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Daiichi-Sankyo

Press Release

Datopotamab Deruxtecan and ENHERTU® Show Promising Early Clinical Activity in Patients with Advanced Non-Small Cell Lung Cancer

- Data at WCLC highlight potential for both antibody drug conjugates as targeted treatments in this setting

Munich and Basking Ridge, NJ – (January 29, 2021) – New research data from Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca's datopotamab deruxtecan and ENHERTU® (trastuzumab deruxtecan) showed encouraging results from both DXd antibody drug conjugates (ADCs) in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

Updated results from the TROPION-PanTumor01 phase 1 trial showed promising clinical activity for datopotamab deruxtecan, a TROP2 directed DXd ADC, in patients with advanced or metastatic NSCLC. Additionally, an interim analysis of the HER2 overexpressing cohort of the DESTINY-Lung01 phase 2 trial showed preliminary evidence of antitumor activity for ENHERTU, a HER2 directed ADC, in patients with metastatic NSCLC. These data were presented today in two oral presentations during the World Conference on Lung Cancer (WCLC) hosted by the International Association for the Study of Lung Cancer (IASLC).

Lung cancer is the leading cause of cancer death among both men and women and accounts for about one-fifth of all cancer deaths globally, with 80 to 85% classified as NSCLC.[1,2,3] For patients with metastatic disease, prognosis is particularly poor, as only 6 to 10% live beyond five years after diagnosis.[4] Currently, there are no TROP2 directed or HER2 directed medicines approved for the treatment of NSCLC.

“Developing innovative therapies for patients with lung cancer, including those that target TROP2 and HER2, are important as few treatment options remain once progression occurs in the metastatic setting following treatment with platinum-based chemotherapy and immune checkpoint inhibitors,” said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology Research and Development, Daiichi Sankyo. “We are encouraged by these preliminary results, which may indicate a durability of effect of datopotamab deruxtecan. We remain committed with AstraZeneca to our bold development plan, particularly the ongoing pivotal phase 3 trial of datopotamab deruxtecan monotherapy in patients with metastatic non-small cell lung cancer.”

"Antibody drug conjugates have transformative potential for the targeted treatment of advanced lung cancer, and the early data for datopotamab deruxtecan and ENHERTU suggest a promising durable benefit in patients who have limited treatment options," said Cristian Massacesi, MD, Senior Vice President, Head of Late Stage Development, Oncology R&D, AstraZeneca. "Both are potent ADCs, and we look forward to further clinical data from these development programs in patients with lung cancer."

TROPION-PanTumor01 Trial Results

In the TROPION-PanTumor01 phase 1 trial, an objective response rate (ORR) ranging from 21 to 25%, as assessed by independent central review, was observed in 159 patients with advanced or metastatic NSCLC receiving different doses of datopotamab deruxtecan (4 mg/kg, 6 mg/kg or 8 mg/kg) as of data cutoff on September 4, 2020. Thirty-two confirmed complete or partial responses were seen, and an additional five complete or partial responses are still too early to confirm. Efficacy data were preliminary due to immaturity of follow-up across dose groups, but preliminary efficacy results may support durability of clinical activity. A disease control rate (DCR) ranging from 67 to 80% was observed with a median progression-free survival (PFS) ranging from 4.3 to 8.2 months across the three doses of datopotamab deruxtecan.

"These updated preliminary results from TROPION-PanTumor01 are encouraging as responses were seen across all three doses of datopotamab deruxtecan, underscoring the potential of targeting TROP2 with an antibody drug conjugate in advanced or metastatic non-small cell lung cancer," said Alexander Spira, MD, PhD, FACP, Oncologist, Virginia Cancer Specialists, U.S. Oncology Research and Johns Hopkins Oncology. "We look forward to seeing the results from the phase 3 trial, which will further evaluate datopotamab deruxtecan versus chemotherapy, the current standard of care for patients with advanced disease that has progressed following treatment with platinum chemotherapy and immunotherapy."

The safety profile of datopotamab deruxtecan seen in this expanded data set of TROPION-PanTumor01 phase 1 trial remains consistent with what has been previously reported. Overall, the 4 mg/kg and 6 mg/kg doses were better tolerated than the 8 mg/kg dose. The most common Grade 3 or greater treatment emergent adverse events (TEAEs) included mucosal inflammation, anemia, stomatitis and fatigue, with patients treated at the 8 mg/kg dose experiencing higher rates overall. The most common TEAEs overall in ≥15% of patients included nausea, stomatitis, alopecia and fatigue. Fourteen cases (8%) of interstitial lung disease (ILD) occurred as determined by an independent adjudication committee. The majority of ILD cases (12/14) were observed with the 8mg/kg cohort, including three deaths (Grade 5). One grade 3 ILD event was seen with the 4 mg/kg dose and one grade 2 ILD was seen with the 6 mg/kg dose.

Based on the efficacy and safety findings, the 6 mg/kg dose has been identified as the recommended dose for the pivotal TROPION-Lung01 phase 3 trial.

The majority of patients across all three doses were previously treated with three or more prior lines of therapy including platinum-based chemotherapy (94%) or immunotherapy (84%). Median duration of follow-up was 7.4 months (range, 0.10-21.7). As of data cutoff on September 4, 2020, 39% of patients remained on treatment with datopotamab deruxtecan.

Summary of TROPION-PanTumor01 Results

Efficacy Measure	**4 mg/kg (n=40[i])**	**6 mg/kg (n=39[i])**	**8 mg/kg (n=80[i])**
ORR (%)[ii]	23% (n=9)	21% (n=8)	25% (n=20)
Confirmed CR/PR (n)[ii]	n=7	n=6	n=19
CR/PR (Too early to be confirmed)[ii]	n=2	n=2	n=1
PD (%)	15% (n=6)	21% (n=8)	9% (n=7)
DCR (%)[iii]	73% (n=29)	67% (n=26)	80% (n=64)

CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response

[i] Includes patients with ≥1 postbaseline scan or who discontinued treatment.

[ii] ORR is CR+PR; Responses are confirmed (CRs/PRs; n=32) plus those CRs/PRs too early to be confirmed (n=5).

[iii] DCR is CR+PR+SD

[iv] Preliminary PFS limited by earlier censoring by data cutoff due to immature duration of follow-up for 4 and 6 mg/kg dose cohorts.

DESTINY-Lung01 Trial Results

In the interim analysis of cohort 1 from the DESTINY-Lung01 phase 2 trial, the primary endpoint of confirmed ORR assessed by independent central review, was 24.5% (12/49) for extensively treated patients with HER2 overexpressing (defined as IHC3+ or IHC2+) metastatic NSCLC treated with ENHERTU (6.4 mg/kg) (n=49), as of the data cutoff on May 30, 2020. One complete response and 11 partial responses were observed. Patients achieved a DCR of 69.4% (34/49 patients [CI 95%, range, 54.6-81.8 patients]) with a median PFS of 5.4 months (95% CI, range, 2.8-7.0 months). After a median follow-up of 6.1 months (range, 0.4-18 months), the estimated median duration of response (DoR) was 6 months (95% CI, range, 3.2-NE months) and the median overall survival (OS) was 11.3 months (95% CI, range 7.8-NE months).

The overall safety and tolerability profile of ENHERTU was consistent with what has been previously observed in other trials. The most common grade 3 or greater (>15%) TEAE was decreased neutrophil count (20.4%). There were eight cases of treatment-related ILD reported, as determined by an independent adjudication committee, including two grade 1, three grade 2, and three deaths (grade 5).

Patients were treated with a median of three prior lines of therapy (range, 1-8) with most receiving platinum-based chemotherapy (91.8%), anti-PD-1 or PD-L1 treatment (73.5%), or docetaxel (24.5%). Median treatment

duration was 18 weeks (range, 3.0-57.1 weeks). As of data cutoff on May 30, 2020, 22% of patients with HER2 overexpressing metastatic NSCLC remained on treatment with ENHERTU.

Results from the HER2 mutant metastatic NSCLC cohort of DESTINY-Lung01, with a data cutoff on November 25, 2019, were previously presented during the 2020 American Society of Clinical Oncology (ASCO) virtual meeting, and also were featured as an encore presentation at WCLC.

About NSCLC

Lung cancer is the leading cause of cancer death among both men and women and accounts for about one-fifth of all cancer deaths.[1] NSCLC accounts for approximately 80 to 85% of all lung cancers.[2,3] For patients with metastatic disease, prognosis is particularly poor, as only 6 to 10% will live beyond five years after diagnosis.[4] The introduction of targeted therapies and checkpoint inhibitors in recent years has improved the treatment landscape for patients with advanced NSCLC; however, new approaches are needed for those who are not eligible for available treatments, or whose cancer continues to progress.[5] Currently, there are no TROP2 directed or HER2 directed medicines approved for the treatment of NSCLC.

TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is overexpressed in many cancers.[6] TROP2 expression has been associated with poor overall and disease-free survival in several types of solid tumors. TROP2 expression has been observed in up to 64% of adenocarcinoma and up to 75% of squamous cell carcinoma NSCLC.[7,8,9]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including lung, breast, gastric and colorectal cancers. HER2 overexpression is associated with a specific HER2 gene alteration known as HER2 amplification and is often associated with aggressive disease and poorer prognosis.[10] It has been reported in up to one-third of patients with NSCLC.[11,12]

Other HER2 gene alterations (called HER2 mutations) have been identified in NSCLC, specifically adenocarcinomas, as distinct molecular targets and have been reported in approximately 2 to 4% of patients with NSCLC.[12,13,14,15] These acquired HER2 gene mutations have been independently associated with cancer cell growth and poor prognosis.[13,14]

About TROPION-PanTumor01

TROPION-PanTumor01 is a first-in-human, open-label, two-part, multicenter phase 1 trial designed to evaluate the safety, tolerability and preliminary efficacy of datopotamab deruxtecan in patients with advanced solid tumors, including NSCLC and triple negative breast cancer (TNBC), that are refractory to or relapsed from standard treatment or for whom no standard treatment is available.

The first part of the study (dose escalation) assessed the safety and tolerability of increasing doses of datopotamab deruxtecan to determine the maximum tolerated dose and/or recommended dose for expansion in patients with unresectable advanced NSCLC. The second part of the study (dose expansion) is further assessing the safety and tolerability of datopotamab deruxtecan at selected dose levels (4 mg/kg, 6 mg/kg and 8 mg/kg) in patients with NSCLC. A cohort of patients with unresectable/advanced or metastatic TNBC evaluating datopotamab deruxtecan (8 mg/kg) was added to the trial in July 2020.

Safety endpoints include dose limiting toxicities and serious adverse events. Efficacy endpoints include ORR, DoR, DCR, time to response, PFS and OS. Pharmacokinetic, biomarker and immunogenicity endpoints also are being evaluated.

About DESTINY-Lung01

DESTINY-Lung01 is a global, phase 2, open-label, multicenter, two-cohort trial evaluating the safety and efficacy of ENHERTU in 170 patients with HER2 mutant (6.4 mg/kg) or HER2 overexpressing (defined as IHC 3+ or IHC 2+; 6.4 mg/kg and 5.4 mg/kg) unresectable and metastatic non-squamous NSCLC. Patients had progressed after one or more systemic therapies including chemotherapy, molecular targeted therapy or immunotherapy. The primary endpoint is ORR by independent central review. Key secondary endpoints include DoR, DCR, PFS and OS.

About the Daiichi Sankyo and AstraZeneca Collaboration

ENHERTU® (T-DXd; trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) and datopotamab deruxtecan (Dato-DXd; DS-1062) are two lead DXd ADCs in the oncology pipeline of Daiichi Sankyo, and the most advanced programs in AstraZeneca's ADC scientific platform.

Each ADC is engineered using Daiichi Sankyo's proprietary and portable DXd ADC technology to target and deliver chemotherapy inside cancer cells that express a specific cell surface antigen. Both ENHERTU (a HER2 directed ADC) and datopotamab deruxtecan (a TROP2 directed ADC) consist of a monoclonal antibody attached to a topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU in March 2019, and datopotamab deruxtecan in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for manufacturing and supply of ENHERTU and datopotamab deruxtecan.

About the Datopotamab Deruxtecan Clinical Development Program

Datopotamab deruxtecan is currently being evaluated in a comprehensive development program across lung cancer and other solid tumors including breast cancer. The development program includes TROPION-Lung01, a pivotal phase 3 head-to-head trial in patients with advanced or metastatic NSCLC without actionable genomic alterations; TROPION-Lung05, a phase 2 trial in patients with advanced or metastatic NSCLC with actionable genomic alterations; TROPION-Lung02, a phase 1b trial in combination with pembrolizumab in patients with advanced or metastatic NSCLC without actionable genomic alterations; TROPION-Lung04, a phase 1b trial in combination with durvalumab in patients with advanced or metastatic NSCLC without actionable genomic alterations; and, TROPION-PanTumor01, a phase 1 dose escalation and expansion study in patients with unresectable advanced NSCLC, and expansion cohort for patients with TNBC whose disease has progressed on standard treatments or for whom no standard treatment is available. Additional expansion cohorts evaluating other tumor types are currently planned.

Datopotamab deruxtecan is an investigational agent that has not been approved for any indication in any country. Safety and efficacy have not been established.

About ENHERTU

ENHERTU® (5.4 mg/kg; trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is approved in the U.S under accelerated approval, in the EU under conditional marketing authorization, and in Japan under the conditional early approval system for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting based on the results from the DESTINY-Breast01 trial.

ENHERTU (6.4 mg/kg) is also approved in the U.S. and Japan for the treatment of patients with HER2 positive unresectable advanced or recurrent gastric cancer 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.

About the ENHERTU Clinical Development Program

A comprehensive development program is underway globally with nine pivotal trials evaluating the efficacy and safety of ENHERTU monotherapy across multiple HER2 targetable cancers including breast, gastric and lung cancers. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

In May 2020, ENHERTU received Breakthrough Therapy Designation (BTD) in the U.S. for the treatment of patients with metastatic non-small cell lung cancer whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy.

U.S. Important Safety Information for ENHERTU

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

- Unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

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

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

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

Contraindications
None.

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

Metastatic Breast Cancer
In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis

occurred in 2.6% of patients treated with ENHERTU. Median time to first onset was 4.1 months (range: 1.2 to 8.3).

Locally Advanced or Metastatic Gastric Cancer
In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

Neutropenia

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

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

Locally Advanced or Metastatic Gastric Cancer
In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, a decrease in neutrophil count was reported in 72% of patients. Fifty-one percent had Grade 3 or 4 decreased neutrophil count. Median time to first onset of decreased neutrophil count was 16 days (range: 4 to 187). Febrile neutropenia was reported in 4.8% of patients.

Left Ventricular Dysfunction

Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment.

Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. When LVEF is >45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure.

Embryo-Fetal Toxicity

ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

Additional Dose Modifications

Thrombocytopenia

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

Adverse Reactions

Metastatic Breast Cancer

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

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

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

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

Locally Advanced or Metastatic Gastric Cancer

The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=55) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group.

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

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

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

Use in Specific Populations

- **Pregnancy:** ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.
- **Lactation:** There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
- **Females and Males of Reproductive Potential:** Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: *Females*: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. *Males*: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
- **Pediatric Use:** Safety and effectiveness of ENHERTU have not been established in pediatric patients.
- **Geriatric Use:** Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were ≥65 years and 5% were ≥75 years. No overall differences in efficacy were observed between patients ≥65 years of age compared to younger patients. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged ≥65 years (53%) as compared to younger patients (42%). Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
- **Hepatic Impairment:** In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

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

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

About Daiichi Sankyo Cancer Enterprise

The mission of Daiichi Sankyo Cancer Enterprise is to leverage our world-class, innovative science and push beyond traditional thinking to create meaningful treatments for patients with cancer. We are dedicated to

transforming science into value for patients, and this sense of obligation informs everything we do. Anchored by our DXd antibody drug conjugate (ADC) technology, our powerful research engines include biologics, medicinal chemistry, modality and other research laboratories in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in Berkeley, CA. For more information, please visit: www.DSCancerEnterprise.com.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 15,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for cardiovascular diseases, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo is primarily focused on providing novel therapies in oncology, as well as other research areas centered around rare diseases and immune disorders. For more information, please visit: www.daiichisankyo.com.

Media Contacts:

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

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

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

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

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

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