

Press Release

ENHERTU[®] Granted Priority Review in the U.S. for Patients with HER2 Low or HER2 Ultralow Metastatic Breast Cancer Who Have Received at Least One Line of Endocrine Therapy

- Based on DESTINY-Breast06 phase 3 trial which demonstrated a statistically significant and clinically meaningful progression-free survival benefit for ENHERTU
- If approved, Daiichi Sankyo and AstraZeneca's ENHERTU will be the first HER2 directed therapy and antibody drug conjugate for patients prior to receiving chemotherapy for metastatic breast cancer

Tokyo and Basking Ridge, NJ – (October 1, 2024) – Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) supplemental Biologics License Application (sBLA) for ENHERTU[®] (fam-trastuzumab deruxtecan-nxki) has been accepted and granted Priority Review in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining) breast cancer who have received at least one endocrine therapy in the metastatic setting.

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

The U.S. Food and Drug Administration (FDA) grants Priority Review to applications for medicines that, if approved, would offer significant improvements over available treatment options by demonstrating safety or efficacy improvements, preventing serious conditions or enhancing patient compliance. The Prescription Drug User Fee Act (PDUFA) date, the FDA action date for their regulatory decision, is February 1, 2025. The Priority Review follows receipt of Breakthrough Therapy Designation [granted](#) by the FDA for ENHERTU based on data from the [DESTINY-Breast06](#) phase 3 trial in August 2024.

Hormone receptor (HR) positive, HER2 negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.¹ Despite being classified as HER2 negative, many of these tumors still carry some level of HER2 expression.² It is estimated that up to 85% to 90% of tumors historically classified as HR positive, HER2 negative, may be HER2 low or HER2 ultralow.^{3,4}

The sBLA is based on data from DESTINY-Breast06 [presented](#) as a late-breaking oral session at the 2024 American Society of Clinical Oncology (#ASCO24) Annual Meeting and recently published in [The New](#)

England Journal of Medicine. In the overall trial population, ENHERTU reduced the risk of disease progression or death by 37% by blinded independent central review (BICR) versus chemotherapy (hazard ratio [HR] 0.63; 95% confidence interval [CI]: 0.53-0.75; $p < 0.0001$). Median progression-free survival (PFS) was 13.2 months with ENHERTU compared to 8.1 months with chemotherapy.

Results were consistent in patients with HER2 low expression and HER2 ultralow expression. In the primary endpoint analysis of patients with HR positive, HER2 low metastatic breast cancer, median PFS was 13.2 months in the ENHERTU arm compared to 8.1 months in the chemotherapy arm (HR 0.62; 95% CI: 0.51-0.74; $p < 0.0001$), as assessed by BICR. In a prespecified exploratory analysis of patients with HER2 ultralow expression, ENHERTU showed a median PFS of 13.2 months versus 8.3 months, respectively (HR 0.78; 95% CI: 0.50-1.21).

The safety profile of ENHERTU in DESTINY-Breast06 was consistent with previous breast cancer clinical trials with no new safety concerns identified. The most common grade 3 or higher treatment related treatment emergent adverse events (TEAEs) occurring in 5% or more of patients treated with ENHERTU were neutropenia (20.7%), leukopenia (6.9%) and anemia (5.8%). Interstitial lung disease (ILD) or pneumonitis occurred in 11.3% of patients treated with ENHERTU. The majority of ILD or pneumonitis events were low grade (grade 1 [n=7; 1.6%] or grade 2 [n=36; 8.3%]). There were three grade 3 ILD events (0.7%), zero grade 4 events and three grade 5 events (0.7%) as determined by an independent adjudication committee.

“This Priority Review highlights the potential to expand the existing indication of ENHERTU in HER2 low metastatic breast cancer to include use in an earlier disease setting as well as in a broader patient population that includes HER2 ultralow,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “We look forward to working closely with the FDA with the goal of bringing ENHERTU to more patients as quickly as possible.”

“While endocrine therapies are widely used in the initial treatment of HR positive metastatic breast cancer, most patients see limited benefit with additional lines of treatment and subsequent chemotherapy is associated with poor response rates and outcomes,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “The results from DESTINY-Breast06 show that ENHERTU has the potential to evolve the current HR positive treatment landscape and become the first targeted treatment for patients with HER2 low or HER2 ultralow expression following endocrine therapy.”

About DESTINY-Breast06

DESTINY-Breast06 is a global, randomized, open-label, phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus investigator’s choice of chemotherapy (capecitabine, paclitaxel or nab paclitaxel) in patients with HR positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (defined as

IHC 0 with membrane staining [IHC >0 <1+]) advanced or metastatic breast cancer. Patients in the trial had no prior chemotherapy for advanced or metastatic disease and received at least two lines of prior endocrine therapy in the metastatic setting. Patients also were eligible if they had received one prior line of endocrine therapy combined with a CDK4/6 inhibitor in the metastatic setting and experienced disease progression within six months of starting first-line treatment or received endocrine therapy as an adjuvant treatment and experienced disease recurrence within 24 months.

The primary endpoint of DESTINY-Breast06 is PFS in the HR positive, HER2 low patient population as measured by BICR. Key secondary endpoints include PFS by BICR in the overall trial population (HER2 low and HER2 ultralow), overall survival (OS) in patients in the HER2 low patient population and OS in the overall trial population. Other secondary endpoints include objective response rate, duration of response, time to first subsequent treatment or death, time to second subsequent treatment or death and safety. Analysis of the HER2 ultralow subgroup was not powered to demonstrate statistical significance.

DESTINY-Breast06 enrolled 866 patients (n=713 for HER2 low and n=153 for HER2 ultralow) at multiple sites in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit ClinicalTrials.gov.

About Breast Cancer and HER2 Expression

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.⁵ More than two million breast cancer cases were diagnosed in 2022 with more than 665,000 deaths globally.⁵ In the U.S., more than 300,000 cases of breast cancer are diagnosed annually.⁶ While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or who progress to metastatic disease are expected to live five years following diagnosis.¹

HR positive, HER2 negative is the most common breast cancer subtype, accounting for approximately 70% of all breast cancers.¹ HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including breast cancer.⁷ Patients with high levels of HER2 expression (IHC 3+ or IHC2+/ISH+) are classified as HER2 positive and treated with HER2 targeted therapies, representing approximately 15 to 20% percent of all breast cancers.⁸ Historically, tumors that were not classified as HER2 positive were classified as HER2 negative, despite the fact that many of these tumors still carry some level of HER2 expression.² It is estimated that approximately 60% to 65% of HR positive, HER2 negative breast cancers are HER2 low and potentially an additional 25% may be HER2 ultralow.^{3,4}

Endocrine therapies are widely given consecutively in the early lines of treatment for HR positive metastatic breast cancer. However, following two lines of endocrine therapy, further efficacy with additional endocrine

treatment is often limited.⁹ The current standard of care following endocrine therapy is chemotherapy, which is associated with poor response rates and outcomes.^{9,10,11,12}

Prior to the approval of ENHERTU following chemotherapy in HER2 low metastatic breast cancer based on the [DESTINY-Breast04](#) trial, there were no targeted therapies approved specifically for patients with HER2 low expression.¹³ There are no targeted therapies specifically approved for patients with HER2 ultralow expression.¹⁴

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 number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

ENHERTU (5.4 mg/kg) is approved in more than 65 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+ or *in-situ* hybridization (ISH)+) 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 the results from the [DESTINY-Breast03](#) trial.

ENHERTU (5.4 mg/kg) is approved in more than 65 countries worldwide 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 systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on the results from the [DESTINY-Breast04](#) trial.

ENHERTU (5.4 mg/kg) is approved in more than 45 countries worldwide for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2 (ERBB2)* mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the [DESTINY-Lung02](#) trial. Continued approval in the U.S. for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in more than 45 countries worldwide for the treatment of adult patients with locally advanced or metastatic HER2 positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the [DESTINY-Gastric01](#), [DESTINY-Gastric02](#) and/or [DESTINY-Gastric06](#) trials. Full approval in

China for this indication will depend on whether a randomized controlled confirmatory clinical trial can demonstrate clinical benefit in this population.

ENHERTU (5.4 mg/kg) is approved in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options based on efficacy results from the [DESTINY-PanTumor02](#), [DESTINY-Lung01](#) and [DESTINY-CRC02](#) trials. Continued approval for this indication in the U.S. may be contingent upon verification and description of clinical benefit in a confirmatory trial.

About the ENHERTU Clinical Development Program

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

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 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.

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADC portfolio currently consists of ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

ENHERTU U.S. 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 (IHC 3+ or ISH 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, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

This indication is approved under accelerated approval based on objective 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 (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen
- Unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

This indication is approved under accelerated approval based on objective 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. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. 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.

HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Median time to first onset was 5.5 months (range: 0.9 to 31.5). Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU.

HER2-Positive 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).

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.

HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 63% of patients. Seventeen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1% of patients.

HER2-Positive 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.

HER2-Positive or HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

In patients with metastatic breast cancer, HER2-mutant NSCLC, and other solid tumors treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.8% of patients, of which 0.6% were Grade 3.

HER2-Positive 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 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 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

HER2-Positive and HER2-Low Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 1799 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 65% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (73%), decreased white blood cell count (70%), decreased hemoglobin (66%), decreased neutrophil count (63%), decreased lymphocyte count (58%), fatigue (56%), decreased platelet count (48%), increased aspartate aminotransferase (47%), increased alanine aminotransferase (43%), vomiting (40%), increased blood alkaline phosphatase (38%), alopecia (34%), constipation (33%), decreased appetite (32%), decreased blood potassium (31%), diarrhea (29%), musculoskeletal pain (24%), and abdominal pain (20%).

HER2-Positive 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 once 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%), decreased blood potassium (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), headache (22%), respiratory infection (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 once 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 decreased blood potassium (25%).

HER2-Mutant Unresectable or Metastatic NSCLC (5.4 mg/kg)

DESTINY-Lung02 evaluated two dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients with HER2-mutant unresectable or metastatic NSCLC who received ENHERTU 5.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. Nineteen percent of patients were exposed for >6 months.

Serious adverse reactions occurred in 30% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, thrombocytopenia, dyspnea, nausea, pleural effusion, and increased troponin I. Fatality occurred in 1 patient with suspected ILD/pneumonitis (1%).

ENHERTU was permanently discontinued in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, diarrhea, decreased blood potassium, hypomagnesemia, myocarditis, and vomiting. Dose interruptions of ENHERTU due to adverse reactions occurred in 23% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia and ILD/pneumonitis. Dose reductions due to an adverse reaction occurred in 11% of patients.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were nausea (61%), decreased white blood cell count (60%), decreased hemoglobin (58%), decreased neutrophil count (52%), decreased lymphocyte count (43%), decreased platelet count (40%), decreased albumin (39%), increased aspartate aminotransferase (35%), increased alanine aminotransferase (34%), fatigue (32%), constipation (31%), decreased appetite (30%), vomiting (26%), increased alkaline phosphatase (22%), and alopecia (21%).

HER2-Positive 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 decreased blood potassium. 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%), decreased blood potassium (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

HER2-Positive (IHC3+) Unresectable or Metastatic Solid Tumors

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast01, DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. The median duration of treatment was 8.3 months (range 0.7 to 30.2).

Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea, pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 15% of patients, of which ILD/pneumonitis accounted for 10%. Dose interruptions due to adverse reactions occurred in 48% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count, anemia, COVID-19, fatigue, decreased white blood cell count, and ILD/pneumonitis. Dose reductions occurred in 27% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, decreased neutrophil count, ILD/pneumonitis, and diarrhea.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (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 after 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 7 months after the last dose. *Males:* Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after 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 1287 patients with HER2-positive or HER2-low breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥ 65 years and 3.8% 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 (59%) as compared to younger patients (49%). Of the 101 patients with HER2-mutant unresectable or metastatic NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥ 65 years and 8% were ≥ 75 years. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients. Of the 125 patients with HER2-positive locally advanced or metastatic 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. Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg in DESTINY-PanTumor02, DESTINY-Lung01, or DESTINY-CRC02, 39% were 65 years or older and 9% were 75 years or older.

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 renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLCr < 30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin > 3 times ULN and any AST).

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 an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical need. For more information, please visit www.daiichisankyo.com.

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