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Daiichi-Sankyo

Press Release

ENHERTU® Reduced the Risk of Disease Progression or Death by 72% Versus Trastuzumab Emtansine (T-DM1) in Patients with HER2 Positive Metastatic Breast Cancer

- Groundbreaking phase 3 head-to-head DESTINY-Breast03 results featured at ESMO Presidential Symposium support ENHERTU as the potential new standard of care in previously treated patients
- DESTINY-Breast01 phase 2 trial data also presented at ESMO showed impressive median overall survival of 29.1 months in HER2 positive patients following two or more HER2 based regimens

Tokyo, Munich and Basking Ridge, NJ – (September 18, 2021) – Detailed positive results from the head-to-head DESTINY-Breast03 phase 3 trial showed that ENHERTU® (trastuzumab deruxtecan), the Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca HER2 directed antibody drug conjugate (ADC), demonstrated superior progression-free survival (PFS) versus trastuzumab emtansine (T-DM1), a HER2 directed ADC currently approved to treat patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. Results were presented as the first late-breaking presentation (#LBA1) in the ESMO Presidential Symposium at the European Society for Medical Oncology (#ESMO21) 2021 Virtual Congress.

At a pre-specified interim analysis of DESTINY-Breast03, ENHERTU demonstrated a 72% reduction in the risk of disease progression or death compared to T-DM1 (hazard ratio [HR] = 0.28; 95% CI: 0.22-0.37; $p=7.8x10^{-22}$). After 15.5 and 13.9 months of follow-up in the ENHERTU and T-DM1 arms respectively, the median PFS for patients treated with ENHERTU was not reached (95% CI: 18.5-NE) compared to 6.8 months for T-DM1 (95% CI: 5.6-8.2) as assessed by blinded independent central review (BICR). In the key secondary endpoint analysis of PFS assessed by investigators, patients treated with ENHERTU experienced a three-fold improvement in PFS of 25.1 months (95% CI: 22.1-NE) compared to 7.2 months (95% CI: 6.8-8.3) for T-DM1 (HR=0.26; 95% CI: 0.20-0.35; $p=6.5x10^{-24}$). A consistent PFS benefit was observed in key subgroups of patients treated with ENHERTU, including those with a history of stable brain metastases.

There was a strong trend towards improved overall survival (OS) with ENHERTU (HR=0.56; 95% CI: 0.36-0.86; p=0.007172), however, this analysis is not yet mature and is not statistically significant. Nearly all patients treated with ENHERTU were alive at one year (94.1%; 95% CI: 90.3-96.4) compared to 85.9% of patients treated with T-DM1 (95% CI: 80.9-89.7).

Confirmed objective response rate (ORR) was more than doubled in the ENHERTU arm versus the T-DM1 arm (79.7%; n=208; 95% CI: 74.3-84.4) versus 34.2% (n=90; 95% CI: 28.5-40.3; p<0.0001). Forty-two

(16.1%) complete responses (CR) and 166 (63.6%) partial responses (PR) were observed in patients treated with ENHERTU compared to 23 (8.7%) CRs and 67 (25.5%) PRs in patients treated with T-DM1.

The safety profile of the most common adverse events with ENHERTU in DESTINY-Breast03 was consistent with previous clinical trials with no new safety concerns identified. The most common grade 3 or higher drug-related treatment emergent adverse events in the ENHERTU arm were neutropenia (19.1%), thrombocytopenia (7.0%), leukopenia (6.6%), nausea (6.6%), anemia (5.8%), fatigue (5.1%), vomiting (1.6%), increase in ALT (1.6%), decreased appetite (1.2%), increase in AST (0.8%), diarrhea (0.4%) and alopecia (0.4%). Overall, 10.5% of patients had confirmed interstitial lung disease (ILD) or pneumonitis related to treatment as determined by an independent adjudication committee. The majority of ILD events (9.7%) were primarily low grade (grade 1 (2.7%) or grade 2 (7.0%)) with two grade 3 (0.8%) events reported. No grade 4 or grade 5 ILD or pneumonitis events occurred.

“Patients with previously treated HER2 positive metastatic breast cancer will typically experience disease progression in less than a year with available HER2 directed treatments,” said Javier Cortés, MD, PhD, Head, International Breast Cancer Center (IBCC), Barcelona, Spain. “The high and consistent benefit seen across efficacy endpoints and key subgroups of patients receiving ENHERTU in DESTINY-Breast03 is remarkable and supports the potential of ENHERTU to become the new standard of care for those who have previously been treated for HER2 positive metastatic breast cancer.”

“The early survival data, which evaluated ENHERTU against another HER2 directed ADC, showed that nearly all patients treated with ENHERTU were alive after a year and is a positive indication of the potential of this medicine to transform the treatment of HER2 positive metastatic breast cancer,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “These landmark data will form the basis of our discussions with global health authorities to potentially bring ENHERTU to patients with previously treated HER2 positive metastatic breast cancer as a more effective treatment option as soon as possible.”

“Today’s results are groundbreaking; ENHERTU tripled progression-free survival as assessed by investigators and provided a disease control rate exceeding 95% compared to 77% for T-DM1 in DESTINY-Breast03,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “In addition, the safety profile was encouraging with no grade 4 or 5 interstitial lung disease events in this trial. These unprecedented data represent a potential paradigm shift in the treatment of HER2 positive metastatic breast cancer and illustrate the potential for ENHERTU to transform more patient lives in earlier treatment settings.”

All patients in DESTINY-Breast03 received at least one prior cancer therapy, including trastuzumab (ENHERTU = 99.6%; T-DM1 = 99.6%), pertuzumab (ENHERTU = 62.1%; T-DM1 = 60.1%), an anti-

HER2 TKI (ENHERTU = 16.1%; T-DM1 = 13.7%) or another anti-HER2 antibody or ADC (ENHERTU = 0.8%; T-DM1 = 1.1%). At the start of the trial, 23.8% of patients in the ENHERTU arm and 19.8% of patients in the T-DM1 arm had stable brain metastases. As of data cut-off on May 21, 2021, 132 patients remained on treatment with ENHERTU and 47 patients on T-DM1.

Summary of DESTINY-Breast03 Results

Efficacy Measure	**ENHERTU (5.4 mg/kg) (n=261)**	**T-DM1 (3.6 mg/kg) (n=263)**
Median PFS (months) (95% CI), per BICR[i] HR=0.28, 95% CI: 0.22-0.37 p=7.8x10^{-22}	NR (18.5-NE)	6.8 months (5.6-8.2)
Landmark 12-month PFS (%) (95% CI) [ii]	75.8% (69.8-80.7)	34.1% (27.7-40.5)
Median PFS (months) (95% CI), investigator assessed[i] HR=0.26, 95% CI: 0.20-0.35 p=6.5x10^{-24}	25.1 months (22.1-NE)	7.2 months (6.8-8.3)
Median OS (months) (95% CI)	NE	NE
Landmark 12-month OS (%) (95% CI) HR=0.56, 95% CI: 0.36-0.86; p=0.007172[iii]	94.1% (90.3-96.4)	85.9% (80.9-89.7)
Confirmed ORR (%) (95% CI; p<0.0001)[ii, iv]	79.7% (74.3-84.4)	34.2% (28.5-40.3)
CR (%)	16.1% (n=42)	8.7% (n=23)
PR (%)	63.6% (n=166)	25.5% (n=67)
SD (%)	16.9% (n=44)	42.6% (n=112)
PD (%) (95% CI)	1.1% (n=3)	17.5% (n=46)
DCR[v]	96.6% (n=252)	76.8% (n=202)

CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease
[i] Median PFS follow-up for ENHERTU was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
[ii] As assessed by BICR
[iii] Not statistically significant
[iv] ORR is (CR + PR)
[v] DCR is (CR+PR+SD)

DESTINY-Breast01 Updated Results

Updated results from the pivotal DESTINY-Breast01 phase 2 trial were also presented at ESMO and showed that ENHERTU (5.4 mg/kg) continued to demonstrate impressive efficacy and durable responses in patients with HER2 positive metastatic breast cancer following two or more prior HER2 based regimens. With a median duration of follow-up of 26.5 months, a continued increase in response was seen in patients treated with ENHERTU with an updated ORR of 62.0% (n=114; 95% CI: 54.4-69.0), including one additional CR (7.1%). A median duration of response (DoR) of 18.2 months (95% CI: 15.0-NE) was also observed. The median PFS was 19.4 months (95% CI: 14.1-25.0). In an exploratory analysis of OS with a median follow-up of 31.1 months (95% CI: 30.7-32.0), evaluated at a greater maturity (52%), the updated median OS was 29.1 months (95% CI: 24.6-36.1).

The overall safety profile seen with ENHERTU in DESTINY-Breast01 continues to be consistent with what has been previously observed. There has been one new case of treatment-related grade 1 ILD or pneumonitis, as determined by an independent adjudication committee as of data cut-off of March 26, 2021.

About DESTINY-Breast03

DESTINY-Breast03 is a global, head-to-head, randomized, open-label, pivotal phase 3 trial evaluating the safety and efficacy of ENHERTU (5.4 mg/kg) versus T-DM1 in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane. The primary efficacy endpoint of DESTINY-Breast03 is PFS based on BICR. Secondary efficacy endpoints include OS, ORR, DoR, clinical benefit rate, PFS based on investigator assessment and safety.

DESTINY-Breast03 enrolled 524 patients at multiple sites in Asia, Europe, North America, Oceania and South America. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Breast01

DESTINY-Breast01 is a global, single-arm, open-label, pivotal phase 2, two-part trial evaluating the safety and efficacy of ENHERTU in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with T-DM1. The primary endpoint of the trial is ORR, as determined by independent central review. Secondary objectives include DoR, disease control rate, clinical benefit rate, PFS, OS and safety.

DESTINY-Breast01 enrolled 253 patients at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About HER2 Positive Breast Cancer

Breast cancer is the most common cancer and one of the leading causes of cancer-related deaths worldwide.[1] More than two million cases of breast cancer were diagnosed in 2020, resulting in nearly 685,000 deaths globally.[1] Approximately one in five cases of breast cancer are considered HER2 positive.[2]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including breast, gastric, lung and colorectal cancers.[3] HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease and poor prognosis in breast cancer.[4]

Despite initial treatment with trastuzumab and a taxane, patients with HER2 positive metastatic breast cancer will often experience disease progression.[5] More effective options are needed to further delay progression and extend survival.[3,6,7]

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 Canada, EU, Israel, Japan, UK and U.S. 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 based on the results from the DESTINY-Breast01 trial.

ENHERTU (6.4 mg/kg) is also approved in Israel, Japan and U.S. for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction 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.

ENHERTU was highlighted in the Clinical Cancer Advances 2021 report as one of two significant advancements in the "ASCO Clinical Advance of the Year: Molecular Profiling Driving Progress in GI Cancers," based on data from both the DESTINY-Gastric01 and DESTINY-CRC01 trials, as well as one of the targeted therapy advances of the year in non-small cell lung cancer (NSCLC) based on the interim results of the *HER2* mutated cohort of the DESTINY-Lung01 trial.

In May 2020, ENHERTU received Breakthrough Therapy Designation in the U.S. for the treatment of patients with metastatic NSCLC whose tumors have a *HER2* mutation and with disease progression on or after platinum-based therapy.

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 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 in Oncology

The oncology portfolio of Daiichi Sankyo is powered by our team of world-class scientists that push beyond traditional thinking to create transformative medicines for people with cancer. Anchored by our DXd antibody drug conjugate (ADC) technology, our research engines include biologics, medicinal chemistry,

modality and other research laboratories in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in the U.S. We also work alongside leading academic and business collaborators to further advance the understanding of cancer as Daiichi Sankyo builds towards our ambitious goal of becoming a global leader in oncology by 2025.

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.

Media Contacts:

Global:
Victoria Amari
Daiichi Sankyo, Inc.
vamari@dsi.com
+1 908 900 3010 (mobile)

US:
Don Murphy
Daiichi Sankyo, Inc.
domurphy@dsi.com
+1 917 817 2649 (mobile)

EU:
Lydia Worms
Daiichi Sankyo Europe GmbH
lydia.worms@daiichi-sankyo.eu
+49 (89) 7808751 (office)
+49 176 11780861 (mobile)

Japan:
Masashi Kawase
Daiichi Sankyo Co., Ltd.
kawase.masashi.a2@daiichisankyo.co.jp
+81 3 6225 1126 (office)

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

References

[1] Sung H, et al. *CA Cancer J Clin*. 2021;10.3322/caac.21660.
[2] Ahn S, et al. *J Pathol Transl Med*. 2020;54(1): 34–44.
[3] Iqbal N, et al. *Mol Biol Int*. 2014;852748.
[4] Pillai R, et al. *Cancer*. 2017;1;123(21):4099-4105.
[5] Barok M, et al. *Breast Cancer Res*. 2014;16(2):209.
[6] Mounsey L, et al. *Clin Breast Cancer*. 2018;18(1):29-37
[7] Martínez-Sáez O, Prat A. *JCO Oncol Pract*. 2021;10.1200/OP.21.00172.