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Daiichi-Sankyo

Press Release

ENHERTU® Approved in the U.S. for HER2 Positive Unresectable or Metastatic Breast Cancer Following Two or More Prior Anti-HER2-Based Regimens

- Accelerated Approval of Daiichi Sankyo and AstraZeneca's ENHERTU® (fam-trastuzumab deruxtecan-nxki) based on the pivotal DESTINY-Breast01 trial that showed clinically meaningful and durable responses

Tokyo, Munich and Basking Ridge, NJ – (December 20, 2019) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca today announced that the U.S. Food and Drug Administration (FDA) has approved ENHERTU® (fam-trastuzumab deruxtecan-nxki), a HER2 directed antibody drug conjugate (ADC), 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.

This press release features multimedia. View the full release here.

"Once patients with HER2 positive metastatic breast cancer progress following at least two HER2 targeted regimens in the metastatic setting, there are limited treatment options," said Shanu Modi, MD, Breast Medical Oncologist, Memorial Sloan Kettering Cancer Center. "ENHERTU has the potential to become a new standard of care."

The FDA approval is based on the results of the single-arm, pivotal phase 2 DESTINY-Breast01 trial of ENHERTU (5.4 mg/kg) monotherapy in 184 female patients with HER2 positive metastatic breast cancer. Trial results showed a confirmed objective response rate (ORR) of 60.3% (n=111; 95% CI: 52.9-67.4), including a 4.3% complete response rate (n=8) and a 56.0% partial response rate (n=103).[1] A median duration of response of 14.8 months (95% CI: 13.8-16.9) was demonstrated as of August 1, 2019. In addition, a median progression free survival of 16.4 months (95% CI: 12.7-Not Estimable), based on a median follow-up of 11.1 months, was recently reported at the San Antonio Breast Cancer Symposium (SABCS) and published online in *The New England Journal of Medicine*.[2]

ENHERTU is approved with a Boxed WARNING for Interstitial Lung Disease (ILD)/pneumonitis and Embryo-Fetal Toxicity. The safety of ENHERTU has been 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 the DESTINY-Breast01 trial and a phase 1 trial. ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in six patients (2.6%) – two deaths already reported from the phase 1 trial and four deaths already reported

in the phase 2 DESTINY-Breast01 trial. Patients and physicians should be aware of ILD/pneumonitis and patients should be actively monitored for potential signs and symptoms. If ILD/pneumonitis is identified, it should be managed as per the FDA approved Prescribing Information. Management may require dose modification or treatment discontinuation and steroid treatment. ENHERTU can cause fetal harm when administered to a pregnant woman. The most common adverse reactions (frequency ≥20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough and thrombocytopenia.

Patients enrolled in DESTINY-Breast01 received a median of five prior regimens (range: 2 -17) in the locally advanced/metastatic setting. All patients received prior trastuzumab, ado-trastuzumab emtansine, and 66% had prior pertuzumab.

“The approval of ENHERTU underscores that this specifically engineered HER2 directed antibody drug conjugate is delivering on its intent to establish an important new treatment for patients with HER2 positive metastatic breast cancer,” said Antoine Yver, MD, MSc, Executive Vice President and Global Head, Oncology R&D, Daiichi Sankyo. “Since the beginning of our clinical trial program four years ago, we have focused on the opportunity to transform the treatment landscape for patients with HER2 positive metastatic breast cancer, and we are extremely proud of how quickly we delivered ENHERTU to patients in the U.S., as ENHERTU represents one of the fastest developed biologics in oncology.”

“ENHERTU has shown impressive results in women with HER2 positive metastatic breast cancer, with the majority of women benefiting from treatment and the median duration of response exceeding 14 months,” said José Baselga, MD, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “With this first approval, we are proud to bring ENHERTU to patients with high unmet need and we look forward to further exploring its potential in additional settings.”

ENHERTU will be available by prescription in the U.S. within the coming weeks. Daiichi Sankyo and AstraZeneca are committed to ensuring that patients in the U.S. who are prescribed ENHERTU can access the medication and receive necessary financial support. Provider and patient support, reimbursement and distribution for ENHERTU in the U.S. will be accessible by visiting www.ENHERTU4U.com or calling 1-833-ENHERTU (1-833-364-3788).

Please visit www.ENHERTU.com for full Prescribing Information, including Boxed WARNING, and Medication Guide.

Important Safety Information

Indication
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 HER2 Positive Breast Cancer

Approximately one in five breast cancers are HER2 positive.[3,4] Despite recent improvements and approvals of new medicines, there remain significant clinical needs for patients with HER2 positive metastatic breast cancer.[5,6] This disease remains incurable with patients eventually progressing after available treatment.[5,6]

About HER2

HER2 is a tyrosine kinase receptor growth-promoting protein found on the surface of some cancer cells that is associated with aggressive disease and poor prognosis in patients with breast cancer.[7] To be considered HER2 positive, tumor cancer cells are usually tested by one of two methods: immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH). IHC test results are reported as: 0, IHC 1+, IHC 2+, or IHC 3+.[7] A finding of IHC 3+ and/or FISH amplification is considered positive.[7]

About DESTINY-Breast01

DESTINY-Breast01 is a pivotal phase 2, single-arm, open-label, global, multicenter, two-part trial evaluating the safety and efficacy of ENHERTU in 184 female patients with HER2 positive unresectable and/or metastatic breast cancer previously treated with ado-trastuzumab emtansine (T-DM1). The primary endpoint of the trial is objective response rate, as determined by independent central review. Secondary objectives include pharmacokinetics, duration of response, disease control rate, clinical benefit rate, progression-free survival, overall survival and safety.

About the Clinical Development Program

A comprehensive development program for fam-trastuzumab deruxtecan-nxki is underway globally with five pivotal trials in HER2 expressing metastatic breast and gastric cancer, including a trial in patients with metastatic breast cancer and low levels of HER2 expression (HER2 low). Phase 2 trials are underway for HER2 expressing advanced colorectal cancer as well as metastatic non-squamous HER2 overexpressing or HER2 mutated non-small cell lung cancer. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

A regulatory submission also has been made to Japan's Ministry of Health, Labour and Welfare (MHLW) for the treatment of HER2 positive metastatic breast cancer, and it has previously received SAKIGAKE designation for the treatment of advanced HER2 positive gastric or gastroesophageal junction cancer by Japan's MHLW.

About ENHERTU

ENHERTU (fam-trastuzumab deruxtecan-nxki), formerly known as DS-8201, is the lead product in the ADC Franchise of the Daiichi Sankyo Cancer Enterprise and the most advanced program in AstraZeneca's ADC Scientific platform. ADCs are targeted cancer medicines that deliver cytotoxic chemotherapy ("payload") to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells.

Designed using Daiichi Sankyo's proprietary DXd ADC technology, ENHERTU is comprised of a HER2 monoclonal antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide-based linker.

ENHERTU received Priority Review, Breakthrough Therapy Designation, and Fast Track Designation from the FDA for the treatment of select patients with HER2 positive metastatic breast cancer.

About the Collaboration between Daiichi Sankyo and AstraZeneca

In March 2019, Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize fam-trastuzumab deruxtecan-nxki as a potential new medicine worldwide, except in Japan where Daiichi Sankyo will maintain exclusive rights. Daiichi Sankyo will be solely responsible for the manufacturing and supply.

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.

Dr. Shanu Modi has received compensation from Daiichi Sankyo for advisory services.

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PP-US-8201a-0527
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