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Daiichi-Sankyo

Press Release

ENHERTU® Type II Variation Application Validated in the EU for Previously Treated Patients with HER2 Positive Metastatic Solid Tumors

- Submission based on three phase 2 trials where Daiichi Sankyo and AstraZeneca's ENHERTU showed clinically meaningful responses across a broad range of tumors
- If approved, ENHERTU would become the first HER2 directed medicine and antibody drug conjugate to receive a tumor agnostic indication in the EU

Tokyo and Munich – (September 11, 2025) – The European Medicines Agency (EMA) has validated the Type II Variation marketing authorization application for ENHERTU® (trastuzumab deruxtecan) for the treatment of adult patients with HER2 positive (immunohistochemistry [IHC] 3+) unresectable or metastatic solid tumors who have received prior treatment and have no satisfactory alternative treatment options.

ENHERTU is a specifically engineered HER2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo (TSE: 4568) and being jointly developed and commercialized by Daiichi Sankyo and AstraZeneca (LSE/STO/Nasdaq: AZN).

The validation confirms the completion of the application and commences the scientific review process by the EMA's Committee for Medicinal Products for Human Use. The application is based on data from three phase 2 trials including DESTINY-PanTumor02, DESTINY-CRC02 and DESTINY-Lung01 where ENHERTU demonstrated clinically meaningful responses across a broad range of tumors.

"ENHERTU has shown a clinically meaningful benefit across several studies in HER2 positive metastatic solid cancers and this validation by the EMA is an important first step toward bringing this medicine to these patients in the EU," said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. "We look forward to working with the EMA to potentially secure a tumor agnostic indication for ENHERTU in the EU, similar to several other regions of the world where this approval has been received."

About DESTINY-PanTumor02

DESTINY-PanTumor02 is a global, multicenter, multi-cohort, open-label phase 2 trial evaluating the efficacy and safety of ENHERTU (5.4 mg/kg) for the treatment of previously treated HER2 expressing tumors, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic cancer or other tumors.

The primary efficacy endpoint of DESTINY-PanTumor02 is confirmed objective response rate (ORR) as assessed by investigator. Secondary endpoints include duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, tolerability and pharmacokinetics. Results from DESTINY-PanTumor02 were published in the *Journal of Clinical Oncology.*

DESTINY-PanTumor02 enrolled 267 patients, including 111 HER2 positive (IHC 3+) adult patients, at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-Lung01

DESTINY-Lung01 is a global phase 2, open-label, two-cohort trial evaluating the efficacy and safety of ENHERTU (6.4 mg/kg and 5.4 mg/kg) in patients with *HER2* mutant (cohort 2, n=91) or HER2 overexpressing (defined as IHC 3+ or IHC 2+) (cohort 1 and 1a, n=90) unresectable or metastatic non-small cell lung cancer (NSCLC) who had progressed after one or more systemic therapies.

The primary endpoint is confirmed ORR by independent central review. Key secondary endpoints include DOR, DCR, PFS, OS and safety. Results from the *HER2* mutant cohort were published in *The New England Journal of Medicine* and results from the HER2 overexpressing cohort were published in *The Lancet Oncology*.

DESTINY-Lung01 enrolled 181 patients, including 17 HER2 positive (IHC 3+) adult patients, at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About DESTINY-CRC02

DESTINY-CRC02 is a global, randomized, two arm, parallel, multicenter phase 2 trial evaluating the efficacy and safety of two doses (5.4 mg/kg or 6.4 mg/kg) of ENHERTU in patients with locally advanced, unresectable or metastatic HER2 positive (IHC 3+ or IHC 2+/ in situ hybridization (ISH)+) colorectal cancer of BRAF wild-type, RAS wild-type or RAS mutant tumor types previously treated with standard therapy. The trial was conducted in two stages. In the first stage, patients (n=80) were randomized 1:1 to receive either 5.4 mg/kg or 6.4 mg/kg of ENHERTU. In the second stage, additional patients (n=42) were enrolled in the 5.4 mg/kg arm.

The primary endpoint is confirmed ORR as assessed by blinded independent central review. Secondary endpoints include DOR, DCR, investigator-assessed confirmed ORR, clinical benefit ratio, PFS, OS and safety. Results from DESTINY-CRC02 were published in *The Lancet Oncology*.

DESTINY-CRC02 enrolled 122 patients, including 64 HER2 positive (IHC 3+) adult patients, at multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

About HER2 Expression in Solid Tumors

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of various tissue cells throughout the body and is involved in normal cell growth.[1] In some cancers, the HER2 gene is amplified or the cells have activating mutations.[2] HER2 protein overexpression may occur as a result of HER2 gene amplification and is often associated with aggressive disease and poor prognosis.[3]

In the EU, HER2 directed therapies have been used to treat breast, gastric and lung cancers. Although HER2 is expressed in solid tumor types including biliary tract, bladder, cervical, endometrial, ovarian and pancreatic cancers, testing is not routinely performed in these additional tumor types and as a result, available literature is limited.[2] In these solid tumors, HER2 overexpression, classified as IHC 3+, has been observed at rates from 1% up to 31%.[4,5,6] Approximately 1% to 5% of patients with NSCLC have tumors with HER2 overexpression (IHC 3+).[4,7] In metastatic colorectal cancer, an estimated 2% to 4% of patients have tumors that are HER2 overexpressing (IHC 3+).[8,9] HER2 positive expression (IHC 3+) has been reported in approximately 4% to 28% of endometrial cancers and 1% to 5% of ovarian cancers.[5,10,11,12,13]

About ENHERTU

ENHERTU (trastuzumab deruxtecan; fam-trastuzumab deruxtecan-nxki in the U.S. only) is a HER2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, ENHERTU is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced program in AstraZeneca's ADC scientific platform. ENHERTU consists of a HER2 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

ENHERTU (5.4 mg/kg) is approved in more than 85 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (immunohistochemistry [IHC] 3+ or in-situ hybridization (ISH)+) breast cancer who have received a prior anti-HER2-based regimen, either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within six months of completing therapy based on the results from the DESTINY-Breast03 trial.

ENHERTU (5.4 mg/kg) is approved in more than 85 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on the results from the DESTINY-Breast04 trial.

ENHERTU (5.4 mg/kg) is approved in more than 40 countries/regions for the treatment of adult patients with unresectable or metastatic hormone receptor (HR) positive, HER2 low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining) breast cancer, as determined by a locally or regionally approved test, that have progressed on one or more endocrine therapies in the metastatic setting based on the results from the DESTINY-Breast06 trial.

ENHERTU (5.4 mg/kg) is approved in more than 60 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 and/or DESTINY-Lung05 trials. Continued approval in China and the U.S. for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in more than 70 countries/regions worldwide for the treatment of adult patients with locally advanced or metastatic HER2 positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01, DESTINY-Gastric02 and/or DESTINY-Gastric06 trials. Continued approval in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (5.4 mg/kg) is approved in more than 10 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options based on efficacy results from the DESTINY-PanTumor02, DESTINY-Lung01 and DESTINY-CRC02 trials. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

About the ENHERTU Clinical Development Program

A comprehensive global clinical development program is underway evaluating the efficacy and safety of ENHERTU as a monotherapy or in combination or sequentially with other cancer medicines across multiple HER2 targetable cancers.

About the Daiichi Sankyo and AstraZeneca Collaboration

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

About the ADC Portfolio of Daiichi Sankyo

The Daiichi Sankyo ADC portfolio consists of seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADC portfolio currently consists of ENHERTU, a HER2 directed ADC, and DATROWAY, a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc, Rahway, NJ, USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world. With more than 120 years of experience, Daiichi Sankyo leverages its world-class science and technology to create new modalities and innovative medicines for people with cancer, cardiovascular and other diseases with high unmet medical need. For more information, please visit www.daiichisankyo.com.

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