

Press Release

Daiichi Sankyo to Present New Data for HER2 and HER3 Directed DXd ADCs at SABCS

- Longer follow-up research data for ENHERTU® based on DESTINY-Breast01, including updated duration of response, progression-free survival, an 18-month landmark analysis of overall survival and longer-term safety profile to be highlighted
- New data from expansion cohorts of phase 1/2 study of patritumab deruxtecan in patients with HR positive, HER2 negative metastatic breast cancer with varying levels of HER3 expression or patients with HER3 high triple negative breast cancer to be presented for first time
- Daiichi Sankyo to hold Virtual R&D Day to discuss key SABCS data and provide future clinical development plans across its oncology portfolio

Munich and Basking Ridge, NJ – (November 17, 2020) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) today announced that it will present new research data for ENHERTU® (fam-trastuzumab deruxtecan-nxki) and patritumab deruxtecan (U3-1402; HER3-DXd), two of its lead DXd antibody drug conjugates (ADC), at the 2020 San Antonio Breast Cancer Symposium (#SABCS20) virtual conference to be held December 8-11, 2020.

Updated results from the pivotal phase 2 DESTINY-Breast01 trial of ENHERTU, a HER2 directed ADC, reporting updated duration of response, progression-free survival, an 18-month landmark analysis of overall survival and longer-term safety seen in previously treated patients with HER2 positive metastatic breast cancer will be presented as a Spotlight Poster Discussion. A first look at new data from the phase 1/2 trial of patritumab deruxtecan, a HER3 directed ADC, reporting on four expansion cohorts of patients with hormone receptor (HR) positive, HER2 negative metastatic breast cancer with varying levels of HER3 expression and triple negative breast cancer with higher levels of HER3 expression will also be presented.

“We look forward to presenting new research data from the DESTINY-Breast01 trial, which will provide updated efficacy and duration of response results, as well as safety outcomes for ENHERTU in patients with previously treated HER2 positive metastatic breast cancer,” said Antoine Yver, MD, MSc, EVP and Global Head, Oncology Research and Development, Daiichi Sankyo. “These research data, as well as the data that will be presented for our HER3 directed ADC, patritumab deruxtecan, continue to reinforce our understanding of the activity of our DXd ADCs and the potential of our DXd ADC technology to provide a potent, durable treatment that selectively targets the cancer cells.”

Additional data to be presented at SABCS includes the initial safety and efficacy results of a phase 1 trial combining ENHERTU with nivolumab in a cohort of patients with HER2 expressing metastatic breast cancer. Trial-in-progress updates from four additional DESTINY-Breast studies will also be presented, including a summary of the first study of ENHERTU in patients with early breast cancer in a head-to-head comparison with ado-trastuzumab emtansine (T-DM1).

Following SABCS, Daiichi Sankyo will hold its R&D Day remotely for investors and analysts on Tuesday, December 15, 2020 at 7-9 pm JST/5-7 am EST. Company executives will provide an overview of the Daiichi Sankyo data presented at SABCS; provide an update on the company's R&D strategy, including updated clinical development plans across the DXd ADC portfolio; and address questions from investors and analysts.

Following is an overview of data from Daiichi Sankyo to be presented at SABCS:

SABCS Abstract	Presentation Details
ENHERTU (HER2 ADC)	
Updated results from DESTINY-Breast01, a phase 2 trial of trastuzumab deruxtecan in HER2 positive metastatic breast cancer	Spotlight Poster Discussion 3 (Abstract 1190; PD3-06) Modi, et al. Advances in the Treatment of HER2+ Disease; Wednesday, December 9, 2020 at 6:30 pm CT
Trastuzumab deruxtecan with nivolumab in patients with HER2 expressing advanced breast cancer: a two-part, phase 1b, multicenter, open-label study	Spotlight Poster Discussion 3 (Abstract 299; PD3-07) Hamilton, et al. Advances in the Treatment of HER2+ Disease; Wednesday, December 9, 2020 at 6:30 pm CT
Novel approach to HER2 quantification: digital pathology coupled with AI-based image and data analysis delivers objective and quantitative HER2 expression analysis for enrichment of responders to T-DXd, specifically in HER2 low patients	Spotlight Poster Discussion 6 (Abstract 1130; PD6-01) Gustavson, et al. Novel Approaches to Pathology and Imaging; Thursday, December 10, 2020 at 3:30 pm CT
Trastuzumab deruxtecan vs. trastuzumab emtansine in high risk patients with HER2 positive, residual invasive early breast cancer after neoadjuvant therapy: a randomized, phase 3 trial (DESTINY-Breast05) [Trial in Progress]	Poster Presentation (Abstract 323) Geyer, et al. Ongoing Trials Poster OT-03-01; Wednesday, December 9, 2020 at 8:00 am CT
Trastuzumab deruxtecan vs. investigator's choice chemotherapy in patients with hormone receptor positive, HER2 low metastatic breast cancer whose disease has progressed on endocrine therapy in the metastatic setting: a randomized, phase 3 trial (DESTINY-Breast06) [Trial in Progress]	Poster Presentation (Abstract 1219) Bardia, et al. Ongoing Trials Poster OT-03-09; Wednesday, December 9, 2020 at 8:00 am CT
Trastuzumab deruxtecan combinations in patients with HER2 positive advanced or metastatic breast cancer: a phase 1b/2 open-label, multicenter, dose finding and dose expansion study (DESTINY-Breast07) [Trial in Progress]	Poster Presentation (Abstract 428) Andre, et al. Ongoing Trials Poster OT-03-04; Wednesday, December 9, 2020 at 8:00 am CT
Trastuzumab deruxtecan combinations in patients with HER2 low metastatic breast cancer: a phase 1b open-label, multicenter, dose finding and expansion study (DESTINY-Breast08) [Trial in Progress]	Poster Presentation (Abstract 532) Jhaveri, et al. Ongoing Trials Poster OT-03-05; Wednesday, December 9, 2020 at 8:00 am CT
A real-world evidence study of treatment patterns among patients with HER2 positive metastatic breast cancer (mBC)	Poster Presentation (Abstract 426) Collins, et al. Epidemiology PS7-82; Wednesday, December 9, 2020 at 8:00am CT

Patritumab Deruxtecan (HER3 ADC)	
Safety and efficacy results from the phase 1/2 study of U3-1402, a human epidermal growth factor receptor 3 (HER3) directed antibody drug conjugate (ADC), in patients with HER3 expressing metastatic breast cancer (MBC)	Spotlight Poster Discussion 1 (Abstract 814) Krop, et al. Novel Therapeutics; Wednesday, December 9, 2020 at 4:00 pm CT

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of seven antibody drug conjugates (ADCs) of which five are currently in clinical development across multiple types of cancer. These include ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (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).

ENHERTU (fam-trastuzumab deruxtecan-nxki) (5.4 mg/kg) is approved in the U.S. under accelerated approval and Japan 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 and is under accelerated assessment in the European Union.

ENHERTU is approved in the U.S. with Boxed WARNINGS for Interstitial Lung Disease and Embryo-Fetal Toxicity.

ENHERTU (6.4 mg/kg) is also approved in Japan for the treatment of patients with HER2 positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy based on the results from the [DESTINY-Gastric01](#) 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 is currently being evaluated in a phase 1 study in previously treated patients with metastatic or unresectable non-small cell lung cancer (NSCLC) and a phase 1/2 study in patients with HER3 expressing metastatic breast cancer. A phase 2 study of patritumab deruxtecan has recently been initiated in patients with advanced or metastatic colorectal cancer who are resistant, refractory, or intolerant to at least two prior lines of systemic therapy. Patritumab deruxtecan is an investigational agent that has not been approved

for any indication in any country. The profile of clinical safety and efficacy for patritumab deruxtecan has 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 $0.5 \times 10^9/L$) 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. Reduce dose by one level. For febrile neutropenia (ANC $<1.0 \times 10^9/L$ and temperature $>38.3^\circ\text{C}$ or a sustained temperature of $\geq 38^\circ\text{C}$ 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 $\geq 20\%$) 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 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.

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