

## Press Release

# ENHERTU<sup>®</sup> Approved in the U.S. for Patients with HER2 Positive Metastatic Breast Cancer Treated with a Prior Anti-HER2-Based Regimen

- Approval broadens indication for Daiichi Sankyo and AstraZeneca's ENHERTU to earlier use in metastatic breast cancer
- Based on groundbreaking DESTINY-Breast03 results showing ENHERTU reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1)

**Tokyo and Basking Ridge, NJ – (May 5, 2022)** – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) ENHERTU<sup>®</sup> (fam-trastuzumab deruxtecan-nxki) has been approved in the U.S. 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.

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

This press release features multimedia. View the full release [here](#).

The approval by the U.S. Food and Drug Administration (FDA) was based on positive results from the pivotal [DESTINY-Breast03](#) phase 3 trial that showed ENHERTU reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1) (hazard ratio [HR] = 0.28; 95% confidence interval [CI]: 0.22-0.37; p<0.0001) in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. The median progression-free survival (PFS) for patients treated with ENHERTU was not reached (95% CI: 18.5-NE) compared to 6.8 months for T-DM1 (95% CI: 5.6-8.2) as assessed by blinded independent central review (BICR).

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 earlier disease setting. The previously granted [accelerated approval](#) of ENHERTU in later line HER2 positive metastatic breast cancer is now converted to regular approval, broadening its breast cancer indication in the U.S. to earlier lines of use in patients with HER2 positive metastatic breast cancer.

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, Israel's Ministry of Health Pharmaceutical Administration, and Switzerland's Swissmedic.

“ENHERTU has demonstrated significant progression-free survival in the earlier metastatic setting, potentially establishing it as a new standard of care in previously treated patients with HER2 positive metastatic breast cancer,” said Erika Hamilton, MD, Director, Breast Cancer and Gynecological Cancer Research Program, Sarah Cannon Research Institute, Nashville, Tennessee. “Today's approval is an important milestone for the clinical community as we will now be able to offer ENHERTU to these patients earlier in their treatment.”

“This is an important day for the breast cancer community,” said Catherine Ormerod, Executive Vice President, Strategy and Mission, Living Beyond Breast Cancer. “With this approval, ENHERTU now provides a new treatment option for patients with HER2 positive metastatic breast cancer, which can be used earlier in treatment to potentially delay progression of disease.”

Additional results from the DESTINY-Breast03 phase 3 trial showed that confirmed objective response rate (ORR) was more than doubled in the ENHERTU arm (82.7%; n=205; 95% CI: 77.4-87.2) versus the T-DM1 arm (36.1%; n=87; 95% CI: 30.0-42.5). Thirty-nine (15.7%) complete responses (CR) and 166 (66.9%) partial responses (PR) were observed in patients treated with ENHERTU compared to 20 (8.3%) CRs and 67 (27.8%) PRs in patients treated with T-DM1. In addition, in the secondary endpoint analysis of PFS as assessed by investigator, which was published online in *The New England Journal of Medicine*, patients treated with ENHERTU had a median PFS of 25.1 months (95% CI: 22.1-NE) compared to 7.2 months (95% CI: 6.8-8.3) for T-DM1 (HR=0.26; 95% CI: 0.20-0.35). Overall survival (OS) was analyzed but immature at time of data cut-off of May 21, 2021 (HR=0.55; 95% CI: 0.36-0.86). Nearly all patients treated with ENHERTU were alive at one year (94.1%; 95% CI: 90.3-96.4) compared to 85.9% of patients treated with T-DM1 (95% CI: 80.9-89.7).

ENHERTU is approved with Boxed WARNINGS for interstitial lung disease (ILD)/pneumonitis and Embryo-Fetal toxicity. 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) in the DESTINY-Breast03 trial. The most common adverse reactions (frequency  $\geq$ 20%), including laboratory abnormalities, were nausea, decreased white blood cell count, decreased neutrophil count, increased aspartate aminotransferase, decreased hemoglobin, decreased lymphocyte count, increased alanine aminotransferase, decreased platelet count, fatigue, vomiting, increased blood alkaline phosphatase, alopecia, hypokalemia, constipation, musculoskeletal pain, diarrhea, decreased appetite, headache, respiratory infection, abdominal

pain, increased blood bilirubin, and stomatitis. Of the 28 ILD events (11%), 0.8% were recorded as grade 3 events. No grade 4 or grade 5 ILD or pneumonitis events were adjudicated as drug-related.

“Today’s FDA approval, which converts the accelerated approval of ENHERTU to regular approval, highlights the importance of the FDA’s accelerated pathway that allows for earlier approval of medicines to treat serious medical conditions such as breast cancer,” said Ken Keller, Global Head, Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “Data from DESTINY-Breast03 not only confirmed the results of DESTINY-Breast01 but also demonstrated the superiority of ENHERTU in prolonging progression-free survival compared to T-DM1 in an earlier setting of HER2 positive metastatic breast cancer.”

“ENHERTU is already established in the later-line treatment of patients with HER2 positive metastatic breast cancer, and we are thrilled that with this approval, patients in the U.S. will now be able to access the transformative potential of ENHERTU earlier in their treatment,” said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. “We look forward to bringing this important, potentially paradigm-shifting medicine to even more patients across the globe in an earlier setting as quickly as possible.”

Based on the DESTINY-Breast03 data, fam-trastuzumab deruxtecan-nxki (ENHERTU) recently was added to the NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) as the Category 1 preferred regimen as second-line therapy for recurrent unresectable (local or regional) or stage IV HER2+ disease.<sup>1</sup>

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](http://www.ENHERTU4U.com) or calling 1-833-ENHERTU (1-833-364-3788).

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

### **Financial Considerations**

Following approval in the U.S., an amount of \$100 million is due from AstraZeneca to Daiichi Sankyo as a second-line milestone payment in HER2 positive metastatic breast cancer.

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-Breast03**

DESTINY-Breast03 is a global, head-to-head, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety 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 PFS based on blinded independent central review. Secondary endpoints include overall survival, ORR, duration of response, PFS 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 HER2 Positive Breast Cancer**

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

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.<sup>6</sup> 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.<sup>7</sup>

Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.<sup>8</sup> More treatment options are needed to further delay progression and extend survival.<sup>8,9,10</sup>

### **About ENHERTU**

ENHERTU<sup>®</sup> (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 the U.S. 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, based on results from the [DESTINY-Breast03](https://clinicaltrials.gov) trial. ENHERTU is also approved in approximately 40 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 (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, are also underway.

Regulatory applications for ENHERTU are currently under review in China, [Europe](#), [Japan](#) and several other countries for the treatment of adult patients with HER2 positive unresectable or metastatic breast cancer who have received a prior anti-HER2 based regimen based on the results from the [DESTINY-Breast03](#) trial.

ENHERTU was granted [Breakthrough Therapy Designation](#) in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH-negative) breast cancer who have received a prior systemic therapy 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. Patients with hormone receptor (HR) positive breast cancer should additionally have received or be ineligible for endocrine therapy.

ENHERTU also is currently under review in the [U.S.](#) for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have a *HER2 (ERBB2)* mutation and who have received a prior systemic therapy based on the results from the [DESTINY-Lung01](#) trial, and in [Europe](#) for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma who have received a prior anti-HER2 based regimen based on the [DESTINY-Gastric01](#) and [DESTINY-Gastric02](#) trials.

### **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
- 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  $\leq 28$  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.,  $\geq 0.5$  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.,  $\geq 1$  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 491 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 13% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.4% of patients treated with ENHERTU. Median time to first onset was 5.5 months (range: 1.1 to 20.8).

### 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 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 68% of patients. Eighteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 6 to 664). Febrile neutropenia was reported in 1.2% 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. 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

In the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, 13 cases (2.6%) of asymptomatic LVEF decrease were reported.

### 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, 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  $25 \times 10^9/L$ ) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets  $<25 \times 10^9/L$ ) interrupt ENHERTU until resolved to Grade 1 or less. Reduce dose by one level.

## **Adverse Reactions**

### Metastatic Breast Cancer

The pooled safety population for patients with metastatic breast cancer reflects exposure to ENHERTU at 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) in 491 patients in DESTINY-Breast03, DESTINY-Breast01, and Study DS8201-A-J101. The median duration of treatment was 13 months (range: 0.7 to 37). In this pooled safety population, the most common ( $\geq 20\%$ ) adverse reactions, including laboratory abnormalities, were nausea (78%), decreased white blood cell count (74%), decreased hemoglobin (68%), decreased neutrophil count (68%), increased aspartate aminotransferase (58%), fatigue (57%), decreased lymphocyte count (56%), vomiting (50%), decreased platelet count (49%), increased alanine aminotransferase (48%), increased blood alkaline phosphatase (45%), alopecia (41%), constipation (35%), hypokalemia (33%), decreased appetite (32%), diarrhea (31%), musculoskeletal pain (28%), increased transaminases (27%), respiratory infection (24%), headache (21%), and abdominal pain (21%).

### *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 in DESTINY-Breast03. ENHERTU was administered by intravenous infusion once every three weeks. 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%).

### 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/m<sup>2</sup> biweekly or paclitaxel (N=7) 80 mg/m<sup>2</sup> 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 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 491 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 22% were  $\geq 65$  years and 4% were  $\geq 75$  years. No overall differences in efficacy within clinical studies were observed between patients  $\geq 65$  years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged  $\geq 65$  years (60%) as compared to younger patients (49%). 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  $\geq 65$  years and 14% were  $\geq 75$  years. No overall differences in efficacy or safety were observed between patients  $\geq 65$  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](http://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](http://www.daiichisankyo.com).

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References:

- <sup>1</sup> 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 May 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.
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