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Press Release

Patritumab Deruxtecan Demonstrated Clinically Meaningful and Durable Responses in Patients with EGFR-Mutated Metastatic Non-Small Cell Lung Cancer in HERTHENA-Lung01 Phase 2 Trial

- An objective response rate of 29.8% was observed with patritumab deruxtecan in heavily pretreated patients
- BLA submission in U.S. planned for the second half of fiscal year 2023

Tokyo and Basking Ridge, NJ – (September 10, 2023) – Results from the HERTHENA-Lung01 phase 2 trial showed that patritumab deruxtecan (HER3-DXd) demonstrated clinically meaningful and durable responses in patients with EGFR-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) following disease progression with an EGFR TKI and platinum-based chemotherapy. These data were presented today during an oral presentation (OA05.03) at the 2023 World Conference on Lung Cancer (#WCLC23) and simultaneously published in the *Journal of Clinical Oncology*.

Patritumab deruxtecan is a specifically engineered potential first-in-class HER3 directed antibody drug conjugate (ADC) designed using Daiichi Sankyo's (TSE: 4568) proprietary DXd ADC technology.

NSCLC accounts for approximately 85% of all lung cancers – 55% having distant spread at diagnosis – with EGFR-activating mutations occurring in 14% to 38% of all NSCLC tumors worldwide.[1,2,3] After disease progression following treatment with an EGFR TKI and platinum-based chemotherapy, currently available therapies offer limited efficacy, highlighting the need for new approaches to improve outcomes.[3,4]

A confirmed objective response rate (ORR) of 29.8% (95% CI: 23.9-36.2) was observed with patritumab deruxtecan (5.6 mg/kg) in 225 patients with EGFR-mutated NSCLC as assessed by blinded independent central review (BICR). One complete response (CR), 66 partial responses (PRs) and 99 cases of stable disease (SD) were seen. A median duration of response (DOR) of 6.4 months (95% CI: 4.9-7.8) and a disease control rate (DCR) of 73.8% (95% CI: 67.5-79.4) were observed. Median progression-free survival (PFS) was 5.5 months (95% CI: 5.1-5.9) and median overall survival (OS) was 11.9 months (95% CI: 11.2-13.1) as of snapshot data cutoff of May 18, 2023.

Efficacy outcomes were consistent across subgroups including a subset of 209 patients previously treated with a third-generation EGFR TKI and platinum-based chemotherapy. Anti-tumor activity with patritumab deruxtecan was observed across diverse mechanisms of EGFR TKI resistance and across a broad range of pretreatment tumor HER3 membrane expression.

In a subset of 30 patients with brain metastases at baseline and no prior radiotherapy treatment, an intracranial ORR of 33.3% (95% CI: 17.3-52.8%) was observed as assessed by central nervous system (CNS) BICR. In these patients, nine intracranial CRs, one intracranial PR and 13 cases of SD were seen. A CNS DOR of 8.4 months (95% CI: 5.8-9.2) was observed.

“The results from HERTHENA-Lung01 provide compelling evidence of efficacy of patritumab deruxtecan in heavily pretreated patients with advanced EGFR-mutated non-small cell lung cancer,” said Helena Yu, MD, Associate Attending Physician, Memorial Sloan Kettering Cancer Center. “The clinically meaningful efficacy observed across a broad range of HER3 expression and diverse mechanisms of EGFR TKI resistance as well as the anti-tumor activity seen in patients with brain metastases, underscore the potential of patritumab deruxtecan to become an important treatment option for a population of patients with lung cancer who have limited treatment options.”

“Disease progression is inevitable in patients with previously treated and relapsed metastatic EGFR-mutated non-small cell lung cancer, reinforcing the need for new and innovative treatments across diverse mechanisms of resistance,” said Ken Takeshita, MD, Global Head, R&D, Daiichi Sankyo. “The results from HERTHENA-Lung01, coupled with early trial results, show that patritumab deruxtecan demonstrates clinically meaningful and durable responses, illustrating the potential of this HER3 directed antibody drug conjugate to become a new standard of care for this patient population with high unmet medical need. These data will support our ongoing discussions with health authorities including our planned submission in the U.S.”

The safety profile of patritumab deruxtecan observed in HERTHENA-Lung01 was consistent with previous clinical trials with a low rate (7.1%) of treatment discontinuation due to treatment-emergent adverse events (TEAEs) at the time of primary data cutoff of November 21, 2022. Grade 3 or higher TEAEs occurred in 64.9% of patients. The most common ($\geq$5%) grade 3 or higher TEAEs were thrombocytopenia (21%), neutropenia (19%), anemia (14%), leukopenia (10%), fatigue (6%), hypokalemia (5%) and asthenia (5%). Twelve patients (5.3%) had confirmed treatment-related interstitial lung disease (ILD) as determined by an independent adjudication committee. The majority of ILD events

were low grade with one grade 1 event and eight grade 2 events. Two grade 3, zero grade 4 and one grade 5 ILD event were observed.

In HERTHENA-Lung01, 51% of patients (n=115) had a history of CNS metastases; 32% (n=72) and 33% of patients (n=75) had brain or liver metastases at baseline by BICR, respectively. In the trial, 63% (n=142) and 36% (n=82) of patients had either an EGFR exon 19 deletion or exon 21 L858R mutation detected at baseline, respectively, and one patient had both.

Patients were heavily pretreated receiving a median of three prior lines of systemic therapy in the locally advanced/metastatic setting (range, 1-11), including platinum-based chemotherapy (100%), third generation EFGR TKI (93%) and immunotherapy (40%). As of the snapshot data cutoff of May 18, 2023, the median trial duration was 18.9 (14.9-27.5) months, and 13 patients were continuing to receive patritumab deruxtecan.

Summary of HERTHENA-Lung01 Results

Efficacy Measure	**Prior treatment with any EGFR TKI and platinum-based chemotherapy n=225**	**Subset with prior treatment with third-generation EGFR TKI and platinum-based chemotherapy n=209**
Confirmed ORR, % (95% CI)	29.8% (23.9-36.2)	29.2.% (23.1-35.9)
CR, n (%)	1 (0.4%)	1 (0.5%)
PR, n (%)	66 (29.3%)	60 (28.7%)
SD, n (%)	99 (44.0%)	91 (43.5%)
PD, n (%)	43 (19.1%)	41 (19.6%)
NE, n (%)	16 (7.1%)	16 (7.7%)
DCR (95% CI), %	73.8% (67.5-79.4)	72.7% (66.2-78.6)
DOR, median (95% CI), months	6.4 months (4.9-7.8)	6.4 months (5.2-7.8)
PFS, median (95% CI), months	5.5 months (5.1-5.9)	5.5 months (5.1-6.4)
OS, median (95% CI), months	11.9 months (11.2-13.1)	11.9 months (10.9-13.1)

CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; PD, progressive disease; SD, stable disease.

About HERTHENA-Lung01

HERTHENA-Lung01 is a global, multicenter, open-label, two-arm phase 2 trial evaluating the safety and efficacy of patritumab deruxtecan in patients with EGFR-mutated locally advanced or metastatic NSCLC following disease progression with an EGFR TKI and platinum-based chemotherapy. Patients were randomized 1:1 to receive 5.6 mg/kg (n=225) or an uptitration regimen (n=50). The uptitration arm was

discontinued as the dose of 5.6 mg/kg of patritumab deruxtecan was selected following a risk-benefit analysis conducted from the phase 1 trial assessing the doses in a similar patient population.

The primary endpoint of HERTHENA-Lung01 was ORR as assessed by BICR. Secondary endpoints included duration of response, PFS, disease control rate, and time to response – all assessed by both BICR and investigator assessment – as well as investigator-assessed ORR, OS, safety and tolerability.

The data presented at WCLC is from the first arm and based on the fixed-dose (5.6 mg/kg) regimen.

HERTHENA-Lung01 enrolled patients in Asia, Europe, North America and Oceania. For more information about the trial, visit ClinicalTrials.gov.

About EGFR-Mutated Non-Small Cell Lung Cancer

Lung cancer is the second most common cancer and the leading cause of cancer-related deaths worldwide.[5] NSCLC accounts for approximately 85% of all lung cancers – 55% having distant spread at diagnosis – with EGFR mutations occurring in 14% to 38% of all NSCLC tumors worldwide.[1,2,3]

The introduction of targeted therapies has improved the treatment landscape for patients with EGFR-mutated locally advanced or metastatic NSCLC. Targeted therapy with EGFR TKIs offers higher response rates, PFS and potential OS advantage, compared to chemotherapy, with third generation EGFR TKIs demonstrating superior efficacy compared to earlier generation inhibitors.[1] However, disease progression from resistance to EGFR TKIs inevitably occurs one to two years following initial treatment.[6]

After failure of EGFR TKI and platinum-based chemotherapy, currently available therapies offer limited efficacy.[3,4] A recent real-world analysis of the treatment of patients in this setting showed that the median PFS in this setting is 3.3 months (95% CI: 2.8-4.4) and median OS is 8.6 months (95% CI: 7.4-9.8). An estimated real-world ORR of 14.1% (95% CI: 3.7%-33.1%) also has been observed.[7,8] New treatment approaches are needed to help improve clinical outcomes in patients with EGFR-mutated NSCLC.

About HER3

HER3 is a member of the EGFR family of receptor tyrosine kinases.[9] It is estimated that about 83% of primary NSCLC tumors and 90% of advanced EGFR-mutated tumors express HER3 after prior EGFR TKI treatment.[10,11] There is currently no HER3 directed therapy approved for the treatment of any cancer.

About Patritumab Deruxtecan

Patritumab deruxtecan (HER3-DXd) is an investigational HER3 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC technology, patritumab deruxtecan is composed of a fully human anti-HER3 IgG1 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Patritumab deruxtecan was granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration in December 2021 for the treatment of patients with EGFR-mutated locally advanced or metastatic NSCLC with disease progression on or after treatment with a third-generation TKI and platinum-based therapies.

Patritumab deruxtecan is currently being evaluated as both a monotherapy and in combination with other therapies in a global development program, which includes HERTHENA-Lung02, a phase 3 trial versus platinum-based chemotherapy in patients with EGFR-mutated locally advanced or metastatic NSCLC following disease progression on or after treatment with a third-generation EGFR TKI; a phase 1 trial in combination with osimertinib in EGFR-mutated locally advanced or metastatic NSCLC; and a phase 1 trial in previously treated patients with advanced NSCLC. A phase 1/2 trial in HER3 expressing metastatic breast cancer also has been completed.

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 (Dato-DXd), a TROP2 directed ADC, are being jointly developed and commercialized globally with AstraZeneca. Four additional Daiichi Sankyo DXd ADCs include patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, raludotatug deruxtecan (R-DXd; DS-6000), a CDH6 directed ADC, and DS-3939, a TA-MUC1 directed ADC.

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 needs. For more information, please visit www.daiichisankyo.com.

Disclosure: Dr. Yu has a consulting relationship with Daiichi Sankyo.

Media Contacts:

Global/US:
Jennifer Brennan
Daiichi Sankyo, Inc.
jbrennan2@dsi.com
+1 908 900 3183 (mobile)

Japan:
Koji Ogiwara
Daiichi Sankyo Co., Ltd.
ogiwara.koji.ay@daiichisankyo.co.jp
+81 3 6225 1126 (office)

Investor Relations Contact:
DaiichiSankyoIR@daiichisankyo.co.jp

References:

[1] Economopoulou P, et al. *Ann Transl Med*. 2018; 6(8):138.
[2] Chen R, et al. *J Hematol Oncol*. 2020; 13(1):58.
[3] Zhang Y-L, et al. *Oncotarget*. 2016; 7(48):78985-78993.
[4] Janne PA, et al. *Cancer Discov*. 2022; 12(1):74-89.
[5] World Health Organization. International Agency for Research on Cancer. Lung Fact Sheet. Accessed January 2023.
[6] Janne PA, et al. *N Engl J Med* 2015; 372:1689-1699.
[7] Patel JD, et al. AACR 2023. Poster 6754.
[8] Patel JD, et al. IASLC 2023 WCLC. Abstract 2201.
[9] Mishra R, et al. *Oncol Rev*. 2018; 12(355):45-62.
[10] Scharpenseel H, et al. *Scientific Reports*. 2019; 9:7406.
[11] Yonesaka K, et al. *Clin Cancer Res*. 2022; 15:28(2):390-403.