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Daiichi-Sankyo

Press Release

ENHERTU® Granted Priority Review in the U.S. for Patients with Previously Treated *HER2* Mutant Metastatic Non-Small Cell Lung Cancer

- Based on pivotal DESTINY-Lung01 results showing Daiichi Sankyo and AstraZeneca's ENHERTU demonstrated a 54.9% tumor response rate
- If approved, ENHERTU to provide patients with a much-needed targeted therapy option

Tokyo and Basking Ridge, NJ – (April 19, 2022) – Daiichi Sankyo (TSE: 4568) and AstraZeneca (LSE/STO/Nasdaq: AZN) have received notification of acceptance of the supplemental Biologics License Application (sBLA) of ENHERTU® (fam-trastuzumab deruxtecan-nxki) for the treatment of adult patients in the U.S. with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have a *HER2* (*ERBB2*) mutation and who have received a prior systemic therapy. The application has also been granted Priority Review.

ENHERTU is a HER2 directed antibody drug conjugate (ADC) being jointly developed by Daiichi Sankyo and AstraZeneca.

The U.S. Food and Drug Administration (FDA) grants Priority Review to applications for medicines that, if approved, would offer significant improvements over available options by demonstrating safety or efficacy improvements, preventing serious conditions or enhancing patient compliance. The Prescription Drug User Fee Act (PDUFA) date, the FDA action date for their regulatory decision, is during the third quarter of the 2022 calendar year. The Priority Review follows receipt of Breakthrough Therapy Designation, granted by the FDA in May 2020 for ENHERTU in this cancer type.

Lung cancer is the second most common form of cancer globally, with more than two million new cases 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] There are currently no HER2 directed therapies approved specifically for the treatment of *HER2* mutant NSCLC, which occurs in approximately 2% to 4% of patients with non-squamous NSCLC.[3,4]

"The results of DESTINY-Lung-01 showed that ENHERTU is the first HER2 directed therapy to demonstrate a strong and robust tumor response in more than half of patients with previously treated *HER2*

mutant metastatic non-small cell lung cancer," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "Seeking approval in the U.S. for a third tumor type in three years further demonstrates the significant potential of ENHERTU in treating multiple HER2 targetable cancers."

"The DESTINY-Lung01 trial confirmed the *HER2* mutation as an actionable biomarker in non-small cell lung cancer," said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "If approved, ENHERTU has the potential to become a new standard treatment in this patient population, offering a much-needed option for patients with *HER2* mutant metastatic non-small cell lung cancer who currently have no targeted treatment options."

The sBLA is based on data from the pivotal DESTINY-Lung01 phase 2 trial published in *The New England Journal of Medicine*, and is supported by the phase 1 trial (DS8201-A-J101) published in *Cancer Discovery*.

Primary results from the *HER2* mutant cohort (cohort 2) of DESTINY-Lung01 in previously-treated *HER2* mutant NSCLC demonstrated a confirmed objective response rate (ORR) of 54.9% (n=50; 95% confidence interval [CI]: 44.2-65.4) in patients treated with ENHERTU (6.4 mg/kg) as assessed by independent central review (ICR). Out of a total of 91 patients, one (1.1%) complete response (CR) and 49 (53.8%) partial responses (PR) were observed. A confirmed disease control rate (DCR) of 92.3% (95% CI: 84.8-96.9) was seen with a reduction in tumor size observed in most patients. After a median follow-up of 13.1 months, the median duration of response (DoR) for ENHERTU was 9.3 months (95% CI: 5.7-14.7). The median progression-free survival (PFS) was 8.2 months (95% CI: 6.0-11.9) and the median overall survival (OS) was 17.8 months (95% CI: 13.8-22.1).

The safety profile of the most common adverse events with ENHERTU in DESTINY-Lung01 was consistent with previous clinical trials. The most common grade 3 or higher drug-related treatment-emergent adverse events were neutropenia (18.7%), anemia (9.9%), nausea (8.8%), fatigue (6.6%), leukopenia (4.4%), diarrhea (3.3%) and vomiting (3.3%). Twenty-three patients (25%) discontinued treatment due to drug-related treatment-emergent adverse events. Overall, 26% of patients had interstitial lung disease (ILD) or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD events (75%) were low grade (grade 1 (12.5%) or grade 2 (62.5%)). Out of the total study population, four grade 3 (4.4%) and two grade 5 (2.2%) ILD or pneumonitis events were reported.

About DESTINY-Lung01

DESTINY-Lung01 is a global phase 2, open-label, two-cohort trial evaluating the efficacy and safety of ENHERTU in patients with *HER2* mutant (6.4 mg/kg) or HER2 overexpressing (defined as IHC3+ or

IHC2+) [6.4 mg/kg and 5.4 mg/kg] unresectable and/or metastatic non-squamous NSCLC who had progressed after one or more systemic therapies. The primary endpoint is confirmed ORR by ICR. Key secondary endpoints include DoR, DCR, PFS, OS and safety. DESTINY-Lung01 enrolled approximately 180 patients at multiple sites, including Asia, Europe 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 new cases diagnosed in 2020.[1] In the U.S., lung cancer is the second most commonly diagnosed cancer, with more than 236,000 new cases expected in 2022.[5] 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* gene alterations (called *HER2* mutations) have been identified in NSCLC as distinct molecular targets and have been reported in approximately 2% to 4% of patients with non-squamous NSCLC.[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.[6] *HER2* gene mutations have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[7] Although the role of anti-HER2 treatment is well established in breast and gastric cancers, HER2 is an emerging biomarker in NSCLC with no approved HER2 directed therapies.[3,8] Next-generation sequencing has been utilized in the identification of *HER2* (*ERBB2*) mutations.[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 40 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 (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 are currently under review in Europe, Japan, U.S. and several other countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a prior anti-HER2-based regimen based on the results from the DESTINY-Breast03 trial.

ENHERTU also is currently under review in Europe for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or GEJ adenocarcinoma who have received a prior anti-HER2 based regimen based on the DESTINY-Gastric01 and DESTINY-Gastric02 trials.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo Company, Limited (referred to as 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 for ENHERTU

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 two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor 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. 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
In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Locally Advanced or Metastatic Gastric Cancer
In DESTINY-Gastric01, of the 125 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 21.0).

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. Reduce dose by one level. For febrile neutropenia (ANC <1.0 x 10^9/L and temperature >38.3ºC or a sustained temperature of ≥38ºC for more than 1 hour), interrupt ENHERTU until resolved. Reduce dose by one level.

Metastatic Breast Cancer
In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4mg/kg, a decrease in neutrophil count was reported in 62% of patients. Sixteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 23 days (range: 6 to 547). Febrile neutropenia was reported in 1.7% of patients.

Locally Advanced or Metastatic Gastric Cancer
In DESTINY-Gastric01, of the 125 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. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. In DESTINY-Gastric01, of the 125 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. 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.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. 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.

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 at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 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. Reduce dose by one level.

Adverse Reactions
Metastatic Breast Cancer
The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31).

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which ILD accounted for 6%. Dose interruptions due to adverse reactions occurred in 33% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, leukopenia, upper respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (79%), white blood cell count decreased (70%), hemoglobin decreased (70%), neutrophil count decreased (62%), fatigue (59%), vomiting (47%), alopecia (46%), aspartate aminotransferase increased (41%), alanine aminotransferase increased (38%), platelet count decreased (37%), constipation (35%), decreased appetite (32%), anemia (31%), diarrhea (29%), hypokalemia (26%), and cough (20%).

Locally Advanced or Metastatic Gastric Cancer
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 once every three 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) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

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 hemoglobin decreased (75%), white blood cell count decreased (74%), neutrophil count decreased (72%), lymphocyte count decreased (70%), platelet count decreased (68%), nausea (63%), decreased appetite (60%), anemia (58%), aspartate aminotransferase increased (58%), fatigue (55%), blood alkaline phosphatase increased (54%), alanine aminotransferase increased (47%), diarrhea (32%), hypokalemia (30%), vomiting (26%), constipation (24%), blood bilirubin increased (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 following 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 at least 7 months following the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following 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 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy 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 (53%) as compared to younger patients (42%). 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.
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

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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