

## Press Release

### **Daiichi Sankyo Continues to Make Bold Strides in Oncology Across DXd ADC Portfolio at 2022 ESMO**

- Late-breaking data from DESTINY-Lung02 phase 2 trial of ENHERTU in patients with previously treated HER2 mutant metastatic non-small cell lung cancer to be featured
- Proffered paper presentation to highlight updated results from phase 1/2 trial of DS-7300 in several types of cancer including lung, esophageal and prostate

**Munich and Basking Ridge, NJ – (September 6, 2022)** – Daiichi Sankyo (TSE: 4568) continues to make bold strides in oncology with the presentation of new clinical research across its innovative DXd antibody drug conjugate (ADC) portfolio in a broad range of cancers including lung, breast, gastric, esophageal and prostate at the 2022 European Society for Medical Oncology (#ESMO22) Congress to be held September 9 to 13, 2022.

Late-breaking results will be featured from an interim analysis of the [DESTINY-Lung02](#) phase 2 trial in patients with previously treated HER2 mutant metastatic non-small cell lung cancer (NSCLC), which formed the basis for the recent [accelerated approval](#) in the U.S. of ENHERTU® (trastuzumab deruxtecan) in this tumor type. Additionally, updated data from both the HER2 mutant and HER2 overexpressing cohorts of the [DESTINY-Lung01](#) phase 2 trial also will be presented.

A proffered paper presentation of extended follow-up data from a [phase 1/2 trial](#) of DS-7300 in patients with heavily pretreated metastatic solid tumors including extensive-stage small cell lung cancer, castration-resistant prostate cancer, esophageal squamous cell carcinoma and squamous NSCLC will be highlighted.

“Following the recent first-of-its-kind approvals of ENHERTU in the U.S. in patients with previously-treated metastatic HER2 low breast cancer and HER2 mutant non-small cell lung cancer, we are proud to continue to report new data across our DXd ADC portfolio in several different tumor types at this year’s ESMO,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “We look forward to sharing results from the DESTINY-Lung02 trial of ENHERTU for the first time along with updated data from DS-7300, our B7-H3 directed ADC, in patients with certain types of lung, esophageal and prostate cancer.”

Other ENHERTU data to be featured at ESMO include a proffered paper presentation on patient-reported outcomes from the [DESTINY-Breast04](#) phase 3 trial, a poster presentation reporting subgroup analyses of the

DESTINY-Breast03 phase 3 trial, and a mini-oral presentation of updated data from the DESTINY-Gastric02 phase 2 trial.

Several trial-in-progress presentations also will provide an overview of ongoing clinical trials across the DXd ADC portfolio including the TROPION-Breast01 phase 3 trial of datopotamab deruxtecan, the HERTHENA-Lung02 phase 3 trial of patritumab deruxtecan and a phase 2 trial of DS-7300. Highlights of Daiichi Sankyo DXd ADC data at 2022 ESMO include:

Presentation Title		Author	Abstract	Presentation
<b>ENHERTU (trastuzumab deruxtecan/T-DXd; HER2 directed ADC)</b>				
<b>Lung</b>	Trastuzumab deruxtecan in patients with HER2 mutated metastatic non-small cell lung cancer: interim results from the phase 2 DESTINY-Lung02 trial	Y. Goto	LBA55	Late-Breaking Presentation Mini Oral Presentation Sunday, September 11, 2022 10:15 - 11:45 CEST
	Trastuzumab deruxtecan in patients with HER2 overexpressing metastatic non-small cell lung cancer: results from the DESTINY-Lung01 trial	E.F. Smit	975P	Poster Presentation Monday, September 12, 2022 12:00 - 13:00 CEST
	Phase 2 trial of trastuzumab deruxtecan in patients with HER2 mutated metastatic non-small cell lung cancer: registrational data from DESTINY-Lung01	B.T. Li	976P	Poster Presentation Monday, September 12, 2022 12:00 - 13:00 CEST
<b>Breast</b>	Patient-reported outcomes from DESTINY-Breast04, a randomized phase 3 study of trastuzumab deruxtecan vs treatment of physician's choice in patients with HER2 low metastatic breast cancer	N.T. Ueno	217OP	Proffered Poster Presentation Sunday, September 11, 2022 9:30 - 9:40 CEST
	Subgroup analysis by disease history and prior treatments of patients with HER2 positive metastatic breast cancer from DESTINY-Breast03, a randomized phase 3 study of trastuzumab deruxtecan vs trastuzumab emtansine	J. Cortes	236P	Poster Presentation Saturday, September 10, 2022 12:00 - 13:00 CEST
	Unraveling the mechanism of action and resistance to trastuzumab deruxtecan (T-DXd): biomarker analyses from patients from DAISY trial	F. Mosele	LBA72	Late-Breaking Presentation Mini Oral Presentation Sunday, September 11, 2022 14:45 - 16:15 CEST
	Antitumor activity of trastuzumab deruxtecan in patients with metastatic breast cancer and brain metastases from DAISY trial	N. Epailard	260P	Poster Presentation Saturday, September 10, 2022 12:00 - 13:00 CEST
<b>Gastric</b>	Updated analysis of DESTINY-Gastric02: a phase 2 single-arm trial of trastuzumab deruxtecan in Western patients with HER2 positive unresectable/metastatic gastric/gastroesophageal junction cancer who progressed on or after trastuzumab-containing regimen	G. Ku	1205MO	Mini Oral Presentation Saturday, September 10, 2022 15:55 - 16:00 CEST
<b>DS-7300 (B7-H3 Directed ADC)</b>				
<b>Lung Esophageal Prostate</b>	B7-H3 DXd antibody drug conjugate shows durable antitumor activity in advanced solid tumors: extended follow-up of a phase 1/2 study	T. Doi	453O	Proffered Paper Presentation Saturday, September 10, 2022 10:35 - 10:45 CEST
<b>Lung</b>	Phase 2, multicenter, randomized, open-label study of DS-7300 in participants with previously treated extensive-stage small cell lung cancer	L. Paz-Ares	1550TiP	Poster Presentation Saturday, September 10, 2022 13:00 - 13:20 CEST
<b>Datopotamab Deruxtecan (Dato-DXd; TROP2 directed ADC)</b>				

<b>Lung</b>	ORCHARD platform study: osimertinib + datopotamab deruxtecan (Dato-DXd) cohort in patients (pts) with advanced NSCLC (aNSCLC) who have progressed on first-line (1L) osimertinib	A.J. de Langen	1188TiP	Poster Presentation Monday, September 12, 2022 12:00 - 13:00 CEST
<b>Breast</b>	Datopotamab deruxtecan, a TROP2 antibody drug conjugate vs investigators' choice of chemotherapy in patients with previously treated, inoperable or metastatic hormone receptor positive, HER2 negative breast cancer: TROPION-Breast01	A. Bardia	274TiP	Poster Presentation Saturday, September 10, 2022 16:20 - 16:40 CEST
<b>Patritumab Deruxtecan (HER3-DXd; HER3 directed ADC)</b>				
<b>Lung</b>	HERTHENA-Lung02: a randomized phase 3 study of patritumab deruxtecan vs platinum-based chemotherapy in locally advanced or metastatic EGFR mutated non-small cell lung cancer after progression on a 3rd-generation EGFR TKI	T. Mok	1195TiP	Poster Presentation Monday, September 12, 2022 12:00 - 13:00 CEST
	Pharmacokinetics, efficacy, and safety of patritumab deruxtecan in EGFR inhibitor-resistant, EGFR mutated non-small cell lung cancer	H. Yu	1190TiP	Poster Presentation Monday, September 12, 2022 12:00 - 13:00 CEST
<b>Breast</b>	TOT-HER3 SOLTI trial: a window of opportunity trial of patritumab deruxtecan in patients with treatment-naïve early breast cancer	M. Olivera	202TiP	Poster Presentation Saturday, September 10, 2022 12:00 - 13:00 CEST
	Increased membrane HER3 expression in brain metastases compared to primary tumors in breast cancer	S. Kusuhara	264P	Poster Presentation Saturday, September 10, 2022 12:00 - 13:00 CEST

### 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 DS-7300 (B7-H3) and DS-6000 (CDH6) are being developed in part through a strategic research collaboration with Sarah Cannon Research Institute.

Each ADC is designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver 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.

ENHERTU is not approved outside the U.S. for the treatment of patients with metastatic HER2 low breast cancer or HER2 mutant NSCLC.

Patritumab deruxtecan, datopotamab deruxtecan, DS-7300 and DS-6000 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

## 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 a prior anti-HER2-based regimen either:
  - In the metastatic setting, or
  - In the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy
- Unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

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

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

### **WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY**

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

### Contraindications

None.

### Warnings and Precautions

#### **Interstitial Lung Disease / Pneumonitis**

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. A higher incidence of Grade 1 and 2 ILD/pneumonitis has been observed in patients with moderate renal impairment. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic ILD/pneumonitis (Grade 1), interrupt ENHERTU until resolved to Grade 0, then if resolved in  $\leq 28$  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.,  $\geq 0.5$  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.,  $\geq 1$  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  $0.5 \times 10^9/L$ ), interrupt ENHERTU until resolved to Grade 2 or less, then maintain dose. For Grade 4 neutropenia (ANC  $<0.5 \times 10^9/L$ ), interrupt ENHERTU until resolved to Grade 2 or less, then reduce dose by one level. For febrile neutropenia (ANC  $<1.0 \times 10^9/L$  and temperature  $>38.3^\circ C$  or a sustained temperature of  $\geq 38^\circ C$  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  $25 \times 10^9/L$ ) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets  $<25 \times 10^9/L$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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<sup>2</sup> biweekly or paclitaxel (N=7) 80 mg/m<sup>2</sup> 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 ( $\geq 20\%$ ) 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  $\geq 65$  years and 3.6% were  $\geq 75$  years. No overall differences in efficacy within clinical studies were observed between patients  $\geq 65$  years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged  $\geq 65$  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  $\geq 65$  years and 8% were  $\geq 75$  years. No overall differences in efficacy or safety were observed between patients  $\geq 65$  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  $\geq 65$  years and 14% were  $\geq 75$  years. No overall differences in efficacy or safety were observed between patients  $\geq 65$  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](http://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](http://www.daiichisankyo.com).

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