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Daiichi-Sankyo

Press Release

ENHERTU® Demonstrated a Median Progression-Free Survival of 13.2 Months in HR Positive, HER2 Low and HER2 Ultralow Metastatic Breast Cancer Following One or More Lines of Endocrine Therapy

- DESTINY-Breast06 results show Daiichi Sankyo and AstraZeneca's ENHERTU is the first HER2 directed medicine and antibody drug conjugate to demonstrate clinically meaningful benefit for patients in this setting
- Additionally, data from DESTINY-Breast03 and DESTINY-Breast07 trials in HER2 positive metastatic breast cancer reinforce ENHERTU as standard of care in second-line setting and highlight potential in first-line setting

Tokyo and Basking Ridge, NJ – (June 2, 2024) – Detailed positive results from the DESTINY-Breast06 phase 3 trial showed that ENHERTU® (trastuzumab deruxtecan) demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to standard of care chemotherapy in patients with HR positive, HER2 low (IHC 1+ or IHC 2+/ISH-) metastatic breast cancer and the overall trial population (patients with HR positive, HER2 low and HER2 ultralow [defined as IHC 0 with membrane staining] expression) following one or more lines of endocrine therapy. Results will be presented today as a late-breaking oral presentation (LBA1000) at the 2024 American Society of Clinical Oncology (#ASCO24) Annual Meeting.

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

In the primary endpoint analysis of patients with HR positive, HER2 low metastatic breast cancer, ENHERTU reduced the risk of disease progression or death by 38% versus chemotherapy (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.51-0.74; $p<0.0001$). Median PFS was 13.2 months in the ENHERTU arm compared to 8.1 months in the chemotherapy arm as assessed by blinded independent central review (BICR).

In the key secondary endpoint analysis of PFS by BICR in the overall trial population, ENHERTU achieved a similar 37% reduction in the risk of disease progression or death versus chemotherapy with a median PFS

of 13.2 months in the ENHERTU arm versus 8.1 months with chemotherapy (HR: 0.63; 95% CI: 0.53-0.75; p<0.0001).

A prespecified exploratory analysis showed the clinically meaningful improvement in PFS was consistent between patients with HER2 low and HER2 ultralow expression. In patients with HER2 ultralow expression, ENHERTU showed a 22% reduction in the risk of disease progression or death compared to chemotherapy with a median PFS of 13.2 months with ENHERTU versus 8.3 months with chemotherapy (HR: 0.78; 95% CI: 0.50-1.21).

In patients with HER2 low expression, confirmed objective response rate (ORR) was 56.5% in the ENHERTU arm with nine complete responses (CRs) and 194 partial responses (PRs) versus 32.2% in the chemotherapy arm with zero CRs and 114 PRs. In the overall trial population, confirmed ORR in the ENHERTU arm was 57.3% with 13 CRs and 237 PRs versus 31.2% in the chemotherapy arm with zero CRs and 134 PRs. In patients with HER2 ultralow expression, the confirmed ORR in the ENHERTU arm was 61.8% with four CRs and 43 PRs versus 26.3% in the chemotherapy arm with zero CRs and 20 PRs.

“Endocrine therapies are widely used early in the treatment of HR positive metastatic breast cancer, but following one or more lines of treatment, patients often derive limited efficacy from further endocrine-based therapy,” said Giuseppe Curigliano, MD, PhD, Professor of Medical Oncology at the University of Milan and the Head of the Division of Early Drug Development at the European Institute of Oncology, IRCCS, Italy and Principal Investigator for the trial. “With a median progression-free survival of more than a year, the results from DESTINY-Breast06 show that ENHERTU could become a new standard of care for patients with HER2 low and HER2 ultralow expressing tumors following endocrine therapy in the metastatic setting.”

The safety profile of ENHERTU in DESTINY-Breast06 was consistent with previous breast cancer clinical trials with no new safety concerns identified. The most common grade 3 or higher treatment related treatment emergent adverse events (TEAEs) occurring in 5% or more of patients treated with ENHERTU were neutropenia (20.7%), leukopenia (6.9%) and anemia (5.8%). Interstitial lung disease (ILD) or pneumonitis occurred in 11.3% of patients treated with ENHERTU. The majority of ILD or pneumonitis events were low grade (grade 1 [n=7; 1.6%] or grade 2 [n=36; 8.3%]). There were three grade 3 ILD events (0.7%), zero grade 4 events and three grade 5 events (0.7%) as determined by an independent adjudication committee.

“ENHERTU continues to deliver pioneering results for a HER2 directed medicine across many different types of cancer,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “These latest results from DESTINY-Breast06 demonstrate clinically meaningful results with ENHERTU even in tumors with very low levels of HER2 expression, suggesting that it may have an important role in treating a wide range of HER2 expressing metastatic breast cancer.”

"DESTINY-Breast06 represents another potential paradigm shift in how we treat patients across the spectrum of HR positive metastatic breast cancer," said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "The results reinforce the potential for ENHERTU to improve outcomes earlier in the treatment landscape and in a broader population of patients with HER2 expressing breast cancer who have never before been eligible for a HER2 directed therapy."

Patients in the DESTINY-Breast06 trial received a median of two prior lines of endocrine therapy in each treatment arm. In the overall trial population, 14.9% of patients (n=65) in the ENHERTU arm had received one prior line of endocrine therapy and 67.8% (n=295) had received two prior lines of endocrine therapy. No patients in the trial had received prior chemotherapy treatment in the metastatic setting. Median duration of follow-up was 18.2 months. As of the data cut-off of March 18, 2024, a total of 119 patients (14.0%) remained on study treatment, with 89 (20.5%) receiving ENHERTU and 30 (7.2%) receiving chemotherapy.

Summary of DESTINY-Breast06 Primary Analysis Results

Efficacy Measure	HER2 low (IHC 1+ and IHC 2+/ISH-)		Overall trial population (HER2 low and HER2 ultralow)		HER2 ultralow (defined as IHC 0 with membrane staining)[i,ii]	
	ENHERTU (n=359)	Chemotherapy (n=354)	ENHERTU (n=436)	Chemotherapy (n=430)	ENHERTU (n=76)	Chemotherapy (n=76)
PFS						
Median PFS[iii] (months) (95% CI)	13.2 months	8.1 months	13.2 months	8.1 months	13.2 months	8.3 months
HR (95% CI)	0.62 (0.51-0.74)		0.63 (0.53-0.75)		0.78 (0.50-1.21)	
p-value	p<0.0001		p<0.0001		---	
OS						
12 month OS Rate (%) (95% CI)	87.6%	81.7%	87.0%	81.1%	84.0%	78.7%
HR (95% CI)	0.83 (0.66-1.05)		0.81 (0.65-1.00)[v]		0.75 (0.43-1.29)	
p-value	p=0.1181[vi]		---		---	
ORR						
Confirmed ORR[i,iii,vii] (%) (n)	56.5% (203)	32.2% (114)	57.3% (250)	31.2% (134)	61.8% (47)	26.3% (20)
Best Overall Response						
CR % (n)	2.5% (9)	0	3.0% (13)	0	5.3% (4)	0
PR % (n)	54.0% (194)	32.2% (114)	54.4% (237)	31.2% (134)	56.6% (43)	26.3% (20)
SD % (n)	34.8% (125)	48.0% (170)	33.9% (148)	49.3% (212)	28.9% (22)	55.3% (42)
Median DOR (months)	14.1 months	8.6 months	14.3 months	8.6 months	14.3 months	14.1 months

CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; NA, not available; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; PR, partial response; SD, stable disease

[i] Descriptive analysis

[ii] Per central lab

[iii] As assessed by BICR

[iv] Less than 40% maturity for interim OS analysis (HER2 low)

[v] No test of significance was performed in line with the multiple testing procedure

[vi] P-value of 0.0046 required for statistical significance at this OS interim analysis

[vii] ORR is (CR + PR)

Additional ENHERTU Data at ASCO

DESTINY-Breast03 Updated Results

Updated overall survival (OS) results from the DESTINY-Breast03 phase 3 trial also presented as a poster show ENHERTU continued to demonstrate a clinically meaningful survival improvement over trastuzumab emtansine (T-DM1) after more than three years of follow-up in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab. In the updated analysis of OS, the key secondary endpoint of median OS has been reached in both treatment arms. Median OS was 52.6 months (95% CI: 48.7-NE) in the ENHERTU arm compared to 42.7 months (95% CI: 35.4-NE) in the T-DM1 arm (HR: 0.73; 95% CI: 0.56-0.94).

The safety profile of ENHERTU continues to be generally manageable and no cumulative toxicities were observed with longer follow-up. Grade 3 or higher treatment related TEAEs occurred in 48.6% of patients receiving ENHERTU. Since the prior data cut-off, there were four new ILD events (all grade 2).

DESTINY-Breast07 Results

Interim results from the DESTINY-Breast07 phase 1b/2 trial of ENHERTU alone or in combination with other anticancer therapies as a first-line treatment for HER2 positive metastatic breast cancer also were presented as an oral presentation. In the analysis, ENHERTU demonstrated promising activity as a monotherapy (n=75) and in combination with pertuzumab (n=50).

Confirmed ORR in the ENHERTU monotherapy arm was 76.0% (80% CI: 68.5-82.4) with six CRs and 51 PRs. In the ENHERTU plus pertuzumab combination arm, confirmed ORR was 84.0% (80% CI: 75.3-90.5) with 10 CRs and 32 PRs. The 12-month PFS rate was 80.8% (80% CI: 73.7-86.1) in the ENHERTU monotherapy arm and 89.4% (80% CI: 81.9-93.9) in the ENHERTU plus pertuzumab combination arm.

The safety of ENHERTU as a monotherapy and in combination with pertuzumab was consistent with known safety profiles of each therapy. Grade 3 or higher TEAEs occurred in 52.0% of patients in the ENHERTU monotherapy arm and 62.0% of patients in the ENHERTU plus pertuzumab combination arm. The most common grade 3 or higher TEAEs occurring in 5% or more of patients were neutropenia (27.0% in ENHERTU monotherapy arm; 24% in ENHERTU plus pertuzumab arm), anemia (4.0% in ENHERTU monotherapy arm; 14.0% in ENHERTU plus pertuzumab arm) and diarrhea (3.0% in ENHERTU monotherapy arm; 6.0% in ENHERTU plus pertuzumab arm). The majority of ILD or pneumonitis events were low grade (grade 1 or 2). In the ENHERTU monotherapy arm, there were two (2.7%) grade 1 events and five (6.7%) grade 2 events. There were no grade 3 or higher events observed in the ENHERTU monotherapy arm. In the ENHERTU plus pertuzumab combination arm, there were six (12.0%) grade 2

events and one (2.0%) grade 3 event. There were no grade 4 or 5 events observed in the ENHERTU plus pertuzumab combination arm.

This is the first dataset of ENHERTU as a first-line treatment of HER2 positive metastatic breast cancer. Analyses from the ongoing DESTINY-Breast09 phase 3 trial will provide further insights regarding the efficacy and safety of ENHERTU in this HER2 positive patient population.

About DESTINY-Breast06

DESTINY-Breast06 is a global, randomized, open-label, phase 3 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) versus investigator's choice of chemotherapy (capecitabine, paclitaxel or nab paclitaxel) in patients with HR positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (defined as IHC 0 with membrane staining) advanced or metastatic breast cancer. Patients in the trial had no prior chemotherapy for advanced or metastatic disease and received at least two lines of prior endocrine therapy in the metastatic setting. Patients also were eligible if they had received one prior line of endocrine therapy combined with a CDK4/6 inhibitor in the metastatic setting and experienced disease progression within six months of starting first-line treatment or received endocrine therapy as an adjuvant treatment and experienced disease recurrence within 24 months.

The primary endpoint is PFS in the HR positive, HER2 low patient population as measured by BICR. Key secondary endpoints include PFS by BICR in the overall trial population (HER2 low and HER2 ultralow), OS in patients in the HER2 low patient population and OS in the overall trial population. Other secondary endpoints include ORR, DOR, time to first subsequent treatment or death, time to second subsequent treatment or death and safety. Analysis of the HER2 ultralow subgroup was not powered to demonstrate statistical significance.

DESTINY-Breast06 enrolled 866 patients (n=713 for HER2 low and n=153 for HER2 ultralow) at multiple sites in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit ClinicalTrials.gov.

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 the 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-Breast07

DESTINY-Breast07 is a global, randomized, open-label phase 1b/2 dose-finding and dose-expansion trial to explore the safety, tolerability and antitumor activity of ENHERTU alone or in combination with other anticancer agents in patients with HER2 positive metastatic breast cancer. The study consists of two phases: a dose escalation phase and a dose expansion phase. The dose escalation phase enrolled patients with locally assessed HER2 positive or advanced metastatic breast cancer in second-line or later treatment. The dose expansion phase enrolled patients with locally assessed HER2 positive breast cancer previously untreated for advanced or metastatic disease.

The primary endpoints of DESTINY-Breast07 are safety and tolerability. Secondary endpoints include ORR and PFS based on investigator assessment.

DESTINY-Breast07 enrolled 244 patients at multiple sites in Asia, Europe, North America and South America. For more information about the trial, visit ClinicalTrials.gov.

About Breast Cancer and HER2 Expression

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] While survival rates are high for those diagnosed with early breast cancer, only about 30% of patients diagnosed with or who progress to metastatic disease are expected to live five years following diagnosis.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including breast cancer.[3] Patients with high levels of HER2 expression (IHC 3+ or IHC2+/ISH+) are classified as HER2 positive and treated with HER2 targeted therapies, representing approximately 15 to 20% percent of all breast cancers.[4] Historically, tumors that were not classified as HER2 positive were classified as HER2 negative, despite the fact that many of these tumors still carry some level of HER2 expression.[5] It is estimated that approximately 60% to 65% of HR positive breast cancers are HER2 low and potentially an additional 25% may be HER2 ultralow.[6,7]

Endocrine therapies are widely given consecutively in the early lines of treatment for HR positive metastatic breast cancer. However, following two lines of endocrine therapy, further efficacy with additional endocrine treatment is often limited. [8] The current standard of care following endocrine therapy is chemotherapy, which is associated with poor response rates and outcomes. [8,9,10,11]

Prior to the approval of ENHERTU following chemotherapy in HER2 low metastatic breast cancer based on the DESTINY-Breast04 trial, there were no targeted therapies approved specifically for patients with HER2 low expression.[12] There are no targeted therapies specifically approved for patients with HER2 ultralow expression.[13]

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 60 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 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 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.

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 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
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/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 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.

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