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Press Release

Valemetostat Pivotal Data Shows Promising Response Rates in Patients with Adult T-Cell Leukemia/Lymphoma

- Oral presentation at ASH 2021 features positive phase 2 data in Japanese patients with relapsed/refractory ATL
- Orphan Drug Designation granted with regulatory filing on track in Japan for FY2021

Tokyo, Munich and Basking Ridge, NJ – (December 11, 2021) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced that valemetostat, a potential first-in-class dual inhibitor of EZH1 and EZH2, demonstrated promising response rates in a pivotal phase 2 study in Japanese patients with relapsed/refractory adult T-cell leukemia/lymphoma (ATL). The results were reported today in an oral presentation (#303) at the 63rd Annual Meeting of the American Society of Hematology (#ASH21).

While ATL is a rare disease, it occurs with greater frequency in parts of Japan and other regions.[1] Currently, there are no optimal standard treatment options for ATL.[1] Nearly 90% of patients relapse after completing intensive first-line treatment, at which point there are few options available.[1,2]

The phase 2 study of valemetostat met its primary endpoint, demonstrating an objective response rate (ORR) of 48% (90% CI: 30.5%-65.9%) in 25 patients with relapsed/refractory ATL, as evaluated by an independent efficacy assessment committee. Five complete remissions, seven partial remissions and 10 cases of stable disease were reported. The median duration of response (DOR) was not reached (95% CI: 1.87 months-NR) at a median follow-up of 6.5 months. Eight patients remained on treatment at the time of data cut-off on April 24, 2021.

The safety profile of valemetostat in the study was consistent with the phase 1 trial in patients with several types of non-Hodgkin lymphoma including peripheral T-cell lymphoma (PTCL) and ATL.[3] Grade 3 or higher treatment emergent adverse events (TEAEs) occurred in 15 of 25 patients (60%), the most common of which (occurring in ≥30% of patients) were platelet count decrease (80%), anemia (48%), alopecia (40%) and dysgeusia (36%). Dose interruptions or reductions due to TEAEs occurred in 20% (n=5) and 8% (n=2) of patients, respectively. Two patients (8%) discontinued treatment due to TEAEs.

Based on these data, valemetostat was granted Orphan Drug designation by the Japan Ministry of Health, Labour and Welfare (MHLW) for the treatment of relapsed/refractory ATL. Therapies receiving Orphan Drug designation from the Japan MHLW are those being developed for serious, difficult-to-treat diseases

that affect fewer than 50,000 patients in Japan, and they qualify for several measures intended to support development including, but not limited to, guidance and subsidies for research and development activities, priority consultation for clinical development and priority review of applications.

"The phase 2 trial of valemetostat demonstrated encouraging response rates in Japanese patients with a history of mogamulizumab therapy for relapsed/refractory ATL," said Makoto Yoshimitsu, MD, PhD, Associate Professor, Kagoshima University Hospital, Japan. "For patients in Japan with aggressive ATL subtypes, median overall survival is about 12 months even with intensive chemotherapy regimens, and potential new options such as valemetostat are greatly needed to improve outcomes, particularly in the relapsed/refractory setting."[4]

"Based on these pivotal data for valemetostat, dual targeting of EZH1 and EZH2, which play important roles in the pathophysiology of T-cell lymphomas, appears to be a promising therapeutic approach for patients with relapsed/refractory ATL, a type of PTCL with particularly poor prognosis," said Ken Takeshita, MD, Global Head of R&D, Daiichi Sankyo. "We are working to deliver valemetostat to ATL patients in Japan as soon as possible while continuing global development in T-cell and B-cell lymphomas."

The study also showed a trend towards a decrease in measurable lesions across all disease sites assessed, including nodal, extranodal, skin and peripheral blood.

The trial included patients with three aggressive subtypes of ATL who received a median of three prior lines of therapy (range, 1-8). Twenty-four of 25 patients had received prior treatment with mogamulizumab.

Summary of Phase 2 Results

Efficacy Measure*	**All Patients (n=25)**	**Acute (n=16)**	**Lymphoma (n=6)**	**Unfavorable chronic (n=3)**
ORR, n (%)	12 (48.0)	10 (62.5)	1 (16.7)	1 (33.3)
CR	5 (20.0)	5 (31.3)	0	0
CRu	0	0	0	0
PR	7 (28.0)	5 (31.3)	1 (16.7)	1 (33.3)
SD	10 (40.0)	4 (25.0)	5 (83.3)	1 (33.3)
RD/PD	3 (12.0)	2 (12.5)	0	1 (33.3)
Median time to first response (months)	1.43 (range 1.0-5.6)	n/a	n/a	n/a
Median DOR (months)	NR (95% CI: 1.87-NR)	n/a	n/a	n/a

*CR, complete remission; CRu, complete remission unconfirmed; DOR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RD, relapsed disease; SD, stable disease

About Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATL) is a rare and aggressive type of peripheral T-cell lymphoma (PTCL) that is caused by human T-cell lymphotropic virus type 1 (HTLV-1).[1] More than 3,000 new cases of ATL are diagnosed each year worldwide.[5] While ATL is rare, it occurs with greater frequency in some regions including parts of Japan, the Caribbean, South America and Australia.[5] In Japan, there are approximately 1,000 new ATL cases and over 1,000 deaths due to ATL annually.[6]

ATL continues to have a dismal prognosis with current therapies.[7] The five-year overall survival rate for patients with ATL is about 14%.[8] A median survival time of approximately eight months (252 days) was reported for patients in Japan with the most common acute ATL subtype.[5]

Treatment of ATL is based on subtype and consists primarily of intensive multi-drug chemotherapy regimens.[7] Nearly 90% of patients relapse after completing intensive first-line treatment, at which point there are few options available.[1,2] Additional therapies are needed to improve the prognosis of ATL in Japan and worldwide.[1,7]

About EZH1 and EZH2

EZH1 (enhancer of zeste homolog 1) and EZH2 (enhancer of zeste homolog 2) enzymes are part of polycomb protein complexes and act through histone methylation to regulate expression of genes involved in maintaining hematopoietic stem cells.[9] EZH1 and EZH2 are recurrently highly expressed or mutated in many hematologic malignancies including T-cell lymphomas.[10] Research has demonstrated that both EZH1 and EZH2 enzymes have a role in hematologic cancer progression and that simultaneous inhibition would be effective in targeting the cancers.[11] There are no dual inhibitors of EZH1 and EZH2 approved for cancer treatment.

About the Phase 2 Study

The pivotal, open-label, multi-center, single-arm phase 2 study evaluated efficacy and safety of valemetostat (200 mg dose daily) as monotherapy in patients with relapsed/refractory ATL who were previously treated with mogamulizumab or at least one systemic chemotherapy in case of intolerance/ contraindication for mogamulizumab and with no history of allogenic hematopoietic stem cell transplant.

The primary endpoint is ORR assessed by independent efficacy assessment committee. Secondary endpoints include investigator-assessed ORR, best response in tumor lesions, complete remission rate, tumor control rate, time to response, duration of response, progression-free survival, overall survival and safety. A total of 25 patients were enrolled in the study in Japan. For more information, visit ClinicalTrials.gov.

About Valemetostat

Valemetostat is a potential first-in-class dual inhibitor of EZH1 and EZH2 currently in clinical development in the Alpha portfolio of Daiichi Sankyo. A potent and selective small molecule inhibitor, valemetostat is designed to counter epigenetic dysregulation by targeting both the EZH1 and EZH2 enzymes.[12]

The valemetostat development program includes VALENTINE-PTCL01, a global pivotal phase 2 trial in patients with relapsed/refractory PTCL and ATL; a pivotal phase 2 trial in patients with relapsed or refractory ATL in Japan; and, a phase 1 study in patients with relapsed/refractory NHL in the U.S. and Japan. Valemetostat received Orphan Drug Designation (ODD) from the U.S. Food & Drug Administration for the treatment of PTCL in December 2021, ODD from the Japan MHLW for the treatment of relapsed/refractory ATL in November 2021 and SAKIGAKE Designation from the Japan MHLW for the treatment of adult patients with relapsed/refractory PTCL in April 2019.

Valemetostat 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 Oncology

The oncology portfolio of Daiichi Sankyo is powered by our team of world-class scientists that push beyond traditional thinking to create transformative medicines for people with cancer. Anchored by our DXd antibody drug conjugate (ADC) technology, our research engines include biologics, medicinal chemistry, modality and other research laboratories in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in the U.S. We also work alongside leading academic and business collaborators to further advance the understanding of cancer as Daiichi Sankyo builds towards our ambitious goal of becoming a global leader in oncology by 2025.

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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