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Daiichi-Sankyo

Press Release

Late-Breaking Data for Daiichi Sankyo's HER3 Directed ADC Patritumab Deruxtecan in EGFR Mutated NSCLC to be Presented at 2020 ESMO Annual Meeting

- Late-breaking results report first findings of phase 1 dose expansion cohort data for patritumab deruxtecan (U3-1402) in patients with EGFR mutated unresectable advanced non-small cell lung cancer
- Data from the HER2 low exploratory cohorts of the pivotal phase 2 DESTINY-Gastric01 trial of ENHERTU® also to be presented

Basking Ridge, NJ and Munich – (September 9, 2020) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that it will present new research data for patritumab deruxtecan (U3-1402) and ENHERTU® (fam-trastuzumab deruxtecan-nxki), two of its lead DXd antibody drug conjugates (ADC), at the 2020 European Society of Medical Oncology (ESMO) Virtual Scientific Program to be held September 19-21, 2020 (#ESMO20).

The late-breaking presentation of patritumab deruxtecan, a potential first-in-class HER3 directed ADC, will feature an analysis that includes the first safety and efficacy results from the dose expansion cohort of a phase 1 clinical trial in patients with EGFR mutated unresectable advanced non-small cell lung cancer (NSCLC) previously treated with a tyrosine kinase inhibitor (TKI) and platinum-based chemotherapy. Data from the HER2 low expression exploratory cohorts of the pivotal phase 2 DESTINY-Gastric01 study of ENHERTU in patients with previously treated advanced gastric or gastroesophageal junction cancer will also be presented.

"We look forward to presenting these new results from the ongoing phase 1 study of patritumab deruxtecan in patients with previously treated, advanced EGFR mutated NSCLC, which reflect encouraging progress in the clinical development of this HER3 directed therapy," said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. "These data, along with the current body of research across our ADC portfolio, demonstrate significant progress in our oncology pipeline and underscore our commitment to translating our DXd ADC technology into potential new treatment options for patients across a number of tumor types."

Following is an overview of the research data from the oncology portfolio of Daiichi Sankyo to be presented at ESMO 2020:

ESMO Virtual Scientific Program Abstract Title	Presentation Details
PATRITUMAB DERUXTECAN (HER3 ADC)	
Efficacy and safety of patritumab deruxtecan (U3-1402), a novel HER3 directed antibody drug conjugate, in patients with EGFR-mutated (EGFRm) NSCLC	Late-Breaker Mini-Oral Presentation (#LBA62): H Yu, et al.; September 18, 2020 at 9:00 a.m. CEST
ENHERTU (HER2 ADC)	
Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2 low, advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: results of the exploratory cohorts in the phase 2, multicenter, open-label DESTINY-Gastric01 study	Mini-Oral Presentation (#1422MO): Yamaguchi, et al. Gastrointestinal tumors, non-colorectal; September 18, 2020 at 9:00 a.m. CEST
A phase 1b/2, multicenter, open-label, dose-escalation and dose-expansion study evaluating trastuzumab deruxtecan (T-DXd; DS-8201) monotherapy and combinations in patients with HER2-overexpressing gastric cancer (DESTINY-Gastric03) [TiP]	E-poster Presentation (#1500TiP): Janjigian, et al.; September 17, 2020 at 9:00 a.m. CEST
Patient preferences for HER2-targeted treatment of advanced or metastatic breast cancer in the United States	E-poster Presentation (#340P): Mansfield, et al.; September 17, 2020 at 9:00 a.m. CEST
Risk factors for interstitial lung disease in patients treated with trastuzumab deruxtecan from two interventional studies	E-poster Presentation (#289P): Powell, et al.; September 17, 2020 at 9:00 a.m. CEST
Artificial intelligence analysis of advanced breast cancer patients from a phase 1 trial of trastuzumab deruxtecan (T-DXd): HER2 and histopathology features as predictors of clinical benefit	E-poster Presentation (#286P): Modi, et al.; September 17, 2020 at 9:00 a.m. CEST

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of seven antibody drug conjugates (ADCs) with five in clinical development across multiple types of cancer. These include ENHERTU, a HER2 directed ADC, and DS-1062, a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca; patritumab deruxtecan (U3-1402), a HER3 directed ADC; and DS-7300, a B7-H3 directed ADC, and DS-6157, a GPR20 directed ADC, which are being developed through a strategic research collaboration with Sarah Cannon Cancer Institute.

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. Each ADC consists of a monoclonal antibody attached by a stable tetrapeptide-based linker to a topoisomerase I inhibitor payload (chemotherapy) with a customized drug to antibody ratio (DAR) to optimize the risk-benefit ratio for the intended patient population.

ENHERTU (5.4 mg/kg) is approved in the U.S. and Japan for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who received two or more prior anti-HER2-based regimens in the metastatic setting based on the DESTINY-Breast01 trial. ENHERTU has not been approved in the EU, or countries outside of the U.S. and Japan for any indication. It is an investigational agent globally for various indications. Safety and effectiveness have not been established for the proposed uses being investigated in ongoing studies. Patritumab deruxtecan (U3-1402) is an investigational agent that has not been approved for any indication in any country. Safety and efficacy have not been established.

U.S. FDA-Approved Indication for ENHERTU
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.

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. In clinical studies, of the 234 patients with unresectable or metastatic HER2-positive breast cancer treated with ENHERTU, 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).

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 prednisolone or equivalent). For symptomatic ILD/pneumonitis (Grade 2 or greater), permanently discontinue ENHERTU. Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected (e.g., ≥1 mg/kg prednisolone or equivalent). Upon improvement, follow by gradual taper (e.g., 4 weeks).

Neutropenia

Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU. Of the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, a decrease in neutrophil count was reported in 30% of patients and 16% had Grade 3 or 4 events. Median time to first onset was 1.4 months (range: 0.3 to 18.2). Febrile neutropenia was reported in 1.7% of patients.

Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Based on the severity of neutropenia, ENHERTU may require dose interruption or reduction. 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.

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. 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. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of <40% or absolute decrease from baseline of >20% is confirmed. 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.

Adverse Reactions
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 adverse reactions (frequency ≥20%) were nausea (79%), fatigue (59%), vomiting (47%), alopecia (46%), constipation (35%), decreased appetite (32%), anemia (31%), neutropenia (29%), diarrhea (29%), leukopenia (22%), cough (20%), and thrombocytopenia (20%).

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%).
- **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 WARNING, 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.

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