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Daiichi-Sankyo

Press Release

ENHERTU® Continues to Demonstrate Clinically Meaningful Tumor Response in Patients with *HER2* Mutant Metastatic Non-Small Cell Lung Cancer

- DESTINY-Lung02 phase 2 trial shows clinically meaningful efficacy and favorable safety at 5.4 mg/kg dose versus 6.4 mg/kg dose of Daiichi Sankyo and AstraZeneca's ENHERTU in *HER2* mutant disease
- Updated results from DESTINY-Lung01 phase 2 trial demonstrate continued durable activity across patient subtypes

Tokyo and Basking Ridge, NJ – (September 11, 2022) – Detailed positive results from an interim analysis of the DESTINY-Lung02 phase 2 trial showed ENHERTU® (trastuzumab deruxtecan) demonstrated clinically meaningful tumor responses in previously treated patients with *HER2* mutant unresectable and/or metastatic non-squamous non-small cell lung cancer (NSCLC). Results will be presented today as a late breaking presentation (LBA55) at the European Society for Medical Oncology (#ESMO22) 2022 Congress.

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).

At a pre-specified interim analysis of DESTINY-Lung02, with a data cutoff of March 24, 2022, patients receiving ENHERTU at a dose of 5.4 mg/kg (n=52) or 6.4 mg/kg (n=28) demonstrated clinically meaningful activity. The safety profile for both doses also was consistent with the overall safety profile of ENHERTU with the 5.4 mg/kg dose demonstrating a favorable safety profile in this patient population. A confirmed objective response rate (ORR) of 53.8% (95% confidence interval [CI], 39.5-67.8) and 42.9% (95% CI, 24.5-62.8) was seen in the 5.4 mg/kg and 6.4 mg/kg arms, respectively, as assessed by blinded independent central review (BICR). One complete response (CR) was observed in each arm (5.4 mg/kg: 1.9%, 6.4 mg/kg: 3.6%) with 27 (51.9%) partial responses (PR) observed in the 5.4 mg/kg arm and 11 (39.3%) PRs observed in the 6.4 mg/kg arm. At the pre-specified interim analysis, a median duration of response (DoR) was not reached in the 5.4 mg/kg arm and a median DoR of 5.9 months (95% CI: 2.8-NE) was seen in the 6.4 mg/kg arm. As median DoR was not reached in the 5.4 mg/kg arm, an additional 90-day follow-up response analysis was conducted, with a data cutoff of June 22, 2022, where ENHERTU demonstrated a confirmed ORR of 57.7% (95% CI, 43.2-71.3) and a median DoR of 8.7 months (95% CI: 7.1-NE) with CRs seen in 1.9% of patients and PRs in 55.8% of patients.

“DESTINY-Lung02 reinforces *HER2* as an actionable mutation in patients with metastatic non-small cell lung cancer and further demonstrates that ENHERTU provides a clinically meaningful tumor response for these patients who have historically had limited treatment options,” said Koichi Goto, MD, Medical Oncologist and Investigator at National Cancer Center Hospital East, Kashiwa, Japan. “The response seen in this trial along with the disease control observed support ENHERTU as a potential treatment option in this type of non-small cell lung cancer.”

In DESTINY-Lung02, a favorable safety profile was observed in patients treated with ENHERTU 5.4 mg/kg with no new safety signals identified at either dose. Grade 3 treatment-emergent adverse events (TEAEs) were higher with ENHERTU 6.4 mg/kg versus 5.4 mg/kg (n=151). Grade 3 or higher treatment-related TEAEs occurred in 31.7% and 58.0% of all patients receiving ENHERTU 5.4 mg/kg or 6.4 mg/kg, respectively. The most common grade 3 or higher treatment-related TEAEs occurring in >10% of patients were neutropenia (11.9% (5.4 mg/kg), 34.0% (6.4 mg/kg)), anemia (8.9% (5.4 mg/kg), 14.0% (6.4 mg/kg)) and leukopenia (2.0% (5.4 mg/kg), 14.0% (6.4 mg/kg)). There were 13 cases (5.9% in the 5.4 mg/kg arm and 14% in the 6.4 mg/kg arm) of treatment-related ILD or pneumonitis reported as determined by an independent adjudication committee. The majority (5.4 mg/kg: 5.0%, 6.4 mg/kg: 14.0%) were low grade (grade 1 or 2), with one grade 3 event (5.4 mg/kg: 1.0%) reported. No grade 4 or grade 5 ILD or pneumonitis events occurred.

“The DESTINY-Lung02 results are consistent with the data previously seen with ENHERTU in non-small cell lung cancer and the efficacy demonstrated in this interim analysis, which supported the recent U.S. FDA accelerated approval of ENHERTU in patients with *HER2* mutant non-small cell lung cancer, reinforces the potential to establish this medicine as a treatment option for these patients,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “These data will help inform future regulatory submissions worldwide with the goal of continuing to offer this innovative medicine to as many patients as possible.”

“The clinically meaningful activity, together with the favorable safety profile seen in the DESTINY-Lung02 trial helps establish the optimal dose of ENHERTU at 5.4 milligrams per kilogram in previously treated *HER2* mutant non-small cell lung cancer,” said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. “As we continue to explore the potential of this important medicine across multiple HER2 targetable tumor types, these data reaffirm the need to undertake HER2 testing in patients diagnosed with lung cancer.”

All patients in DESTINY-Lung02 received at least one prior cancer therapy, including platinum-based chemotherapy. In the pre-specified early cohort, 71.2% and 78.6% of patients received prior anti-PD-1 therapy in the 5.4 mg/kg and 6.4 mg/kg arms, respectively. Median follow-up was 5.6 months (1.1-11.7) in the 5.4 mg/kg arm and 5.4 months (0.6-12.1) in the 6.4 mg/kg arm.

Summary of DESTINY-Lung02 Results

Efficacy Measure	ENHERTU (5.4 mg/kg) n=52	ENHERTU (5.4 mg/kg) n=52 Additional 90-day Follow-up[i]	ENHERTU (6.4 mg/kg) n=28
Confirmed ORR (%) (95% CI)[ii,iii]	53.8% (39.5-67.8)	57.7% (43.2-71.3)	42.9% (24.5-62.8)
CR (%)	1.9%	1.9%	3.6%
PR (%)	51.9%	55.8%	39.3%
SD (%)	36.5%		50.0%
PD (%)	3.8%		3.6%
NE (%)[iv]	5.8%		3.6%
DCR (95% CI) [ii,v]	90.4% (79.0-96.8)		92.9% (76.5-99.1)
Median DoR (months) (95% CI)[ii]	NE (4.2-NE)	8.7 (7.1-NE)	5.9 (2.8-NE)
Median TTIR (months) (95% CI)	1.4 (1.2-5.8)		1.4 (1.2-3.0)

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTIR, time to initial response
Data from subset of patients randomized ≥4.5 months prior to the data cut-off

[i] As the median DoR for the 5.4 mg/kg dose arm was not reached at the March 24, 2022 cutoff, an additional 90-day follow-up response analysis was conducted; data cutoff for the 90-day follow-up was June 22, 2022

[ii] As assessed by blinded independent central review

[iii] ORR is (CR + PR)

[iv] Three patients were NE at 5.4 mg/kg (one patient never received treatment due to COVID; two patients discontinued before first tumor assessment); one NE at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment).

[v] DCR is (CR + PR + SD)

DESTINY-Lung01 Updated Results

Updated results from the DESTINY-Lung01 phase 2 trial, which evaluated ENHERTU in *HER2* mutant (cohort 2) or HER2 overexpressing (cohort 1 and cohort 1a) NSCLC, also were presented at ESMO and showed that ENHERTU continues to demonstrate consistent efficacy, safety and survival with longer follow-up.

After a median follow-up of 16.7 months, results of previously-treated patients with *HER2* mutant NSCLC (cohort 2) showed the median duration of response (DoR) for ENHERTU in the overall patient population increased to 10.6 months (95% CI: 5.6-18.3) with median overall survival (OS) increasing to 18.6 months (95% CI: 13.8-25.8). Subgroup analyses of patients with or without a presence of baseline asymptomatic brain metastases showed that treatment with ENHERTU resulted in a median PFS of 7.1 months (95% CI: 5.5-9.8) and 9.7 months (95% CI: 4.5-16.9), respectively and a median OS of 14.0 months (95% CI: 9.8-19.5) and 27.0 months (95% CI: 15.3-NE), respectively. The subgroup analysis of patients who had received either two or fewer prior therapies or more than two prior therapies showed a median PFS of 8.3 months (95% CI: 5.8-15.2) and 6.8 months (95% CI: 4.4-9.8), respectively and a median OS of 22.1 months (95% CI: 14.0-31.3) and 13.8 months (95% CI: 7.1-18.6), respectively.

Additionally, updated results from cohort 1 (ENHERTU 6.4 mg/kg; n=49) and cohort 1a (ENHERTU 5.4 mg/kg; n=41), which evaluated patients with previously-treated metastatic HER2 overexpressing NSCLC, highlight encouraging anti-tumor activity. At the data cutoff of December 3, 2021, in cohort 1, a confirmed ORR of 26.5% (95% CI: 15.0-41.1) was seen in patients receiving ENHERTU 6.4 mg/kg with a median PFS of 5.7 months (95% CI: 2.8-7.2) and a median OS of 12.4 months (95% CI: 7.8-17.2). In cohort 1a, a confirmed ORR of 34.1% (95% CI: 20.1-50.6) was seen in patients receiving ENHERTU 5.4 mg/kg, with a median PFS of 6.7 months (95% CI: 4.2-8.4) and a median OS of 11.2 months (95% CI: 8.4-NE). Median duration of follow-up was 12.0 months (95% CI: 0.4-36.0) and 10.6 months (95% CI: 0.6-16.9) in the 6.4 mg/kg and 5.4 mg/kg treatment groups, respectively.

The overall safety profile of ENHERTU in DESTINY-Lung01 was consistent with previous data, with no new safety signals identified with the longer follow-up. In the *HER2* mutant NSCLC patient cohort, there was one additional case of treatment-related ILD or pneumonitis observed, as determined by an independent adjudication committee. ILD has been observed in 27.5% of patients treated with ENHERTU 6.4 mg/kg in the *HER2* mutant cohort with the majority identified as low-grade and two grade 5 events occurring. In the HER2 overexpressing NSCLC patient cohorts, there were two additional cases of treatment-related ILD or pneumonitis observed in the 6.4 mg/kg dose arm and two cases observed in the 5.4 mg/kg dose cohort, as determined by an independent adjudication committee. ILD has been observed in 20.4% and 4.9% of patients treated with ENHERTU at the 6.4 mg/kg and 5.4 mg/kg doses, respectively, in the HER2 overexpressing cohort with the majority identified as low-grade and four grade 5 events occurring. Data from the DESTINY-Lung01 phase 2 trial were previously published in *The New England Journal of Medicine*.

ENHERTU is not approved outside the U.S. for the treatment of patients with metastatic *HER2* mutant NSCLC.

About DESTINY-Lung02

DESTINY-Lung02 is a global, randomized phase 2 trial evaluating the safety and efficacy of ENHERTU in patients with *HER2* mutant metastatic NSCLC with disease recurrence or progression during or after at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy. Patients were randomized 2:1 to receive ENHERTU 5.4 mg/kg (Cohort 1; n=102) or ENHERTU 6.4 mg/kg (Cohort 2; n=50). The primary endpoint of the study is confirmed ORR as assessed by BICR. Secondary endpoints include confirmed disease control rate (DCR), DoR and PFS assessed by investigator and BICR, investigator-assessed OS and safety. DESTINY-Lung02 enrolled 152 patients at multiple sites, including Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Lung01

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

About *HER2* Mutant and HER2 Overexpressing NSCLC

Lung cancer is the second most common form of cancer globally, with more than two million patients diagnosed in 2020.[1] For patients with metastatic NSCLC, prognosis is particularly poor, as only approximately 8% will live beyond five years after diagnosis.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including lung, breast, gastric and colorectal cancers. Certain *HER2 (ERBB2)* gene alterations (called *HER2* mutations) have been identified in patients with non-squamous NSCLC as a distinct molecular target, and occur in approximately 2 to 4% of patients with this type of lung cancer.[3,4] While *HER2* gene mutations can occur in a range of patients, they are more commonly found in patients with NSCLC who are younger, female and have never smoked.[5] *HER2* gene mutations have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[6]

Although the role of anti-HER2 treatment is well established in breast and gastric cancers, there were no approved HER2 directed therapies in NSCLC prior to the accelerated U.S. FDA approval of ENHERTU in unresectable or metastatic *HER2* mutant NSCLC.[7] Next-generation sequencing has been utilized in the identification of *HER2* (*ERBB2*) mutations.[8]

HER2 overexpression is associated with a specific HER2 gene alteration known as HER2 amplification and is often associated with aggressive disease and poorer prognosis.[9] It has been reported in approximately 10% to 15% of patients with NSCLC, with an incidence as high as 30% in those with adenocarcinoma (a subtype of cancer that grows in the glands that line the insides of organs).[10,11,12,13]

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

ENHERTU (5.4 mg/kg) is approved in more than 30 countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a (or one or more) prior anti-HER2-based regimen, either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within six months of completing therapy based on the results from the DESTINY-Breast03 trial. ENHERTU also is approved in several countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast01 trial.

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

ENHERTU (5.4 mg/kg) is approved under accelerated approval in the U.S. for the treatment of adult patients with unresectable or metastatic 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 for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in several countries for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 trial.

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

About the ENHERTU Clinical Development Program

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

Regulatory applications for ENHERTU in breast and gastric cancer are currently under review in several countries based on the DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, DESTINY-Gastric01 and DESTINY-Gastric02 trials, respectively.

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.

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 who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

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

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

- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.**

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

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

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

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

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

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

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. For Grade 3 neutropenia (Absolute Neutrophil Count [ANC] <1.0 to 0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC <0.5 x 10^9/L), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3º C or a sustained temperature of ≥38º C for more than 1 hour), interrupt ENHERTU until resolved, then reduce dose by one level.

Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)

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

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

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

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt

ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

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

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

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

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

Adverse Reactions
Metastatic Breast Cancer and HER2-Mutant NSCLC (5.4 mg/kg)
The pooled safety population reflects exposure to ENHERTU 5.4 mg/kg intravenously every 3 weeks in 984 patients in Study DS8201-A-J101 (NCT02564900), DESTINY-Breast01, DESTINY-Breast03, DESTINY-Breast04, and DESTINY-Lung02. Among these patients 65% were exposed for >6 months and 39% were exposed for >1 year. In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (76%), decreased white blood cell count (71%), decreased hemoglobin (66%), decreased neutrophil count (65%), decreased lymphocyte count (55%), fatigue (54%), decreased platelet count (47%), increased aspartate aminotransferase (48%), vomiting (44%), increased alanine aminotransferase (42%), alopecia (39%), increased blood alkaline phosphatase (39%), constipation (34%), musculoskeletal pain (32%), decreased appetite (32%), hypokalemia (28%), diarrhea (28%), and respiratory infection (24%).

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

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and

urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

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

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

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

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

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

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

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

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

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

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

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

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

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

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

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg every 3 weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) for patients who received ENHERTU.

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

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

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

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months after the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse

reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for 7 months after the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 883 patients with breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 3.6% were ≥75 years. No overall differences in efficacy within clinical studies were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (60%) as compared to younger patients (48%). Of the 101 patients with unresectable or metastatic HER2-mutant NSCLC treated with ENHERTU 5.4 mg/kg, 40% were ≥65 years and 8% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients. Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **Renal Impairment:** A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Monitor patients with moderate renal impairment more frequently. The recommended dosage of ENHERTU has not been established for patients with severe renal impairment (CLcr <30 mL/min).
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. The recommended dosage of ENHERTU has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

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

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

About Daiichi Sankyo

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

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