

Press Release

ENHERTU® Granted Breakthrough Therapy Designation in U.S. for Patients with HER2 Positive Metastatic Breast Cancer Treated with One or More Prior Anti-HER2-Based Regimens

- Based on groundbreaking DESTINY-Breast03 results where ENHERTU reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1)
- ENHERTU has now been granted four Breakthrough Therapy Designations, including two in breast cancer

Tokyo, Munich and Basking Ridge, NJ – (October 4, 2021) – The U.S. Food and Drug Administration (FDA) has granted ENHERTU® (fam-trastuzumab deruxtecan-nxki) Breakthrough Therapy Designation (BTD) in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received one or more prior anti-HER2-based regimens. ENHERTU is a HER2 directed antibody drug conjugate (ADC) jointly developed by Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca.

The U.S. FDA's BTD is designed to accelerate the development and regulatory review of potential new medicines that are intended to treat a serious condition and address a significant unmet medical need. The new medicine needs to have shown encouraging preliminary clinical results that demonstrate substantial improvement on a clinically significant endpoint over available medicines.

Breast cancer remains the most common cancer worldwide, with more than two million cases diagnosed in 2020, resulting in nearly 685,000 deaths globally.¹ Approximately one in five cases of breast cancer are considered HER2 positive.² Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.³ More effective options are needed to further delay progression and extend survival.^{3,4,5}

“By granting a fourth Breakthrough Therapy Designation to ENHERTU, the FDA continues to recognize the significant potential of this medicine across multiple HER2 targetable tumors,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “With the unprecedented data recently reported from the DESTINY-Breast03 trial, we look forward to working closely with the FDA to bring ENHERTU to patients who have been previously treated for HER2 positive metastatic breast cancer as soon as possible.”

“This is an important step in bringing ENHERTU as a potential new option in earlier lines of treatment for HER2 positive metastatic breast cancer, given the urgent need to improve outcomes,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “This recognition by the FDA underscores the transformative possibility of ENHERTU seen with the remarkable DESTINY-Breast03 results presented at ESMO just two weeks ago.”

The FDA granted BTB based on data from the [DESTINY-Breast03](#) pivotal trial [presented](#) during the 2021 European Society for Medical Oncology (ESMO) Congress. In the trial, ENHERTU demonstrated a 72% reduction in the risk of disease progression or death compared to T-DM1 (hazard ratio [HR] = 0.28; 95% CI: 0.22-0.37; $p=7.8 \times 10^{-22}$) in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane.

The safety profile of the most common adverse events with ENHERTU in DESTINY-Breast03 was consistent with previous clinical trials with no new safety concerns identified. The most common grade 3 or higher drug-related treatment emergent adverse events in the ENHERTU arm were neutropenia (19.1%), thrombocytopenia (7.0%), leukopenia (6.6%), nausea (6.6%), anemia (5.8%), fatigue (5.1%), vomiting (1.6%), increase in ALT (1.6%), decreased appetite (1.2%), increase in AST (0.8%), diarrhea (0.4%) and alopecia (0.4%). Overall, 10.5% of patients had interstitial lung disease (ILD) or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD events (9.7%) were low grade (grade 1 (2.7%) or grade 2 (7.0%)) with two grade 3 (0.8%) events reported. No grade 4 or grade 5 ILD or pneumonitis events occurred.

Previous BTBs for ENHERTU were in late-line HER2 positive metastatic breast cancer in 2017 and *HER2* mutant metastatic non-small cell lung cancer (NSCLC) and HER2 positive metastatic gastric cancer in 2020.

About HER2 Positive Breast Cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.¹ More than two million cases of breast cancer were diagnosed in 2020, resulting in nearly 685,000 deaths globally.¹ Approximately one in five cases of breast cancer are considered HER2 positive.²

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.⁶ HER2 protein overexpression may occur as a result of *HER2* gene amplification and is often associated with aggressive disease and poor prognosis in breast cancer.⁷

Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.³ More effective options are needed to further delay progression and extend survival.^{3,4,5}

About DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomized, open-label, pivotal phase 3 trial evaluating the safety and efficacy of ENHERTU (5.4 mg/kg) versus T-DM1 in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. The primary efficacy endpoint of DESTINY-Breast03 is progression-free survival (PFS) based on blinded independent central review. Secondary efficacy endpoints include overall survival, objective response rate, duration of response, progression-free survival based on investigator assessment and safety.

DESTINY-Breast03 enrolled 524 patients at multiple sites in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit [ClinicalTrials.gov](https://clinicaltrials.gov).

About ENHERTU

ENHERTU® (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed 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. ENHERTU consists of a HER2 monoclonal antibody attached to a topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

ENHERTU (5.4 mg/kg) is approved in Canada, EU, Israel, Japan, UK and U.S. 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 results from the [DESTINY-Breast01](#) trial.

ENHERTU (6.4 mg/kg) is also approved in Israel, Japan and U.S. for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the [DESTINY-Gastric01](#) trial.

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

About the ENHERTU Clinical Development Program

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

ENHERTU was highlighted in the [Clinical Cancer Advances 2021](#) report as one of two significant advancements in the “ASCO Clinical Advance of the Year: Molecular Profiling Driving Progress in GI Cancers,” based on data from both the [DESTINY-Gastric01](#) and [DESTINY-CRC01](#) trials, as well as one of the targeted therapy advances of the year in NSCLC based on the interim results of the *HER2* mutated cohort of the [DESTINY-Lung01](#) trial.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in [March 2019](#) and datopotamab deruxtecan (Dato-DXd) in [July 2020](#), except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and datopotamab deruxtecan.

U.S. Important Safety Information for ENHERTU

Indications

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.

- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

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. 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/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥ 1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

Metastatic Breast Cancer

In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 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).

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. 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.

Metastatic Breast Cancer

In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4mg/kg, a decrease in neutrophil count was reported in 62% of patients. Sixteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 23 days (range: 6 to 547). Febrile neutropenia was reported in 1.7% of patients.

Locally Advanced or Metastatic Gastric Cancer

In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

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. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF. 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. 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.

Additional Dose Modifications

Thrombocytopenia

For Grade 3 thrombocytopenia (platelets <50 to 25 x 10⁹/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10⁹/L) interrupt ENHERTU until resolved to Grade 1 or less. Reduce dose by one level.

Adverse Reactions

Metastatic Breast Cancer

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 ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea (79%), white blood cell count decreased (70%), hemoglobin decreased (70%), neutrophil count decreased (62%), fatigue (59%), vomiting (47%), alopecia (46%), aspartate aminotransferase increased (41%), alanine aminotransferase increased (38%), platelet count decreased (37%), constipation (35%), decreased appetite (32%), anemia (31%), diarrhea (29%), hypokalemia (26%), and cough (20%).

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m² biweekly or paclitaxel (N=7) 80 mg/m² weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were hemoglobin decreased (75%), white blood cell count decreased (74%), neutrophil count decreased (72%), lymphocyte count decreased (70%), platelet count decreased (68%), nausea (63%), decreased appetite (60%), anemia (58%), aspartate aminotransferase increased (58%), fatigue (55%), blood alkaline phosphatase increased (54%), alanine aminotransferase increased (47%), diarrhea (32%), hypokalemia (30%), vomiting (26%), constipation (24%), blood bilirubin increased (24%), pyrexia (24%), and alopecia (22%).

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%). Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥ 65 years and 14% were ≥ 75 years. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients.
- **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 in Oncology

The oncology portfolio of Daiichi Sankyo is powered by our team of world-class scientists that push beyond traditional thinking to create transformative medicines for people with cancer. Anchored by our DXd antibody drug conjugate (ADC) technology, our 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 the U.S. We also work alongside leading academic and business collaborators to further advance the understanding of cancer as Daiichi Sankyo builds towards our ambitious goal of becoming a global leader in oncology by 2025.

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose “to contribute to the enrichment of quality of life around the world.” In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an “Innovative Global Healthcare Company Contributing to the Sustainable Development of Society.” For more information, please visit: www.daiichisankyo.com.

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