

Press Release

Datopotamab Deruxtecan Improved Progression-Free Survival Versus Chemotherapy in Patients with Previously Treated Non-Small Cell Lung Cancer in TROPION-Lung01 Phase 3 Trial

- Daiichi Sankyo and AstraZeneca's datopotamab deruxtecan reduced the risk of disease progression or death by 25% in overall population and by 37% in patients with non-squamous tumors
- Datopotamab deruxtecan is the first antibody drug conjugate to demonstrate statistically significant improvement in PFS over docetaxel in this setting of high unmet need

Tokyo and Basking Ridge, NJ – (October 23, 2023) – Positive results from the pivotal [TROPION-Lung01](#) phase 3 trial showed that datopotamab deruxtecan (Dato-DXd) demonstrated a statistically significant improvement for the primary endpoint of progression-free survival (PFS) compared to docetaxel, the current standard of care, in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) treated with at least one prior line of therapy. These data, the second of two positive late-breaking presentations ([LBA12](#)) from the datopotamab deruxtecan clinical development program, were featured during Presidential Symposium 3 at the European Society for Medical Oncology (#ESMO23) 2023 Congress.

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

Datopotamab deruxtecan reduced the risk of disease progression or death by 25% compared to docetaxel (hazard ratio [HR]=0.75; 95% confidence interval [CI]: 0.62-0.91; p=0.004) as assessed by blinded independent central review (BICR). Median PFS was 4.4 months in patients treated with datopotamab deruxtecan compared to 3.7 months with docetaxel. Results also showed a confirmed objective response rate (ORR) of 26.4% in patients treated with datopotamab deruxtecan compared to an ORR of 12.8% in patients treated with docetaxel. Median duration of response (DoR) was 7.1 months (95% CI: 5.6-10.9) in the datopotamab deruxtecan arm compared to 5.6 months (95% CI: 5.4-8.1) in the docetaxel arm.

In patients with non-squamous NSCLC, datopotamab deruxtecan demonstrated a clinically meaningful benefit, reducing the risk of disease progression or death by 37% compared to docetaxel (HR=0.63; 95% CI: 0.51-0.78) as assessed by BICR. Median PFS was 5.6 months in patients treated with datopotamab deruxtecan compared to 3.7 months in those treated with docetaxel. A confirmed ORR of 31.2% was observed in the datopotamab deruxtecan arm, including four complete responses (CRs), versus 12.8% with docetaxel which elicited no CRs. Median DoR was 7.7 months in the datopotamab deruxtecan arm compared

with 5.6 months in the docetaxel arm. Datopotamab deruxtecan did not demonstrate a PFS benefit in patients with squamous NSCLC.

For the dual primary endpoint of overall survival (OS), interim results numerically favored datopotamab deruxtecan over docetaxel in the overall population (HR=0.90; 95% CI: 0.72-1.13) and in patients with non-squamous tumors (HR=0.77; 95% CI: 0.59-1.01), however, results did not reach statistical significance at the time of this data cut-off. The trial is ongoing and OS will be assessed at a final analysis.

“For patients with advanced non-small cell lung cancer, current standard of care second-line docetaxel is associated with limited benefit and substantial toxicity,” said Aaron Lisberg, MD, UCLA Health, Thoracic Medical Oncology and investigator in the trial. “The improvement in progression-free survival observed with datopotamab deruxtecan, particularly in patients with non-squamous tumors, and the improved tolerability of this antibody drug conjugate compared to docetaxel, represent a meaningful advance for patients with lung cancer.”

In the TROPION-Lung01 trial, no new safety concerns were identified with datopotamab deruxtecan. The median treatment duration for datopotamab deruxtecan was 4.2 versus 2.8 months for docetaxel. Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 25% and 41% of patients in the datopotamab deruxtecan and docetaxel arms, respectively. The most common grade 3 or higher TRAEs were neutropenia (1% vs. 23%), stomatitis (6% vs. 1%), anemia (4% vs. 4%), asthenia (3% vs. 2%), nausea (2% vs. 1%) and fatigue (1% vs. 2%) for datopotamab deruxtecan versus docetaxel, respectively. Grade 3 or higher adjudicated drug-related interstitial lung disease (ILD) events occurred in 3% and 1% of patients in the datopotamab deruxtecan and docetaxel arms, respectively. In the datopotamab deruxtecan arm, there were seven grade 5 ILD events (2%) adjudicated as drug-related by an independent committee. The primary cause of death in four of these cases was attributed to disease progression by the treating investigator. Of the seven adjudicated grade 5 ILD events, four (1.7%) were in patients with non-squamous NSCLC and three (4.6%) were in patients with squamous NSCLC. In the docetaxel arm, one adjudicated drug-related grade 5 ILD event (0.3%) occurred.

“These results shown at ESMO from the second of two pivotal trials of datopotamab deruxtecan provide further support for the practice-changing potential of our DXd antibody drug conjugate technology across different targets and types of cancer,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “The benefit seen in patients with non-squamous tumors is particularly impressive and, coupled with the data from TROPION-Lung05, provides promising evidence that datopotamab deruxtecan may play an important role in treating patients with non-small cell lung cancer who currently have limited effective options following initial treatment.”

“Datopotamab deruxtecan is central to the future we envision where antibody drug conjugates improve upon and ultimately displace entrenched standards of care, like chemotherapy, in multiple cancer types,” said Susan Galbraith, MBBChir, PhD, Executive Vice President, Oncology R&D, AstraZeneca. “The TROPION-Lung01 results demonstrate for the first time that an antibody drug conjugate can delay disease progression or death for longer than conventional chemotherapy in patients with advanced non-small cell lung cancer. This is particularly noteworthy considering datopotamab deruxtecan was also associated with a lower burden of treatment-related severe adverse events than chemotherapy.”

Patient enrollment by tumor histology was consistent across treatment arms and with real world incidence with 78% and 77% of patients in the datopotamab deruxtecan and docetaxel arms, respectively, having non-squamous tumors.¹ In the datopotamab deruxtecan arm, patients were previously treated with platinum containing therapy (99%), anti-PD-1/PD-L1 therapy (88%) or targeted therapy (15%). In the docetaxel arm, patients were previously treated with platinum containing therapy (100%), anti-PD-1/PD-L1 therapy (88%) or targeted therapy (16%). In both arms, 17% of patients had tumors expressing actionable genomic alterations, such as epidermal growth factor receptor (EGFR) mutations. At the March 29, 2023 data cut-off, 52 patients remained on treatment with datopotamab deruxtecan and 17 remained on docetaxel.

Summary of TROPION-Lung01 Efficacy Results

Overall Trial Population		
	Datopotamab Deruxtecan (n=299)	Docetaxel (n=305)
Median PFS (months) ⁱ (95% CI)	4.4 months (4.2-5.6)	3.7 months (2.9-4.2)
Hazard Ratio (95% CI)	0.75 (0.62-0.91)	
p-value ⁱⁱ	p=0.004	
Median OS (months) (95% CI) ⁱⁱⁱ	12.4 months (10.8-14.8)	11.0 months (9.8-12.5)
Hazard Ratio (95% CI)	0.90 (0.72-1.13)	
ORR (confirmed), % (95% CI) ^{i, iv}	26.4% (21.5-31.8)	12.8% (9.3-17.1)
CR rate, %	1.3%	0%
PR rate, %	25.1%	12.8%
Median DoR (months) ⁱ (95% CI)	7.1 months (5.6-10.9)	5.6 months (5.4-8.1)
Non-Squamous Histology		
	Datopotamab Deruxtecan (n=229)	Docetaxel (n=232)
Median PFS (months) ⁱ (95% CI)	5.6 months (4.4-7.0)	3.7 months (2.9-4.2)
Hazard Ratio (95% CI)	0.63 (0.51-0.78)	
OS Hazard Ratio (95% CI)	0.77 (0.59-1.01)	
ORR (confirmed), % ^{i, iv}	31.2%	12.8%
Median DoR (months) ⁱ	7.7 months	5.6 months
Squamous Histology		
	Datopotamab Deruxtecan (n=70)	Docetaxel (n=73)
Median PFS (months) ⁱ	2.8 months (1.9-4.0)	3.9 months (2.8-4.5)
Hazard Ratio (95% CI)	1.38 (0.94-2.02)	
OS Hazard Ratio (95% CI)	1.32 (0.87-2.00)	
ORR (%) ^{i, iv}	9.2%	12.7%

Median DoR (months) ⁱ	5.9 months	8.1 months
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CI, confidence interval; CR, complete response; DoR, duration of response; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response

ⁱ As assessed by BICR

ⁱⁱ p-value prespecified boundary of 0.008

ⁱⁱⁱ With median follow-up of 11.8 and 11.7 months for the datopotamab deruxtecan and docetaxel arms, respectively; OS data were not mature

^{iv} ORR is (complete response + partial response)

TROPION-Lung05 Results

Initial results from the [TROPION-Lung05](#) phase 2 trial showed datopotamab deruxtecan demonstrated encouraging antitumor activity in patients with heavily pretreated locally advanced or metastatic NSCLC with actionable genomic alterations including those with EGFR mutations and anaplastic lymphoma kinase (ALK) rearrangements. The data were presented in a mini-oral session on Saturday, October 21 at the ESMO 2023 Congress ([1314MO](#)).

In the overall population (n=137), datopotamab deruxtecan demonstrated a confirmed ORR of 35.8% (95% CI: 27.8-44.4), including four CRs and 45 partial responses, and a disease control rate (DCR) of 78.8%. Median PFS was 5.4 months (95% CI: 4.7-7.0). In patients with EGFR mutations (n=78), the largest group of genomic alterations, datopotamab deruxtecan demonstrated an ORR of 43.6% and DCR of 82.1%.

In the TROPION-Lung05 trial, the most common grade 3 or higher treatment-emergent adverse events (TEAEs) were stomatitis (10%), anemia (6%), decreased appetite (4%) and fatigue (4%). There were five ILD events (4%) adjudicated as drug-related by an independent committee, including four grade 1 or 2 events and one grade 5 event.

About TROPION-Lung01

[TROPION-Lung01](#) is an ongoing global, randomized, multicenter, open-label phase 3 trial evaluating the efficacy and safety of datopotamab deruxtecan versus docetaxel in patients with locally advanced or metastatic NSCLC with and without actionable genomic alterations previously treated with at least one prior therapy. Patients with actionable genomic alterations were previously treated with platinum-based chemotherapy and an approved targeted therapy. 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, time to response, DCR as assessed by both BICR and investigator, and safety.

TROPION-Lung01 enrolled approximately 600 patients at sites in Asia, Europe, North America and South America. For more information visit [ClinicalTrials.gov](#).

About TROPION-Lung05

[TROPION-Lung05](#) is an ongoing global, multicenter, single-arm, open-label phase 2 study evaluating the efficacy and safety of datopotamab deruxtecan in patients with locally advanced or metastatic NSCLC with actionable genomic alterations with disease progression on or after at least one tyrosine kinase inhibitor and at least one regimen of platinum-based chemotherapy (with or without other systemic therapies). Patients with one or more genomic alterations including EGFR, ALK, ROS1, NTRK, BRAF, RET, or MET and who received up to four prior lines of treatment were eligible for the study.

The primary trial endpoint is ORR as assessed by BICR. Secondary efficacy endpoints include DoR, best percentage change in the sum of diameters of measurable tumors, DCR, clinical benefit rate, PFS, time to response and OS. Safety endpoints include TEAEs and other safety parameters. TROPION-Lung05 enrolled 137 patients globally. For more information visit [ClinicalTrials.gov](#).

About Non-Small Cell Lung Cancer

More than one million people worldwide are diagnosed with advanced NSCLC each year.^{2,3} Approximately 30% and 70% of NSCLC tumors are of squamous or non-squamous histology, respectively, the latter including adenocarcinoma and large cell carcinoma.¹ While immunotherapy and targeted therapies have improved outcomes in the first-line setting, most patients eventually experience disease progression and receive chemotherapy.^{4,5,6} For decades, chemotherapy has been the last treatment available for patients with advanced NSCLC in the absence of other treatment options and despite limited effectiveness and known side effects.^{4,5,6}

TROP2, a transmembrane glycoprotein, is broadly expressed in a large majority of NSCLC tumors.⁷ There are currently no TROP2 directed ADCs approved for the treatment of lung cancer.^{8,9}

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 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 development program called TROPION is underway globally with more than 12 trials

evaluating the efficacy and safety of datopotamab deruxtecan across multiple tumors, including NSCLC, triple negative breast cancer and HR positive, HER2 low or negative breast cancer. Beyond the TROPION program, datopotamab deruxtecan also is being evaluated in novel combinations in several ongoing trials.

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 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 DXd ADC Portfolio of Daiichi Sankyo

The DXd ADC portfolio of Daiichi Sankyo currently consists of six ADCs in clinical development across multiple types of cancer. ENHERTU, a HER2 directed ADC, and datopotamab deruxtecan, a TROP2 directed ADC, 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 & Co., Inc., Rahway, N.J. USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

Designed using Daiichi Sankyo's proprietary DXd ADC technology to target and deliver a cytotoxic payload inside cancer cells that express a specific cell surface antigen, 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.

Datopotamab deruxtecan, ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan and DS-3939 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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