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Press Release

Novel Computational Pathology-Based TROP2 Biomarker for Datopotamab Deruxtecan Was Predictive of Clinical Outcomes in Patients with Non-Small Cell Lung Cancer in TROPION-Lung01 Phase 3 Trial

- Daiichi Sankyo and AstraZeneca's datopotamab deruxtecan demonstrated meaningfully greater magnitude of progression-free survival benefit in patients with this biomarker
- AstraZeneca and Roche Tissue Diagnostics are collaborating to co-develop and commercialize the TROP2-QCS biomarker companion diagnostic

Tokyo and Basking Ridge, NJ – (September 8, 2024) – Results from an exploratory analysis of the TROPION-Lung01 phase 3 trial showed TROP2 as measured by quantitative continuous scoring (QCS), AstraZeneca's proprietary computational pathology platform, was predictive of clinical outcomes in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who were treated with datopotamab deruxtecan (Dato-DXd). In patients with TROP2-QCS biomarker positive tumors, datopotamab deruxtecan demonstrated a meaningfully greater magnitude of efficacy versus docetaxel than in the overall trial population. Results will be presented today during a Presidential Symposium (PL02.11) at the IASLC 2024 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer (#WCLC24).

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

TROP2 is a protein broadly expressed in NSCLC on the surface of and inside tumor cells.[1,2] When assessed using conventional immunohistochemistry (IHC)-based pathology, TROP2 expression has not been predictive of patient responses to TROP2 directed ADCs.[3,4] QCS is a fully supervised computational pathology platform developed by AstraZeneca that analyzes digitized images of patient tissue samples and precisely quantifies targets like TROP2 on the surface of and inside every tumor cell.

In this analysis, QCS was used to analyze tissue samples collected from patients in TROPION-Lung01. This produced a normalized membrane ratio for each tumor cell in each sample. Patient tumors were

considered TROP2-QCS biomarker positive if the majority (≥75%) of tumor cells exhibited a ratio below a predetermined value (≤0.56), indicating a greater proportion of TROP2 in the cytoplasm.

The analysis showed a greater proportion of patients with nonsquamous NSCLC were considered TROP2-QCS biomarker positive than those with squamous NSCLC (66% versus 44%, respectively). The threshold for biomarker positivity was optimized for progression-free survival (PFS) in the subgroup of patients with nonsquamous NSCLC without actionable genomic alterations because it represents a population with significant unmet medical need.

In patients with TROP2-QCS biomarker positive tumors (60% of the biomarker evaluable population including patients with nonsquamous and squamous NSCLC), datopotamab deruxtecan reduced the risk of disease progression or death by 43% versus docetaxel (median PFS of 6.9 months versus 4.1 months; hazard ratio [HR]=0.57; 95% confidence interval [CI]: 0.41-0.79). By comparison, in the primary analysis of the overall trial population, datopotamab deruxtecan reduced the risk of disease progression or death by 25% versus docetaxel (median PFS of 4.4 months versus 3.7 months; HR=0.75; 95% CI: 0.62-0.91; p=0.004) as presented at the European Society for Medical Oncology (#ESMO23) 2023 Congress.

In the subgroup of patients with nonsquamous NSCLC without actionable genomic alterations and with TROP2-QCS biomarker positive tumors, datopotamab deruxtecan reduced the risk of disease progression or death by 48% versus docetaxel (median PFS of 7.2 months versus 4.1 months; HR=0.52; CI: 95% 0.35-0.78).

“TROP2 is broadly expressed on solid tumor cells including non-small cell lung cancer, but it has yet to be established as a predictive biomarker for any TROP2 directed antibody drug conjugate,” said Marina Garassino, MD, Professor of Medicine, The University of Chicago and investigator in the trial. “We have shown with this analysis that the more precise quantitative measurement of TROP2 on and inside tumor cells, enabled by AstraZeneca’s computational pathology platform, can identify which patients with non-small cell lung cancer are most likely to benefit from treatment with datopotamab deruxtecan.”

“The results from the QCS analysis support the potential of TROP2, as measured by quantitative continuous scoring, as a predictive biomarker for datopotamab deruxtecan and begin to answer the question of why certain patients with non-small cell lung cancer respond better to treatment,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “These insights are critical to advancing our

understanding of how we can more precisely identify patients with non-small cell lung cancer who may benefit from treatment with our TROP2 directed antibody drug conjugate."

"This analysis demonstrates the power of our computational pathology platform to discover new predictive biomarkers and substantially improve patient selection for datopotamab deruxtecan. It also has great potential to help more precisely select patients across our broader antibody drug conjugate portfolio," said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. "We are excited to extend our collaboration with Roche Tissue Diagnostics with the aim of validating this exploratory approach for TROP2, developing the companion diagnostic and bringing it to the clinic as quickly as possible."

In the biomarker evaluable population, no new safety concerns were identified and rates of grade 3 or higher treatment-related adverse events (TRAE) were similar regardless of TROP2 status. In patients with TROP2-QCS biomarker positive tumors, grade 3 or higher TRAEs occurred in 30% and 46% of patients in the datopotamab deruxtecan and docetaxel arms, respectively. The most common grade 3 or higher TRAEs were stomatitis (7% vs. 3%) and ocular surface events (3% vs. 0%). Grade 3 or higher adjudicated drug-related interstitial lung disease events occurred in 3% and 1% of patients in the datopotamab deruxtecan and docetaxel arms, respectively.

Summary of TROPION-Lung01 QCS Analysis Results

Overall biomarker evaluable population (n=352)				
	TROP2-QCS biomarker positive		**TROP2-QCS biomarker negative**	
	Datopotamab Deruxtecan (n=107)	**Docetaxel (n=107)**	**Datopotamab Deruxtecan (n=65)**	**Docetaxel (n=73)**
Median PFS (months)	6.9 months	4.1 months	2.9 months	4.0 months
HR (95% CI)	0.57 (0.41-0.79)		1.16 (0.79-1.70)	
ORR	32.7%	10.3%	16.9%	15.1%
Nonsquamous histology without actionable genomic alterations biomarker-evaluable subgroup, n=221				
	Datopotamab Deruxtecan (n=68)	**Docetaxel (n=72)**	**Datopotamab Deruxtecan (n=40)**	**Docetaxel (n=41)**
Median PFS	7.2 months	4.1 months	4.0 months	4.4 months
HR (95% CI)	0.52 (0.35-0.78)		1.22 (0.74-2.00)	
ORR	36.8%	15.3%	22.5%	12.2%

CI, confidence interval; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival

About TROPION-Lung01

TROPION-Lung01 is a global, randomized, multicenter, open-label phase 3 trial evaluating the efficacy and safety of datopotamab deruxtecan (6.0 mg/kg) versus docetaxel (75 mg/m^2) 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, either in combination 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 blinded independent central review (BICR) and OS. Key secondary endpoints include investigator-assessed PFS, ORR, duration of response, time to response, disease control rate 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.

About Advanced Non-Small Cell Lung Cancer

Nearly 2.5 million lung cancer cases were diagnosed globally in 2022.[5] NSCLC is the most common type of lung cancer, accounting for about 80% of cases.[6] Approximately 75% and 25% of NSCLC tumors are of nonsquamous or squamous histology, respectively.[7] While immunotherapy and targeted therapies have improved outcomes in the first-line metastatic setting, most patients eventually experience disease progression and receive chemotherapy.[8,9,10] For decades, chemotherapy has been the last treatment available for patients with advanced NSCLC, despite limited effectiveness and known side effects.[9,10,11]

TROP2 is a protein broadly expressed in the majority of NSCLC tumors.[1] There is currently no TROP2 directed ADC approved for the treatment of lung cancer.[11,12]

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 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.

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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