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Datopotamab deruxtecan new BLA submitted for accelerated approval in the US for patients with previously treated advanced *EGFR*-mutated non-small cell lung cancer

AstraZeneca and Daiichi Sankyo's new application is based on the TROPION-Lung05 Phase II trial and supported by data from additional trials including TROPION-Lung01

Previously submitted BLA based on TROPION-Lung01 Phase III trial for patients with nonsquamous NSCLC has been voluntarily withdrawn

AstraZeneca and Daiichi Sankyo have submitted a new Biologics License Application (BLA) for accelerated approval in the US for datopotamab deruxtecan (Dato-DXd) for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor-mutated (*EGFR*) 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The companies have voluntarily withdrawn the BLA in the US for datopotamab deruxtecan for patients with advanced or metastatic nonsquamous NSCLC based on the TROPION-Lung01 Phase III trial.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 US Food and Drug Administration (FDA).

The new BLA is based on results from the TROPION-Lung05 Phase II trial and supported by data from the TROPION-Lung01 Phase III and TROPION-PanTumor01 Phase I 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).

Susan Galbraith, Executive Vice President, Oncology R&D, AstraZeneca, said: "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. TROPION-Lung01 has also provided exciting exploratory data supporting our biomarker development, which will be validated in ongoing and planned Phase III lung cancer trials."

Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo, said: "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. The potential approval of datopotamab deruxtecan could offer renewed hope for patients with this formidable disease."

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

AstraZeneca and Daiichi Sankyo are evaluating datopotamab deruxtecan alone and with *Tagrisso* (osimertinib) as treatment for patients with advanced or metastatic *EGFR*-mutated nonsquamous NSCLC in the ongoing TROPION-Lung14 and TROPION-Lung15 Phase III trials. In addition, ongoing Phase III trials in 1st-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 tumours in the 2nd-line nonsquamous NSCLC setting is also planned.

Notes

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-cell lung cancer (SCLC) or NSCLC, the latter accounting for about 80% of cases.[2] Approximately 10-15% of patients with NSCLC in the US and Europe, and 30-40% of patients in Asia have an *EGFR* mutation.[3,4] The majority of *EGFR* mutations occur in tumours of nonsquamous histology.[5]

For patients with tumours that have an *EGFR* mutation, the established 1st-line treatment in the metastatic setting is an *EGFR*-tyrosine kinase inhibitor (TKI).[6] While *EGFR*-TKIs have improved outcomes in the 1st-line setting, most patients eventually experience disease progression and receive chemotherapy.[7-10]

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

TROPION-Lung05
TROPION-Lung05 is a global, multicentre, single-arm, open-label Phase II 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 tumours 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, 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.

TROPION-Lung01
TROPION-Lung01 is a global, randomised, multicentre, open-label Phase III 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 and interim OS results from TROPION-Lung01 were presented at the ESMO 2023 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 and simultaneously published in the *Journal of Clinical Oncology* in September 2024.

TROPION-PanTumor01
TROPION-PanTumor01 is a first-in-human, open-label, two-part, multicentre Phase I trial evaluating the safety and preliminary efficacy of datopotamab deruxtecan in patients with advanced solid tumours 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 (TNBC), HR-positive, HER2-low or negative breast cancer, SCLC, 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.

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 programmes 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 programme is underway with more than 20 trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple cancers, including NSCLC, TNBC and HR-positive, HER2-low or negative breast cancer. The programme includes seven Phase III trials in lung cancer and five Phase III trials in breast cancer evaluating datopotamab deruxtecan as a monotherapy and in combination with other anticancer treatments in various settings.

Daiichi Sankyo collaboration
AstraZeneca and Daiichi Sankyo entered into a global collaboration to jointly develop and commercialise *Enhertu* (trastuzumab deruxtecan) in March 2019 and datopotamab deruxtecan 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.

AstraZeneca in lung cancer
AstraZeneca is working to bring patients with lung cancer closer to cure through the detection and treatment of early-stage disease, while also pushing the boundaries of science to improve outcomes in the resistant and advanced settings. By defining new therapeutic targets and investigating innovative approaches, the Company aims to match medicines to the patients who can benefit most.

The Company's comprehensive portfolio includes leading lung cancer medicines and the next wave of innovations, including *Tagrisso* (osimertinib) and *Iressa* (gefitinib); *Imfinzi* (durvalumab) and *Imjudo* (tremelimumab); *Enhertu* (trastuzumab deruxtecan) and datopotamab deruxtecan in collaboration with Daiichi Sankyo; *Orpathys* (savolitinib) in collaboration with HUTCHMED; as well as a pipeline of potential new medicines and combinations across diverse mechanisms of action.

AstraZeneca is a founding member of the Lung Ambition Alliance, a global coalition working to accelerate innovation and deliver meaningful improvements for people with lung cancer, including and beyond treatment.

AstraZeneca in oncology
AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca
AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in

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Contacts

For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

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