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Daiichi-Sankyo

Press Release

ENHERTU® Reduced the Risk of Disease Recurrence or Death by 53% Versus T-DM1 in Patients with High-Risk HER2 Positive Early Breast Cancer Following Neoadjuvant Therapy in DESTINY-Breast05 Phase 3 Trial

- More than 92% of patients treated with Daiichi Sankyo and AstraZeneca's ENHERTU were free of invasive disease at three years
- DESTINY-Breast05 presented in ESMO Presidential Symposium I alongside DESTINY-Breast11 reinforces potential for ENHERTU to become a foundational treatment in curative-intent early breast cancer setting

Tokyo and Basking Ridge, NJ – (October 18, 2025) – Positive results from the DESTINY-Breast05 phase 3 trial showed ENHERTU® (trastuzumab deruxtecan) demonstrated a highly statistically significant and clinically meaningful improvement in invasive disease-free survival (IDFS) compared to trastuzumab emtansine (T-DM1) as a post-neoadjuvant treatment (after surgery) in patients with HER2 positive early breast cancer with residual invasive disease in the breast and/or axillary lymph nodes after neoadjuvant treatment and a high risk of disease recurrence. Results were presented today (LBA1) alongside the results of DESTINY-Breast11 (291O) in Presidential Symposium I at the 2025 European Society for Medical Oncology (#ESMO25) Congress.

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, ENHERTU significantly reduced the risk of invasive disease recurrence or death (invasive disease-free survival [IDFS]) by 53% (hazard ratio [HR]=0.47; 95% confidence interval [CI]: 0.34-0.66; p<0.0001) compared to T-DM1 as a post-neoadjuvant treatment. ENHERTU demonstrated a three-year IDFS rate of 92.4% (95% CI: 89.7-94.4) compared to 83.7% with T-DM1 (95% CI: 80.2-86.7). IDFS findings were consistent across all prespecified subgroups.

In the key secondary endpoint analysis of disease-free survival (DFS), ENHERTU also significantly reduced the risk of disease recurrence or death by 53% (HR=0.47; 95% CI: 0.34-0.66; p<0.0001) compared to T-DM1 as a post-neoadjuvant treatment. The three-year DFS rate for ENHERTU was 92.3% (95% CI: 89.5-94.3) compared to 83.5% with T-DM1 (95% CI: 79.9-86.4). Treatment with ENHERTU also reduced the

risk of distant disease recurrence (distant recurrence-free interval [DRFI]) by 51% (HR=0.49; 95% CI: 0.34-0.71) and the risk of brain metastases (brain metastasis-free interval [BMFI]) by 36% (HR=0.64; 95% CI: 0.35-1.17) versus T-DM1. DRFI at three years was 93.9% with ENHERTU (95% CI: 91.4-95.7) compared to 86.1% with T-DM1 (95% CI: 82.5-89.1). BMFI at three years was 97.6% with ENHERTU (95% CI: 96.2-98.5) compared to 95.8% with T-DM1 (95% CI: 93.6-97.2).

Overall survival (OS) was not mature at the time of this planned interim analysis (2.9% maturity at data cut-off) and will be assessed in future analyses (HR=0.61; 95% CI: 0.34-1.10).

"For patients with residual disease after neoadjuvant treatment, the post-neoadjuvant setting represents a critical second opportunity to reduce recurrence risk, and in DESTINY-Breast05 ENHERTU reduced the risk of early recurrence or death by 53% compared to the current standard of T-DM1," said Charles Geyer, MD, Chief Scientific Officer of the NSABP Foundation, Professor of Medicine at the UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania and Principal Investigator for the trial. "These results, coupled with the safety data from the trial, are likely to transform clinical practice in the post-neoadjuvant setting for patients with high-risk disease, with the potential for ENHERTU to set a new standard of care."

The safety profile of ENHERTU observed in DESTINY-Breast05 was consistent with its known profile with no new safety concerns identified. Grade 3 or higher treatment emergent adverse event (TEAE) rates were comparable between ENHERTU (50.6%) and T-DM1 (51.9%). The most common grade 3 or higher TEAEs occurring in 5% or more of patients treated with ENHERTU were decreased neutrophil count (15.5%), decreased white blood cell count (10.0%) and decreased platelet count (6.7%). Rates of interstitial lung disease (ILD) or pneumonitis were low in both arms with ILD events occurring in 9.6% of the ENHERTU arm and 1.6% of the T-DM1 arm. The majority of ILD or pneumonitis events were low grade (grade 1 [ENHERTU=16; 2.0%; T-DM1=8; 1.0%] or grade 2 [n=52; 6.5%; T-DM1=5; 0.6%]). There were no grade 3 or higher ILD or pneumonitis events for T-DM1. In the ENHERTU arm, there were seven grade 3 events (0.9%), zero grade 4 events and two grade 5 events (0.2%) as determined by an independent adjudication committee.

"The results of DESTINY-Breast05 demonstrate a clear benefit of ENHERTU over the current standard of care following surgery in patients with HER2 positive early breast cancer at high risk of recurrence after neoadjuvant treatment, improving their chance for sustained long-term outcomes," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "These results, coupled with the results of DESTINY-Breast11, illustrate the continued promise of ENHERTU to move earlier in the breast cancer treatment paradigm where it can have the greatest impact on the lives of patients."

"Progress in treating HER2 positive early breast cancer has been significant, yet managing patients at a higher-risk of recurrence remains challenging," said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology Hematology R&D, AstraZeneca. "These landmark data, alongside those from DESTINY-Breast11, underscore the potential of ENHERTU to become a foundational treatment in early-stage breast cancer, increasing the likelihood that more patients could be cured in this setting."

All patients in the DESTINY-Breast05 trial had received prior neoadjuvant chemotherapy and HER2 targeted therapy and the majority of patients received either concurrent (ENHERTU=53.5%; T-DM1=58.8%) or sequential (ENHERTU=39.9%; T-DM1=34.1%) radiotherapy treatment. The majority of patients were pathologic node positive following neoadjuvant treatment (ENHERTU=80.7%; T-DM1=80.5%). As of the data cut-off date of July 2, 2025, the median study duration was 29.9 months in the ENHERTU arm (range: 0.3-53.4) and 29.7 months in the T-DM1 arm (range: 0.1-54.4).

Summary of DESTINY-Breast05 Interim Analysis Results

Efficacy Measure	**ENHERTU (5.4 mg/kg) (n=818)**	**T-DM1 (n=817)**
IDFS [i,ii,iii,iv]		
HR (95% CI) = 0.47 (0.34-0.66); p<0.0001		
3-year IDFS % (95% CI)	92.4% (89.7-94.4)	83.7% (80.2-86.7)
Total IDFS events n (%)	51 (6.2)	102 (12.5)
Category of first IDFS event, n[iii]		
Distant recurrent CNS	17	25
Distant recurrence (non-CNS)	25	52
Local invasive recurrence	1	5
Regional recurrence	1	6
Contralateral invasive recurrence	0	6
Death without prior event	7	8
DFS [i,ii,v]		
HR (95% CI) = 0.47; (0.34-0.66); p<0.0001		
3-year DFS % (95% CI)	92.3% (89.5-94.3)	83.5% (79.9-86.4)
Total DFS events n (%)	52 (6.4)	103 (12.6)
DRFI [ii,vi]		
Patients with events (recurrence), n (%)	42 (5.1)	81 (9.9)
3-year event-free rate, % (95% CI)	93.9 (91.4-95.7)	86.1 (82.5-89.1)
HR (95% CI) = 0.49 (0.34-0.71)		
BMFI[ii,vii]		
Patients with events (recurrence), n (%)	17 (2.1)	26 (3.2)
3-year event-free rate, % (95% CI)	97.6 (96.2-98.5)	95.8 (93.6-97.2)
HR (95% CI) = 0.64 (0.35-1.17)		
OS[viii]		
Patients with events (deaths), n (%)	18 (2.2)	29 (3.5)
Survival at 3 years, % (95% CI)	97.4 (95.8-98.4)	95.7 (93.5-97.2)
HR (95% CI) = 0.61; (0.34-1.10)		

BMFI, brain-metastasis-free interval; CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hazard ratio; IDFS, invasive disease-free survival; OS, overall survival

[i] IDFS and DFS, the primary and key secondary efficacy endpoints, were statistically evaluated using the pre-specified hierarchical testing procedure.

[ii] Based on investigator assessment
[iii] IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence or death from any cause
[iv] Patients who experienced multiple types of IDFS events within 61 days after their first event are reported in the category according to the following hierarchy: distant recurrence CNS, distant recurrence non-CNS, local invasive recurrence, regional recurrence, contralateral breast cancer, death without a previous event
[v] DFS is defined as the time between randomization and the date of first occurrence of an IDFS event per STEEP criteria, including second primary non-breast cancer event or contralateral or ipsilateral ductal carcinoma *in situ* (DCIS)
[vi] DRFI is defined as the time between randomization and the date of distant breast cancer recurrence
[vii] BMFI is defined as the time between randomization and the date of documentation of brain metastases or leptomeningeal disease
[viii] OS was 2.9% mature at interim analysis

DESTINY-Breast05 was conducted in collaboration with the National Surgical Adjuvant Breast and Bowel Project Foundation (NSABP), the German Breast Group (GBG), Arbeitsgemeinschaft Gynäkologische Onkologie (AGO-B) and SOLTI Breast Cancer Research Group.

About DESTINY-Breast05

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

The primary endpoint of DESTINY-Breast05 is investigator-assessed IDFS. IDFS is defined as the time from randomization until first recurrence, distant recurrence or death from any cause. The key secondary endpoint is investigator-assessed DFS. Other secondary endpoints include OS, DRFI, BMFI and safety.

DESTINY-Breast05 enrolled 1,635 patients in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit ClinicalTrials.gov.

About Post Neoadjuvant HER2 Positive Early Breast Cancer

Breast cancer is the second most common cancer and one of the leading causes of cancer-related deaths worldwide.[1] More than two million breast cancer cases were diagnosed in 2022, with more than 665,000 deaths globally.[1]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast cancer.[2] HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease and poor prognosis in breast cancer.[2] Approximately one in five cases of breast cancer are considered HER2 positive.[3]

For patients with HER2 positive early breast cancer, achieving pCR with neoadjuvant treatment is the earliest indicator of improved long-term survival.[4] However, approximately half of patients who receive neoadjuvant treatment do not reach pCR and have poorer long-term outcomes, putting them at increased risk of disease recurrence.[4,5,6,7,8,9]

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

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

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 85 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (immunohistochemistry [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 85 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on the results from the DESTINY-Breast04 trial.

ENHERTU (5.4 mg/kg) is approved in more than 45 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic hormone receptor (HR) positive, HER2 low (IHC 1+ or IHC 2+/ ISH-) or HER2 ultralow (IHC 0 with membrane staining) breast cancer, as determined by a locally or

regionally approved test, that have progressed on one or more endocrine therapies in the metastatic setting based on the results from the DESTINY-Breast06 trial.

ENHERTU (5.4 mg/kg) is approved in more than 60 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 and/or DESTINY-Lung05 trials. Continued approval in China and the U.S. for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in more than 70 countries/regions worldwide for the treatment of adult patients with locally advanced or metastatic HER2 positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01, DESTINY-Gastric02 and/or DESTINY-Gastric06 trials. Continued approval in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (5.4 mg/kg) is approved in more than 10 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options based on efficacy results from the DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 trials. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

About the ENHERTU Clinical Development Program

A comprehensive global clinical development program is underway evaluating the efficacy and safety of ENHERTU as a monotherapy or in combination or sequentially with other cancer medicines across multiple HER2 targetable cancers.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in March 2019 and DATROWAY® in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of ENHERTU and DATROWAY.

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where 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. The DXd ADC portfolio currently consists of ENHERTU, a HER2 directed ADC, and DATROWAY, a TROP2 directed ADC, which 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, NJ, USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 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:
  - Hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by an FDA-approved test, that has progressed on one or more endocrine therapies in the metastatic setting
  - 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 (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

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

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 1 level. Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥0.5 mg/kg/day prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate systemic corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by gradual taper for at least 4 weeks.

<u>HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)</u>
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 0.9% of patients treated with ENHERTU.

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

Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated.

For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by 1 level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3º C or a sustained temperature of ≥38º C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by 1 level.

HER2-Positive, HER2-Low, and HER2-Ultralow 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 65% of patients. Nineteen percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 2 to 939). Febrile neutropenia was reported in 1.2% of patients.

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 20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of 20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

HER2-Positive, HER2-Low, and HER2-Ultralow Metastatic Breast Cancer, HER2-Mutant NSCLC, and Solid Tumors (Including IHC 3+) (5.4 mg/kg)
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 4.6% of patients, of which 0.6% were Grade 3 or 4.

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

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

Additional Dose Modifications
Thrombocytopenia
For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then reduce dose by 1 level.

Adverse Reactions

HER2-Positive, HER2-Low, and HER2-Ultralow 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 2233 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Breast06, DESTINY-Lung01, DESTINY-Lung02, DESTINY-CRC02, and DESTINY-PanTumor02. Among these patients, 67% were exposed for >6 months and 38% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (73%), nausea (72%), decreased hemoglobin (67%), decreased neutrophil count (65%), decreased lymphocyte count (60%), fatigue (55%), decreased platelet count (48%), increased aspartate aminotransferase (46%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (39%), vomiting (38%), alopecia (37%), constipation (32%), decreased blood potassium (32%), decreased appetite (31%), diarrhea (30%), and musculoskeletal pain (24%).

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 1 dose of ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast03. The median duration of treatment was 14 months (range: 0.7 to 30) for patients who received ENHERTU.

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

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (74%), decreased neutrophil count (70%), increased aspartate aminotransferase (67%), decreased hemoglobin (64%), decreased lymphocyte count (55%), increased alanine aminotransferase (53%), decreased platelet count (52%), fatigue (49%), vomiting (49%), increased blood alkaline phosphatase (49%), alopecia (37%), decreased blood potassium (35%), constipation (34%), musculoskeletal pain (31%), diarrhea (29%), decreased appetite (29%), headache (22%), respiratory infection (22%), abdominal pain (21%), increased blood bilirubin (20%), and stomatitis (20%).

HER2-Low and HER2-Ultralow Metastatic Breast Cancer

DESTINY-Breast06

The safety of ENHERTU was evaluated in 434 patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks in DESTINY-Breast06. The median duration of treatment was 11 months (range: 0.4 to 39.6) for patients who received ENHERTU.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were ILD/pneumonitis, COVID-19, febrile neutropenia, and hypokalemia. Fatalities due to adverse reactions occurred in 2.8% of patients including ILD (0.7%); sepsis (0.5%); and COVID-19 pneumonia, bacterial meningoencephalitis, neutropenic sepsis, peritonitis, cerebrovascular accident, general physical health deterioration (0.2% each).

ENHERTU was permanently discontinued in 14% of patients. The most frequent adverse reaction (>2%) associated with permanent discontinuation was ILD/pneumonitis. Dose interruptions due to adverse reactions occurred in 48% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were COVID-19, decreased neutrophil count, anemia, pyrexia, pneumonia, decreased white blood cell count, and ILD. Dose reductions occurred in 25% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were nausea, fatigue, decreased platelet count, and decreased neutrophil count.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (86%), decreased neutrophil count (75%), nausea (70%), decreased hemoglobin (69%), decreased lymphocyte count (66%), fatigue (53%), decreased platelet count (48%), alopecia (48%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (43%), increased aspartate aminotransferase (41%), decreased blood potassium (35%), diarrhea (34%), vomiting (34%), constipation (32%), decreased appetite (26%), COVID-19 (26%), and musculoskeletal pain (24%).

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

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

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

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

<u>HER2-Mutant Unresectable or Metastatic NSCLC (5.4 mg/kg)</u>
DESTINY-Lung02 evaluated 2 dose levels (5.4 mg/kg [n=101] and 6.4 mg/kg [n=50]); however, only the results for the recommended dose of 5.4 mg/kg intravenously every 3 weeks are described below due to increased toxicity observed with the higher dose in patients with NSCLC, including ILD/pneumonitis.

The safety of ENHERTU was evaluated in 101 patients with HER2-mutant unresectable or metastatic NSCLC who received ENHERTU 5.4 mg/kg intravenously once every 3 weeks until disease progression or unacceptable toxicity in DESTINY-Lung02. 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 1 dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in 1 patient each (0.8%).

ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, lymphopenia, upper respiratory tract infection, diarrhea, and decreased blood potassium. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

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

HER2-Positive (IHC 3+) Unresectable or Metastatic Solid Tumors

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

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

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

The most common (≥20%) adverse reactions, including laboratory abnormalities, were decreased white blood cell count (75%), nausea (69%), decreased hemoglobin (67%), decreased neutrophil count (66%), fatigue (59%), decreased lymphocyte count (58%), decreased platelet count (51%), increased aspartate aminotransferase (45%), increased alanine aminotransferase (44%), increased blood alkaline phosphatase (36%), vomiting (35%), decreased appetite (34%), alopecia (34%), diarrhea (31%), decreased blood potassium (29%), constipation (28%), decreased sodium (22%), stomatitis (20%), and upper respiratory tract infection (20%).

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 1741 patients with HER2-positive, HER2-low, or HER2-ultralow breast cancer treated with ENHERTU 5.4 mg/kg, 24% were ≥65 years and 4.9% 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 (61%) as compared to younger patients (52%). Of the 101 patients with HER2-mutant unresectable or metastatic NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥65 years and 8% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 125 patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 192 patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors treated with ENHERTU 5.4 mg/kg in DESTINY-PanTumor02, DESTINY-Lung01, or DESTINY-CRC02, 39% were ≥65 years and 9% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **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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