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Daiichi-Sankyo

Press Release

Data Across Daiichi Sankyo DXd ADC Portfolio at 2022 SABCS Demonstrates Bold Progress in Advancing Treatment for Patients with Breast Cancer

- Survival data from DESTINY-Breast03 and DESTINY-Breast02 phase 3 trials in patients with HER2 positive metastatic breast cancer further confirms efficacy of ENHERTU
- First presentation of datopotamab deruxtecan results in patients with HR positive, HER2 negative metastatic breast cancer shows promising clinical activity
- Annual R&D Day following SABCS to provide updates across Daiichi Sankyo R&D portfolio

Basking Ridge, NJ – (November 21, 2022) – Daiichi Sankyo (TSE: 4568) continues to boldly challenge the breast cancer treatment landscape with the presentation of 30 abstracts from its innovative DXd antibody drug conjugate (ADC) portfolio at the 2022 San Antonio Breast Cancer Symposium (#SABCS22) to be held December 6 to 10, 2022.

ENHERTU® (trastuzumab deruxtecan) data from DESTINY-Breast03 and DESTINY-Breast02, two head-to-head phase 3 trials in patients with previously treated HER2 positive metastatic breast cancer, will be highlighted in back-to-back oral presentations and included in the SABCS Press Program. A Spotlight Poster Discussion will feature the first reported results of datopotamab deruxtecan (Dato-DXd) in patients with HR positive, HER2 negative metastatic breast cancer from the TROPION-PanTumor01 phase 1 trial.

"Three years after unveiling the impressive results of DESTINY-Breast01 at SABCS, we look forward to showcasing data from two additional head-to-head trials confirming the efficacy and safety profile of ENHERTU, including updated results from DESTINY-Breast03 and the first presentation of results from DESTINY-Breast02," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "We will present for the first time preliminary data of datopotamab deruxtecan in patients with HR positive, HER2 negative metastatic breast cancer, as well as updated results in metastatic triple negative breast cancer. With these new data, Daiichi Sankyo continues reaching for our goal of changing the standard of care for patients across all breast cancer subtypes with our innovative DXd ADC portfolio."

In patients with metastatic triple negative breast cancer (TNBC), updated results from the TROPION-PanTumor01 phase 1 trial of datopotamab deruxtecan will be featured as a poster presentation and a Spotlight Poster Discussion will provide updated data from the datopotamab deruxtecan and durvalumab arm of the BEGONIA phase 1b/2 trial.

Additionally, updates from other ongoing breast cancer trials from the DESTINY and TROPION clinical development programs of ENHERTU and datopotamab deruxtecan as well as collaborative trials across Daiichi Sankyo's DXd ADC portfolio including DEBBRAH, TRIO-US B-12 TALENT and SOLTI-TOT-HER3 will be presented.

Following SABCS, Daiichi Sankyo will hold its annual R&D Day for investors and analysts on Monday, December 12, 2022 at 5:30 pm ET. Company executives will provide an overview of Daiichi Sankyo's research data presented at SABCS, provide updates on the company's R&D strategy, and address questions from investors and analysts.

Highlights of the data from the DXd ADC portfolio of Daiichi Sankyo to be presented at SABCS 2022 include:

Presentation Title		Author	Abstract	Presentation
ENHERTU (trastuzumab deruxtecan/T-DXd; HER2 directed ADC)				
HER2 Positive	Trastuzumab deruxtecan vs. treatment of physician's choice in patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine: primary results of the phase 3 study DESTINY-Breast02	I. Krop	GS2-01	Oral Presentation: General Session 2 Wednesday, December 7, 2022 9:00 am CT
	Trastuzumab deruxtecan vs. trastuzumab emtansine in patients with HER2 positive metastatic breast cancer: updated survival results of the randomized, phase 3 study DESTINY-Breast03	S. A. Hurvitz	GS2-02	Oral Presentation General Session 2 Wednesday, December 7, 2022 9:15 am CT
	Trastuzumab deruxtecan for the treatment of patients with HER2 positive breast cancer with brain and/or leptomeningeal metastases: a multicenter retrospective study (ROSET-BM study)	Y. Takashi	PD7-01	Spotlight Poster Discussion 7 Wednesday, December 7, 2022 5:00 pm CT
	Dose-expansion study of trastuzumab deruxtecan as monotherapy or combined with pertuzumab in patients with metastatic human epidermal growth factor receptor 2-positive (HER2 positive) breast cancer in DESTINY-Breast07	E.P. Hamilton	PD18-11	Spotlight Poster Discussion 18 Friday, December 9, 2022 7:00 am CT
	Open-label, phase 3b/4 study of trastuzumab deruxtecan in patients with or without baseline brain metastasis with advanced/metastatic human epidermal growth factor receptor 2 positive (HER2 positive) breast cancer: DESTINY-Breast12	N. U. Lin	OT2-16-02	Poster Presentation Wednesday, December 7, 2022 5:00 pm CT
HER2 Low	TRIO-US B-12 TALENT: neoadjuvant trastuzumab deruxtecan with or without anastrozole for HER2 low, HR positive early-stage breast cancer	S.A. Hurvitz	GS2-03	Oral Presentation General Session 2 Wednesday, December 7, 2022 9:30 am CT

	Trastuzumab deruxtecan in patients with unstable central nervous system involvement from HER2 low advanced breast cancer: the DEBBRAH trial	J.M. Perez-Garcia	PD7-02	Spotlight Poster Discussion 7 Wednesday, December 7, 2022 5:00 pm CT
	Trastuzumab deruxtecan + durvalumab as first-line treatment for unresectable locally advanced/metastatic hormone receptor-negative (HR negative), HER2 low breast cancer: updated results from BEGONIA, a phase 1b/2 study	P. Schmid	PD11-08	Spotlight Poster Discussion 11 Thursday, December 8, 2022 7:00 am CT
	Trastuzumab deruxtecan vs. treatment of physician's choice in patients with HER2 low unresectable and/or metastatic breast cancer: subgroup analyses from DESTINY-Breast04	N. Harbeck	P1-11-01	Poster Presentation Tuesday, December 6, 2022 5:00 pm CT
HER2 Testing	Retrospective study to estimate the prevalence and describe the clinicopathological characteristics, treatment patterns, and outcomes of HER2 low breast cancer	G. Viale	HER2-15	HER2 Low: A Separate Entity Special Session – Hall 3 Wednesday, December 7, 2022 9:45 am CT
	Determination of HER2 low status in tumors of patients with unresectable and/or metastatic breast cancer in DESTINY-Breast04	A. Prat	HER2-18	
	Proficiency assessment of HER2 low breast cancer scoring with the Ventana PATHWAY 4B5 and Dako HercepTest HER2 assays and the impact of pathologist training	J. Rüschoff	HER2-13	
	A fully automatic artificial intelligence system for accurate and reproducible HER2 IHC scoring in breast cancer	Y. Globerson	P6-04-05	Poster Presentation Friday, December 9, 2022 7:00 am CT
	Computational pathology based HER2 expression quantification in HER2 low breast cancer	A. Spitzmüller	P6-04-03	Poster Presentation Friday, December 9, 2022 7:00 am CT
	ART: Automated region segmentation of tumor on HER2-stained breast cancer tissue	A. Kapil	P6-04-16	Poster Presentation Friday, December 9, 2022 7:00 am CT
	High intra- and inter-block concordance of HER2 immunohistochemistry scores across breast cancer samples and impact of decalcification procedures	A. Tsirka	P6-04-17	Poster Presentation Friday, December 9, 2022 7:00 am CT
Datopotamab Deruxtecan (Dato-DXd; TROP2 directed ADC)				
HR Positive, HER2 Negative	Phase 1 TROPION-PanTumor01 study evaluating datopotamab deruxtecan in unresectable or metastatic hormone receptor positive (HR positive), HER2 negative breast cancer	F. Meric-Bernstam	PD13-08	Spotlight Poster Discussion 13 Thursday, December 8, 2022 5:00 pm CT
	Datopotamab deruxtecan, a TROP2 antibody-drug conjugate, vs. investigators' choice of chemotherapy in previously-treated, inoperable or metastatic HR positive, HER2 negative breast cancer: TROPION-Breast01	A. Bardia	OT1-03-04	Poster Presentation Tuesday, December 6, 2022 5:00 pm CT

TNBC	Datopotamab deruxtecan + durvalumab as first-line treatment for unresectable locally advanced/metastatic triple negative breast cancer: updated results from BEGONIA, a phase 1b/2 study	P. Schmid	PD11-09	Spotlight Poster Discussion 11 Thursday, December 8, 2022 7:00 am CT
	Datopotamab deruxtecan in advanced triple-negative breast cancer: updated results from the Phase 1 TROPION-PanTumor01 Study	A. Bardia	P6-10-03	Poster Presentation Friday, December 9, 2022 7:00 am CT
	TROPION-Breast02: Phase 3, open-label, randomized study of first-line datopotamab deruxtecan versus chemotherapy in patients with locally recurrent inoperable or metastatic triple negative breast cancer who are not candidates for anti-PD-(L)1 therapy	R. Dent	OT1-03-05	Poster Presentation Tuesday, December 6, 2022 5:00 pm CT
Patritumab Deruxtecan (HER3-DXd; HER3 directed ADC)				
HR positive, HER2 negative	Genetic determinants of response to patritumab deruxtecan in hormone receptor positive (HR positive), HER2 negative breast cancer: a correlative analysis from SOLTI-TOT-HER3 trial	F. Brasó-Maristany	P5-02-31	Poster Presentation Thursday, December 8, 2022 5:00 pm CT

About the DXd ADC Portfolio of Daiichi Sankyo

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

Each ADC is 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 and DS-6000 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

ENHERTU U.S. Important Safety Information

Indications

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

- Unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  - In the metastatic setting, or
  - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy

- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy

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

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

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

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

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

Contraindications

None.

Warnings and Precautions

Interstitial Lung Disease / Pneumonitis

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

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

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

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

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

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

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

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

Left Ventricular Dysfunction
Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

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

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

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

the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for 4 months after the last dose of ENHERTU.

Additional Dose Modifications

Thrombocytopenia

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

Adverse Reactions

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

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

HER2-Positive Metastatic Breast Cancer

DESTINY-Breast03

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

Serious adverse reactions occurred in 19% of patients receiving ENHERTU. Serious adverse reactions in >1% of patients who received ENHERTU were vomiting, interstitial lung disease, pneumonia, pyrexia, and urinary tract infection. Fatalities due to adverse reactions occurred in 0.8% of patients including COVID-19 and sudden death (one patient each).

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

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

HER2-Low Metastatic Breast Cancer

DESTINY-Breast04

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Use in Specific Populations

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

and any AST).

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

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

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 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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