

Press Release

ENHERTU[®] Plus Pertuzumab Approved in the U.S. as First New Treatment in More Than a Decade for First-Line Treatment of Patients with HER2 Positive Metastatic Breast Cancer

- Based on DESTINY-Breast09 phase 3 trial results that showed Daiichi Sankyo and AstraZeneca's ENHERTU in combination with pertuzumab reduced the risk of disease progression by 44% versus THP with a median progression-free survival of more than three years

Tokyo and Basking Ridge, NJ – (December 15, 2025) – ENHERTU[®] (fam-trastuzumab deruxtecan-nxki) in combination with pertuzumab has been approved in the U.S. as a first-line treatment for adult patients with unresectable or metastatic HER2 positive (immunohistochemistry [IHC] 3+ or in-situ hybridization (ISH)+) breast cancer, as determined by a U.S Food and Drug Administration (FDA)-approved test.

ENHERTU is a specifically engineered HER2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca (LSE/STO/Nasdaq: AZN).

The approval was based on results from the [DESTINY-Breast09](#) phase 3 trial, [presented](#) during a special late-breaking oral session at the 2025 American Society of Clinical Oncology (#ASCO25) Annual Meeting and subsequently published in [The New England Journal of Medicine](#). The FDA completed the review under its Real Time Oncology Review (RTOR) program, an initiative of the FDA, following [Priority Review](#) and [Breakthrough Therapy Designation](#) of ENHERTU in combination with pertuzumab in the U.S. in this setting. The expanded approval for ENHERTU in the U.S. enables its use earlier as part of a combination regimen in the first-line setting of patients with HER2 positive metastatic breast cancer.

In DESTINY-Breast09, ENHERTU in combination with pertuzumab reduced the risk of disease progression or death by 44% versus taxane, trastuzumab and pertuzumab (THP) (hazard ratio [HR]: 0.56; 95% confidence interval [CI]: 0.44-0.71; p<0.0001) in patients with HER2 positive metastatic breast cancer who had not received prior chemotherapy or HER2 targeted therapy or had received neoadjuvant or adjuvant HER2 targeted therapy more than six months before the diagnosis of advanced or metastatic disease. Median progression-free survival (PFS) was 40.7 months (95% CI: 36.5-not estimable [NE]) with ENHERTU in

combination with pertuzumab compared to 26.9 months (95% CI: 21.8-NE) for THP as assessed by blinded independent central review (BICR).

Confirmed objective response rate (ORR) was 87% (95% CI: 83-90) with ENHERTU in combination with pertuzumab compared to 81% (95% CI: 77-85) with THP. The ENHERTU in combination with pertuzumab arm showed that 15% of patients achieved a complete response (CR) and 72% achieved a partial response (PR) while in the THP arm, 8% of patients achieved a CR and 73% achieved a PR.

“Trastuzumab deruxtecan plus pertuzumab is the only first-line treatment approved in more than a decade to demonstrate a statistically significant improvement in progression-free survival over the current standard regimen for patients with HER2 positive metastatic breast cancer,” said Sara Tolaney, MD, MPH, Chief of the Division of Breast Oncology, Dana-Farber Cancer Institute and Principal Investigator for the DESTINY-Breast09 trial. “With a median progression-free survival exceeding three years versus approximately two years with THP, trastuzumab deruxtecan combined with pertuzumab should become a new first-line standard of care in this setting.”

ENHERTU is approved with Boxed WARNINGS for interstitial lung disease (ILD)/pneumonitis and Embryo-Fetal toxicity. The safety of ENHERTU in combination with pertuzumab was evaluated in 381 patients with unresectable or metastatic HER2 positive breast cancer in DESTINY-Breast09. The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased white blood cell count, decreased hemoglobin, decreased neutrophil count, nausea, increased alanine aminotransferase, diarrhea, increased aspartate aminotransferase, decreased lymphocyte count, decreased platelet count, increased blood alkaline phosphatase, decreased blood potassium, fatigue, alopecia, vomiting, upper respiratory tract infection, constipation, decreased appetite, decreased weight, COVID-19, musculoskeletal pain, increased blood bilirubin and abdominal pain. Serious adverse reactions occurred in 27% of patients receiving ENHERTU in combination with pertuzumab. Serious adverse reactions in $>1\%$ of patients who received ENHERTU in combination with pertuzumab were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis. Fatalities due to adverse reactions occurred in 3.4% of patients.

“Since its initial approval six years ago, ENHERTU has transformed the treatment of HER2 positive metastatic breast cancer,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “With this approval in the first-line metastatic setting, ENHERTU once again offers significant improvements in progression-free survival and has practice-changing potential when used in combination with pertuzumab.”

“With this approval, we are bringing ENHERTU to the earliest treatment setting for HER2 positive metastatic breast cancer, where optimizing efficacy has an important impact on long-term outcomes,” said Dave Fredrickson, Executive Vice President, Oncology Hematology Business Unit, AstraZeneca. “The treatment approach with ENHERTU plus pertuzumab in DESTINY-Breast09 sets a new benchmark of more than three years without disease progression or death for patients in this setting.”

This application in the U.S. also was reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. As part of Project Orbis, reviews are ongoing in Switzerland and with other regulatory authorities. A separate regulatory application also is under review in [Japan](#) based on DESTINY-Breast09.

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 this approval in the U.S., an amount of \$150 million is due from AstraZeneca to Daiichi Sankyo as a milestone payment for the first-line unresectable or metastatic HER2 positive breast cancer indication. 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-Breast09

[DESTINY-Breast09](#) is a global, multicenter, randomized, open-label, phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) either alone or in combination with pertuzumab versus standard of care THP as first-line treatment in patients with HER2 positive metastatic breast cancer.

Patients were randomized 1:1:1 to receive either ENHERTU monotherapy with a pertuzumab matching placebo; ENHERTU in combination with pertuzumab; or THP. Randomization was stratified by prior treatment (*de novo* metastatic disease versus progression from early-stage disease), hormone receptor (HR) status and *PIK3CA* mutation status.

The primary endpoint of DESTINY-Breast09 is PFS as assessed by BICR in the ENHERTU monotherapy and ENHERTU combination arms. Secondary endpoints include investigator-assessed PFS, overall survival,

ORR, duration of response, pharmacokinetics and safety. The investigational arm assessing ENHERTU monotherapy versus THP remains blinded to patients and investigators and will continue to the final PFS analysis.

DESTINY-Breast09 enrolled 1,157 patients across multiple sites in Africa, Asia, Europe, North America and South America. For more information about the trial, visit [ClinicalTrials.gov](https://clinicaltrials.gov).

About HER2 Positive Metastatic Breast Cancer

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.¹ More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.¹ In the U.S., more than 300,000 cases of breast cancer are diagnosed annually with more than 42,000 deaths.² While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or that have progressed to metastatic disease are expected to live five years following diagnosis.³

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast cancer.⁴ HER2 positive metastatic breast cancer is an aggressive disease driven by overexpression or amplification of HER2.⁵ Approximately one in five cases of breast cancer are considered HER2 positive.⁶

While HER2 targeted therapies have improved outcomes across several lines of treatment in the metastatic setting, prognosis remains poor with most patients experiencing disease progression within two years after first-line treatment with THP, which has been the standard of care for more than a decade.^{5,7,8,9}

Approximately 10,000 patients in the U.S. are treated in the first-line HER2 positive metastatic setting with 25% to 30% of these patients not receiving any further treatment following first-line therapy due to discontinuation of therapy or death.^{10,11,12}

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) in combination with pertuzumab is approved in the U.S. as a first-line treatment for adult patients with unresectable or metastatic HER2 positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test based on the results from the [DESTINY-Breast09](#) trial.

ENHERTU (5.4 mg/kg) is approved in more than 90 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+ or 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 85 countries/regions 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 55 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic hormone receptor (HR) positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining) breast cancer, as determined by a locally or regionally approved test, that have progressed on one or more endocrine therapies in the metastatic setting based on the results from the [DESTINY-Breast06](#) trial.

ENHERTU (5.4 mg/kg) is approved in more than 60 countries/regions 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](#) and/or [DESTINY-Lung05](#) trials. Continued approval in China and 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 70 countries/regions 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. Continued approval in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (5.4 mg/kg) is approved in more than 10 countries/regions worldwide 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 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 as a monotherapy or in combination or sequentially with other cancer medicines across multiple HER2 targetable cancers.

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 DATROWAY® 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 DATROWAY.

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of eight ADCs in clinical development crafted from ADC technology discovered in-house by Daiichi Sankyo.

The DXd ADC Technology platform of Daiichi Sankyo consists of six ADCs in clinical development where each ADC is comprised of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADCs include ENHERTU and DATROWAY®, which are being jointly developed and commercialized globally with AstraZeneca, and ifinatamab deruxtecan (I-DXd), raludotatug deruxtecan (R-DXd) and patritumab deruxtecan (HER3-DXd), which are being jointly developed and commercialized globally with Merck & Co., Inc, Rahway, NJ, USA. DS-3939 is being developed by Daiichi Sankyo.

Additional ADCs being developed by Daiichi Sankyo include DS-9606, which consists of a monoclonal antibody attached to a modified pyrrolbenzodiazepine (PBD) payload and DS3610, which consists of an antibody attached to a novel immunomodulatory payload that acts as an agonist of STING.

Ifinatamab deruxtecan, raludotatug deruxtecan, patritumab deruxtecan, DS-3939, DS-9606, and DS3610 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:

- HER2-Positive Metastatic Breast Cancer

- In combination with pertuzumab as first-line treatment for unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test
- As monotherapy for the treatment of unresectable or metastatic HER2-positive (IHC 3+ or 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
- HER2-Low and HER2-Ultralow Metastatic Breast Cancer
 - As monotherapy for the treatment of unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
 - As monotherapy for the treatment of 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
- HER2-Mutant Unresectable or Metastatic Non-Small Cell Lung Cancer (NSCLC)
 - As monotherapy for the treatment of unresectable or metastatic 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.

- HER2-Positive Locally Advanced or Metastatic Gastric Cancer
 - As monotherapy for the treatment of 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
- HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors
 - As monotherapy for the treatment of unresectable or metastatic HER2-positive (IHC 3+) 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 monotherapy or ENHERTU 5.4 mg/kg in combination with pertuzumab. 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 1 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, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

In patients 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 0.9% of patients treated with ENHERTU.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), ILD occurred in 12% of patients. Median time to first onset was 8.0 months (range: 0.6 to 33.8). Fatal outcomes due to ILD and/or pneumonitis occurred in 0.5% of patients treated with ENHERTU in combination with pertuzumab.

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 monotherapy or ENHERTU 5.4 mg/kg in combination with pertuzumab. 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 1 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 1 level.

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

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Nineteen 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 1.2% of patients.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), decreased neutrophil count occurred in 79% of patients. Median time to first onset was 22 days (range: 5 to 994).

Twenty-nine percent had Grade 3 or 4 decreased neutrophil count. Febrile neutropenia was reported in 2.6% 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, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)

ENHERTU as Monotherapy

In patients treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 4.6% of patients, of which 0.6% were Grade 3 or 4.

ENHERTU in Combination with Pertuzumab

In patients treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), LVEF decrease was reported in 11% of patients, of which 2.1% were Grade 3 or 4.

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 $25 \times 10^9/L$) 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, then reduce dose by 1 level.

Adverse Reactions

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

ENHERTU as Monotherapy

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Breast06, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

ENHERTU in Combination with Pertuzumab

The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg in combination with pertuzumab intravenously every 3 weeks in 431 patients in DESTINY-Breast07 (n=50), and DESTINY-Breast09 (n=381). Among these patients, 86% were exposed for >6 months and 73% were exposed for >1 year. In this pooled safety population, the most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased hemoglobin (80%), decreased neutrophil count (79%), nausea (74%), increased alanine aminotransferase (65%), diarrhea (64%), increased aspartate aminotransferase (63%), decreased lymphocyte count (61%), decreased platelet count (55%), increased blood alkaline phosphatase (54%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (32%), constipation (31%), decreased appetite (31%), decreased weight (28%), musculoskeletal pain (23%), abdominal pain (22%), and increased blood bilirubin (23%).

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast09

The safety of ENHERTU 5.4 mg/kg in combination with pertuzumab was evaluated in DESTINY-Breast09, a randomized, three-arm, multicenter study including 763 patients with HER2-positive (IHC 3+ or ISH+) unresectable or metastatic breast cancer. Three hundred eighty-one patients received ENHERTU in combination with pertuzumab and 382 patients received THP (taxane [docetaxel or paclitaxel], trastuzumab, and pertuzumab). Among patients who received ENHERTU in combination with pertuzumab, the median duration of treatment was 22 months (range: 0.3 months to 44.5 months).

Serious adverse reactions occurred in 27% of patients receiving ENHERTU in combination with pertuzumab. Serious adverse reactions in >1% of patients were diarrhea, pneumonia, febrile neutropenia, hypokalemia, vomiting, ILD, pulmonary embolism, and sepsis. Fatalities due to adverse reactions occurred in 3.4% of patients including pneumonia (n=3), ILD (n=2), sepsis (n=2), pulmonary embolism, septic shock, acute kidney injury, dyspnea, febrile neutropenia, and intestinal ischemia (one patient each).

ENHERTU was discontinued for adverse reactions in 21% of patients. The most frequent adverse reaction ($>2\%$) associated with permanent discontinuation was ILD/pneumonitis (6.6%). Dose interruptions due to adverse reactions occurred in 69% of patients. The most frequent adverse reactions ($>2\%$) associated with dose interruption were COVID-19, neutropenia, upper respiratory tract infection, fatigue, anemia, hypokalemia, ILD/pneumonitis, thrombocytopenia, pneumonia, diarrhea, transaminase increased, leukopenia, cough, pyrexia, decreased appetite, and blood bilirubin increased. Dose reductions occurred in 46% of patients treated with ENHERTU in combination with pertuzumab. The most frequent adverse reactions ($>2\%$) associated with dose reduction were fatigue, neutropenia, nausea, diarrhea, ILD/pneumonitis, thrombocytopenia, vomiting, transaminases increased, decreased weight, febrile neutropenia, and hypokalemia.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (87%), decreased hemoglobin (80%), decreased neutrophil count (78%), nausea (75%), increased alanine aminotransferase (66%), diarrhea (64%), decreased lymphocyte count (62%), increased aspartate aminotransferase (62%), decreased platelet count (56%), increased blood alkaline phosphatase (55%), decreased blood potassium (54%), fatigue (53%), alopecia (48%), vomiting (46%), upper respiratory tract infection (33%), constipation (33%), decreased appetite (32%), decreased weight (30%), COVID-19 (28%), musculoskeletal pain (24%), increased blood bilirubin (23%), and abdominal pain (23%).

DESTINY-Breast03

The safety of ENHERTU was evaluated in 257 patients with unresectable or metastatic HER2-positive breast cancer who received at least 1 dose of ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU.

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in $>1\%$ of patients who received ENHERTU were vomiting, ILD, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (1 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 and HER2-Ultralow Metastatic Breast Cancer

DESTINY-Breast06

The safety of ENHERTU was evaluated in 434 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast06. The median duration of treatment was 11 months (range: 0.4 to 39.6) for patients who received ENHERTU.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in $>1\%$ of patients who received ENHERTU were ILD/pneumonitis, COVID-19, febrile neutropenia, and hypokalemia. Fatalities due to adverse reactions occurred in 2.8% of patients including ILD (0.7%); sepsis (0.5%); and COVID-19 pneumonia, bacterial meningoencephalitis, neutropenic sepsis, peritonitis, cerebrovascular accident, general physical health deterioration (0.2% each).

ENHERTU was permanently discontinued in 14% of patients. The most frequent adverse reaction ($>2\%$) associated with permanent discontinuation was ILD/pneumonitis. Dose interruptions due to adverse reactions occurred in 48% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose interruption were COVID-19, decreased neutrophil count, anemia, pyrexia, pneumonia, decreased white blood cell count, and ILD. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions ($>2\%$) associated with dose reduction were nausea, fatigue, decreased platelet count, and decreased neutrophil count.

The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased neutrophil count (75%), nausea (70%), decreased hemoglobin (69%), decreased lymphocyte count (66%), fatigue (53%), decreased platelet count (48%), alopecia (48%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (43%), increased aspartate aminotransferase (41%), decreased blood potassium (35%), diarrhea (34%), vomiting (34%), constipation (32%), decreased appetite (26%), COVID-19 (26%), and musculoskeletal pain (24%).

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 2 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 3 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 1 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 1 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 (IHC 3+) Unresectable or Metastatic Solid Tumors

The safety of ENHERTU was evaluated in 347 adult patients with unresectable or metastatic HER2-positive (IHC 3+) 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 1 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:** *ENHERTU as Monotherapy:* Of the 2355 patients with HER2-positive, HER2-low, or HER2-ultralow breast cancer treated with ENHERTU 5.4 mg/kg, 23% were ≥ 65 years and 5% 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 (55%) as compared to younger patients (50%). 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 and 9% were ≥ 75 years. No overall differences in efficacy or safety were observed between patients ≥ 65 years of age compared to younger patients. *ENHERTU in Combination with Pertuzumab:* In patients with HER2-positive unresectable or metastatic breast cancer treated with ENHERTU 5.4 mg/kg in combination with pertuzumab (N=431), 17% were ≥ 65 years and 3% 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 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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