

Press Release

ENHERTU® Granted Breakthrough Therapy Designation in the U.S. as Post-Neoadjuvant Therapy for Patients with HER2 Positive Early Breast Cancer

- Tenth Breakthrough Therapy Designation for Daiichi Sankyo and AstraZeneca's ENHERTU with the latest based on DESTINY-Breast05 phase 3 trial results
- Sixteenth Breakthrough Therapy Designation granted by the FDA across the oncology portfolio of Daiichi Sankyo

Tokyo and Basking Ridge, NJ – (December 22, 2025) – ENHERTU® (trastuzumab deruxtecan) has been granted Breakthrough Therapy Designation (BTD) in the U.S. for adult patients with HER2 positive early breast cancer with residual invasive disease in the breast and/or axillary lymph nodes after neoadjuvant treatment and high risk of disease recurrence.

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

The FDA granted this BTD based on results from the [DESTINY-Breast05](#) phase 3 trial [presented in](#) Presidential Symposium I at the 2025 European Society of Medical Oncology (#ESMO25) Congress and subsequently published in [The New England Journal of Medicine](#), marking the ninth pivotal trial of ENHERTU to be published in the prestigious journal.

“This tenth Breakthrough Therapy Designation reinforces how ENHERTU continues to deliver transformational results that advance the treatment of breast cancer,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “We look forward to working with the FDA with the goal of bringing ENHERTU to the post-neoadjuvant setting of HER2 positive early breast cancer, as DESTINY-Breast05 clearly

demonstrated that ENHERTU may help halt invasive disease recurrence over the current standard of care, resulting in potentially more patients achieving a cure.”

“For patients with residual disease after neoadjuvant treatment, the post-neoadjuvant setting represents a critical opportunity to reduce the risk of recurrence and prevent progression to metastatic disease,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology Hematology R&D, AstraZeneca. “This Breakthrough Therapy Designation highlights the impressive clinical benefit of ENHERTU over the current standard of care and underscores its potential to become an important treatment option in the post-neoadjuvant setting.”

ENHERTU has received 10 BTDs, with six BTDs for breast cancer, including HER2 positive early breast cancer, second-line HER2 positive metastatic breast cancer, later-line HER2 positive metastatic breast cancer, later-line HER2 low metastatic breast cancer and HER2 low or HER2 ultralow metastatic breast cancer. ENHERTU has also received four additional BTDs for HER2 positive metastatic solid tumors, HER2 positive metastatic colorectal cancer, *HER2 (ERBB2)* mutant metastatic non-small cell lung cancer (NSCLC) and HER2 positive metastatic gastric/gastroesophageal junction cancer. The latest BTD for ENHERTU represents the sixteenth BTD across the oncology portfolio of Daiichi Sankyo.

An application for ENHERTU followed by paclitaxel, trastuzumab and pertuzumab (THP) is under [review](#) in the U.S. for the neoadjuvant treatment (prior to surgery) of patients with HER2 positive early-stage breast cancer based on the results from the [DESTINY-Breast11](#) trial.

About DESTINY-Breast05

[DESTINY-Breast05](#) is a global, multicenter, randomized, open-label, phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus trastuzumab emtansine (T-DM1) in patients with HER2 positive early breast cancer with residual invasive disease in breast or axillary lymph nodes following neoadjuvant therapy and a high risk of recurrence. High risk of recurrence was defined as presentation with inoperable cancer (prior to neoadjuvant therapy) or pathologically positive axillary lymph nodes following neoadjuvant therapy.

The primary endpoint of DESTINY-Breast05 is investigator-assessed invasive disease-free survival (IDFS). IDFS is defined as the time from randomization until first invasive local, axillary or distant recurrence or death from any cause. The key secondary endpoint is investigator-assessed disease-free survival. Other secondary endpoints include overall survival, distant recurrence-free interval, brain metastases-free interval and safety.

DESTINY-Breast05 enrolled 1,635 patients in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit [ClinicalTrials.gov](https://www.clinicaltrials.gov).

About Post Neoadjuvant Treatment for HER2 Positive Early 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

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast cancer.² 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.² Approximately one in five cases of breast cancer is considered HER2 positive.³

For patients with HER2 positive early breast cancer, achieving pathologic complete response (pCR) with neoadjuvant treatment is the earliest indicator of improved long-term survival.⁶ However, approximately half of patients who receive neoadjuvant treatment do not experience pCR, putting them at increased risk of disease recurrence.^{4,5,6,7,8,9}

Despite receiving additional treatment with T-DM1 for residual disease in the post-neoadjuvant setting, approximately 20% of patients still experience invasive disease or death, with no reduction in the risk of central nervous system recurrence.^{10,11} Once patients are diagnosed with metastatic disease, the five-year survival rate drops from nearly 90% to approximately 30%.¹²

Post-neoadjuvant therapy represents a key opportunity to minimize the risk of recurrence and prevent progression to metastatic disease for patients with residual disease. New treatment options are needed in the early breast cancer setting to help reduce the likelihood of disease progression and improve long-term outcomes for more patients.^{13,14}

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) 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 pyrrolobenzodiazepine (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:

- **HER2-Positive Metastatic Breast Cancer**
 - In combination with pertuzumab as first-line treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer, as determined by an FDA-approved test
 - As monotherapy 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
- **HER2-Low and HER2-Ultralow Metastatic Breast Cancer**
 - As monotherapy 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 an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
 - As monotherapy for the treatment of adult patients with 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 adult patients with 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 adult patients with 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 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

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.

Important Safety Information

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 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 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 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 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 (≥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 (≥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%), increased aspartate aminotransferase (62%), decreased lymphocyte count (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.

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