Press Release

Daiichi-Sankyo

Enhertu® Approved in the U.S. for Two New Indications for Patients with HER2 Positive Early Breast Cancer

- Approved for use before surgery based on DESTINY-Breast11 phase 3 trial or following surgery based on DESTINY-Breast05 phase 3 trial
- Two new indications bring Daiichi Sankyo and AstraZeneca's Enhertu into curative-intent setting, reinforcing its role across stages of HER2 positive breast cancer
- Enhertu now approved for nine indications with six across both early and metastatic HER2 positive breast cancer

Tokyo – (May 15, 2026) – Enhertu® (fam-trastuzumab deruxtecan-nxki) has been approved by the U.S. Food and Drug Administration (FDA) for two new breast cancer indications in the neoadjuvant and adjuvant settings of patients with HER2 positive early breast cancer.

In the neoadjuvant setting, Enhertu followed by a taxane, trastuzumab and pertuzumab (THP) has been approved for the treatment of adult patients with HER2 positive stage 2 or stage 3 breast cancer. In the adjuvant setting, Enhertu has been approved for the treatment of adult patients with HER2 positive breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment.

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/NYSE: AZN).

The neoadjuvant approval was based on results from the DESTINY-Breast11 phase 3 trial published in *Annals of Oncology* and the adjuvant approval was based on the results from the DESTINY-Breast05 phase 3 trial published in *The New England Journal of Medicine*. Data from both trials were presented at the 2025 European Society for Medical Oncology (ESMO) Congress.

In DESTINY-Breast11, Enhertu followed by THP demonstrated a statistically significant and clinically meaningful improvement in the pathologic complete response (pCR) rate compared to dose-dense doxorubicin and cyclophosphamide followed by THP (ddAC-THP) in patients with high-risk, locally advanced HER2 positive early-stage breast cancer. Pathologic complete response is defined as no evidence of invasive cancer cells in the removed breast tissue and lymph nodes following treatment. The pCR rate with Enhertu followed by THP was 67.3% compared with 56.3% with ddAC-THP, representing a difference of 11.2% (95% confidence interval [CI]: 3.9-18.3; p=0.003).

In DESTINY-Breast05, Enhertu significantly reduced the risk of invasive disease recurrence or death (invasive disease-free survival [IDFS]) by 53% (hazard ratio [HR]=0.47; 95% CI: 0.34-0.66; p<0.0001) compared to trastuzumab emtansine (T-DM1) in patients with HER2 positive breast cancer with residual invasive disease following neoadjuvant therapy. Enhertu demonstrated a three-year IDFS rate of 92.4% (95% CI: 89.7-94.4) and 83.7% with T-DM1 (95% CI: 80.2-86.7). Data also showed that Enhertu significantly reduced the risk of disease recurrence or death (disease-free survival [DFS]) by 53% (HR=0.47; 95% CI: 0.34-0.66; p<0.0001) compared to T-DM1. Results showed a three-year DFS rate of 92.3% (95% CI: 89.5-94.3) in the Enhertu arm and 83.5% with T-DM1 (95% CI: 79.9-86.4).

Based on the results from DESTINY-Breast05, fam-trastuzumab deruxtecan-nxki (Enhertu) has been included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a Category 1 recommended treatment in the adjuvant setting for patients with HER2 positive early breast cancer with residual disease following preoperative therapy and high risk of recurrence. See NCCN Guidelines® for detailed recommendations.

“HER2 positive breast cancer is an aggressive disease, and our goal is to reduce the risk of recurrence as early as possible to achieve the best long-term outcomes. The neoadjuvant setting offers the earliest opportunity to improve outcomes, while the adjuvant setting provides another important chance to prevent recurrence for patients with residual disease after surgery,” said Shanu Modi, MD, medical oncologist, Memorial Sloan Kettering Cancer Center and principal investigator for the DESTINY-Breast11 trial. “These two new indications in HER2 positive early breast cancer will evolve how we treat patients in these settings and support trastuzumab deruxtecan as a potential new standard of care in early-stage disease.”

“Providing patients with early breast cancer more options to help prevent progression to metastatic disease can lead to improved outcomes,” said Victoria Smart, Senior Vice President, Mission, Susan G. Komen. “Progression and recurrence remain among the most significant unmet needs for those diagnosed with early breast cancer, and continued advances in treatment bring new hope to patients and families facing this disease.”

Enhertu is approved with Boxed WARNINGS for interstitial lung disease (ILD)/pneumonitis and Embryo-Fetal toxicity. The safety of Enhertu followed by THP was evaluated in 320 patients with HER2 positive (IHC 3+ or ISH+) early breast cancer who received at least one dose of Enhertu followed by THP in DESTINY-Breast11. The safety of Enhertu was evaluated in 806 patients with HER2 positive breast cancer with residual invasive disease following neoadjuvant therapy who received at least one dose of Enhertu in DESTINY-Breast05.

In DESTINY-Breast11, the most common adverse reactions (≥20%), including laboratory abnormalities, were decreased hemoglobin, increased alanine aminotransferase, increased aspartate aminotransferase, decreased white blood cell count, nausea, peripheral neuropathy, diarrhea, decreased neutrophil count, alopecia, fatigue, decreased lymphocyte count, rash, musculoskeletal pain, decreased blood potassium, constipation, vomiting, stomatitis and decreased appetite. Serious adverse reactions occurred in 11% of patients receiving Enhertu followed by THP, including COVID-19 (0.9%) and ILD/pneumonitis (0.6%). Fatal adverse reactions occurred in 0.6% of patients, including ILD or pneumonitis and death not otherwise specified (one patient each).

In DESTINY-Breast05, the most common adverse reactions (≥20%), including laboratory abnormalities, were decreased white blood cell count, decreased lymphocyte count, decreased neutrophil count, nausea, decreased hemoglobin, increased aspartate aminotransferase, fatigue, increased alanine aminotransferase, decreased platelet count, increased blood alkaline phosphatase, constipation, vomiting, decreased blood potassium, diarrhea, musculoskeletal pain and decreased appetite. Serious adverse reactions occurred in 17% of patients receiving Enhertu. Serious adverse reactions in ≥1% of patients who received Enhertu were ILD/pneumonitis, radiation pneumonitis and decreased platelet count. Fatal adverse reactions occurred in 0.4% of patients, including ILD/pneumonitis (two patients) and respiratory tract infection (one patient).

“Enhertu has redefined the treatment of HER2 expressing breast cancer with practice-changing data across six breast cancer indications in seven years,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “Enhertu is now approved in the U.S. across both early and metastatic HER2 positive breast cancer, accomplishing what we set out to achieve a little over a decade ago for patients at the start of our comprehensive clinical development program.”

“HER2 positive early disease is considered highly curable, however, up to one in four patients still experience disease recurrence, underscoring the need for new options in this setting,” said Dave Fredrickson, Executive Vice President, Oncology Hematology Business Unit, AstraZeneca. “These approvals mark an important step forward, expanding the possibility of cure to more patients for the first time in many years and positioning Enhertu as a foundational treatment in early breast cancer.”

These applications in the U.S. were 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 for both DESTINY-Breast11 and DESTINY-Breast05 are ongoing in Australia, Brazil, Canada, Israel, Singapore and the UK. Additional regulatory submissions for Enhertu based on DESTINY-Breast05 are under review in Japan, the EU and Switzerland.

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 these approvals in the U.S., an amount of $155 million ($30 million for the neoadjuvant approval and $125 million for the adjuvant approval) is due from AstraZeneca to Daiichi Sankyo as milestone payments for these HER2 positive early-stage breast cancer indications. 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-Breast11

DESTINY-Breast11 is a global, multicenter, randomized, open-label, phase 3 trial evaluating the efficacy and safety of neoadjuvant Enhertu (5.4 mg/kg) monotherapy or Enhertu followed by THP compared to ddAC-THP in patients with high-risk HER2 positive early-stage breast cancer.

Patients were randomized 1:1:1 to receive either eight cycles of Enhertu monotherapy; four cycles of Enhertu followed by four cycles of THP; or four cycles of ddAC followed by four cycles of THP.

The primary endpoint of DESTINY-Breast11 is rate of pCR (absence of invasive disease in the breast and lymph nodes). Secondary endpoints include event-free survival, IDFS, overall survival (OS) and safety.

DESTINY-Breast11 enrolled 927 patients across multiple sites in Asia, Europe, North America and South America. For more information about the trial, visit ClinicalTrials.gov.

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 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 IDFS, which 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 DFS. Other secondary endpoints include OS, 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.

About 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] In the U.S., approximately 320,000 cases of breast cancer are diagnosed annually with more than 42,000 deaths.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including breast cancer.[3] 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.[3] An estimated one in five cases of breast cancer is considered HER2 positive.[4] Approximately one in three patients with HER2 positive early-stage breast cancer is considered high-risk, meaning they are more likely to experience disease recurrence and have a poor prognosis.[5]

There are two treatment settings for HER2 positive early breast cancer: neoadjuvant (before surgery) and adjuvant (after surgery). In the neoadjuvant setting, the current standard of care varies across regions but generally consists of combination chemotherapy regimens. In the U.S., the current standard of care consists of a combination regimen of carboplatin, trastuzumab, pertuzumab and a taxane.[6] For patients with HER2 positive early breast cancer, reaching pCR with neoadjuvant treatment is an early indicator of improved long-term survival.[7] However, 39% to 66% of patients who receive neoadjuvant treatment do not reach pCR, putting them at increased risk of disease recurrence.[8,9,10,11,12]

In the adjuvant setting, despite receiving additional treatment with current standard of care for residual disease, some patients still experience invasive disease or death.[13] Once patients are diagnosed with metastatic disease, the five-year survival rate drops from nearly 90% to approximately 30%.[14,] Adjuvant therapy represents a key opportunity to minimize the risk of recurrence and prevent progression to metastatic disease for patients with residual disease.[15,16]

About Enhertu

Enhertu (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, Enhertu is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced program in AstraZeneca's ADC scientific platform. Enhertu consists of a HER2 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Enhertu (5.4 mg/kg) is approved in the U.S. for the treatment of adult patients with HER2 positive breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment based on the DESTINY-Breast05 trial.

Enhertu (5.4 mg/kg) followed by THP is approved in China and the U.S. as a neoadjuvant treatment for adult patients with HER2 positive (IHC 3+ or ISH+) stage 2 or stage 3 breast cancer based on the results from the DESTINY-Breast11 trial. 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) in combination with pertuzumab is approved in Israel, Saudi Arabia, Switzerland, the United Arab Emirates and 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 95 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 95 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 70 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 75 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 90 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-Gastric04 trials.

Enhertu (5.4 mg/kg) is approved in more than 15 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, DESTINY-CRC02 and/or HERALD trials. Continued approval in the U.S. 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.

Enhertu U.S. Indications and Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for:

- HER2-Positive Early Breast Cancer
  - As neoadjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer, as determined by an FDA-authorized test followed by a taxane, trastuzumab, and pertuzumab (THP)

  - As adjuvant treatment of adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following neoadjuvant trastuzumab (with or without pertuzumab) and taxane-based treatment

- 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-authorized 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-authorized 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-authorized 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-authorized 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 severe, life-threatening, and fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Contraindications
None.

Warnings and Precautions
Interstitial Lung Disease / Pneumonitis
Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose 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. In the adjuvant HER2+ breast cancer setting, if drug-induced ILD is suspected, rule out radiotherapy-related pneumonitis. If only radiotherapy-related pneumonitis is suspected, consider interruption of ENHERTU for Grade 2 and permanently discontinue ENHERTU for Grade ≥3.

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

ENHERTU followed by THP
In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, ILD occurred in 4.4% of patients. Median time to first onset was 2.7 months (range: 1.1 to 6.0). Fatal outcomes due to ILD and/or pneumonitis occurred in 1 patient (0.3%) treated with ENHERTU followed by THP.

<u>HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)</u>
In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21).

Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by 1 level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3º C or a sustained temperature of ≥38º C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by 1 level.

<u>HER2-Positive, HER2-Low, and HER2-Ultralow Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)</u>
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% 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.

ENHERTU followed by THP
In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, a decrease in neutrophil count was reported in 58% of patients. Seventeen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 42 days (range: 11 to 165). Febrile neutropenia was reported in 0.9% 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 dysfunction (LVD) has been observed with anti-HER2 therapies, including ENHERTU. Assess left ventricular ejection fraction (LVEF) prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVD 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 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, LVD 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.

ENHERTU followed by THP
In patients treated with ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11, LVD was reported in 1.3% of patients, of which 0.3% were Grade 3.

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)
In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Embryo-Fetal Toxicity
ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for 7 months after the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU.

Additional Dose Modifications
Thrombocytopenia
For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 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 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 39% 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 (43%), 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%), increased blood bilirubin (23%), and abdominal pain (22%).

HER2-Positive Early Breast Cancer
DESTINY-Breast11
The safety of ENHERTU followed by THP was evaluated in 320 patients with HER2-positive (IHC 3+ or ISH+) early breast cancer who received at least 1 dose of ENHERTU 5.4 mg/kg followed by THP in DESTINY-Breast11. ENHERTU was administered by intravenous infusion once every three weeks for 4 cycles followed by THP for 4 cycles. The median duration of treatment was 5.6 months (range: 0.7 to 9.1) for patients who received ENHERTU followed by THP.

Serious adverse reactions occurred in 11% of patients receiving ENHERTU followed by THP, including COVID-19 (0.9%) and ILD/pneumonitis (0.6%). Fatal adverse reactions occurred in 0.6% of patients, including ILD/pneumonitis and death not otherwise specified (1 patient each).

In patients treated with ENHERTU followed by THP, the permanent discontinuation of ENHERTU due to adverse reactions occurred in 1.3%, of which ILD/pneumonitis accounted for 0.6%. Dose interruptions of ENHERTU due to adverse reactions occurred in 11% of patients. The most frequent adverse reactions (>2%) associated with dose interruption were decreased neutrophil count and COVID-19. Dose reductions of ENHERTU occurred in 2.5% of patients treated with ENHERTU.

The most common (≥20%) adverse reactions in patients treated with ENHERTU followed by THP, including laboratory abnormalities, were decreased hemoglobin (83%), increased alanine aminotransferase (79%), increased aspartate aminotransferase (74%), decreased white blood cell count (67%), nausea (65%), peripheral neuropathy (59%), diarrhea (59%), decreased neutrophil count (58%), alopecia (48%), fatigue (41%), decreased lymphocyte count (40%), rash (31%), musculoskeletal pain (30%), decreased blood potassium (29%), constipation (29%), vomiting (29%), stomatitis (23%), and decreased appetite (20%).

DESTINY-Breast05
The safety of ENHERTU was evaluated in 806 patients with HER2-positive breast cancer with residual invasive disease following neoadjuvant HER2-targeted therapy who then received at least one dose of ENHERTU 5.4 mg/kg. ENHERTU was administered by intravenous infusion once every three weeks for 14 cycles. The median duration of treatment was 10 months (range: 0.7 to 16) for patients who received ENHERTU.

Serious adverse reactions occurred in 17% of patients receiving ENHERTU. Serious adverse reactions in ≥1% of patients who received ENHERTU were ILD/pneumonitis, radiation pneumonitis, pneumonia, and platelet count decreased. Fatal adverse reactions occurred in 0.4% of patients including ILD/pneumonitis (2 patients) and respiratory tract infection (1 patient).

Permanent discontinuation of ENHERTU due to an adverse reaction occurred in 18% of patients. The adverse reaction which resulted in permanent discontinuation of ENHERTU >2% included ILD/pneumonitis. Dose interruptions of ENHERTU due to an adverse reaction occurred in 50% of patients. Adverse reactions which required dosage interruptions in >2% included radiation pneumonitis, neutrophil count decreased, COVID-19, white blood cell count decreased, ILD/pneumonitis, platelet count decreased, upper respiratory tract infection, fatigue, cough, and pyrexia. Dose reductions of ENHERTU due to an adverse reaction occurred in 26% of patients. Adverse reactions which required dose reductions in >2% of patients included nausea, fatigue, platelet count decreased, ILD/pneumonitis, and neutrophil count decreased.

The most common (≥20%) adverse reactions, including laboratory abnormalities, in patients receiving ENHERTU were decreased white blood cell count (80%), decreased lymphocyte count (72%), decreased neutrophil count (72%), nausea (71%), decreased hemoglobin (61%), increased aspartate aminotransferase (60%), fatigue (54%), increased alanine aminotransferase (53%), decreased platelet count (46%), increased blood alkaline phosphatase (39%), constipation (32%), vomiting (31%), decreased blood potassium (27%), diarrhea (23%), musculoskeletal pain (23%), and decreased appetite (20%).

ILD was reported in 17% of patients receiving ENHERTU, which included COVID-19 pneumonia, interstitial lung disease, lung opacity, organizing pneumonia, pneumocystis jirovecii pneumonia, pneumonia, and pneumonitis which was adjudicated as ILD (irrespective of causality). Adjudicated drug-related ILD for ENHERTU was 10% for all Grades and 0.9% for Grades 3 or 4.

<u>HER2-Positive Metastatic Breast Cancer</u>
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 (1 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%). 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 (≥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 (≥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 (≥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 (≥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%).

<u>HER2-Mutant Unresectable or Metastatic NSCLC (5.4 mg/kg)</u>
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. The median duration of treatment was 8 months (range: 0.7 to 28) for patients who received ENHERTU.

Serious adverse reactions occurred in 40% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pleural effusion, thrombocytopenia, dyspnea, nausea, pneumonia, vomiting, myocarditis, pulmonary embolism, and increased troponin I. Fatalities due to adverse reactions occurred in 3% of patients including ILD/pneumonitis, cerebrovascular accident, and pneumococcal sepsis (1 patient each).

ENHERTU was permanently discontinued in 17% of patients. Adverse reactions which resulted in permanent discontinuation of ENHERTU were ILD/pneumonitis, pneumonia, blood bilirubin increased, hypokalemia, metastases to meninges, and myocarditis. Dose interruptions of ENHERTU due to adverse reactions occurred in 50% of patients. Adverse reactions which required dose interruption (>2%) included neutropenia, COVID-19, ILD/pneumonitis, fatigue, anemia, and pneumonia. Dose reductions due to an adverse reaction occurred in 20% of patients. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, fatigue, and decreased appetite.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (68%), nausea (67%), decreased white blood cell count (66%), decreased neutrophil count (59%), decreased lymphocyte count (56%), increased aspartate aminotransferase (51%), decreased albumin (50%), decreased platelet count (49%), fatigue (48%), increased alanine aminotransferase (41%), decreased appetite (41%),

constipation (38%), increased alkaline phosphatase (37%), vomiting (32%), decreased blood potassium (29%), diarrhea (24%), alopecia (22%), and musculoskeletal pain (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/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 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 (≥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 (≥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 2233 patients treated with ENHERTU 5.4 mg/kg, 28% were ≥65 years and 6% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (56%) as compared to younger patients (49%). 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. *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 compared to younger patients. *ENHERTU followed by THP*: Of the 320 patients with HER2-positive early breast cancer treated with ENHERTU 5.4 mg/kg followed by THP, 12% were ≥65 years and 1.6% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients ≥65 years (38%) as compared to younger patients (30%).
- **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, monitor for increased adverse reactions 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 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 seven 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 and DS3790 are being developed by Daiichi Sankyo.

An additional ADC being developed by Daiichi Sankyo is DS3610, which consists of an antibody attached to a novel payload that acts as an agonist of STING.

Ifinatamab deruxtecan, raludotatug deruxtecan, patritumab deruxtecan, DS-3939, DS3610 and DS3790 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo

Daiichi Sankyo (TSE: 4568) is a global healthcare company committed to becoming a trusted healthcare innovator, transforming the lives of people through its strength in science and technology. The company discovers and develops new standards of care to address diverse medical needs to fulfill its purpose of contributing to the enrichment of quality of life around the world. With a strategic focus on oncology, Daiichi Sankyo is advancing an industry-leading antibody drug conjugate portfolio along with identifying new breakthrough generating technologies to deliver practice-changing medicines to patients, healthcare professionals and society. For more information, please visit www.daiichisankyo.com.

Disclosure: Dr. Modi provides consulting and advisory services to Daiichi Sankyo (and AstraZeneca)

MEDIA CONTACTS:

Global:
Jennifer Brennan
jennifer.brennan@daiichisankyo.com
+1 908 900 3183 (mobile)

Japan:
DS-PR_jp@daiichisankyo.com

INVESTOR RELATIONS CONTACT:
DaiichiSankyoIR_jp@daiichisankyo.com

References:

[1] World Health Organization. Breast Fact Sheet. Accessed May 2026.
[2] Siegel RL, et al. *CA Cancer J Clin*. 2026;76(1):e70043.
[3] Cheng X. *Genes (Basel)*. 2024;15(7):903.
[4] Tarantino P, et al. *Ann Oncol.* 2023;34(8):645-659.
[5] Mahtani R, et al. *Cancers* (Basel). 2025;17(11):1848.
[6] Wang J, et al. *Breast Cancer*. 2023;15:721-730.
[7] Spring LM, et al. *Clin Cancer Res*. 2020;26(12):2838-2848.
[8] Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-2284.
[9] Swain SM, et al. *Ann Oncol*. 2018;29(3):646-653.
[10] Huober J, et al. *J Clin Oncol.* 2022;40(25):2946-2956.
[11] Masuda N, et al. *Breast Cancer Res Treat*. 2020;180(1):135-146.
[12] Gao HF, et al. Presented at ASCO Annual Meeting 2025.
[13] Geyer CE, et al. *N Engl J Med*. 2025;392:249-257.
[14] National Cancer Institute. SEER Cancer Stat Facts: Female Breast Cancer. Accessed May 2026.
[15] von Minckwitz G, et al. *N Engl J Med*. 2019;380(7):617-628.
[16] Zaborowski AM and Wong SM. *BJS.* 2023;110(7):765-772.

PP-US-ENB-5118-1
05/26