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Daiichi-Sankyo

Press Release

ENHERTU® Achieved Statistically Significant Overall Survival Reducing the Risk of Death by 36% Versus Trastuzumab Emtansine (T-DM1) in Patients with HER2 Positive Metastatic Breast Cancer in DESTINY-Breast03

- Daiichi Sankyo and AstraZeneca's ENHERTU also improved progression-free survival by 22 months versus T-DM1 in patients previously treated with HER2 directed therapy in the DESTINY-Breast03 phase 3 trial
- ENHERTU showed significant progression-free and overall survival improvements versus chemotherapy in later-line HER2 positive setting in the DESTINY-Breast02 phase 3 trial

Tokyo, Munich and Basking Ridge, NJ – (December 7, 2022) – Updated results from the DESTINY-Breast03 phase 3 trial (Abstract #GS2-02) showed that ENHERTU® (trastuzumab deruxtecan) demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) compared to trastuzumab emtansine (T-DM1) in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. These results and primary results from the DESTINY-Breast02 phase 3 trial (Abstract #GS2-01) will be presented today at the 2022 San Antonio Breast Cancer Symposium (#SABCS22), with the updated results from DESTINY-Breast03 simultaneously published in *The Lancet.*

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

In the key secondary endpoint analysis of OS in DESTINY-Breast03, ENHERTU demonstrated a 36% reduction in risk of death versus T-DM1 (hazard ratio [HR] = 0.64; 95% confidence interval [CI] 0.47-0.87; p=0.0037). In both treatment arms, median OS was not yet reached (ENHERTU [40.5-NE] versus T-DM1 [34.0-NE]) after a median duration of follow-up of 28.4 months for ENHERTU and 26.5 months for T-DM1. In the ENHERTU arm, an estimated 77.4% of patients were alive at two years (95% CI: 71.7-81.2) compared to 69.9% of patients treated with T-DM1 (95% CI: 63.7-75.2). The observed survival benefit was consistent across all analyzed subgroups, including patients with or without baseline brain metastases, with or without baseline visceral disease, those who were hormone receptor (HR) positive or HR negative and patients regardless of prior pertuzumab or lines of systemic therapy.

"The main goals of therapy for advanced breast cancer are to control the disease and improve survival, and it is therefore critical to continue to improve upon existing treatment options, particularly in the metastatic

setting," said Sara Hurvitz, MD, Medical Oncologist, Professor of Medicine and Director of the Breast Cancer Clinical Trials Program in the Division of Hematology-Oncology at the David Geffen School of Medicine at UCLA, and Medical Director for the Clinical Research Unit at the UCLA Jonsson Comprehensive Cancer Center in Santa Monica, CA. "For patients with HER2 positive breast cancer who experience disease progression following initial treatment in the metastatic setting, ENHERTU has shown significant improvement in survival compared to T-DM1, further confirming this medicine as the new standard of care."

With the additional follow-up in DESTINY-Breast03, ENHERTU also continued to demonstrate a clinically meaningful improvement in progression-free survival (PFS) with a 22 month improvement in median PFS over T-DM1, reaffirming the statistically significant finding at the previous interim analysis. The updated exploratory analysis was not tested for statistical significance and not powered to show differences between treatment arms. The median PFS for patients in the ENHERTU arm was 28.8 months (HR=0.33; 95% CI: 22.4-37.9) compared to 6.8 months for T-DM1 (95% CI: 5.6-8.2) as assessed by blinded independent central review (BICR). Confirmed objective response rate (ORR) was 78.5% in the ENHERTU arm with 21.1% of patients demonstrating a complete response (CR) versus an ORR of 35.0% in the T-DM1 arm where 9.5% of patients achieved a CR. The median duration of response (DoR) was 36.6 months in the ENHERTU arm and 23.8 months in the T-DM1 arm.

The safety profile observed with ENHERTU in DESTINY-Breast03 was consistent with previous clinical trials with no new safety concerns identified. Grade 3 or higher treatment-related treatment emergent adverse events (TEAEs) occurred in 47.1% of patients receiving ENHERTU. The most common grade 3 or higher treatment-related TEAEs in the ENHERTU arm were decreased neutrophil count (16.0%), anemia (9.3%), decreased platelet count (7.8%), nausea (7.0%), decreased white blood cell count (6.2%) and fatigue (5.8%). In the ENHERTU arm, 15.2% of patients (n=39) experienced interstitial lung disease (ILD) or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD or pneumonitis events were low grade (grade 1 or grade 2) with two grade 3 events and no grade 4 or grade 5 events observed in patients treated with ENHERTU.

"The overall survival benefits shown in both the DESTINY-Breast03 and DESTINY-Breast02 trials further validate the role of ENHERTU in potentially extending the lives of patients with previously treated HER2 positive breast cancer," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "Additionally, median progression-free survival was four times longer with one in five patients showing no detectable signs of disease when treated with ENHERTU compared to T-DM1 in DESTINY-Breast03, which is particularly impressive in the metastatic setting of HER2 positive breast cancer."

"The updated results for DESTINY-Breast03 showing that ENHERTU extends patients' lives and also delays progression by nearly two years reinforces our belief that this medicine has the potential to set a new standard of care for patients with HER2 positive metastatic breast cancer treated in the second-line setting," said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "Complemented by DESTINY-Breast02, we now have two phase 3 trials in HER2 positive metastatic breast cancer showing patients in these trials have more disease-free time and live longer when they receive ENHERTU versus the previous standard of care."

All patients in DESTINY-Breast03 received at least one prior cancer therapy, including trastuzumab (ENHERTU = 99.6%; T-DM1 = 99.6%) or pertuzumab (ENHERTU = 62.1%; T-DM1 = 60.1%). In the ENHERTU arm, 41.4% of patients had received one prior line of therapy in the metastatic setting. At baseline, 16.5% of patients in the ENHERTU arm and 14.8% of patients in the T-DM1 arm had a history of brain metastases. As of data cut-off on July 25, 2022, 75 patients remained on treatment with ENHERTU and 18 patients on T-DM1.

Summary of Updated DESTINY-Breast03 Results

Efficacy Measure	**ENHERTU (5.4 mg/kg) n=261**	**Trastuzumab Emtansine (T-DM1; 3.6 mg/kg) n=263**
Median OS, months (95% CI)	Not reached (40.5-NE)	Not reached (34.0-NE)
	HR=0.64 (0.47-0.87) p=0.0037[i]	
OS rate (%) (95% CI)		
12 months	94.1% (90.4-96.4)	86.0% (81.1-89.8)
24 months	77.4 % (71.7-82.1)	69.9% (63.7-75.2)
Median PFS by BICR, months (95% CI)	28.8 months (22.4-37.9)	6.8 months (5.6-8.2)
	HR=0.33 (0.26-0.43) p<000001[i,ii]	
Median PFS2 by investigator, months (95% CI)[iii]	40.5 months (40.5-NE)	25.7 months (18.5-34.0)
	HR=0.47 (0.35-0.62) p=0.000001[i,ii]	
Confirmed ORR, % (95% CI)	78.5% (73.1-83.4)	35.0% (29.2-41.1)
	p<0.0001[i,ii]	
CR (%)	21.1% (n=55)	9.5% (n=25)
PR (%)	57.5% (n=150)	25.5% (n=67)
SD (%)	18.0% (n=47)	41.8% (n=110)
PD (%)	1.1% (n=3)	17.9% (n=47)
Median DoR, months (95% CI)[iv]	36.6 months (22.4-NE)	23.8 months (12.6-34.7)

BICR, blinded independent central review; CI, confidence interval; CR, complete response, DoR, duration of response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second progression-free survival; PR, partial response; SD, stable disease

[i] Two-sided

[ii] Nominal p value. Updated exploratory analysis was not tested for statistical significance and not powered to show differences between treatment arms

[iii] From the time of randomization to second progression

[iv] Based on BICR

DESTINY-Breast02 Primary Results

In the primary results from the DESTINY-Breast02 phase 3 trial, ENHERTU demonstrated a 64% reduction in the risk of disease progression or death in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with T-DM1 compared to physician's choice of treatment (trastuzumab plus capecitabine or lapatinib plus capecitabine) (HR=0.36; 95% CI: 0.28-0.45; p<0.000001). The median PFS for patients in the ENHERTU arm was 17.8 months (95% CI: 14.3-20.8) compared to 6.9 months (95% CI: 5.5-8.4) for those treated with physician's choice of therapy as assessed by BICR. Treatment with ENHERTU also showed a 34% reduction in the risk of death compared to physician's choice of treatment (HR=0.66; 95% CI: 0.50-0.86; p=0.0021) with a median OS of 39.2 months with ENHERTU (95% CI: 32.7-NE) versus 26.5 months with physician's choice of therapy (95% CI: 21.0-NE).

The data from DESTINY-Breast02 confirm the data seen in the DESTINY-Breast01 phase 2 trial, which supported the first approvals of ENHERTU in patients with HER2 positive metastatic breast cancer who received two or more prior anti-HER2-based regimens.

The safety profile observed with ENHERTU in DESTINY-Breast02 was consistent with previous clinical trials with no new safety concerns identified. Grade 3 or higher treatment-related TEAEs occurred in 41.3% of patients receiving ENHERTU. The most common grade 3 or higher treatment-related TEAEs in the ENHERTU arm were decreased neutrophil count (10.6%), anemia (7.9%), neutropenia (7.7%), nausea (6.7%) and asthenia (5.0%). In the ENHERTU arm, 10.4% of patients (n=42) experienced ILD or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD or pneumonitis events were low grade (grade 1 or grade 2), with three grade 3 events, no grade 4 events and two grade 5 events observed.

About DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus T-DM1 in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. The primary efficacy endpoint of DESTINY-Breast03 is PFS based on BICR. OS is a key secondary efficacy outcome measure. Other secondary endpoints include ORR, DoR, PFS based on investigator assessment and safety. DESTINY-Breast03 enrolled 524 patients at multiple sites in Asia, Europe, North America, Oceania and South America. Primary results from DESTINY-Breast03 were published in *The New England Journal of Medicine,* with updated OS results published in *The Lancet*. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Breast02

DESTINY-Breast02 is a global, randomized, open-label, pivotal phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus physician's choice of treatment (trastuzumab/capecitabine or lapatinib/capecitabine) in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with T-DM1. Patients were randomized 2:1 to receive either ENHERTU or physician's choice of treatment. The primary endpoint of DESTINY-Breast02 is PFS based on BICR. The key secondary endpoint is OS. Other secondary endpoints include ORR based on BICR and investigator assessment, DoR based on BICR, PFS based on investigator assessment and safety. DESTINY-Breast02 enrolled approximately 600 patients at multiple sites in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit ClinicalTrials.gov.

About HER2 Positive Breast Cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.[1] More than two million breast cancer cases were diagnosed in 2020, with nearly 685,000 deaths globally.[1] Approximately one in five cases of breast cancer are considered HER2 positive.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast, gastric, lung and colorectal cancers.[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.[4]

Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[5,6]

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 topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

ENHERTU (5.4 mg/kg) is approved in more than 35 countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a (or one or more) 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 also is approved in several countries for the treatment of adult

patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast01 trial.

ENHERTU (5.4 mg/kg) is approved in Brazil and the U.S. for the treatment of adult patients with unresectable or metastatic HER2 low (immunohistochemistry (IHC) 1+ or IHC 2+/*in-situ* hybridization (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 under accelerated approval in the U.S. for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2 (ERBB2*) mutations, as detected by a FDA-approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 trial. Continued approval 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 several countries for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 trial.

ENHERTU is approved in the U.S. with Boxed WARNINGS for Interstitial Lung Disease and Embryo-Fetal Toxicity. For more information, please see the accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

About the ENHERTU Clinical Development Program

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

Regulatory applications for ENHERTU in breast and gastric cancer are currently under review in several countries.

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.

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 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 gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen

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.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, ILD occurred in 12% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.0% of patients treated with ENHERTU. Median time to first onset was 5 months (range: 0.9 to 23).

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 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 one 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 one level.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 65% of patients. Sixteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 664). Febrile neutropenia was reported in 1.1% of patients.

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.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
In patients with metastatic breast cancer and HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, LVEF decrease was reported in 3.6% of patients, of which 0.4% were Grade 3.

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 one level.

Adverse Reactions
Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients 65% 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 nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

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 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%), hypokalemia (35%), constipation (34%), musculoskeletal pain

(31%), diarrhea (29%), decreased appetite (29%), respiratory infection (22%), headache (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 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 hypokalemia (25%).

Unresectable or Metastatic HER2-Mutant 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 unresectable or metastatic HER2-mutant NSCLC who received ENHERTU 5.4 mg/kg intravenously every three weeks 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, hypokalemia, 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%).

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/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 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 hypokalemia. 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%), hypokalemia (30%), vomiting (26%), constipation (24%), increased blood bilirubin (24%), pyrexia (24%), and alopecia (22%).

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 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.6% 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 (60%) as compared to younger patients (48%). Of the 101 patients with unresectable or metastatic HER2-mutant 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

locally advanced or metastatic HER2-positive 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.

- **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. 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 dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit: www.daiichisankyo.com.

Media Contacts:

Global:
Victoria Amari
Daiichi Sankyo, Inc.
vamari@dsi.com
+1 908 900 3010 (mobile)

Japan:
Koji Ogiwara
Daiichi Sankyo Co., Ltd.
ogiwara.koji.ay@daiichisankyo.co.jp
+81 3 6225 1126 (office)

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

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