

Press Release

Patritumab Deruxtecan Continues to Show Encouraging Clinical Activity in Distinct Patient Populations with Metastatic Lung and Breast Cancer in Updated Results of Two Early Trials

- Updated results from phase 1 trial, including first presentation of data from a cohort of patients with EGFR-mutated metastatic non-small cell lung cancer, featured during a Presidential Session at JSMO
- Subgroup analysis by HER2 expression from phase 1/2 trial of patients with HER3 expressing metastatic breast cancer highlighted in a second Presidential Session

Tokyo and Basking Ridge, NJ – (March 20, 2023) – New data from Daiichi Sankyo’s (TSE: 4568) patritumab deruxtecan (HER3-DXd) from two early trials in patients with previously treated EGFR-mutated metastatic non-small cell lung cancer (NSCLC) (#PS1-2) or HER3 expressing metastatic breast cancer (#PS2-4) were presented during two Presidential Sessions at the Japanese Society of Medical Oncology (#JSMO2023) Annual Meeting.

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

Lung and breast cancer are the first and fifth leading causes of cancer-related deaths worldwide, accounting for approximately 1.8 million and 685,000 deaths in 2020, respectively.^{1,2} New therapeutic approaches are needed to improve outcomes for these cancers and HER3 is a promising target for therapeutic development as it is broadly expressed in both lung and breast tumors.^{3,4,5}

“Most patients with lung or breast cancer involved in these two early-stage trials were heavily pre-treated, underscoring the need for new and innovative treatment options to help improve outcomes,” said Mark Rutstein, MD, Global Head, Oncology Clinical Development, Daiichi Sankyo. “These results further add to the growing body of evidence that targeting HER3 with patritumab deruxtecan may be a promising therapeutic option for a wide array of patients across several subtypes of metastatic lung and breast cancer.”

EGFR-Mutated NSCLC Phase 1 Trial Results

Updated data from a pooled analysis of a phase 1 trial of patritumab deruxtecan (5.6 mg/kg), including the first presentation of results from heavily pretreated patients with EGFR-mutated locally advanced or

metastatic NSCLC (cohort 3a), demonstrated promising clinical efficacy after a median follow up of 23 months (range, 11.8-36.0). These data were presented during the Presidential Session on March 16, 2023.

An objective response rate (ORR) of 40.2% (95% CI: 30.6-50.4), as assessed by blinded independent central review (BICR), was observed with patritumab deruxtecan in the pooled analysis of 102 patients with EGFR-mutated NSCLC. One complete response (CR), 40 partial responses (PRs) and 39 cases of stable disease (SD) were seen. A disease control rate (DCR) of 78.4% (95% CI: 69.2-86.0) and a median duration of response (DOR) of 7.6 months (95% CI: 6.9-14.7) were observed. Median progression-free survival (PFS) was 6.4 months (95% CI: 5.3-8.3) and median overall survival (OS) was 15.8 months (95% CI: 10.8-21.5). Efficacy outcomes were consistent in a subgroup of 78 patients previously treated with third-generation EGFR TKI and platinum-based chemotherapy.

Responses with patritumab deruxtecan were seen in patients across a broad range of HER3 expression and across multiple mechanisms of EGFR TKI resistance. Additionally, confirmed ORRs of 36.4% (95% CI: 23.8-50.4) and 44.7% (95% CI: 30.2-59.9) were observed in patients with and without a history of central nervous system (CNS) metastases, respectively.

“Patritumab deruxtecan demonstrated a median overall survival of more than 15 months, which is particularly impressive in heavily pretreated patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer,” said Hidetoshi Hayashi, MD, PhD, Associate Professor, Department of Medical Oncology at Kindai University, Osaka, Japan. “Further clinical evaluation of patritumab deruxtecan in EGFR-mutated NSCLC is underway.”

Patients were heavily pre-treated receiving a median of four prior lines of systemic therapy in the locally advanced/metastatic setting (range, 1-14) and median treatment duration was 5.5 months (range, 0.7-27.5). Safety of patritumab deruxtecan seen in this phase 1 trial was consistent with that previously observed in patients with EGFR-mutated NSCLC. Treatment-emergent adverse events (TEAEs) grade ≥ 3 were reported in 58 patients (56.9%) and included platelet count decrease (26%), neutrophil count decrease (21%), fatigue (10%), anemia (9%), white blood cell count decrease (8%), nausea (7%), hypokalemia (7%), lymphocyte count decrease (7%), dyspnea (6%) and febrile neutropenia (6%). Eight patients (7.8%) had confirmed treatment-related interstitial lung disease (ILD) as determined by independent adjudication committee. The majority of these ILD events were low-grade with two grade 1, three grade 2, one grade 3 and two grade 5 events. As of the data cut-off on January 28, 2022, eight patients remained on study treatment with patritumab deruxtecan.

Summary of Results in EGFR-Mutated NSCLC Phase 1 Trial

Efficacy Measure	Patritumab deruxtecan 5.6 mg/kg n=102	Subset with prior third-generation EGFR TKI and platinum-based chemotherapy n=78
Confirmed ORR, % (95% CI)	40.2% (30.6-50.4)	41.0% (30.0-52.7)
Confirmed BOR		
CR, % (n)	1.0% (1)	1.3% (1)
PR, % (n)	39.2% (40)	39.7% (31)
SD, % (n)	38.2% (39)	34.6% (27)
PD, % (n)	12.7% (13)	14.1% (11)
NE, % (n)	8.8% (9)	10.3% (8)
DCR % (n) (95% CI)	78.4% (80) (69.2-86.0)	75.6% (59) (64.6-84.7)
DOR, median (95% CI), months	7.6 months (6.9-14.7)	11.2 months (7.0-NE)
PFS, median (95% CI), months	6.4 months (5.3-8.3)	6.4 months (4.4-10.8)
OS, median (95% CI), months	15.8 months (10.8-21.5)	16.2 months (11.2-21.9)

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

Subgroup Analysis of HER2 Expression in HER3 Expressing Metastatic Breast Cancer Phase 1/2 Trial

Newly reported exploratory subgroup analysis of HER2 expression (HER2 low defined as IHC 1+ or IHC2+/ISH-; or HER2 zero) from a three-part, first-in-human phase 1/2 trial evaluating patritumab deruxtecan (n=182) in patients with heavily pretreated HER3 expressing metastatic breast cancer, including HR positive/HER2 negative and triple negative breast cancer (TNBC), demonstrated promising clinical activity. These data were presented during a second Presidential Session on March 17, 2023.

In patients with HR positive breast cancer, confirmed ORRs of 36.2% (95%, CI: 24.0-49.9) in patients with HER2 low (n=58) and 28.2% (95% CI: 15.0-44.9) in patients with HER2 zero (n=39) disease were observed. Median DOR was 7.2 months (95% CI: 5.5-NE) and 7.0 months (95% CI: 3.0-NE), median PFS was 5.8 months (95% CI: 4.1-8.5) and 8.2 months (95% CI: 5.8-9.1) and median OS was 13.7 months (95% CI: 8.5-20.1) and 14.6 months (95% CI: 11.0-21.0) in the HER2 low and HER2 zero subgroups, respectively.

In patients with TNBC, a confirmed ORR of 20.7% (95% CI: 8.0-39.7) was observed in patients with HER2 low expression (n=29) and 26.3% (95%, CI: 9.1-51.2) in patients with HER2 zero expression (n=19). Median DOR was 4.1 months (95% CI: 2.7-6.0) and 8.4 months (95% CI: 4.2-NE), median PFS was 4.4 months (95% CI: 2.6-5.6) and 8.4 months (95% CI: 3.9-13.9), and OS was 12.7 months (95% CI: 9.2-21.8) and 16.6 months (95% CI: 9.3-23.8) in the HER2 low and HER2 zero subgroups, respectively.

Pooled safety of patritumab deruxtecan previously reported was further analyzed by dose (4.8 mg/kg and 6.4 mg/kg) and location of patients in Japan (n=142) or the U.S. (n=40) with an overall similar rate for TEAEs, excluding ILD, seen between Japan and U.S. subgroups. Grade \geq 3 TEAEs occurred in 99 patients (69.7%)

in Japan and 21 patients (52.5%) in the U.S. Twelve patients (8.5%) from Japan and zero patients from U.S. had confirmed treatment related ILD as determined by an independent adjudication committee. The majority of ILD events were low-grade with three grade 1 (2.1%), five grade 2 (3.5%), three grade 3 (2.1%) and one grade 5 (0.7%) event.

“These data extend previous observations and demonstrate patritumab deruxtecan has shown clinical activity in patients with metastatic breast cancer and HER2 low or HER2 zero expression,” said Hiroji Iwata, MD, PhD, Vice Director and Chief of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan. “These data support the further evaluation of patritumab deruxtecan as a potential treatment option for breast cancer and learning more about appropriate sequencing approaches with other therapies.”

Patients across subgroups were heavily pre-treated, receiving a median of seven prior lines of systemic therapy in the HR positive, HER2 low and HER2 zero subgroups, four prior lines of systemic therapy in the HR negative, HER2 low subgroup, and three prior lines of systemic therapy in the HR negative, HER2 zero subgroup. Median treatment duration was 5.5 months (range, 0.7-28.4) in the HR positive, HER2 low subgroup, 7.6 months (range, 1.4-22.8) in the HR positive, HER2 zero subgroup, 4.9 months (range, 0.7-19.8) in the HR negative, HER2 low subgroup and 5.7 months (range, 0.7-22.5) in the HR negative, HER2 zero subgroup. As of data cut-off of August 16, 2021, four patients (10.6%) remained on treatment with patritumab deruxtecan.

Summary of HER2 Expression Subgroup Analysis in HER3 Expressing Metastatic Breast Cancer Phase 1/2 Trial

	HR positive/HER2 negative		TNBC	
Efficacy Measure	HR positive /HER2 low (n=58)	HR positive/ HER2 zero (n=39)	HR negative /HER2 low (n=29)	HR negative/ HER2 zero (n=19)
Confirmed ORR, % (95% CI)	36.2% (24.0-49.9)	28.2% (15.0-44.9)	20.7% (8.0-39.7)	26.3% (9.1-51.2)
Confirmed BOR				
PR, %	36.2%	28.2%	20.7%	26.3%
SD, %	43.1%	61.5%	48.3%	68.4%
PD, %	10.3%	7.7%	24.1%	5.3%
NE, % (n)	10.3%	2.6%	6.9%	0.0%
DOR, median (95% CI), months	7.2 months (5.5-NE)	7.0 months (3.0-NE)	4.1 months (2.7-6.0)	8.4 months (4.2-NE)
PFS, median (95% CI), months	5.8 months (4.1-8.5)	8.2 months (5.8-9.1)	4.4 months (2.6-5.6)	8.4 months (3.9-13.9)
OS, median (95% CI), months	13.7 months (8.5-20.1)	14.6 months (11.0-21.0)	12.7 months (9.2-21.8)	16.6 months (9.3-23.8)

BOR, best overall response; DOR, duration of response; HER, human epidermal growth factor receptor; HR, hormone receptor; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; NE, not evaluable; TNBC, triple negative breast cancer.
95% exact binomial confidence interval (by Clopper-Pearson method)

About the Phase 1 Non-Small Cell Lung Cancer Trial

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

The dose escalation part of the trial is evaluating 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 trial was to assess the safety and tolerability of patritumab deruxtecan and determine the recommended dose for expansion (RDE).

The dose expansion part of the trial 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). Cohort 4 includes patients with NSCLC, including any histology other than small cell or combined small and non-small cell.

The primary objective of Cohorts 1, 2 and 3 in the dose expansion part of the trial is to assess efficacy of patritumab deruxtecan as measured by confirmed ORR assessed by BICR. Secondary trial endpoints include investigator-assessed ORR, DCR, DOR, PFS, OS, safety and pharmacokinetics. The primary objective of Cohort 4 is to assess the relative bioavailability of clinical study versus commercial patritumab deruxtecan in Cohort 3a. The trial enrolled 264 patients at multiple sites in Asia, Europe and North America. For more information, visit [ClinicalTrials.gov](https://clinicaltrials.gov).

About the Phase 1/2 Breast Cancer Trial

The global, open-label, three-part phase 1/2 trial is evaluating the safety and efficacy of patritumab deruxtecan in patients with HER3 expressing advanced/unresectable metastatic breast cancer who are refractory or intolerant to standard treatment, or for whom no standard treatment is available.

The dose escalation part of the trial assessed the safety and tolerability of increasing doses of patritumab deruxtecan to determine the maximum tolerated dose. The dose finding part of the trial assessed the safety and efficacy of patritumab deruxtecan at selected dosing levels to determine the recommended dose for expansion. Patients in the dose escalation and dose finding parts of the trial must have received six or fewer prior chemotherapy regimens, at least two of which were administered for treatment of advanced/unresectable metastatic disease, and at least one prior chemotherapeutic regimen must have included a taxane, administered in the neoadjuvant, adjuvant or advanced setting, except in the dose expansion part of the TNBC cohort.

The phase 2 part of the trial evaluated the safety and efficacy of patritumab deruxtecan at the recommended dose for expansion in four different cohorts of patients with HER3 expressing and HER2 negative locally advanced or metastatic breast cancer, including HR positive and triple negative breast cancer. The trial enrolled 182 patients at multiple sites in the United States and Japan. For more information, 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.¹ Approximately 80% to 85% of lung cancer is classified as NSCLC, which is typically diagnosed at an advanced stage in more than 50% of cases.^{6,7} EGFR mutations occur in up to 30% of all NSCLC tumors worldwide.⁸

The introduction of targeted therapies has improved the treatment landscape for patients with EGFR-mutated metastatic or locally advanced NSCLC. Targeted therapy with EGFR TKIs offers higher response rates and progression-free survival compared to chemotherapy.⁶ However, disease progression from resistance to EGFR TKIs inevitably occurs one to two years following initial treatment.⁹ Subsequent standard treatments following first-line progression offer limited efficacy.¹⁰ New treatment approaches are needed to help improve survival in patients with EGFR-mutated NSCLC.

About Breast Cancer

Breast cancer is the most common cancer and is one of the leading causes of cancer-related deaths worldwide.¹¹ More than two million cases of breast cancer were diagnosed in 2020 with nearly 685,000 deaths globally.^{2,11} Despite recent advancements across the three main subtypes of breast cancer, including HER2 positive, HR positive/HER2 low or negative and triple negative, it remains incurable and new treatment strategies are needed for refractory disease.

About HER3

HER3 is a member of the EGFR family of receptor tyrosine kinases.¹² It is estimated that about 83% of primary NSCLC tumors express HER3 and 90% of advanced EGFR-mutated tumors after prior EGFR TKI treatment express HER3.^{5,13} HER3 also is highly expressed in about 30% to 50% of breast tumors.^{3,4,14} There is currently no HER3 directed medicine 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 (BTD) by the U.S. Food and Drug Administration (FDA) in December 2021 for the treatment of patients with metastatic or locally advanced EGFR-mutated 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-Lung01](#), a phase 2 trial in patients with EGFR-mutated locally advanced or metastatic NSCLC previously treated with two prior systemic therapies including at least one EGFR TKI and at least one platinum-based chemotherapy based regimen; [HERTHENA Lung02](#), a phase 3 trial versus platinum-based chemotherapy in patients with EGFR-mutated locally advanced or metastatic NSCLC following treatment with one or more EGFR TKIs; 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 unresectable or metastatic 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 five ADCs in clinical development across multiple types of cancer. The company's clinical trial stage DXd ADCs include ENHERTU, a HER2 directed ADC and datopotamab deruxtecan (Dato-DXd), a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca; and patritumab deruxtecan (HER3-DXd), a HER3 directed ADC. Two additional ADCs including ifinatamab deruxtecan (I-DXd; DS-7300), a B7-H3 directed ADC, and DS-6000, a CDH6 directed ADC, are being developed through a strategic early-stage research collaboration with Sarah Cannon Research Institute.

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 and DS-6000 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 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 need. 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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