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Daiichi-Sankyo

Press Release

ENHERTU® Demonstrated Clinically Meaningful and Durable Responses in Patients Across Multiple HER2 Expressing Advanced Solid Tumors

- Daiichi Sankyo and AstraZeneca's ENHERTU showed an objective response rate of 37.1% in the overall population of the DESTINY-PanTumor02 phase 2 trial
- ENHERTU is the first therapy to show broad activity across HER2 expressing advanced solid tumors where there are currently no approved HER2 directed therapies
- DESTINY-CRC02 phase 2 trial also demonstrated positive antitumor activity and consistent safety in patients with previously treated HER2 positive metastatic colorectal cancer

Tokyo, Munich and Basking Ridge, NJ – (June 5, 2023) – Positive results from an interim analysis of the ongoing DESTINY-PanTumor02 phase 2 trial showed that ENHERTU® (trastuzumab deruxtecan) demonstrated clinically meaningful and durable responses across a broad range of HER2 expressing advanced solid tumors in previously treated patients. These results will be presented today as a late-breaking oral presentation (abstract #LBA3000) at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting.

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 trial, previously treated patients (n=267) with HER2 expressing advanced solid tumors including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic cancers or other tumors were treated with ENHERTU. The results showed a confirmed objective response rate (ORR) of 37.1% as assessed by investigator at an interim analysis. Complete response (CR) was achieved in 5.6% (n=15) of patients, 31.5% (n=84) achieved a partial response (PR) and 46.1% (n=123) had stable disease. The disease control rate (DCR) in the overall trial population was 68.2% as assessed by investigator at an interim analysis. The highest response rates were seen in patients with tumor HER2 expression of immunohistochemistry (IHC) 3+ as confirmed by central testing, where ENHERTU demonstrated a confirmed ORR of 61.3%.

Nearly half (49.6%) of all patients in DESTINY-PanTumor02 who achieved a response remained in response at one year. Median duration of response (DoR) was 11.8 months (95% confidence interval [CI]: 9.8-NE) in the overall trial population and 22.1 months (95% CI: 9.3-NE) in patients with IHC 3+ expression.

"The DESTINY-PanTumor02 data showed encouraging and durable response rates across a broad range of HER2 expressing solid tumors where there are currently no approved HER2 targeted treatments," said Funda Meric-Bernstam, MD, Chair of the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center and Principal Investigator for the trial. "Based on these results, ENHERTU has the potential to benefit specific patients with HER2 expressing advanced disease who currently have limited options and may face a poor prognosis."

The safety profile observed in DESTINY-PanTumor02 was consistent with previous clinical trials of ENHERTU with no new safety concerns identified. Grade 3 or higher treatment related treatment emergent adverse events (TEAEs) occurred in 38.6% of patients. The most common grade 3 or higher treatment related TEAEs occurring in ≥5% of patients were neutropenia (19.1%), anemia (8.6%), fatigue (6.0%) and thrombocytopenia (5.2%). In DESTINY-PanTumor02, 7.5% of patients experienced interstitial lung disease (ILD) or pneumonitis related to treatment with ENHERTU as determined by an independent adjudication committee. The majority of ILD or pneumonitis events were low grade (grade 1 or 2) with one grade 3 event, no grade 4 events and one grade 5 event observed.

"Nearly half of patients who achieved a response with ENHERTU as a late-line treatment for HER2 expressing advanced solid tumors in DESTINY-PanTumor02 remained in response at one year, demonstrating the potential of this important medicine to provide benefit to patients with hard-to-treat cancers in need of new options," said Mark Rutstein, MD, Global Head, Oncology Development, Daiichi Sankyo. "The results further reinforce the important role of antibody drug conjugates like ENHERTU to provide potential new solutions to advance current standards of care in areas of high unmet need and improve the outcomes of patients."

"While HER2 is an established biomarker in breast, gastric, lung and colorectal cancers, data from the DESTINY-PanTumor02 trial validate HER2 as an actionable biomarker across a broad range of tumor types," said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. "ENHERTU is the first treatment to demonstrate broad activity across HER2 expressing solid tumors where there are currently no approved HER2 directed therapies. These data will support our ongoing conversations with global health authorities as we look to bring ENHERTU to as many patients as possible."

In DESTINY-PanTumor02, patients had received a median of two prior cancer therapies (range: 0-13). Of the 267 patients that had received treatment, 75 were IHC 3+ and 125 were IHC 2+ as determined by central testing. As of data cut-off on November 16, 2022, 44 patients remained on treatment.

Summary of DESTINY-PanTumor02 Results

Efficacy Measure	All Patients	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other[i]
All IHC Expression Levels[ii]								
(N)	267	40	40	40	41	25	41	40
Confirmed ORR (%) (Investigator Assessed)	37.1%	50.0%	57.5%	45.0%	22.0%	4.0%	39.0%	30.0%
CR (%)	5.6% (n=15)	5.0% (n=2)	17.5% (n=7)	10.0% (n=4)	2.4% (n=1)	0% (n=0)	2.4% (n=1)	0% (n=0)
PR (%)	31.5% (n=84)	45.0% (n=18)	40.0% (n=16)	35.0% (n=14)	19.5% (n=8)	4.0% (n=1)	36.6% (n=15)	30.0% (n=12)
SD (%)	46.1% (n=123)	30.0% (n=12)	32.5% (n=13)	35.0% (n=14)	61.0% (n=25)	68.0% (n=17)	43.9% (n=18)	60.0% (n=24)
PD (%)	15.7% (n=42)	17.5% (n=7)	10.0% (n=4)	17.5% (n=7)	17.1% (n=7)	28.0% (n=7)	17.1% (n=7)	7.5% (n=3)
DCR[iii] at 12 weeks (%)	68.2% (n=182)	67.5% (n=27)	80.0% (n=32)	70.0% (n=28)	65.9% (n=27)	36.0% (n=9)	70.7% (n=29)	75.0% (n=30)
Median DoR, months (95% CI)	11.8 (9.8-NE)	9.8 (4.2-NE)	NR (9.9-NE)	11.3 (4.1-NE)	8.6 (2.1-NE)	NR	8.7 (4.3-11.8)	NR (4.1-NE)
IHC 3+[ii]								
(N)	75	8	13	11	16	2	16	9
Confirmed ORR (%)	61.3%	75.0%	84.6%	63.6%	56.3%	0.0%	56.3%	44.4%
IHC 2+[ii]								
(N)	125	20	17	19	14	19	20	16
Confirmed ORR (%)	27.2%	40.0%	47.1%	36.8%	0.0%	5.3%	35.0%	18.8%

BTC, biliary tract cancer; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; IHC, immunohistochemistry; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

[i]Responses in extramammary Paget disease, head and neck cancer, oropharyngeal neoplasm and salivary gland cancer

[ii]IHC based on central HER2 testing; 67 patients had IHC 1+ (n=25), IHC 0 (n=30) or unknown IHC status (n=12) by central testing

[iii]Confirmed complete response, confirmed partial response or stable disease

DESTINY-CRC02 Primary Results

Primary results from the DESTINY-CRC02 phase 2 trial, which evaluated ENHERTU at the 5.4 mg/kg and 6.4 mg/kg doses in patients with previously treated locally advanced, unresectable or metastatic HER2 positive (IHC 3+ or IHC 2+/*in-situ* hybridization [ISH]+) colorectal cancer of BRAF wild-type, RAS wild-type or RAS mutant tumor types, also were presented at ASCO.

Analysis of the primary endpoint showed that ENHERTU achieved a confirmed ORR of 37.8% (95% CI: 27.3-49.2) in patients treated with the 5.4 mg/kg dose (n=82) and 27.5% (95% CI: 14.6-43.9) in patients treated with the 6.4 mg/kg dose (n=40) as assessed by blinded independent central review (BICR). All responses were partial (n=31 [5.4 mg/kg]; n=11 [6.4 mg/kg]) with 48.8% of patients in the 5.4 mg/kg arm

and 57.5% of patients in the 6.4 mg/kg arm achieving stable disease. Greater efficacy was observed in patients with the highest levels of HER2 expression (IHC 3+) (46.9% ORR [95% CI: 34.3-59.8]) compared to those with IHC 2+/ISH+ HER2 status in the 5.4 mg/kg treatment arm (5.6% ORR [95% CI: 0.1-27.3]). Antitumor efficacy was observed regardless of RAS mutation status (39.7% ORR with RAS mutations; 28.6% ORR without RAS mutations) and in those with prior HER2 directed therapy (41.2% ORR) in the 5.4 mg/kg arm.

With a median duration of follow-up of 8.9 months and 10.3 months in the 5.4 mg/kg and 6.4 mg/kg arms respectively, ENHERTU also demonstrated a median DoR of 5.5 months in both the 5.4 mg/kg (95% CI: 4.2-8.1) and 6.4 mg/kg (95% CI: 3.7-NE) arms. Median progression-free survival (PFS) was 5.8 months (95% CI: 4.6-7.0) in the 5.4 mg/kg arm and 5.5 months (95% CI: 4.2-7.0) in the 6.4 mg/kg arm. Median overall survival (OS) was 13.4 months (95% CI: 12.5-16.8) in the 5.4 mg/kg arm and not reached (95% CI: 9.9-NE) in the 6.4 mg/kg arm.

The safety profile observed in DESTINY-CRC02 at the 5.4 mg/kg and 6.4 mg/kg dose levels was consistent with other clinical trials of ENHERTU, with no new safety signals identified at either dose. A more favorable benefit-risk profile was observed in patients treated with ENHERTU 5.4 mg/kg resulting in its selection as the recommended dose. Grade 3 or higher treatment related TEAEs were numerically higher with ENHERTU 6.4 mg/kg versus 5.4 mg/kg. Grade 3 or higher treatment related TEAEs occurred in 41.0% and 48.7% of patients receiving ENHERTU 5.4 mg/kg or 6.4 mg/kg, respectively. The most common grade 3 or higher TEAEs occurring in ≥10% of patients receiving ENHERTU were neutropenia (16.9% [5.4 mg/kg]; 28.2% [6.4 mg/kg]), anemia (9.6% [5.4 mg/kg]; 23.1% [6.4 mg/kg]) and thrombocytopenia (6.0% [5.4 mg/kg]; 12.8% [6.4 mg/kg]). There were 12 cases of treatment related ILD or pneumonitis reported as determined by an independent adjudication committee (8.4% [n=7/83] in the 5.4 mg/kg arm; 12.8% [n=5/39] in the 6.4 mg/kg arm). The majority of ILD or pneumonitis events (8.4% [5.4 mg/kg]; 10.2% [6.4 mg/kg]) were low grade (grade 1 or 2) with no grade 3, no grade 4 and one grade 5 event observed (2.6% [6.4 mg/kg]).

The results of DESTINY-CRC02 support 5.4 mg/kg as the optimal dose of ENHERTU monotherapy in patients with HER2 positive metastatic colorectal cancer.

About DESTINY-PanTumor02

DESTINY-PanTumor02 is a global, multicenter, multi-cohort, open-label phase 2 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) for the treatment of previously treated HER2 expressing tumors, including biliary tract cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer and other tumors. The primary efficacy endpoint of DESTINY-PanTumor02 is confirmed ORR as assessed by investigator. Secondary endpoints include DoR, DCR, PFS, OS, safety, tolerability and

pharmacokinetics. DESTINY-PanTumor02 has enrolled 267 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-CRC02

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

About HER2 Expression in Solid Tumors

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of various tissue cells throughout the body and is involved in normal cell growth.[1,2] In some cancers, HER2 expression is amplified or the cells have activating mutations.[1,3] HER2 protein overexpression may occur as a result of *HER2* gene amplification and is often associated with aggressive disease and poor prognosis.[4]

While HER2 directed therapies have been used to treat breast, gastric, lung and colorectal cancers, more research is needed evaluating their potential role in treating other HER2 expressing tumor types.[2,5,6]

HER2 is an emerging biomarker in biliary tract, bladder, cervical, endometrial, ovarian and pancreatic cancers.[3] Testing is not routinely performed in these additional tumor types and as a result, available literature is limited. HER2 overexpression (IHC 3+) has been observed at rates from 1% to 28% in these solid tumors.[7,8] There is an unmet need for effective therapies for certain HER2 expressing solid tumors, particularly for those who have progressed on or are refractory to standard of care therapies as there are currently no approved HER2 directed therapies for these cancers.[2,9]

Colorectal cancer is the third most common and second most common cause of cancer deaths worldwide with more than 1.9 million patients diagnosed and more than 935,000 deaths globally in 2020.[10] Approximately 25% of patients have metastatic disease at diagnosis, meaning the disease has spread to distant organs and about 50% of patients with colorectal cancer will eventually develop metastases.[11] For patients with metastatic disease, approximately 2% to 3% are HER2 overexpressing.[6,12]

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 50 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 (5.4 mg/kg) is approved in more than 40 countries for the treatment of adult patients with unresectable or metastatic HER2 low (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 in Israel and under accelerated approval in the U.S. for the treatment of adult patients with 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 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 30 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 and/or DESTINY-Gastric02 trials.

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. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

About the Daiichi Sankyo and AstraZeneca Collaboration

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

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of five ADCs in clinical development across multiple types of cancer. The company's clinical trial stage DXd ADCs include ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca; and patritumab deruxtecan (HER3-DXd), a HER3 directed ADC. Two additional ADCs including ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd; DS-6000), a CDH6 directed ADC, are being developed through a strategic early-stage research collaboration with Sarah Cannon Research Institute.

Designed using Daiichi Sankyo's proprietary DXd ADC technology, each ADC targets and delivers 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 and raludotatug deruxtecan 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 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 17,000 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.

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