

Press Release

Patritumab Deruxtecan Data at ASCO Demonstrates Tumor Response Across Multiple Resistance Mechanisms in Patients with Advanced EGFR-Mutated NSCLC

- Oral presentation highlighting extended follow-up data from phase 1 study in patients with locally advanced or metastatic TKI-resistant, EGFR-mutated NSCLC shows promising clinical activity
- Data from this study informed the design of the recently initiated pivotal HERTHENA-Lung01 trial in similar patient population

Tokyo, Munich and Basking Ridge, NJ – (June 4, 2021) – New data from Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo's) patritumab deruxtecan (HER3-DXd), a HER3 directed antibody drug conjugate (ADC), demonstrated preliminary evidence of clinically meaningful and durable tumor response in patients with locally advanced or metastatic TKI-resistant, EGFR-mutated non-small cell lung cancer (NSCLC).

These extended follow-up data from the dose escalation portion and one expansion cohort of a phase 1 study of patritumab deruxtecan were presented today during an oral presentation (Abstract #9007) at the 2021 American Society of Clinical Oncology (#ASCO21) Virtual Scientific Program.

While the efficacy of targeted therapy with EGFR TKIs is well-established in the treatment of patients with advanced EGFR-mutated NSCLC, the development of a broad range of resistance mechanisms commonly leads to disease progression.^{1,2} Subsequent salvage therapies after EGFR TKI and platinum-based chemotherapy have limited efficacy with progression-free survival (PFS) of approximately 2.8 to 3.2 months.³ New treatment approaches are needed to overcome resistance and improve survival in these patients.

An objective response rate (ORR), as assessed by blinded central review, was 39% (CI 95%; 26-52%) in 57 evaluable patients treated with patritumab deruxtecan (5.6 mg/kg). One confirmed complete response and 21 partial responses were observed. The disease control rate was 72% (CI 95%; 59-83%). After a median follow-up of 10.2 months (range, 5.2-19.9 months), the estimated median duration of response was 6.9 months (CI 95%; range, 3.1-NE months) and the estimated median PFS was 8.2 months (CI 95%; range, 4.4-8.3 months). Confirmed responses were observed in patients across a spectrum of baseline tumor HER3 membrane expression levels, EGFR activating mutations and EGFR TKI resistance mechanisms, including EGFR activating mutations (Ex19del, L858R, G719Y), other EGFR mutations (T790M, C797S, Ex20ins),

amplifications (EGFR, CCNE1, MET) and non-EGFR mutations and fusions (MET, KRAS). A subgroup of patients treated with osimertinib and platinum-based chemotherapy (n=44) prior to enrollment in the study demonstrated similar efficacy. An ORR of 39% (CI 95%; 24-55%) and PFS of 8.2 months (CI 95%; 4.0-NE) was observed in this subgroup. Additionally, the confirmed ORR and median PFS were similar in patients with or without a history of brain metastases.

“EGFR TKIs are the standard of care for patients with advanced EGFR-mutated NSCLC. However, the activity of these agents is limited by the development of acquired resistance mechanisms,” said Pasi A. Jänne, MD, PhD, Director, Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute. “In this study, where patients were heavily pre-treated, efficacy was observed in patients with and without known EGFR TKI resistance mechanisms in a population that is often difficult to treat. Targeting HER3 with patritumab deruxtecan may be a novel and promising strategy, and we look forward to further evaluating clinical activity and safety in the pivotal HERTHENA-Lung01 trial.”

The safety profile of patritumab deruxtecan in patients treated with the 5.6 mg/kg dose (n=57) is consistent with that seen across all patients (n=81) in both the dose escalation and dose expansion cohort 1 of the study (doses range from 3.2 to 6.4 mg/kg). Grade 3 or higher treatment emergent events (TEAEs) occurred in 64% of all patients (n=81). TEAEs grade 3 or higher severity occurring in $\geq 5\%$ of all patients were platelet count decreased, neutrophil count decreased, fatigue, anemia, dyspnea, febrile neutropenia, hypoxia, white blood cell count decreased, hypokalemia and lymphocyte count decreased. There were four cases of treatment-related interstitial lung disease (ILD) reported, as determined by an independent adjudication committee, including two of grade 1 severity, one grade 2, and one grade 3. The median time to adjudicated onset of treatment-related ILD was 53 days (range, 13-130 days). There were five TEAEs associated with death including two cases of disease progression, two cases of respiratory failure and one case of shock. All TEAEs associated with death were considered not related to the study drug.

“Treatment options that provide meaningful therapeutic benefit for patients with EGFR-mutated non-small cell lung cancer with disease progression following standard treatment with EGFR TKIs and platinum-based chemotherapy are limited,” said Gilles Gallant, BPharm, PhD, FOPQ, Senior Vice President, Global Head, Oncology Development, Oncology R&D, Daiichi Sankyo. “HER3 represents a novel target for therapeutic development as it is broadly expressed in non-small cell lung cancer. These results are encouraging since the safety profile was consistent with previous findings and response to patritumab deruxtecan was seen irrespective of the level of HER3 expression or mechanism of resistance to prior therapies.”

Patients receiving 5.6 mg/kg (n=57) of patritumab deruxtecan were pre-treated with a median of four prior lines of therapy (range, 1-9), including EGFR TKIs (100%), platinum-based chemotherapy (91%) and immunotherapy (40%). A majority (86%) were previously treated with osimertinib. Of the 57 patients, 27 patients had brain metastases at baseline. As of data cut-off on September 24, 2020, 32% of patients remain on treatment with patritumab deruxtecan.

Summary of Results

| Efficacy Measure | HER3-DXd Dose Escalation 5.6 mg/kg Plus Dose Expansion 5.6 mg/kg (n=57) ^{iv} | |
|-----------------------------------|--|-----------------------------|
| | Prior TKI±PBC (n=57) | Prior OSI and PBC (n=44) |
| ORR (%) (95% CI) ^{i, ii} | 39% (26-52) | 39% (24-55) |
| CR (%) | 2% | 2% |
| PR (%) | 37% | 36% |
| SD (%) | 33% | 30% |
| PD (%) | 16% | 18% |
| NE (%) | 12% | 14% |
| DCR (%) (95% CI) ⁱⁱⁱ | 72% (59-83) | 68% (52-81) |
| Time to response (months) | 2.6 months (1.2-5.4) | 2.7 months (1.2-5.4) |
| Median DOR (months) (95% CI) | 6.9 months (3.1-NE) | 7.0 months (3.1-NE) |
| Median PFS (months) (95% CI) | 8.2 months (4.4-8.3) | 8.2 months (4.0-NE) |

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; OSI, osimertinib; NE, not estimable; PBC, platinum-based chemotherapy; PD, progressive disease; PR, partial response; PFS, progression-free survival; SD, stable disease; TKI; tyrosine kinase inhibitor

ⁱ As assessed by independent central review

ⁱⁱ ORR is (CR + PR)

ⁱⁱⁱ DCR is (CR + PR + SD)

^{iv} Median follow up: 10.2 (range, 5.2-19.9) months

About the Phase 1 Non-Small Cell Lung Cancer Study

The global, multicenter, open label, two-part phase 1 study is evaluating patritumab deruxtecan in previously treated patients with metastatic or unresectable NSCLC.

The dose escalation part of the study evaluated patients with EGFR-mutated disease either with progression on osimertinib or T790M-negative after progression on erlotinib, gefitinib or afatinib. The primary objective of this part of the study was to assess the safety and tolerability of patritumab deruxtecan and determine the recommended dose for expansion (RDE).

The dose expansion part of the study is evaluating patritumab deruxtecan at the RDE (5.6 mg/kg every three weeks) in three cohorts. Cohort 1 includes patients with locally advanced or metastatic EGFR-mutated

NSCLC who experienced disease progression after taking one or more EGFR TKIs and one or more platinum based chemotherapy regimens. Cohort 2 includes patients with squamous or non-squamous NSCLC without EGFR-activating mutations following platinum-based chemotherapy and following an anti-PD-1 or anti-PD-L1 antibody regimen. Cohort 3 includes patients with NSCLC with EGFR-activating mutations including any histology other than combined small cell and non-small cell lung cancer; patients in Cohort 3 are randomized 1:1 to receive the 5.6 mg/kg RDE regimen (Cohort 3a) or an escalating up-titration regimen of patritumab deruxtecan (Cohort 3b).

Preliminary data from the dose escalation part of the study were [presented](#) previously at the 2019 World Conference on Lung Cancer, and early data from the dose escalation part (5.6 mg/kg dose) and Cohort 1 of the dose expansion were [presented](#) at the 2020 European Society of Medical Oncology (ESMO) Virtual Congress. Exploratory biomarker analyses assessing genomic alterations of patient tumors were [presented](#) at the 2020 World Conference on Lung Cancer.

The primary objective of the dose expansion part of the study is to assess efficacy of patritumab deruxtecan as measured by confirmed objective response rate assessed by blinded independent central review. Secondary study endpoints include investigator-assessed objective response rate; safety, tolerability and preliminary efficacy; and characterization of the pharmacokinetics of patritumab deruxtecan. The study enrolled patients at multiple sites in the U.S., Europe, Japan and other countries in Asia. For more information, visit [ClinicalTrials.gov](https://clinicaltrials.gov).

About Non-Small Cell Lung Cancer

Lung cancer is the most common cancer and the leading cause of cancer mortality worldwide. There were an estimated 2.2 million new cases of lung cancer and 1.8 million deaths in 2020.⁴ Most lung cancers are diagnosed at an advanced or metastatic stage.⁵ Non-small cell lung cancer (NSCLC) accounts for 80 to 85% of all lung cancers.⁶

The introduction of targeted therapies and checkpoint inhibitors in the past decade has improved the treatment landscape for patients with advanced or metastatic NSCLC; however, the prognosis is particularly poor among patients who have progressed after treatment with standard therapies. For patients who are not eligible for current treatments, or whose cancer continues to progress, new therapeutic approaches are needed.⁷

The mutationally-activated EGFR tyrosine kinase is a well-established oncogenic driver and molecular target for management of advanced stage NSCLC.⁸ For patients with advanced EGFR-mutated NSCLC, targeted therapy with EGFR TKIs offer higher response rates and progression-free survival compared to chemotherapy.⁷ However, most patients eventually develop resistance to these therapies, and standard treatment options are limited.⁹ Treatment options used in this setting historically have demonstrated limited efficacy with progression free survival of up to 6.4 months for platinum-based chemotherapy and 3.2 months for other salvage therapies.^{3, 10} New treatment approaches are needed to overcome resistance and improve survival in these patients.

About HER3

HER3 is a member of the EGFR family of receptor tyrosine kinases, which are associated with aberrant cell proliferation and survival.¹¹ Approximately 25 to 30% of lung cancers worldwide have an EGFR-activating mutation, and it is estimated that about 83% of all NSCLC tumors express the HER3 protein, which can be associated with an increased incidence of metastases, reduced survival and resistance to standard of care treatment.^{12,13,14} Currently, no HER3 directed medicines are approved for the treatment of cancer.

About Patritumab Deruxtecan

Patritumab deruxtecan (HER3-DXd) is one of three lead DXd ADCs in the oncology pipeline of Daiichi Sankyo. Designed using Daiichi Sankyo's proprietary DXd ADC technology, patritumab deruxtecan is comprised of a human anti-HER3 antibody attached to a topoisomerase I inhibitor payload, an exatecan derivative, via a stable tetrapeptide-based cleavable linker.

Patritumab deruxtecan is currently being evaluated in a comprehensive development program across multiple cancers as both a monotherapy and in combination with other anticancer treatments. The development program includes [HERTHENA-Lung01](#), a pivotal phase 2 study in patients with locally advanced or metastatic EGFR-mutated NSCLC previously treated with a TKI and platinum-based chemotherapy; a [phase 2 study](#) in patients with advanced/metastatic colorectal cancer with disease progression following at least two prior lines of systemic therapy; a [phase 1/2 study](#) in HER3 expressing metastatic breast cancer; a [phase 1 study](#) in combination with osimertinib in locally advanced/metastatic EGFR-mutated NSCLC; and, a [phase 1 study](#) in previously treated patients with metastatic or unresectable NSCLC.

Patritumab deruxtecan is an investigational medicine that has not been approved for any indication in any country. Safety and efficacy have not been established.

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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