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Press Release

Datopotamab Deruxtecan Shows Encouraging Tumor Response in Patients with Advanced Non-Small Cell Lung Cancer with Actionable Genomic Alterations

- Sub-analysis of TROPION-PanTumor01 phase 1 trial of datopotamab deruxtecan featured as late-breaking Mini Oral presentation at ESMO
- TROPION-Lung05 phase 2 trial currently enrolling patients to further evaluate the safety and efficacy of datopotamab deruxtecan in this patient population

Tokyo, Munich and Basking Ridge, NJ – (September 19, 2021) – New data for datopotamab deruxtecan (Dato-DXd), a TROP2 directed DXd antibody drug conjugate (ADC) being developed by Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) and AstraZeneca, show an encouraging tumor response rate in patients with advanced non-small cell lung cancer (NSCLC) with actionable genomic alterations. A sub-analysis of the NSCLC cohort of the TROPION-PanTumor01 phase 1 trial was presented as a late-breaking Mini Oral presentation (#LBA49) at the European Society for Medical Oncology (#ESMO21) 2021 Virtual Congress.

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality worldwide, with 80 to 85% classified as NSCLC.[1,2,3] For patients with advanced NSCLC with certain genomic alterations, treatment with targeted therapy offers improved response rates or survival compared to traditional chemotherapy.[4] However, once these targeted therapies are exhausted, treatment options are more limited.[5] While TROP2 has been found to be highly expressed in NSCLC and associated with poor survival, there currently are no TROP2 directed therapies approved for the treatment of patients with NSCLC.[6,7]

A confirmed objective response rate (ORR) of 35% was observed in 34 evaluable patients with NSCLC with actionable genomic alterations treated with datopotamab deruxtecan as assessed by blinded independent central review. Twelve partial responses (35%) and 14 cases of stable disease (41%) were observed. With a median follow-up of 13.4 months (range, 7-28 months), the median duration of response (DOR) was 9.5 months (95% CI: 3.3-NE). Clinical activity was observed in patients with EGFR mutations (Ex19del, L858R), including after osimertinib therapy, and across other actionable genomic alterations.

The safety profile of datopotamab deruxtecan was consistent with that observed in the overall NSCLC population of the TROPION-PanTumor01 trial. The most common treatment-emergent adverse events (TEAEs) were nausea and stomatitis. One case of interstitial lung disease (grade 5 at the 8 mg/kg dose) was observed and adjudicated as treatment-related.

"Identification of genomic alterations serves as an important roadmap for the treatment of patients with non-small cell lung cancer. However, prognosis is poor after progression on currently available therapies targeted to the underlying oncogenic alteration," said Edward B. Garon, MD, Director of Thoracic Oncology, Jonsson Comprehensive Cancer Center at University of California, Los Angeles. "We are highly encouraged by the tumor responses seen in this analysis as these results support the potential of datopotamab deruxtecan in patients with advanced non-small cell lung cancer with actionable genomic alterations and disease progression following standard treatment."

"These data provide preliminary evidence that datopotamab deruxtecan elicits tumor responses in patients with previously treated advanced non-small cell lung cancer with actionable genomic alterations," said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. "Further validation of these initial results is underway in the TROPION-Lung05 phase 2 trial where datopotamab deruxtecan is being evaluated in this specific type of NSCLC with disease progression following targeted therapy and platinum-based chemotherapy."

"TROP2 may be associated with poor prognosis and short median overall survival in some patients with advanced non-small cell lung cancer, one of the most common forms of cancer," said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. "This setting represents high unmet need as the patients in this trial have exhausted many of the available options. These updated results from our TROPION clinical development program, add to the evidence for the potential role of datopotamab deruxtecan across non-small cell lung cancer disease."

The majority of patients (82%) in this sub-analysis had received three or more prior lines of therapy including platinum-based chemotherapy (91%), TKIs (85%), and immunotherapy (41%). Patients included in this analysis had tumors with EGFR mutations (85%), ALK fusion (9%), ROS1 fusion (3%), and RET fusion (3%). Of those with EGFR mutations, 69% had received prior treatment with osimertinib. As of data cut-off on April 6, 2021, 12% of patients remained on treatment with datopotamab deruxtecan.

Summary of TROPION-PanTumor01 Results in NSCLC with Actionable Genomic Alterations

Efficacy Measure	**Total Evaluable (n=34)**[i,ii,iii]
Confirmed ORR (%, n)[iv]	35% (n=12)
CR (%, n)	0% (n=0)
PR (%, n)	35% (n=12)
SD (%, n)	41% (n=14)
DoR, median (95% CI), months	9.5 months (3.3-NE)

CI, confidence interval; CR, complete response; DoR, duration of response; ORR, objective response rate; PR, partial response; SD, stable disease;

[i] Assessed across doses [4 mg/kg (n=8), 6 mg/kg (n=10), and 8 mg/kg (n=16)]
[ii] As assessed by blinded independent central review
[iii] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment.
[iv] ORR is (CR + PR)

About TROPION-PanTumor01

TROPION-PanTumor01 is a first-in-human, open-label, two-part, multicenter phase 1 trial evaluating the safety, tolerability and preliminary efficacy of datopotamab deruxtecan in patients with advanced solid tumors refractory to or relapsed from standard treatment or for whom no standard treatment is available, including NSCLC, triple negative breast cancer (TNBC), hormone receptor (HR) positive breast, urothelial, gastric and esophageal cancers.

The dose escalation part of the study assessed the safety and tolerability of increasing doses of datopotamab deruxtecan to determine the maximum tolerated dose and/or recommended dose for expansion in patients with unresectable advanced NSCLC. The dose expansion part of the study further assessed the safety and tolerability of datopotamab deruxtecan at selected dose levels (4 mg/kg, 6 mg/kg and 8 mg/kg) in patients with NSCLC. Based on the preliminary efficacy and safety profile, the 6 mg/kg dose has been chosen for further development.[8,9]

Safety endpoints include dose limiting toxicities and serious adverse events. Efficacy endpoints include ORR, disease control rate, DOR, time to response, progression-free survival and overall survival. Pharmacokinetic, biomarker and immunogenicity endpoints also are being evaluated.

About Non-Small Cell Lung Cancer (NSCLC)

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality worldwide, with 80 to 85% classified as NSCLC.[1,3] NSCLC is diagnosed at an advanced stage in more than 50% of patients and often has a poor prognosis with worsening outcomes after each line of subsequent therapy.[10,11,12]

The majority of patients with advanced NSCLC traditionally received platinum-based chemotherapy as first-line treatment.[13] The introduction of targeted therapies and immune checkpoint inhibitors in the past two decades has created new options and shifted treatment to a more personalized approach.[13]

A number of targeted therapies offer improved efficacy over traditional chemotherapy regimens and are approved for treatment of NSCLC with specific genomic alterations.[4] The most common alterations for which targeted therapies are approved are EGFR (approximately 10 to 35% frequency) and ALK rearrangement (approximately 3 to 7%). Patients eventually develop resistance to available therapies.[5]

About TROP2

TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is widely expressed in several types of solid tumors, including NSCLC.[6,14] Research indicates that TROP2 expression is associated with increased tumor progression and poor overall and disease free survival in several types of solid tumors.[6,14] While TROP2 is expressed across all lung cancer subtypes, results from one NSCLC study demonstrated TROP2 expression in all adenocarcinoma cases and 92% of squamous cell carcinoma cases (the most common forms of NSCLC), while a separate study found high TROP2 expression in 64% of adenocarcinoma and 75% of squamous cell carcinoma cases.[6,15] However, no TROP2 directed therapies are currently approved for the treatment of patients with NSCLC.[7]

About Datopotamab Deruxtecan (Dato-DXd)

Datopotamab deruxtecan (Dato-DXd) is an investigational TROP2 directed antibody drug conjugate (ADC). Designed using Daiichi Sankyo's proprietary DXd ADC technology, datopotamab deruxtecan is one of three lead 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[3] monoclonal antibody, developed in collaboration with Sapporo Medical University, attached to a topoisomerase I inhibitor payload, an exatecan derivative, via a tetrapeptide-based cleavable linker.[16]

A comprehensive development program called TROPION is underway globally with trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple solid tumors, including NSCLC, TNBC, HR positive breast, urothelial, gastric and esophageal cancer. Trials in combination with other anticancer treatments, such as immunotherapy, are also underway.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize datopotamab deruxtecan in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights. Daiichi Sankyo is responsible for the manufacturing and supply of datopotamab deruxtecan.

About Daiichi Sankyo in Oncology

The oncology portfolio of Daiichi Sankyo is powered by our team of world-class scientists that push beyond traditional thinking to create transformative medicines for people with cancer. Anchored by our DXd antibody drug conjugate (ADC) technology, our research engines include biologics, medicinal chemistry, modality and other research laboratories in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in the U.S. We also work alongside leading academic and business collaborators to further

advance the understanding of cancer as Daiichi Sankyo builds towards our ambitious goal of becoming a global leader in oncology by 2025.

About Daiichi Sankyo

Daiichi Sankyo is dedicated to creating new modalities and innovative medicines by leveraging our world-class science and technology for our purpose "to contribute to the enrichment of quality of life around the world." In addition to our current portfolio of medicines for cancer and cardiovascular disease, Daiichi Sankyo is primarily focused on developing novel therapies for people with cancer as well as other diseases with high unmet medical needs. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 16,000 employees around the world draw upon a rich legacy of innovation to realize our 2030 Vision to become an "Innovative Global Healthcare Company Contributing to the Sustainable Development of Society." For more information, please visit: www.daiichisankyo.com.

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