Daiichi-Sankyo

Press Release

Datopotamab Deruxtecan-Based Combinations Show Promising Clinical Activity in Patients with Advanced Non-Small Cell Lung Cancer

- Late-breaking oral presentation at WCLC features first results from TROPION-Lung02 trial of Daiichi Sankyo and AstraZeneca's TROP2 directed antibody drug conjugate

Tokyo and Basking Ridge, NJ – (August 9, 2022) – Initial results from the TROPION-Lung02 phase 1b trial showed that datopotamab deruxtecan (Dato-DXd) in combination with pembrolizumab with or without platinum chemotherapy demonstrated promising clinical activity and a tolerable safety profile in patients with previously untreated or pretreated advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations. Results were presented today during a late-breaking mini-oral presentation (#MA13.07) at the IASLC 2022 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer (#WCLC22).

Datopotamab deruxtecan is a specifically designed TROP2 directed DXd antibody drug conjugate (ADC) being jointly developed by Daiichi Sankyo (TSE:4568) and AstraZeneca (LSE/STO/Nasdaq: AZN).

NSCLC is diagnosed at an advanced stage in nearly 50% of patients and often has a poor prognosis with worsening outcomes after each line of subsequent therapy.[1,2,3] While first-line treatment consisting of immunotherapy with or without chemotherapy has improved outcomes in patients with NSCLC without actionable genomic alterations, disease progression still occurs in the majority of patients and additional treatment strategies in this setting are needed.[4,5]

An interim analysis of the ongoing TROPION-Lung02 trial in patients with previously untreated or pretreated advanced or metastatic NSCLC without actionable genomic alterations demonstrated a promising overall response rate (ORR) in the overall population of 37% (median follow-up of 6.5 months) of 38 patients receiving datopotamab deruxtecan in combination with pembrolizumab (doublet therapy) and an ORR of 41% (median follow-up of 4.4 months) of 37 patients receiving datopotamab deruxtecan in combination with pembrolizumab and platinum chemotherapy (triplet therapy). A disease control rate (DCR) of 84% was seen with both the doublet and triplet combination therapy in the overall population that comprised both first-line and second-line settings.

In previously untreated patients, ORRs of 62% (eight of the 13 patients receiving doublet therapy) and 50% (10 of 20 patients receiving triplet therapy) were observed. Eight partial responses (PRs) were seen in patients receiving doublet therapy and 10 PRs (three pending confirmation) were seen in patients receiving triplet therapy. A DCR of 100% was observed with doublet therapy and a DCR of 90% was observed with triplet therapy.

“Many patients with advanced non-small cell lung cancer still experience disease progression following initial treatment, underscoring the need for new therapeutic approaches,” said Benjamin Philip Levy, MD, Clinical Director of Medical Oncology, Johns Hopkins Sidney Kimmel Cancer Center, at Sibley Memorial Hospital and Associate Professor of Oncology at Johns Hopkins University School of Medicine. “The initial results from the TROPION-Lung02 trial show encouraging safety and efficacy results when combining datopotamab deruxtecan and pembrolizumab with or without platinum chemotherapy and warrant further study in the first-line metastatic setting.”

Combinations with datopotamab deruxtecan demonstrated a tolerable safety profile, which supports further evaluation in ongoing studies. Grade 3 or greater treatment-emergent adverse events (TEAEs) occurred in 40% and 60% of patients in the doublet and triplet cohorts, respectively. The most frequent TEAEs of any grade in the doublet and triplet cohorts respectively were stomatitis (56% and 29%), nausea (41% and 48%), decreased appetite (28% and 38%), fatigue (25% and 36%) and anemia (16% and 36%). There were four interstitial lung disease (ILD) events determined as drug-related by an independent adjudication committee across both cohorts; two were adjudicated as grade 1/2 and two were adjudicated as grade 3. No grade 4 or grade 5 ILD events were adjudicated as drug-related. At the time of the data cut-off, there were three potential ILD events pending adjudication. Three deaths occurred (two within the doublet cohort, one in the triplet cohort), none of which were determined as drug-related. Treatment discontinuations due to adverse events occurred in less than 21% of patients and datopotamab deruxtecan dose discontinuation occurred in 13% of patients.

“These early findings from TROPION-Lung02 are promising and represent the first lung cancer trial to report results combining a TROP2 directed antibody drug conjugate with an immune checkpoint inhibitor with or without platinum chemotherapy in patients with advanced or metastatic non-small cell lung cancer,” said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. “These data support the initiation of the TROPION-Lung08 phase 3 trial to further evaluate datopotamab deruxtecan in combination with pembrolizumab as a first-line combination treatment in patients with advanced non-small cell lung cancer without actionable genomic alterations.”

"Building on preliminary findings of datopotamab deruxtecan combination therapy in triple negative breast cancer shared earlier this year, these initial results from TROPION-Lung02 reflect the broader promise of combining existing treatments with antibody drug conjugates," said Cristian Massacesi, MD, Chief Medical Officer and Oncology Chief Development Officer, AstraZeneca. "We look forward to continuing this important research with the goal of providing a new treatment option for patients with advanced non-small cell lung cancer."

Patients in TROPION-Lung02 receiving doublet therapy were previously-treated with one median line of therapy, including platinum chemotherapy (60%) and immunotherapy (30%). In the triplet cohort, patients previously received platinum chemotherapy (35%) and immunotherapy (38%). Datopotamab deruxtecan-based combination as first-line therapy accounted for 33% and 63% of patients in doublet and triplet cohorts, respectively. As of the May 2, 2022 data cut-off, 53% and 77% of patients remained on the doublet and triplet therapy, respectively.

Summary of TROPION-Lung02 Results

Overall Population		
	Doublet (n=40)	**Triplet (n=48)**
Median Follow-Up	6.5 months	4.4 months
Efficacy Measure	**Doublet (n=38)**	**Triplet (n=37)**
ORR, % (confirmed and pending)	37%	41%
DCR, %	84%	84%
As First Line Therapy		
Efficacy Measure	**Doublet (n=13)**	**Triplet (n=20)**
ORR, %[1]	62%	50%
PR (confirmed)	62%	35%
PR (pending confirmation)	0%	15%
DCR, %[2]	100%	90%
As Second or Later Line Therapy		
Efficacy Measure	**Doublet (n=25)**	**Triplet (n=17)**
ORR, % (confirmed and pending)	24%	29%

DCR, disease control rate; ORR, overall response rate; PR, partial response
[1] ORR is CR + PR
[2] DCR is CR + PR + SD

About TROPION-Lung02

TROPION-Lung02 is an ongoing global, open-label, six-cohort phase 1b trial evaluating the safety and efficacy of datopotamab deruxtecan at two dose levels (4 mg/kg and 6 mg/kg) in combination with pembrolizumab (200 mg) with or without four cycles of platinum chemotherapy (carboplatin or cisplatin) in

both previously untreated and pretreated patients with advanced or metastatic NSCLC without actionable genomic alterations (e.g., EGFR, ALK, ROS1, NTRK, BRAF, RET, MET or other known actionable alterations).

The primary endpoints of TROPION-Lung02 are dose-limiting toxicities (DLTs) and TEAEs. Secondary endpoints include ORR, duration of response, progression-free survival, overall survival, pharmacokinetics and anti-drug antibodies for datopotamab deruxtecan and pembrolizumab.

TROPION-Lung02 is one of two clinical trial collaborations with Merck & Co., Inc., Rahway, NJ., USA (known as MSD outside of the United States and Canada) evaluating datopotamab deruxtecan in combination with pembrolizumab with or without platinum chemotherapy. The second clinical trial collaboration for the TROPION-Lung08 phase 3 trial is currently enrolling previously untreated patients with PD-L1 high (tumor proportion score ≥ 50%) advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations to evaluate the safety and efficacy of datopotamab deruxtecan in combination with pembrolizumab compared to pembrolizumab alone.

About Non-Small Cell Lung Cancer Without Actionable Genomic Alterations

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality worldwide.[6] NSCLC is diagnosed at an advanced stage in nearly 50% of patients and often has a poor prognosis with worsening outcomes after each line of subsequent therapy.[1,2,3]

While the introduction of targeted therapies and checkpoint inhibitors in recent years have improved outcomes for patients with advanced NSCLC, the majority of tumors do not have known actionable genomic alterations.[7,8,9,10] Current standard of care in the first-line treatment of patients with advanced NSCLC without actionable genomic alterations is immunotherapy with or without platinum-based chemotherapy, based upon PD-L1 expression. While these therapies may improve survival, at least 40 to 60% of tumors do not respond to initial treatment and disease progression occurs, underscoring the need for new therapeutic approaches and options.[11,12,13,14]

About TROP2 in Non-Small Cell Lung Cancer

TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is widely expressed in several types of solid tumors, including NSCLC.[15,16,17,18] TROP2 is expressed across all lung cancer subtypes, with the highest expression seen in the majority of adenocarcinoma and squamous cell carcinoma (the most common forms of NSCLC).[17,19] No TROP2 directed therapies are currently approved for the treatment of patients with NSCLC.[14,20,21]

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 three leading 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, via tetrapeptide-based cleavable linkers.

A comprehensive development program called TROPION is underway globally with trials evaluating the efficacy and safety of datopotamab deruxtecan across multiple solid tumors, including triple negative breast cancer, HR positive/HER2 negative breast cancer, NSCLC, small cell lung cancer, urothelial, gastric and esophageal cancer. Trials in combination with other anticancer treatments, such as immunotherapy, also are underway.

About the Daiichi Sankyo and AstraZeneca Collaboration

Daiichi Sankyo Company, Limited (referred to as 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

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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