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Daiichi-Sankyo

Press Release

Daiichi Sankyo Showcases Bold Leadership in Oncology with Survival Improvements for Certain Patients with Cancer at ASCO and EHA

- ENHERTU data from historic DESTINY-Breast04 trial in patients with HER2 low metastatic breast cancer has the potential to redefine how breast cancer is categorized and treated
- First presentation of DS-6000 and new patritumab deruxtecan results further support the strength of Daiichi Sankyo's DXd ADC technology across multiple cancers including breast, lung, ovarian and renal cell carcinoma
- Survival benefit of quizartinib in combination with chemotherapy demonstrated in QuANTUM-First trial in patients with newly diagnosed *FLT3*-ITD positive AML

Basking Ridge, NJ – (May 23, 2022) – Daiichi Sankyo (TSE: 4568) will present new clinical research across its oncology portfolio at the 2022 American Society of Clinical Oncology Scientific Program (#ASCO22) and the European Hematology Association Congress (#EHA22).

Presentations, including a Plenary Session (LBA#3) at ASCO featuring the DESTINY-Breast04 trial of ENHERTU® (trastuzumab deruxtecan) and a Presidential Symposium at EHA (S100) highlighting the QuANTUM-First trial of quizartinib, underscore the company's leadership in developing multiple transformative medicines that significantly improve survival for certain patients with cancer. Both DESTINY-Breast04 and QuANTUM-First data will be featured in press briefings at ASCO and EHA.

"We will be showcasing impressive data from two of our late-stage clinical development programs at ASCO and EHA, where our medicines are demonstrating significant survival advantage in certain patients with metastatic breast cancer and acute myeloid leukemia," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "Our ambition is to push the boundaries of science to change the way cancer is treated. The results of the DESTINY-Breast04 trial of ENHERTU will transform the practice of how breast cancer is treated, as this is the first time that a HER2 directed therapy has demonstrated an improvement in survival in patients with HER2 low metastatic breast cancer, a cancer category distinct from HER2 positive breast cancer."

Redefining How Breast Cancer is Categorized and Treated

Data from the historic DESTINY-Breast04 phase 3 trial evaluating ENHERTU versus the current standard of care of physician's choice of chemotherapy in patients with HER2 low metastatic breast cancer will be highlighted during the ASCO Plenary Session (LBA#3) and included in an ASCO Press Briefing on Sunday, June 5.

ENHERTU is the first ever HER2 directed medicine to show efficacy in HER2 low breast cancer. ENHERTU demonstrated a statistically significant and clinically meaningful benefit in progression-free survival (PFS) and overall survival (OS) compared to standard treatment in patients with HER2 low metastatic breast cancer (defined as IHC 1+ or IHC 2+/ISH-negative), potentially redefining how breast cancer will be categorized and treated in the future.

The safety profile of ENHERTU in DESTINY-Breast04 was consistent with previous clinical trials with no new safety concerns identified. Overall interstitial lung disease (ILD) rates were consistent with that observed in late-line HER2 positive breast cancer trials of ENHERTU with a lower rate of grade 5 ILD observed, as determined by an independent adjudication committee.

Other ENHERTU data being presented at ASCO includes an update of safety data from the head-to-head DESTINY-Breast03 phase 3 trial versus trastuzumab emtansine and preliminary data from DESTINY-Breast07 and DESTINY-Breast08, two phase 2 dose-finding trials evaluating ENHERTU in combination with other breast cancer treatments in patients with HER2 positive and HER2 low breast cancer, respectively.

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

Strength of the Daiichi Sankyo DXd ADC Technology Across Multiple Cancers

Data from a phase 1/2 trial of patritumab deruxtecan (HER3-DXd), a potential first-in-class HER3 directed ADC, in patients with HER3 expressing metastatic breast cancer will be featured at ASCO. These results show promising clinical activity in several HER3 high breast cancer subtypes including HER2 positive breast cancer, hormone receptor positive/HER2 negative breast cancer and triple negative breast cancer. Additionally, preliminary phase 1 data of patritumab deruxtecan from a cohort of patients with metastatic non-small cell lung cancer (NSCLC) without EGFR-activating mutations will be presented for the first time.

First ever preliminary phase 1 results of DS-6000 in patients with advanced ovarian cancer and renal cell carcinoma also will be highlighted. DS-6000 is a potential first-in-class CDH6 directed ADC and the fifth DXd ADC from Daiichi Sankyo's pipeline to report encouraging early clinical data.

A trial-in-progress presentation of the TROPION-Lung08 phase 3 trial of datopotamab deruxtecan (Dato-DXd) in combination with pembrolizumab as first-line treatment of patients with metastatic NSCLC in PD-L1 ≥50%, without actionable genomic alterations will be presented.

Daiichi Sankyo will hold a conference call for investors and analysts on Tuesday, June 7 from 5:30 to 7:00 pm CDT. Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo and Gilles Gallant, BPharm, PhD, FOPQ, Global Head, Oncology Development will provide an overview of the ASCO research data and address questions from investors and analysts.

Improving Survival for Patients with Newly Diagnosed *FLT3*-ITD AML

Data from the pivotal QuANTUM-First phase 3 trial of quizartinib in combination with standard chemotherapy in patients with newly diagnosed *FLT3*-ITD positive acute myeloid leukemia (AML) will be featured during the EHA Presidential Symposium and included in an EHA Press Briefing on Saturday, June 11.

Results from QuANTUM-First demonstrated that patients who received quizartinib in combination with standard induction and consolidation chemotherapy and then continued with single agent quizartinib for up to 36 cycles had a statistically significant and clinically meaningful improvement in OS compared to those who received standard treatment alone. The safety of quizartinib was shown to be manageable and consistent with the known safety profile.

Highlights of Daiichi Sankyo data at 2022 ASCO include:

Presentation Title		Author	Abstract	Presentation
ENHERTU (trastuzumab deruxtecan; T-DXd)				
Breast	Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients with HER2 low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study	S. Modi	LBA #3	Plenary Session Sunday, June 5 1:00 – 4:00 pm CDT
	Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with HER2 positive (HER2+) unresectable and/or metastatic breast cancer (mBC): Safety follow-up of the randomized, phase 3 study DESTINY-Breast03	E. Hamilton	#1000	Oral Presentation Saturday, June 4 1:15 – 4:15 pm CDT
	Dose-finding and dose expansion studies of trastuzumab deruxtecan in combination with other anti-cancer agents in patients with advanced/metastatic HER2+ (DESTINY-Breast07 [DB-07]) and HER2-low (DESTINY-Breast08 [DB-08]) breast cancer (BC)	F. Andre	#3025	Poster Presentation Sunday, June 5 8:00 – 11:00 am CDT
	Monitoring and management of interstitial lung disease (ILD)/pneumonitis among metastatic breast cancer (mBC) patients treated with trastuzumab deruxtecan (T-DXd)	J. Kish	#1036	Poster Presentation Monday, June 6 8:00 – 11:00 am CDT
	Retrospective study to estimate the prevalence of HER2 low breast cancer (BC) and describe its clinicopathological characteristics	G. Viale	#1087	Poster Presentation Monday, June 6 8:00 – 11:00 am CDT
Lung	Open-label, randomized, multicenter, phase 3 study evaluating trastuzumab deruxtecan (T-DXd) as first-line treatment in patients with unresectable, locally advanced, or metastatic non-small cell lung cancer (NSCLC) harboring HER2 exon 19 or 20 mutations (DESTINY-Lung04)	B. Li	TPS9137	Poster Presentation Monday, June 6 8:00 – 11:00 am CDT

Patritumab Deruxtecan (HER3-DXd)				
Breast	Results from the phase 1/2 study of patritumab deruxtecan, a HER3 directed antibody drug conjugate (ADC), in patients with HER3 expressing metastatic breast cancer (MBC)	I. Krop	#1002	Oral Presentation Saturday, June 4 1:15 – 4:15 pm CDT
Lung	Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic non-small cell lung cancer (NSCLC) without EGFR-activating mutations	C. Steuer	#9017	Poster Presentation Monday, June 6 1:15 – 2:45 pm CDT
	Phase 1 study of patritumab deruxtecan (HER3-DXd; U3-1402) in combination with osimertinib in patients with advanced EGFR-mutated NSCLC	P. Jänne	#TPS3161	Poster Presentation Saturday, June 5 8:00 – 11:00 am CDT
DS-6000				
RCC and Ovarian	Phase 1, two-part, multi-center, first-in-human (FIH) study of DS-6000 in subjects with advanced renal cell carcinoma (RCC) and ovarian cancer (OVC)	E. Hamilton	#3002	Oral Presentation Tuesday, June 7 9:45 – 12:45 pm CDT
Datopotamab deruxtecan (Dato-DXd)				
Lung	TROPION-Lung08: Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab in treatment-naïve advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC) with PD-L1 ≥50% and without actionable genomic alterations	B. Levy	#TPS3162	Poster Presentation Sunday, June 5 8:00 – 11:00 am CDT
DS-6157				
GIST	A phase 1, multicenter, open-label, first-in-human study of DS-6157 in patients with advanced gastrointestinal stromal tumor (GIST)	S. George	#11512	Poster Discussion Sunday, June 5 11:30 – 1:00 pm CDT

Highlights of Daiichi Sankyo data at 2022 EHA include:

Presentation Title		Author	Abstract	Presentation
Quizartinib				
Acute Myeloid Leukemia (AML)	Quizartinib prolongs survival compared with placebo in combination with intensive induction and consolidation therapy followed by single agent continuation in newly diagnosed *FLT3*-ITD+ AML aged 18-75	H. Erba	S100	Presidential Symposium Presentation Saturday, June 11 2:45 – 4:15 pm CEST
	Initial results of phase 1/2 study of azacitidine in combination with quizartinib for patients with myelodysplastic syndrome and myelodysplastic/myeloproliferative neoplasm with FLT3 or CBL mutation	T. Abuasab	#3453	Poster Presentation Friday, June 10 4:30 – 5:45 pm CEST
	Preliminary results of VEN-A-QUI study: A phase 1-2 trial to assess the safety and efficacy of the combination of azacitidine or low-dose cytarabine with venetoclax and quizartinib in newly diagnosed unfit AML patients	J.M. Bergua-Burgues	#3585	Poster Presentation Friday, June 10 4:30 – 5:45 pm CEST
	Quizartinib with decitabine and venetoclax (triplet) is active in patients with *FLT3*-ITD mutated acute myeloid leukemia – a phase 1/2 study	M. Yilmaz	#2636	Oral Presentation Saturday, June 11 4:30 – 5:45 pm CEST
	Risk factors and incidence of cardiac events in a large cohort of 525 adult patients with newly diagnosed non-M3 acute myeloid leukemia	B. Boluda	#2381	Poster Presentation Friday, June 10 4:30 – 5:45 pm 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 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.

Patritumab deruxtecan, datopotamab 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.

About Quizartinib

Quizartinib is an oral, highly potent and selective type II FLT3 inhibitor currently in clinical development for the treatment of *FLT3*-ITD positive AML. In addition to QuANTUM-First, the quizartinib development program also includes a phase 1/2 trial in pediatric and young adult patients with relapsed/refractory *FLT3*-ITD AML in Europe and North America. Several phase 1/2 combination trials with quizartinib also are underway at The University of Texas MD Anderson Cancer Center as part of a strategic research collaboration focused on accelerating development of Daiichi Sankyo pipeline therapies for AML.

Quizartinib is currently approved for use in Japan under the brand name VANFLYTA® for the treatment of adult patients with relapsed/refractory *FLT3*-ITD AML, as detected by an approved test. Quizartinib is an investigational medicine in all countries outside of Japan.

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 the U.S. 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, based on results from the DESTINY-Breast03 trial. ENHERTU is also approved in approximately 40 countries for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2-based regimens based on the results from the DESTINY-Breast01 trial.

ENHERTU (6.4 mg/kg) is approved in several countries for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 trial.

ENHERTU is approved in the U.S. with Boxed WARNINGS for Interstitial Lung Disease and Embryo-Fetal Toxicity. For more information, please see the accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

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

- 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 491 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 13% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 1.4% of patients treated with ENHERTU. Median time to first onset was 5.5 months (range: 1.1 to 20.8).

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 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, a decrease in neutrophil count was reported in 68% of patients. Eighteen percent had Grade 3 or 4 decrease in neutrophil count. Median time to first onset of decreased neutrophil count was 22 days (range: 6 to 664). Febrile neutropenia was reported in 1.2% 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. 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
In the 491 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU 5.4 mg/kg, 13 cases (2.6%) of asymptomatic LVEF decrease were reported.

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, 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 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 pooled safety population for patients with metastatic breast cancer reflects exposure to ENHERTU at 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) in 491 patients in DESTINY-Breast03, DESTINY-Breast01, and Study DS8201-A-J101. The median duration of treatment was 13 months (range: 0.7 to 37). In this pooled safety population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea (78%), decreased white blood cell count (74%), decreased hemoglobin (68%), decreased neutrophil count (68%), increased aspartate aminotransferase (58%), fatigue (57%), decreased lymphocyte count (56%), vomiting (50%), decreased platelet count (49%), increased alanine aminotransferase (48%), increased blood alkaline phosphatase (45%), alopecia (41%), constipation (35%), hypokalemia (33%), decreased appetite (32%), diarrhea (31%), musculoskeletal pain (28%), increased transaminases (27%), respiratory infection (24%), headache (21%), and abdominal pain (21%).

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 in DESTINY-Breast03. ENHERTU was administered by intravenous infusion once every three weeks. 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%).

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 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 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 491 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 22% were ≥65 years and 4% 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 (49%). 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 or severe renal impairment.
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

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

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

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit www.daiichisankyo.com.

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