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Daiichi-Sankyo

Press Release

ENHERTU® Recommended for Approval in the EU by CHMP for Patients with *HER2* Mutant Advanced Non-Small Cell Lung Cancer

- Recommendation based on DESTINY-Lung02 trial results, which showed Daiichi Sankyo and AstraZeneca's ENHERTU achieved strong and durable tumor responses in previously treated *HER2* mutant disease
- ENHERTU showed a confirmed objective response rate of 49.0% and median duration of response of 16.8 months

Tokyo and Munich – (September 15, 2023) –ENHERTU® (trastuzumab deruxtecan) has been recommended for approval in the European Union (EU) as a monotherapy for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have an activating *HER2* (*ERBB2*) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

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

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) based its positive opinion on the primary results from the DESTINY-Lung02 phase 2 trial presented at the IASLC 2023 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer (#WCLC23) and simultaneously published in the *Journal of Clinical Oncology*. The recommendation will now be reviewed by the European Commission, which has the authority to grant marketing authorizations for medicines in the EU.

In the trial, ENHERTU (5.4 mg/kg) demonstrated a confirmed objective response rate (ORR) of 49.0% (95% confidence interval [CI]: 39.0-59.1) and disease control rate (DCR) of 93.1% (95% CI: 86.4-97.2), as assessed by blinded independent central review (BICR) in patients with previously treated advanced or metastatic *HER2* mutant NSCLC. One (1.0%) complete response (CR) and 49 (48.0%) partial responses (PR) were observed. The median duration of response (DoR) was 16.8 months (95% CI: 6.4-not estimable [NE]). Median follow-up was 11.5 months in the 5.4 mg/kg arm (n=102) at time of data cutoff of December 23, 2022.

“ENHERTU is the first therapy to demonstrate a strong and durable tumor response in patients with previously treated *HER2* mutant advanced non-small cell lung cancer, validating HER2 as an actionable target in lung cancer and supporting the potential to provide a much-needed option for these patients,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “This CHMP opinion is a positive step forward in advancing this HER2 directed antibody drug conjugate for these patients and we look forward to the European Commission’s decision.”

“*HER2* mutant non-small cell lung cancer is an aggressive form of lung cancer that often affects younger patients and has a poor prognosis, with limited approved therapies,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “This milestone recognizes the unmet need in the European Union and if approved, ENHERTU will provide the first targeted treatment option for these patients.”

In DESTINY-Lung02, the safety profile of ENHERTU at the 5.4 mg/kg and 6.4 mg/kg doses were consistent with other trials of ENHERTU with no new safety signals observed. A favorable safety profile was observed in patients treated with ENHERTU 5.4 mg/kg. Grade 3 or higher treatment-related treatment emergent adverse events (TEAEs) occurred in 38.6% of all patients receiving ENHERTU 5.4 mg/kg. The most common grade 3 or higher TEAEs were neutropenia (18.8%) and anemia (10.9%). There were 13 cases (12.9%) of treatment-related interstitial lung disease (ILD) or pneumonitis reported in the 5.4 mg/kg arm as determined by an independent adjudication committee. The majority were low grade (grade 1 or 2 [10.9%; four grade 1 and seven grade 2 events]), with one grade 3 event, zero grade 4 events and one grade 5 event observed.

About DESTINY-Lung02

DESTINY-Lung02 is a global, randomized phase 2 trial evaluating the safety and efficacy of ENHERTU in patients with *HER2* mutant unresectable and/or metastatic NSCLC with disease recurrence or progression during or after at least one regimen of prior anticancer therapy that must have contained a platinum-based chemotherapy. Patients were randomized 2:1 to receive ENHERTU 5.4 mg/kg (n=102) or ENHERTU 6.4 mg/kg (n=50).

The primary endpoint of the trial is confirmed ORR as assessed by BICR. Secondary endpoints include DCR, DoR and progression free survival (PFS) assessed by investigator and BICR, investigator-assessed overall survival (OS) and safety. DESTINY-Lung02 enrolled 152 patients at multiple sites, including Asia, Europe, Oceania and North America. For more information about the trial, visit ClinicalTrials.gov.

About *HER2* Mutant NSCLC

Lung cancer is the second most common form of cancer globally with more than two million cases diagnosed in 2020.[1] In Europe, lung cancer is the third most commonly diagnosed cancer with more than 477,000 cases diagnosed in 2020.[2] Lung cancer is also the leading cause of cancer-related deaths in Europe, with nearly 400,000 deaths reported in 2020.[2] Prognosis is particularly poor for patients with metastatic NSCLC as only approximately 9% will live beyond five years after diagnosis.[3]

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumors, including lung, breast, gastric and colorectal cancers. Certain *HER2* (*ERBB2*) gene alterations (called *HER2* mutations) have been identified in patients with non-squamous NSCLC as a distinct molecular target, and occur in approximately 2% to 4% of patients with this type of lung cancer.[4,5] While *HER2* gene mutations can occur in a range of patients, they are more commonly found in patients with NSCLC who are younger, female and have never smoked.[6] *HER2* gene mutations have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[7] Next-generation sequencing has been utilized in the identification of *HER2* (*ERBB2*) mutations.[8,9]

Although the role of anti-HER2 treatment is well established in breast and gastric cancers, there were no approved HER2 directed therapies in NSCLC prior to the approvals of ENHERTU by the Israel Ministry of Health (MOH) Pharmaceutical Division, the Japan Ministry of Health, Labour and Welfare and the accelerated U.S. Food and Drug Administration (FDA) approval of ENHERTU in unresectable or metastatic *HER2* mutant NSCLC.[10,11]

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 topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

ENHERTU (5.4 mg/kg) is approved in more than 50 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 positive breast cancer who have received a (or one or more) 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 40 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2 low (IHC 1+ or IHC 2+/*in-situ* hybridization (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 Israel, Japan and under accelerated approval in the U.S. 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 trial. Continued approval for this indication in the U.S. may be contingent upon verification and description of clinical benefit in a confirmatory trial.

ENHERTU (6.4 mg/kg) is approved in more than 30 countries worldwide for the treatment of adult patients with locally advanced or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01 and/or DESTINY-Gastric02 trials.

About the ENHERTU Clinical Development Program

A comprehensive global clinical development program is underway evaluating the efficacy and safety of ENHERTU monotherapy across multiple HER2 targetable cancers. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

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 datopotamab deruxtecan (Dato-DXd) 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 datopotamab deruxtecan.

About the DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, are being jointly developed and commercialized globally with AstraZeneca. Four additional Daiichi Sankyo DXd ADCs include patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, raludotatug deruxtecan (R-DXd; DS-6000), a CDH6 directed ADC, and DS-3939, a TA-MUC1 directed ADC.

Designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, 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.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan and DS-3939 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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References

[1] WHO. Cancer Today. 2020. Accessed September 2023.
[2] WHO. Fact Sheets: Europe. Accessed September 2023.
[3] American Cancer Society. Lung Cancer Survival Rates. Accessed September 2023.
[4] Liu S, et al. *Clin Cancer Res.* 2018;24(11):2594-2604.
[5] Riudavets M, et al. *ESMO Open.* 2021;6(5): 100260.
[6] Pillai RN, et al. *Cancer*. 2017;123:4099-105.
[7] Offin M, et al. *Cancer*. 2019;125:4380-7.
[8] Hechtman J, et al. *Cancer Cytopathol.* 2019;127(7): 428-431.
[9] Gulilat, M, et al, *BMC Med Gen.* 2019;12(1):81.
[10] Zhou J, et al. *Ther Adv Med Oncol*. 2020;12.
[11] Ren S, et al. *ESMO Open*. 2022; 1:7.