NEWS RELEASE

ENHERTU® Approved in the U.S. as First Tumor Agnostic HER2 Directed Therapy for Previously Treated Patients with Metastatic HER2 Positive Solid Tumors

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- Based on three phase 2 trials of Daiichi Sankyo and AstraZeneca's ENHERTU that showed clinically meaningful responses across a broad range of tumors
- ENHERTU now has five approved indications with the latest in HER2 expressing (IHC 3+) metastatic cancers

TOKYO & BASKING RIDGE, N.J.--(BUSINESS WIRE)-- Daiichi Sankyo (TSE: 4568) and AstraZeneca's (LSE/STO/Nasdaq: AZN) ENHERTU® (fam-trastuzumab deruxtecan-nxki) has been approved in the U.S. for the treatment of adult patients with unresectable or metastatic HER2 positive (immunohistochemistry [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 (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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

The first tumor agnostic approval of a HER2 directed therapy and ADC was based on efficacy data in 192 adult patients with previously treated unresectable or metastatic HER2 positive (IHC 3+) solid tumors who were enrolled in one of three multicenter phase 2 trials from the DESTINY clinical development program, including **DESTINY-**

PanTumor02, **DESTINY-Lung01** or **DESTINY-CRC02**. The major efficacy outcome measure in all three of the studies was confirmed ORR and an additional efficacy outcome measure was DOR.

In DESTINY-PanTumor02, efficacy was assessed in a subgroup of previously treated patients (n=111) with centrally or locally assessed HER2 positive (IHC 3+) solid tumors including either biliary tract, bladder, cervical, endometrial, ovarian, pancreatic or other tumors. Confirmed ORR was 51.4% (95% confidence interval [CI]: 41.7-61.0) and median DOR range was 19.4 months (range: 1.3, 27.9+ ['+' denotes ongoing responses at data cutoff]). In DESTINY-Lung01, efficacy was assessed in a subgroup of patients (n=17) with centrally confirmed HER2 positive (IHC 3+) non-small cell lung cancer (NSCLC). A confirmed ORR of 52.9% (95% CI: 27.8-77.0) and median DOR range of 6.9 months (range: 4.0, 11.7+) was seen. In DESTINY-CRC02, efficacy was assessed in the subgroup of patients (n=64) with centrally confirmed HER2 positive (IHC 3+) colorectal cancer. Confirmed ORR was 46.9% (95% CI: 34.3-59.8) and median DOR range was 5.5 months (range: 1.3+, 9.7+).

The approval was received following the U.S. Food and Drug Administration's (FDA) review of the application using the Real-Time Oncology Review (RTOR) program and under **Priority Review** and **Breakthrough Therapy Designation**. The submission was reviewed under Project Orbis, which provides a framework for concurrent submission and review of oncology medicines among participating international partners. As part of Project Orbis, ENHERTU also is under regulatory review for the same indication by regulatory authorities in Australia, Brazil and Singapore.

"Until the approval of trastuzumab deruxtecan, patients with metastatic HER2 positive solid tumors have had limited treatment options," said Funda Meric-Bernstam, MD, Chair of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center. "Based on the clinically meaningful response rates seen across clinical trials, this tumor-agnostic approval means that patients may now be treated with a HER2 directed medicine."

ENHERTU is approved with Boxed WARNINGS for interstitial lung disease (ILD)/pneumonitis and Embryo-Fetal toxicity. 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) in **DESTINY-Breast01**, DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02. The most common adverse reactions (frequency ≥20%), including laboratory abnormalities, were decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, fatigue, decreased lymphocyte count, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, decreased appetite, alopecia, diarrhea, decreased blood potassium, constipation, decreased sodium, stomatitis, and upper respiratory tract infection. Serious adverse reactions occurred in 34% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were sepsis, pneumonia, vomiting, urinary tract infection, abdominal pain, nausea,

pneumonitis, pleural effusion, hemorrhage, COVID-19, fatigue, acute kidney injury, anemia, cellulitis, and dyspnea. Fatalities due to adverse reactions occurred in 6.3% of patients including ILD/pneumonitis (2.3%), cardiac arrest (0.6%), COVID-19 (0.6%), and sepsis (0.6%). The following events occurred in one patient each (0.3%): acute kidney injury, cerebrovascular accident, general physical health deterioration, pneumonia, and hemorrhagic shock.

“This fifth indication in the U.S. is a significant milestone as eligible patients with previously treated metastatic HER2 positive solid tumors may now be treated with ENHERTU,” said Ken Keller, Global Head of Oncology Business, and President and CEO, Daiichi Sankyo, Inc. “The accelerated approval by the FDA for this tumor agnostic indication is based on the clinically meaningful efficacy seen with ENHERTU across numerous types of metastatic cancers.”

“As the first antibody drug conjugate to be granted a tumor agnostic indication, ENHERTU is truly delivering on its potential across metastatic HER2 targetable tumors,” said Dave Fredrickson, Executive Vice President, Oncology Business Unit, AstraZeneca. “This approval also elevates the importance of testing for biomarkers, including HER2, across a broad range of tumors to ensure these patients with advanced cancer who have few options know whether a targeted medicine might be right for them.”

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**.

Based on these results, fam-trastuzumab deruxtecan-nxki (ENHERTU) has been included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a treatment option for multiple metastatic tumors. See NCCN Guidelines® for detailed recommendations.1

About DESTINY-PanTumor02

DESTINY-PanTumor02 is a global, multicenter, multi-cohort, open-label phase 2 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) for the treatment of previously treated HER2 expressing tumors, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic cancer or other tumors.

The primary efficacy endpoint of DESTINY-PanTumor02 is confirmed ORR as assessed by investigator. Secondary endpoints include DOR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, tolerability and pharmacokinetics. DESTINY-PanTumor02 enrolled 267 patients, including 111 HER2 positive (IHC 3+)

adult patients, at multiple sites in Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov**.

The primary analysis of this study was **presented** in a late-breaking mini-oral session at the 2023 European Society for Medical Oncology (ESMO) Congress and simultaneously published in the **Journal of Clinical Oncology** .

About DESTINY-Lung01

DESTINY-Lung01 is a global phase 2, open-label, two-cohort trial evaluating the efficacy and safety of ENHERTU (6.4 mg/kg and 5.4 mg/kg) in patients with HER2 mutant (cohort 2, n=91) or HER2 overexpressing (defined as IHC 3+ or IHC 2+) (cohort 1 and 1a, n=90) unresectable or metastatic NSCLC who had progressed after one or more systemic therapies. The primary endpoint is confirmed ORR by independent central review. Key secondary endpoints include DOR, DCR, PFS, OS and safety. DESTINY-Lung01 enrolled 181 patients, including 17 HER2 positive (IHC 3+) adult patients, at multiple sites, including Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov.**

Full results from the HER2 mutant cohort were **presented** at the 2021 ESMO Congress and simultaneously published in **The New England Journal of Medicine** . Updated results from both cohorts of DESTINY-Lung01 were **presented** at the 2022 ESMO Congress. Full results from the HER2 overexpressing cohort were published in **The Lancet Oncology** in March 2024.

About DESTINY-CRC02

DESTINY-CRC02 is a global, randomized, two arm, parallel, multicenter phase 2 trial evaluating the efficacy and safety of two doses (5.4 mg/kg or 6.4 mg/kg) of ENHERTU in patients with locally advanced, unresectable or metastatic HER2 positive colorectal cancer of BRAF wild-type, RAS wild-type or RAS mutant tumor types previously treated with standard therapy. The trial was conducted in two stages. In the first stage, patients (n=80) were randomized 1:1 to receive either 5.4 mg/kg or 6.4 mg/kg of ENHERTU. In the second stage, additional patients (n=42) were enrolled in the 5.4 mg/kg arm. The primary endpoint is confirmed ORR as assessed by blinded independent central review. Secondary endpoints include DOR, DCR, investigator-assessed confirmed ORR, clinical benefit ratio, PFS, OS and safety. DESTINY-CRC02 enrolled 122 patients, including 64 HER2 positive (IHC 3+) adult patients, at multiple sites in Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov**.

Primary results from the DESTINY-CRC02 phase 2 trial were **presented** at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting.

About DESTINY-Breast01

DESTINY-Breast01 is a global single-arm, open-label, two-part multicenter phase 2 trial evaluating the safety and efficacy of ENHERTU in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine (T-DM1). The primary endpoint of the trial is ORR, as determined by independent central review. Secondary objectives include DOR, DCR, clinical benefit rate, PFS, OS and safety. DESTINY-Breast01 enrolled 253 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit **ClinicalTrials.gov.**

Updated data from DESTINY-Breast01 were **presented** at the ESMO 2021 Virtual Congress. The initial analysis was presented at SABCS 2019 and simultaneously published in **The New England Journal of Medicine** in December 2019.

About HER2 Expression in Solid Tumors

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of various tissue cells throughout the body and is involved in normal cell growth.2,3 In some cancers, HER2 expression is amplified or the cells have activating mutations.2,4 HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease and poor prognosis.5

HER2 directed therapies have been used to treat breast, gastric, lung and colorectal cancers for a number of years. Although HER2 is expressed in solid tumor types including biliary tract, bladder, cervical, endometrial, ovarian and pancreatic cancers,4 testing is not routinely performed in these additional tumor types and as a result, available literature is limited. In these solid tumors, HER2 positive expression, classified as IHC 3+, has been observed at rates from 1% to 28%.6,7 Approximately 1% to 5% of patients with NSCLC have tumors with HER2 overexpression (IHC 3+), however, the levels of protein expression reported vary in the literature.6,8 Approximately 1% to 4% of patients with metastatic colorectal cancer have tumors that are HER2 overexpressing (IHC 3+).6,9,10

About ENHERTU

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

ENHERTU (5.4 mg/kg) is approved in more than 60 countries worldwide for the treatment of adult patients with

unresectable or metastatic HER2 positive (IHC 3+ or in-situ hybridization (ISH)+) breast cancer who have received a prior anti-HER2-based regimen, either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within six months of completing therapy based on the results from the **DESTINY-Breast03** trial.

ENHERTU (5.4 mg/kg) is approved in more than 55 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ (ISH)-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on the results from the **DESTINY-Breast04** trial.

ENHERTU (5.4 mg/kg) is approved in more than 35 countries worldwide for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the **DESTINY-Lung02** trial. Continued approval in the U.S. for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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

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

About the ENHERTU Clinical Development Program

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

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in **March 2019** and datopotamab deruxtecan (Dato-DXd) in **July 2020**, except in Japan where Daiichi Sankyo

maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and datopotamab deruxtecan.

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc., Rahway, N.J. USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

Designed using Daiichi Sankyo's proprietary DXd ADC Technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

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

ENHERTU U.S. Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive (IHC 3+ or ISH positive) breast cancer who have received a prior anti-HER2-based regimen either:
    - In the metastatic setting, or
    - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

  This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

- Locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH positive) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen

- Unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

  This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher

ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
- Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in ≤28 days from date of onset, maintain dose. If resolved in >28 days from date of onset, reduce dose one level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

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

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

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

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

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 109/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 109/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 109/L and temperature >38.3° C or a sustained temperature of ≥38° C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

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

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

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

In patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients

with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

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

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

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

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

Embryo-Fetal Toxicity

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

Additional Dose Modifications

Thrombocytopenia

For Grade 3 thrombocytopenia (platelets <50 to 25 x 109/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 109/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by one level.

Adverse Reactions

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

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

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

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

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

ENHERTU was permanently discontinued in 14% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 44% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, leukopenia, anemia, thrombocytopenia, pneumonia, nausea, fatigue, and ILD/pneumonitis. Dose reductions occurred in 21% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, neutropenia, and fatigue.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), decreased blood potassium (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased

appetite (29%), headache (22%), respiratory infection (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

The safety of ENHERTU was evaluated in 371 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast04. The median duration of treatment was 8 months (range: 0.2 to 33) for patients who received ENHERTU.

Serious adverse reactions occurred in 28% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, pneumonia, dyspnea, musculoskeletal pain, sepsis, anemia, febrile neutropenia, hypercalcemia, nausea, pyrexia, and vomiting. Fatalities due to adverse reactions occurred in 4% of patients including ILD/pneumonitis (3 patients); sepsis (2 patients); and ischemic colitis, disseminated intravascular coagulation, dyspnea, febrile neutropenia, general physical health deterioration, pleural effusion, and respiratory failure (1 patient each).

ENHERTU was permanently discontinued in 16% of patients, of which ILD/pneumonitis accounted for 8%. Dose interruptions due to adverse reactions occurred in 39% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, fatigue, anemia, leukopenia, COVID-19, ILD/pneumonitis, increased transaminases, and hyperbilirubinemia. Dose reductions occurred in 23% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, thrombocytopenia, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (70%), decreased hemoglobin (64%), decreased neutrophil count (64%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (44%), alopecia (40%), vomiting (40%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (36%), constipation (34%), increased blood alkaline phosphatase (34%), decreased appetite (32%), musculoskeletal pain (32%), diarrhea (27%), and decreased blood potassium (25%).

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

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

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

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

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

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

HER2-Positive Locally Advanced or Metastatic Gastric Cancer (6.4 mg/kg)

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m2 biweekly or paclitaxel (N=7) 80 mg/m2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%)

associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and decreased blood potassium. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (75%), decreased white blood cell count (74%), decreased neutrophil count (72%), decreased lymphocyte count (70%), decreased platelet count (68%), nausea (63%), decreased appetite (60%), increased aspartate aminotransferase (58%), fatigue (55%), increased blood alkaline phosphatase (54%), increased alanine aminotransferase (47%), diarrhea (32%), decreased blood potassium (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

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

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

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

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%),

increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (20%).

Use in Specific Populations

- Pregnancy: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- Lactation: There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- Females and Males of Reproductive Potential: Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- Pediatric Use: Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- Geriatric Use: Of the 1287 patients with HER2-positive or HER2-low breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.8% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (59%) as compared to younger patients (49%). Of the 101 patients with HER2-mutant unresectable or metastatic NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥65 years and 8% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 125 patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg in DESTINY-PanTumor02, DESTINY-Lung01, or DESTINY-CRC02, 39% were 65 years or older and 9% were 75 years or older. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- Renal Impairment: A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The

recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).

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

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch.

Please see accompanying full **Prescribing Information** , including Boxed WARNINGS, and **Medication Guide.**

About Daiichi Sankyo

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

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