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Daiichi-Sankyo

Press Release

ENHERTU® Demonstrated Strong and Durable Tumor Responses in Previously Treated *HER2* Mutant Advanced Lung Cancer in DESTINY-Lung02 Phase 2 Trial

- Daiichi Sankyo and AstraZeneca's ENHERTU showed objective response rates of 49% and 56% with 5.4 mg/kg and 6.4 mg/kg doses, respectively, in primary analysis
- ENHERTU provided a median progression free survival of 9.9 months at 5.4 mg/kg dose and 15.4 months at 6.4 mg/kg dose with a median duration of response of 16.8 months seen at the 5.4 mg/kg dose and not reached at the 6.4 mg/kg dose
- Favorable safety profile confirms 5.4 mg/kg as optimal dose in this tumor type and reinforces role of ENHERTU in this setting

Tokyo, Munich and Basking Ridge, NJ – (September 11, 2023) – Results from the primary analysis of the DESTINY-Lung02 phase 2 trial showed ENHERTU® (trastuzumab deruxtecan) continued to demonstrate strong and durable tumor responses in previously treated patients with *HER2* mutant unresectable and/or metastatic non-squamous non-small cell lung cancer (NSCLC). These results, along with the first report on progression-free survival (PFS) and overall survival (OS), were presented today (MA 13.10) at the IASLC 2023 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer (#WCLC23) and simultaneously published in the *Journal of Clinical Oncology*.

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 the primary analysis, a confirmed objective response rate (ORR) of 49.0% (95% confidence interval [CI]: 39.0-59.1) in the 5.4 mg/kg arm and 56.0% (95% CI: 41.3-70.0) in the 6.4 mg/kg arm was observed as assessed by blinded independent central review (BICR). One (1.0%) complete response (CR) and 49 (48.0%) partial responses (PR) were observed in the 5.4 mg/kg arm and two (4.0%) CRs and 26 (52.0%) PRs were observed in the 6.4 mg/kg arm. The disease control rate (DCR) was 93.1% (95% CI: 86.4-97.2) at the 5.4 mg/kg dose and 92.0% (95% CI: 80.8-97.8) at the 6.4 mg/kg dose. The median duration of response (DoR) was 16.8 months (95% CI: 6.4-not estimable [NE]) in the 5.4 mg/kg arm and was not reached in the 6.4 mg/kg arm (95% CI: 8.3-NE).

Median PFS as assessed by BICR was 9.9 months (95% CI: 7.4-NE) in the 5.4 mg/kg arm and 15.4 months (95% CI: 8.3-NE) in the 6.4 mg/kg arm. Median OS was 19.5 months (95% CI: 13.6-NE) in the 5.4 mg/kg

arm and not reached (95% CI: 12.1-NE) in the 6.4 mg/kg arm. Median follow-up was 11.5 months in the 5.4 mg/kg arm (n=102) and 11.8 months in the 6.4 mg/kg arm (n=50) at time of data cutoff of December 23, 2022.

“The primary results from DESTINY-Lung02 demonstrate that ENHERTU continues to show strong and durable tumor responses for patients treated at either dose,” said Pasi A. Jänne, MD, PhD, Director, Lowe Center for Thoracic Oncology and Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute. “The favorable safety profile seen at the 5.4 mg/kg dose continues to support the use of ENHERTU in the treatment of patients with *HER2* mutant non-small cell lung cancer, a particularly aggressive form of the disease where patients face a poor prognosis and have historically had few options.”

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 or higher treatment-related treatment emergent adverse events (TEAEs) were lower with ENHERTU 5.4 mg/kg versus 6.4 mg/kg. Grade 3 or higher treatment-related TEAEs occurred in 38.6% 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 TEAEs were neutropenia (18.8% [5.4 mg/kg]; 36.0% [6.4 mg/kg]) and anemia (10.9% [5.4 mg/kg]; 16.0% [6.4 mg/kg]). There were 27 cases of treatment-related interstitial lung disease (ILD) or pneumonitis reported as determined by an independent adjudication committee (12.9% [n=13/101] in the 5.4 mg/kg arm; 28.0% [n=14/50] in the 6.4 mg/kg arm). In the 5.4 mg/kg arm, the majority of ILD cases were low grade (grade 1 or 2 [10.9%; four grade 1 and seven grade 2 events]) with one grade 3 event, zero grade 4 events and one grade 5 event observed. In the 6.4 mg/kg arm, the majority of ILD cases were low grade (grade 1 or 2 [26.0%; four grade 1 and nine grade 2 events]) with zero grade 3 events, zero grade 4 events and one grade 5 event observed.

“The disease control achieved by more than 90% of patients with previously treated *HER2* mutant non-small cell lung cancer in the primary analysis of DESTINY-Lung02 reinforces the efficacy we have already seen with ENHERTU in this hard-to-treat disease,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “These results, along with encouraging progression-free survival and overall survival findings reported for the first time, demonstrate the potential role of ENHERTU as an important treatment option for this patient population.”

“These results from DESTINY-Lung02 highlight that HER2 is an actionable target in lung cancer and reinforce the importance of testing for predictive biomarkers, including HER2 alterations in lung cancer, at the time of diagnosis to accurately identify patients who may be able to benefit from a targeted treatment,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “The data also reaffirm our belief in ENHERTU as a potential new targeted treatment option for patients who have historically had limited options.”

Patients in the DESTINY-Lung02 trial received a median of two prior cancer therapies in each ENHERTU arm (5.4 mg/kg: range 1-12; 6.4 mg/kg: range 1-7). *HER2* mutations were primarily in the kinase domain (5.4 mg/kg: 97.1%; 6.4 mg/kg: 100%). Baseline central nervous system metastases were present in 34.3% of patients in the 5.4 mg/kg arm and 44.0% of patients in the 6.4 mg/kg arm. Median follow-up was 11.5 months (range 1.1-20.6) in the 5.4 mg/kg arm and 11.8 months (range 0.6-21.0) in the 6.4 mg/kg arm.

Summary of DESTINY-Lung02 Primary Analysis Results

Efficacy Measure	**ENHERTU (5.4 mg/kg) n=102[i]**	**ENHERTU (6.4 mg/kg) n=50[i]**
Confirmed ORR (%) (95% CI)[ii,iii]	49.0% (39.0-59.1)	56.0% (41.3-70.0)
CR (%)	1.0%	4.0%
PR (%)	48.0%	52.0%
SD (%)	44.1%	36.0%
PD (%)	3.9%	4.0%
NE (%)[iv]	2.9%	4.0%
DCR (95% CI) [v, vi]	93.1% (86.4-97.2)	92.0% (80.8-97.8)
Median DoR (months) (95% CI)[vi, vii]	16.8 months (6.4-NE)	NE (8.3-NE)
Median TTIR (months)[vi]	1.8 months (1.2-7.0)	1.6 months (1.2-11.2)
Median PFS (months) (95% CI)[vi, viii]	9.9 months (7.4-NE)	15.4 months (8.3-NE)
Median OS (months) (95% CI)[vi, ix]	19.5 months (13.6-NE)	NE (12.1-NE)

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTIR, time to initial response

[i] Data cut-off: As of December 23, 2022

[ii] Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1

[iii] ORR is (CR + PR)

[iv] Three patients were NE at 5.4 mg/kg (one patient never received treatment due to COVID-19; two patients discontinued before first tumor assessment); two patients were NE at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment)

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

[vi] As assessed by BICR

[vii] 60.0% and 75.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms, respectively, were censored

[viii] 56.9% and 60.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms, respectively, were censored

[ix] 63.7% and 72.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms, respectively, were censored

About DESTINY-Lung02

DESTINY-Lung02 is a global, randomized phase 2 trial evaluating the safety and efficacy of ENHERTU in patients with *HER2* mutant unresectable and/or 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 (n=102) or ENHERTU 6.4 mg/kg (n=50).

The primary endpoint of the trial is confirmed ORR as assessed by BICR. Secondary endpoints include DCR, DoR and PFS assessed by investigator and BICR, OS and safety. DESTINY-Lung02 enrolled 152

patients at multiple sites, including Asia, Europe, Oceania and North America. For more information about the trial, visit ClinicalTrials.gov.

About *HER2* Mutant NSCLC

Lung cancer is the second most common form of cancer globally, with more than two million cases diagnosed in 2020.[1] Prognosis is particularly poor for patients with metastatic NSCLC as only approximately 9% 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] Next-generation sequencing has been utilized in the identification of *HER2* (*ERBB2*) mutations.[7,8]

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 approvals of ENHERTU by the Israel Ministry of Health (MOH) Pharmaceutical Division, the Japan Ministry of Health, Labour and Welfare and the accelerated U.S. Food and Drug Administration (FDA) approval in unresectable or metastatic *HER2* mutant NSCLC.[9]

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 worldwide 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 worldwide 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, Japan and under accelerated approval in the U.S. for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 trial. Continued approval for this indication in the U.S. 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 worldwide 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 clinical development program is underway evaluating the efficacy and safety of ENHERTU monotherapy across multiple HER2 targetable cancers. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in March 2019 and datopotamab deruxtecan (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 six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, are being jointly developed and commercialized globally with AstraZeneca. Four additional Daiichi Sankyo DXd ADCs include patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, raludotatug deruxtecan (R-DXd; DS-6000), a CDH6 directed ADC, and DS-3939, a TA-MUC1 directed ADC.

Designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan and DS-3939 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

ENHERTU U.S. Important Safety Information

Indications

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable or metastatic HER2-positive 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 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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