers are HER2 positive.² Gastric cancer is usually diagnosed in the advanced stage, but even when diagnosed in earlier stages of the disease the survival rate remains modest.⁴ Recommended first-line treatment for HER2 positive advanced or metastatic gastric cancer is combination

chemotherapy plus trastuzumab, an anti-HER2 medicine, which has been shown to improve outcomes when added to chemotherapy.⁵ For gastric cancer that progresses on first line treatment, trastuzumab has not shown any further benefit and there are no other approved HER2 targeting medicines.⁵

DESTINY-Gastric01

[DESTINY-Gastric01](#) is an open-label, multi-center, randomized, pivotal phase 2 trial evaluating the safety and efficacy of ENHERTU in a primary cohort of 188 patients from Japan and South Korea with HER2 expressing advanced gastric cancer or gastroesophageal junction adenocarcinoma (defined as IHC3+ or IHC2+/ISH+) who had progressed on two or more prior treatment regimens including fluoropyrimidine (5-FU), platinum chemotherapy and trastuzumab. Patients were randomized 2:1 to receive ENHERTU or investigator's choice of chemotherapy (paclitaxel or irinotecan monotherapy). Patients were treated with ENHERTU 6.4 mg/kg once every three weeks or chemotherapy.

The primary endpoint of the study is ORR, as assessed by independent central review. ORR, or tumor response rate, represents the percentage of patients whose disease decreased and/or disappears. Overall survival was a key secondary endpoint to be statistically evaluated hierarchically if the primary endpoint was statistically significant. Other secondary endpoints include PFS, DoR, DCR and confirmed ORR assessed in those responses confirmed by a follow-up scan of at least 4 weeks after initial independent central review.

About ENHERTU

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

ENHERTU (5.4 mg/kg) 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 U.S., 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 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 [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 [sNDA](#) 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 $0.5 \times 10^9/L$) interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC $< 0.5 \times 10^9/L$) interrupt ENHERTU until resolved to Grade 2 or less. Reduce dose by one level. For febrile neutropenia (ANC $< 1.0 \times 10^9/L$ and temperature $> 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ 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 $\geq 20\%$) 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 American Cancer Society. About Stomach Cancer. [Targeted Therapies for Stomach Cancer](#). December 2017.

³ Iqbal N, et al. *Mol Biol Int.* 2014; 2014: 852748

⁴ CUREA et al. *Cancer Biotherapy & Radiopharmaceuticals.* 2017;32 (10).

⁵ NCCN Guidelines® Gastric Cancer. Version 4.2019. December 20, 2019: MS-22-36.