

Press Release

ENHERTU® Granted Breakthrough Therapy Designation in the U.S. for HER2 Mutant Metastatic Non-Small Cell Lung Cancer

- Designation based on phase 2 DESTINY-Lung01
- This is the third Breakthrough Therapy Designation for ENHERTU, highlighting its potential to treat multiple HER2 cancers

Tokyo, Basking Ridge, NJ and Munich - (May 18, 2020) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca’s ENHERTU® (fam-trastuzumab deruxtecan-nxki) has been granted Breakthrough Therapy Designation (BTD) in the U.S. for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a HER2 mutation and with disease progression on or after platinum-based therapy.

NSCLC is the most common type of lung cancer, and prognosis is particularly poor for patients with metastatic disease as only about six to 10 percent will be alive five years after diagnosis.^{1,2} Approximately two to four percent of patients with NSCLC have a HER2 mutation.^{3,4}

The U.S. Food and Drug Administration’s (FDA) BTD is designed to accelerate the development and regulatory review of potential new medicines that are intended to treat a serious condition and address a significant unmet medical need. The new medicine needs to have shown encouraging preliminary clinical results that demonstrate substantial improvement on a clinically significant endpoint over available medicines.

“We are encouraged by the promising evidence of activity seen with ENHERTU in patients with advanced lung cancer and a HER2 mutation,” said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. “We look forward to working closely with the FDA on the potential for ENHERTU to become the first HER2 directed therapy approved for non-small cell lung cancer.”

“Today’s news is very welcome as we continue to evaluate the potential of ENHERTU to help patients with this devastating type of lung cancer,” said José Baselga, MD, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “Targeted treatments and immunotherapies are demonstrating tremendous

advancements, but there remains an unmet medical need for patients with HER2 mutations who are not benefiting from such therapies or for those whose cancer continues to progress.”

The FDA granted BTM based on data from ongoing phase 2 [DESTINY-Lung01](#) trial currently assessing ENHERTU, a HER2 directed antibody drug conjugate (ADC), in patients with HER2 mutant metastatic NSCLC and data from the phase 1 trial published in *Cancer Discovery*. An interim analysis from DESTINY-Lung01 will be presented at the 2020 American Society of Clinical Oncology (ASCO20) Virtual Scientific Program.

The overall safety and tolerability profile of ENHERTU in the ongoing DESTINY-Lung01 trial is consistent with that seen in the phase 1 trial. The most common adverse events to date (n=42) are gastrointestinal and hematological including nausea, alopecia, anemia, decreased appetite and decreased neutrophil count. There have been five cases of drug-related interstitial lung disease (ILD) and pneumonitis in patients with HER2 mutant NSCLC, all of which were grade 2. There have been no ILD-related deaths.

This is the third BTM granted for ENHERTU in the U.S., and the fourth expedited regulatory designation received globally. Last week, ENHERTU received [BTM](#) in patients with HER2 positive unresectable gastric or gastroesophageal junction adenocarcinoma who have received two or more prior regimens including trastuzumab.

ENHERTU recently received accelerated approval in the [U.S.](#) and approval in [Japan](#) under the conditional early approval system for the treatment of adult patients with unresectable or metastatic HER2 positive metastatic breast cancer who have received two or more prior anti-HER2 based regimens.

About HER2

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors including gastric, breast and lung cancers. In some tumors, HER2 overexpression is associated with a specific HER2 gene alteration known as amplification and is often associated with aggressive disease and poorer prognosis.⁵

Other HER2 gene alterations (called HER2 mutations) have been identified in NSCLC, specifically adenocarcinomas, as distinct molecular targets.^{4,6} Approximately two to four percent of patients with NSCLC have HER2 mutations, which have been independently associated with cancer cell growth and poor prognosis.^{3,4}

About Non-Small Cell Lung Cancer (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.⁷ In the U.S., it is estimated that 228,820 new cases of lung cancer will be diagnosed in 2020 and more than 135,000 people will die from the disease.⁸

NSCLC accounts for approximately 80 to 85 percent of all lung cancers.⁹ For patients with metastatic disease, prognosis is particularly poor, as only six to 10 percent will be alive five years after diagnosis.¹ 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.¹⁰ Currently, no medicine is specifically approved for patients with HER2 mutant NSCLC.

About DESTINY-Lung01

[DESTINY-Lung01](#) is a global, phase 2, open-label, multicenter, two-cohort study evaluating the safety and efficacy of ENHERTU in 170 patients with HER2 mutant (n=90) or HER2 overexpressing (defined as IHC 3+ or IHC 2+, n=80) unresectable and metastatic non-squamous NSCLC whose cancer has progressed after one or more systemic therapies including chemotherapy, molecular targeted therapy or immunotherapy. The primary endpoint is objective response rate (ORR). Key secondary endpoints include duration of response, disease control rate, progression free survival, and overall survival.

About ENHERTU

ENHERTU (fam-trastuzumab deruxtecan-nxki in the U.S. only; trastuzumab deruxtecan outside the U.S.) is a HER2 directed antibody drug conjugate (ADC) and is the lead ADC in the oncology portfolio of Daiichi Sankyo 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 has been approved for use only in the U.S. and Japan. 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 subject proposed use.

About the ENHERTU Clinical Development Program

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

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 ENHERTU worldwide, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is solely responsible for the manufacturing and supply.

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 $> 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ 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 WARNING, and [Medication Guide](#).

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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References:

- ¹ Goldstraw P, et al. *J Thorac Oncol*. 2016; 11(1):39–51.
- ² American Cancer Society. [Lung Cancer. Early Detection, Diagnosis and Staging](#). January 2020.
- ³ Campbell JD, et al. *Nat Genet*. 2016 Jun;48(6):607-16.
- ⁴ Li BT, et al. *J Thorac Oncol*. 11(3):414-9.
- ⁵ Iqbal N, et al. *Mol Biol Int*. 2014;2014:852748.
- ⁶ Pillai RN, et al. *Cancer*. 2017 Nov 1;123(21):4099-4105.
- ⁷ Bray, F, et al. *CA: Cancer J. Clin* 2018;68:394-424.
- ⁸ American Cancer Society. About Lung Cancer. [Key Statistics for Lung Cancer](#). January 2020.
- ⁹ American Cancer Society. About Lung Cancer. [Types of Lung Cancer](#). January 2020.
- ¹⁰ Economopoulou P, et al. *Ann Transl Med* 2018 Apr; 6(8):138.