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Daiichi-Sankyo

Press Release

Datopotamab Deruxtecan New BLA Submitted for Accelerated Approval in the U.S. for Patients with Previously Treated Advanced EGFR-Mutated Non-Small Cell Lung Cancer

- Daiichi Sankyo and AstraZeneca's new application is based on the TROPION-Lung05 phase 2 trial and supported by data from additional trials including TROPION-Lung01
- Previously submitted BLA based on TROPION-Lung01 phase 3 trial for patients with nonsquamous NSCLC has been voluntarily withdrawn

Tokyo and Basking Ridge, NJ – (November 12, 2024) – Daiichi Sankyo (TSE: 4568) and AstraZeneca (LSE/STO/Nasdaq: AZN) have submitted a new Biologics License Application (BLA) for accelerated approval in the U.S. for datopotamab deruxtecan (Dato-DXd) for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor-mutated (EGFR-mutated) non-small cell lung cancer (NSCLC) who have received prior systemic therapies, including an EGFR-directed therapy.

The companies have voluntarily withdrawn the BLA in the U.S. for datopotamab deruxtecan for patients with advanced or metastatic nonsquamous NSCLC based on the TROPION-Lung01 phase 3 trial.

The decision to submit a new BLA for EGFR-mutated NSCLC and withdraw the previously submitted BLA for nonsquamous NSCLC was informed by feedback from the U.S. Food and Drug Administration (FDA).

The new BLA is based on results from the TROPION-Lung05 phase 2 trial and supported by data from the TROPION-Lung01 phase 3 and TROPION-PanTumor01 phase 1 trials. New results from a pooled analysis of patients with previously treated EGFR-mutated NSCLC in the TROPION-Lung05 and TROPION-Lung01 trials will be featured in a late-breaking presentation at the upcoming European Society for Medical Oncology (ESMO) Asia 2024 Congress (LBA7).

Datopotamab deruxtecan is a specifically engineered TROP2 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed by Daiichi Sankyo and AstraZeneca.

"Treating EGFR-mutated non-small cell lung cancer is incredibly challenging following disease progression given that the complexity and variability of these mutations often lead to resistance," said Ken Takeshita,

MD, Global Head, R&D, Daiichi Sankyo. “The potential approval of datopotamab deruxtecan could offer renewed hope for patients with this formidable disease.”

“TROPION-Lung01 was designed to test the potential to improve upon standard-of-care chemotherapy in a broad, previously treated, advanced lung cancer patient population. The results, together with data from TROPION-Lung05, showed an especially pronounced benefit for patients with an EGFR mutation which informed our discussions with the FDA and the decision to seek accelerated approval of datopotamab deruxtecan in this patient population,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “TROPION-Lung01 has also provided exciting exploratory data supporting our biomarker development, which will be validated in ongoing and planned phase 3 lung cancer trials.”

Daiichi Sankyo and AstraZeneca are evaluating datopotamab deruxtecan alone and with osimertinib, AstraZeneca’s EGFR tyrosine kinase inhibitor (TKI), as treatment for patients with advanced or metastatic EGFR-mutated nonsquamous NSCLC in the ongoing TROPION-Lung14 and TROPION-Lung15 phase 3 trials. In addition, ongoing phase 3 trials in first-line advanced or metastatic nonsquamous NSCLC, AVANZAR and TROPION-Lung10, have the potential to validate the QCS (quantitative continuous scoring) biomarker for TROP2 identified in an exploratory analysis of TROPION-Lung01. An additional trial in patients with biomarker-positive tumors in the second-line nonsquamous NSCLC setting is also planned.

About TROPION-Lung05

TROPION-Lung05 is a global, multicenter, single-arm, open-label phase 2 trial evaluating the efficacy and safety of datopotamab deruxtecan in patients with locally advanced or metastatic NSCLC with actionable genomic alterations who have progressed on or after one regimen of platinum-based chemotherapy and at least one TKI (with or without other systemic therapies). Patients receiving up to four prior lines of treatment with tumors with one or more genomic alterations including EGFR, ALK, ROS1, NTRK, BRAF, RET or MET were eligible for the trial.

The primary trial endpoint of TROPION-Lung05 is objective response rate (ORR) as assessed by blinded independent central review (BICR). Secondary efficacy endpoints include duration of response (DoR), disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), time to response (TTR), overall survival (OS) and safety.

TROPION-Lung05 enrolled 137 patients globally in Asia, Europe and North America. For more information visit ClinicalTrials.gov.

About TROPION-Lung01

TROPION-Lung01 is a global, randomized, multicenter, open-label phase 3 trial evaluating the efficacy and safety of datopotamab deruxtecan versus docetaxel in adult patients with locally advanced or metastatic NSCLC with and without actionable genomic alterations who require systemic therapy following prior treatment. Patients with actionable genomic alterations were previously treated with an approved targeted therapy and platinum-based chemotherapy. Patients without known actionable genomic alterations were previously treated, concurrently or sequentially, with platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor.

The dual primary endpoints of TROPION-Lung01 are PFS as assessed by BICR and OS. Key secondary endpoints include investigator-assessed PFS, ORR, DoR, TTR, and DCR as assessed by both BICR and investigator, and safety.

TROPION-Lung01 enrolled approximately 600 patients in Asia, Europe, North America, Oceania and South America. For more information visit ClinicalTrials.gov.

Primary PFS results and interim OS results from TROPION-Lung01 were presented at the 2023 ESMO (#ESMO23) Congress. Final OS results were presented at IASLC 2024 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer (#WCLC24) and simultaneously published in the *Journal of Clinical Oncology* in September 2024.

About TROPION-PanTumor01

TROPION-PanTumor01 is a first-in-human, open-label, two-part, multicenter phase 1 trial evaluating the safety and preliminary efficacy of datopotamab deruxtecan in patients with advanced solid tumors that have relapsed or are refractory to standard treatment or for which no standard treatment is available. The dose escalation portion of the trial enrolled patients with NSCLC to assess the safety and tolerability of datopotamab deruxtecan to determine the recommended dose for expansion (6 mg/kg). The dose expansion part of TROPION-PanTumor01 is enrolling several different cohorts including patients with NSCLC, triple negative breast cancer, HR positive, HER2 low or negative breast cancer, small cell lung cancer, urothelial, gastric, pancreatic, castration resistant prostate and esophageal cancer.

Safety endpoints include dose-limiting toxicities and serious adverse events. Efficacy endpoints include ORR, DoR, TTR, PFS and OS. Pharmacokinetic, biomarker and immunogenicity endpoints also are being evaluated.

TROPION-PanTumor01 enrolled approximately 900 patients in Asia and North America. For more information visit ClinicalTrials.gov.

About Advanced Non-Small Cell Lung Cancer

Nearly 2.5 million lung cancer cases were diagnosed globally in 2022.[1] Lung cancer is broadly split into small or non-small cell lung cancer, the latter accounting for about 80% of cases.[2] Approximately 10 to 15% of patients with NSCLC in the U.S. and Europe, and 30 to 40% of patients in Asia have an EGFR mutation.[3,4] The majority of EGFR mutations occur in tumors of nonsquamous histology.[5]

For patients with tumors that have an EGFR mutation, the established first-line treatment in the metastatic setting is an EGFR-TKI.[6] While EGFR TKIs have improved outcomes in the first-line setting, most patients eventually experience disease progression and receive chemotherapy.[7,8,9,10]

TROP2 is a protein broadly expressed in the majority of NSCLC tumors.[11] There is currently no TROP2 directed ADC approved for the treatment of lung cancer.[6,12]

About Datopotamab Deruxtecan (Dato-DXd)

Datopotamab deruxtecan (Dato-DXd) is an investigational TROP2 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, datopotamab deruxtecan is one of six DXd ADCs in the oncology pipeline of Daiichi Sankyo, and one of the most advanced programs in AstraZeneca's ADC scientific platform. Datopotamab deruxtecan is comprised of a humanized anti-TROP2 IgG1 monoclonal antibody, developed in collaboration with Sapporo Medical University, attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

A comprehensive global clinical development program is underway with more than 20 trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple cancers, including NSCLC, triple negative breast cancer and HR positive, HER2 low or negative breast cancer. The program includes seven phase 3 trials in lung cancer and five phase 3 trials in breast cancer evaluating datopotamab deruxtecan as a monotherapy and in combination with other anticancer treatments in various settings.

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 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 datopotamab deruxtecan (Dato-DXd), 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. 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.

Datopotamab deruxtecan, 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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