

Press Release

ENHERTU[®] Approved in the U.S. as the First HER2 Directed Therapy for Patients with HER2 Low Metastatic Breast Cancer

- Based on DESTINY-Breast04 results which showed Daiichi Sankyo and AstraZeneca's ENHERTU reduced risk of disease progression or death by 50% and increased overall survival by more than six months versus chemotherapy

Tokyo and Basking Ridge, NJ – (August 5, 2022) – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) ENHERTU[®] (fam-trastuzumab deruxtecan-nxki) has been approved in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

ENHERTU is a specifically engineered HER2 directed antibody drug conjugate (ADC) being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca.

The approval was granted under the FDA's Real-Time Oncology Review (RTOR) program following the recent [Priority Review](#) and [Breakthrough Therapy Designation](#) of ENHERTU in the U.S. in this setting. The expanded approval for ENHERTU in the U.S. enables its use across a wide spectrum of HER2 expression, including patients with HER2 low disease.

The approval by the U.S. Food and Drug Administration (FDA) was based on positive results from the [DESTINY-Breast04](#) phase 3 trial of previously treated patients with HER2 low metastatic breast cancer. In the trial, ENHERTU demonstrated a 49% reduction in the risk of disease progression or death versus physician's choice of chemotherapy in patients with HER2 low metastatic breast cancer with hormone receptor (HR) positive disease (hazard ratio [HR] = 0.51; 95% confidence interval [CI]: 0.40-0.64; $p < 0.0001$). A median progression-free survival (PFS) of 10.1 months (95% CI: 9.5-11.5) was seen in patients treated with ENHERTU compared to 5.4 months (95% CI: 4.4-7.1) with chemotherapy, as assessed by blinded independent central review (BICR). Results also showed a 36% reduction in the risk of death with ENHERTU compared to chemotherapy in patients with HR positive disease (HR=0.64; 95% CI: 0.48-0.86; $p = 0.0028$) with a median overall survival (OS) of 23.9 months with ENHERTU (95% CI: 20.8-24.8) versus 17.5 months with chemotherapy (95% CI: 15.2-22.4).

In the overall trial population of patients with HER2 low metastatic breast cancer with HR positive or HR negative disease and across levels of HER2 expression (both IHC 1+ and IHC 2+/ISH-) a similar 50%

reduction in the risk of disease progression or death was observed between ENHERTU and chemotherapy (HR=0.50; 95% CI:0.40-0.63; p<0.0001), with a median PFS of 9.9 months (95% CI: 9.0-11.3) for ENHERTU versus 5.1 months (95% CI: 4.2-6.8) in those treated with chemotherapy, as assessed by BICR. A median OS of 23.4 months (95% CI: 20.0-24.8) was seen in patients treated with ENHERTU versus 16.8 months (95% CI: 14.5-20.0) in those treated with chemotherapy (HR=0.64; 95% CI: 0.49-0.84; p=0.001).

“Approximately half of all patients with breast cancer have tumors that are HER2 low, which have previously been classified as HER2 negative and have not had effective treatment options with HER2 targeted medicines,” said Shanu Modi, MD, medical oncologist, Memorial Sloan Kettering Cancer Center and principal investigator for the trial. “Based on the promising results of the DESTINY-Breast04 trial, clinicians are starting to differentiate levels of HER2 expression and redefine how metastatic breast cancer is classified with a distinct HER2 low patient population that may be eligible for trastuzumab deruxtecan.”

Additional results from the DESTINY-Breast04 trial showed that in patients with HR positive disease, the confirmed objective response rate (ORR) more than tripled in the ENHERTU arm versus the chemotherapy arm (52.9% [n=175; 95% CI: 47.3-58.4] versus 16.6% [n=27; 95% CI: 11.2-23.2], respectively). Twelve (3.6%) complete responses (CR) and 164 (49.5%) partial responses (PR) were observed in patients with HR positive disease treated with ENHERTU compared to one (0.6%) CR and 26 (16%) PRs in those treated with chemotherapy. Median duration of response was 10.7 months for ENHERTU versus 6.8 months for chemotherapy.

In the overall trial population, confirmed ORR more than tripled in the ENHERTU arm (52.3% [n=195; 95% CI: 47.1-57.4]) versus those treated with chemotherapy (16.3% [n=30; 95% CI: 11.3-22.5]). Thirteen (3.5%) CRs and 183 (49.1%) PRs were observed in patients treated with ENHERTU compared to two (1.1%) CRs and 28 (15.2%) PRs in those treated with chemotherapy. Median duration of response was 10.7 months for ENHERTU versus 6.8 months for chemotherapy.

ENHERTU is approved with Boxed WARNINGS for interstitial lung disease (ILD)/pneumonitis and Embryo-Fetal toxicity. The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH-) breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in the DESTINY-Breast04 trial. The most common adverse reactions (frequency $\geq 20\%$), including laboratory abnormalities, were nausea, decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, alopecia, vomiting, increased aspartate aminotransferase, increased alanine aminotransferase, constipation, increased blood alkaline phosphatase, decreased appetite, musculoskeletal pain, diarrhea and hypokalemia. Overall, 12% of patients had confirmed ILD or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD events were primarily low grade, with five grade 3 (1.3%) and no grade 4 events reported. Fatalities due to adverse reactions occurred in 4% of patients

including ILD/pneumonitis (three patients); sepsis (two patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion and respiratory failure.

“Today’s FDA approval marks a monumental moment in breast cancer treatment as ENHERTU is the first-ever HER2 directed medicine to be approved for the treatment of patients with HER2 low metastatic breast cancer,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “With the groundbreaking survival benefit seen in the DESTINY-Breast04 trial, this milestone confirms the importance of targeting lower levels of HER2 expression in the treatment of metastatic breast cancer and we are thrilled that we can now offer ENHERTU to even more patients.”

“The rapid approval of ENHERTU in HER2 low metastatic breast cancer by the FDA underscores the urgency to bring this transformational medicine to patients as quickly as possible,” said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. “Patients with HER2 low tumors, who are identified through existing HER2 testing methods, will now have the opportunity to be treated based upon their HER2 status.”

Based on the DESTINY-Breast04 data, fam-trastuzumab deruxtecan-nxki (ENHERTU) was added to the NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines[®]) in June 2022 as the Category 1 preferred regimen for patients with tumors that are HER2 IHC 1+ or 2+ and ISH negative who have received at least one prior line of chemotherapy for metastatic disease and, if tumor is HR+, are refractory to endocrine therapy.¹

As part of Project Orbis, ENHERTU also is under regulatory review for the same indication by the Australian Therapeutic Goods Administration, Brazilian Health Regulatory Agency (ANVISA), Health Canada and Switzerland’s Swissmedic.

Daiichi Sankyo and AstraZeneca are committed to ensuring that patients in the U.S. who are prescribed ENHERTU can access the medication and receive necessary financial support. Provider and patient support, reimbursement and distribution for ENHERTU in the U.S. will be accessible by visiting www.ENHERTU4U.com or calling 1-833-ENHERTU (1-833-364-3788).

Please visit www.ENHERTU.com for full [Prescribing Information](#), including Boxed WARNINGS, and [Medication Guide](#).

Financial Considerations

Following approval in the U.S., an amount of \$200 million is due from AstraZeneca to Daiichi Sankyo as a milestone payment for an indication for ENHERTU in patients with HER2 low metastatic breast cancer who were previously treated with one or two lines of chemotherapy.

Sales of ENHERTU in the U.S. are recognized by Daiichi Sankyo. For further details on the financial arrangements, please consult the collaboration agreement from [March 2019](#).

About DESTINY-Breast04

DESTINY-Breast04 is a global, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) in patients with HR positive or HR negative, HER2 low unresectable and/or metastatic breast cancer previously treated with one or two prior lines of chemotherapy. Patients were randomized 2:1 to receive either ENHERTU or chemotherapy.

The primary endpoint of DESTINY-Breast04 is PFS in patients with HR positive disease based on BICR. Key secondary endpoints include PFS based on BICR in all randomized patients (HR positive and HR negative disease), OS in patients with HR positive disease and OS in all randomized patients (HR positive and HR negative disease). Other secondary endpoints include PFS based on investigator assessment, objective response rate based on BICR and on investigator assessment, duration of response based on BICR and safety. DESTINY-Breast04 enrolled 557 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit [ClinicalTrials.gov](#).

About Breast Cancer and HER2 Expression

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide and in the U.S.^{2,3} More than two million patients with breast cancer were diagnosed in 2020 with nearly 685,000 deaths globally.² In the U.S., more than 290,000 patients are expected to be diagnosed in 2022, with more than 43,000 deaths.⁴ Approximately one in five patients with breast cancer are considered HER2 positive.⁵

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, and is one of many biomarkers expressed in breast cancer tumors.⁶

HER2 expression is currently determined by an IHC test which estimates the amount of HER2 protein on a cancer cell, and/or an ISH test, which counts the copies of the HER2 gene in cancer cells.^{6,7} HER2 tests provide IHC and ISH scores across the full HER2 spectrum and are routinely used to determine appropriate treatment options for patients with metastatic breast cancer. HER2 positive cancers are currently defined as

HER2 expression measured as IHC 3+ or IHC 2+/ISH+, and HER2 negative cancers are defined as HER2 expression measured as IHC 0, IHC 1+ or IHC 2+/ISH-.⁶ However, approximately half of all breast cancers are HER2 low, defined as a HER2 score of IHC1+ or IHC 2+/ISH-.^{8,9,10} HER2 low occurs in both HR positive and HR negative disease.¹¹

Previously, patients with HR positive metastatic breast cancer and HER2 low disease had limited effective treatment options following progression on endocrine (hormone) therapy.^{9,12} Additionally, few targeted options were available for those with HR negative disease.¹³ Now with the approval of ENHERTU, patients with HER2 low tumors may be eligible for HER2 directed therapy.

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 more than 30 countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a (or one or more) prior anti-HER2-based regimen, either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within six months of completing therapy, based on the results from the [DESTINY-Breast03](#) trial. ENHERTU also is approved in several countries 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 based on the results from the [DESTINY-Breast01](#) trial.

ENHERTU (5.4 mg/kg) is approved in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 low (immunohistochemistry (IHC) 1+ or IHC 2+/*in-situ* hybridization (ISH)-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy, based on the results of the [DESTINY-Breast04](#) trial.

ENHERTU (6.4 mg/kg) is approved in several countries for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) 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, also are underway.

Regulatory applications for ENHERTU in breast, gastric and non-small cell lung cancers are currently under review in several countries based on the DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Gastric01, DESTINY-Gastric02 and DESTINY-Lung01 trials, respectively.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo Company, Limited (referred to as 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.

Important Safety Information

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 a prior anti-HER2-based regimen either:
 - In the metastatic setting, or
 - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- 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 and HER2-Mutant Solid Tumors (5.4 mg/kg)

In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In 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, then 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, then reduce dose by one level.

Metastatic Breast Cancer and HER2-Mutant Solid Tumors (5.4 mg/kg)

In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In 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. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. 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. 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.

Metastatic Breast Cancer and HER2-Mutant Solid Tumors (5.4 mg/kg)

In patients with metastatic breast cancer and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In 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.

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, then reduce dose by one level.

Adverse Reactions

Metastatic Breast Cancer and HER2-Mutant Solid Tumors (5.4 mg/kg)

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and NCT04644237. Among these patients 65% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

Metastatic Breast Cancer

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg intravenously every three weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30).

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), hypokalemia (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), respiratory infection (22%), headache (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in $>1\%$ of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and hypokalemia (25%).

Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

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 every 3 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) for patients who received ENHERTU.

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 decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), hypokalemia (30%), vomiting (26%), constipation (24%), increased blood bilirubin (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 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥ 65 years and 3.6% were ≥ 75 years. No overall differences in efficacy within clinical studies 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 (60%) as compared to younger patients (48%). 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.
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate or severe renal impairment.
- **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

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.

Disclosure: Dr. Modi has financial interests related to AstraZeneca and Daiichi Sankyo.

Media Contacts:

U.S.:

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

Japan:

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

References:

- ¹ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed August 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
- ² Sung H, et al. *CA Cancer J Clin*. 2021;10.3322/caac.21660.
- ³ CDC. [United States Cancer Statistics: Data Visualizations](#). Accessed August 2022
- ⁴ American Cancer Society. [Cancer Facts & Figures 2022](#). Accessed August 2022.
- ⁵ Ahn S, et al. *J Pathol Transl Med*. 2020;54(1): 34-44.
- ⁶ Iqbal N, et al. *Mol Biol Int*. 2014;852748.
- ⁷ Wolff A, et al. *Arch Pathol Lab Med*. 2018;142(11):1364–1382.
- ⁸ Schalper K, et al. *Arch Pathol Lab Med*. 2014;138:213-219.
- ⁹ Schettini F, et al. *NPJ Breast Cancer*. 2021;7:1.
- ¹⁰ Denkert C, et al. *Lancet Oncol*. 2021;22:1151-61.
- ¹¹ Miglietta F, et al. *NPJ Breast Cancer*. 2021;7:137.
- ¹² Matutino A, et al. *Current Oncology*. 2018; 25(S1):S131-S141.
- ¹³ American Cancer Society. [Breast Cancer Hormone Receptor Status](#). Accessed August 2022.

ENHERTU® is a registered trademark of Daiichi Sankyo Company, Limited.
PP-US-EN-1764
08/22