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Press Release

Valemetostat Data at EHA Shows Promising Durable Tumor Response in Patients with Peripheral T-Cell Lymphoma and Adult T-Cell Leukemia/Lymphoma

- Oral presentation highlights data from phase 1 study of valemetostat showing promising clinical activity in patients with relapsed/refractory PTCL and ATL
- Pivotal phase 2 study VALENTINE-PTCL01 underway globally to further evaluate efficacy and safety of valemetostat in similar patient population

Tokyo, Munich, Basking Ridge, N.J. – **(June 11, 2021)** – New data from Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) for valemetostat, a potential first-in-class specific and potent dual inhibitor of EZH1 and EZH2, showed promising and durable tumor response in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) and adult T-cell leukemia/lymphoma (ATL).[1] [2] The data were reported today during an oral presentation (Abstract #S218) at the Annual Congress of the European Hematology Association (#EHA2021).

PTCL is a group of rare and heterogenous malignancies, including ATL, which represent about 10-15% of all non-Hodgkin lymphomas (NHL).[3] The majority of patients with PTCL experience disease progression following initial treatment with a multi-drug chemotherapy-based regimen, and median overall survival following relapse is approximately 5.8 months.[4] New innovative treatment strategies are needed to improve survival in these patients.

In this first-in-human phase 1 study of valemetostat in B-cell and T-cell NHL, data were reported at EHA in the subset of patients with relapsed/refractory PTCL and ATL. The objective response rate (ORR), based on investigator's assessment, was 54.5% (CI 95%: 38.8-69.6) in 44 patients with PTCL including 12 complete responses (CRs) and 12 partial responses (PRs). A median duration of response (DOR) of 56.00 weeks (CI 95%: 44.43-NE) and a median progression-free survival (PFS) of 52.00 weeks (CI 95%: 16.14-NE) were observed after a median follow-up of 19.93 weeks (range: 3.1-68.1).

The ORR in 14 patients with ATL was 57.1% (CI 95%: 28.9-82.3), with four CRs and four PRs. Median DOR and PFS were not estimable for patients with ATL after a median follow up of 23.07 weeks (range: 3.3-125.0). Twelve patients with PTCL and six patients with ATL remained on treatment with valemetostat at the time of data cut-off on November 2, 2020.

The safety profile of valemetostat in patients with PTCL and ATL (n=58) was similar with that seen across all patients with NHL (n=77). Grade 3 or higher treatment emergent adverse events (TEAEs) occurred in 54

of 77 NHL patients (70.1%) and included neutrophil count decrease (23.4%), lymphocyte count decrease (22.1%), platelet count decrease (16.9%), white blood cell count decrease (15.6%), anemia (11.7%), diarrhea (1.3%) and alanine aminotransferase (ALT) increase (1.3%). Dose interruption or reductions due to TEAEs occurred in 41.6% (n=32) and 10.4% (n=8) of all patients with NHL, respectively.

"The proportion of patients who responded to valemetostat and the durability of responses observed in this trial are very encouraging for patients with PTCL, including ATL, which remains one of the most significant areas of unmet need in the treatment of hematologic cancers," said Shigeru Kusumoto, MD, Associate Professor, Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Japan. "Because both EZH1 and EZH2 play important roles for the pathophysiology of PTCL and ATL, dual targeting of EZH1 and EZH2 with valemetostat may be an innovative approach for these difficult-to-treat diseases."

"We are committed to translating the novel mechanism of valemetostat into a potential treatment option for patients with PTCL and ATL in various regions around the world where these types of blood cancers are most prevalent," said Ken Takeshita, MD, Global Head of Research and Development, Daiichi Sankyo. "Based on the promising clinical activity seen in this phase 1 study, we have initiated VALENTINE-PTCL01, a global pivotal study that will further evaluate the efficacy and safety of valemetostat in patients with relapsed or refractory PTCL including ATL."

Patients with PTCL enrolled in the study had received a median of two prior treatments (range: 1-8), including prior hematopoietic stem cell transplantation (HSCT; 20.5%). Patients with ATL had received a median of two prior treatments (range: 1-8), including HSCT (14.3%).

Summary of Phase 1 Results

Efficacy Measure	**Valemetostat Phase 1 Dose Expansion 200 mg (n=58)**	
	PTCL[iii, iv] (n=44)	**ATL[v,vi] (n=14)**
ORR (%) (95% CI) [i,ii]	54.5% (38.8-69.6)	57.1% (28.9-82.3)
CR	12 (27.3)	4 (28.6)
PR	12 (27.3)	4 (28.6)
SD	5 (11.4)	2 (14.3)
PD	8 (18.2)	3 (21.4)
NE	1 (2.3)	0 (0)
Not done	6 (13.6)	1 (7.1)
Time to response (weeks)	8.14 weeks (4.1-24.1)	8.14 weeks (7.3-84.1)
Median DOR (weeks) (95% CI)	56.00 weeks (44.43-NE)	NE (6.14-NE)
Median PFS (weeks) (95% CI)	52.00 weeks (16.14-NE)	NE (8.14-NE)

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DOR, duration of response; PFS, progression-free survival

[i] As assessed by investigator

[ii] ORR is CR+PR (including uncertified CR [CRu] for ATL)

[iii] Includes PTCL subtypes: AITL (angioimmunoblastic T-cell lymphoma), PTCL-NOS (not otherwise specified), ALCL (anaplastic large cell lymphoma) and "other" PTCL
[iv] Median follow-up: 19.93 weeks (range: 3.1-68.1)
[v] Includes 7 patients with acute and 7 patients with lymphomatous ATL subtypes
[vi] Median follow-up: 23.07 weeks (range: 3.3-125.0)

About the Phase 1 Study

The open-label, single-arm, multi-center, first-in-human, two-part phase 1 study is evaluating the safety and efficacy of valemetostat in adult patients with relapsed/refractory NHL, including B-cell and T-cell lymphomas. Following the dose escalation portion of the study, which evaluated safety, pharmacokinetics and determined the recommended dose for expansion (200 mg once daily), the dose expansion part enrolled patients into one of two cohorts based on NHL subtype (PTCL and ATL) to further evaluate safety and assess preliminary efficacy. For more information about this study, visit ClinicalTrials.gov.

About VALENTINE-PTCL01 Trial

Data from the phase 1 study of valemetostat presented at EHA informed the design of the recently initiated pivotal VALENTINE-PTCL01 study. A global, open-label, single-arm, two-cohort phase 2 study, VALENTINE-PTCL01 is evaluating the efficacy and safety of valemetostat in patients with relapsed/refractory PTCL and ATL who have received at least one systemic therapy and are ineligible for HSCT. The first cohort will enroll patients with PTCL, and a second cohort will enroll patients with ATL.

The primary efficacy endpoint of the study is ORR according to blinded independent central review. Secondary efficacy endpoints include CR, PR, DOR, PFS and overall survival. The study will analyze safety endpoints including adverse events as well as pharmacokinetic and exploratory biomarker endpoints. Up to 176 patients will be enrolled at approximately 70 sites in Asia, Europe, North America and Oceania. For more information about this study, visit ClinicalTrials.gov.

About PTCL and ATL

PTCL is a group of rare and heterogenous hematologic malignancies, including ATL, that represent approximately 10-15% of all NHLs.[3] Approximately 544,000 new cases of NHL were diagnosed worldwide in 2020.[5] There are at least 29 recognized subtypes of PTCL, which occur with significant geographic variation.[6] The most common subtypes of PTCL occur frequently in Western countries and in Asia, while ATL is generally more frequent in Japan and parts of the Caribbean and Latin America.[7] ATL is associated with the human T-cell lymphotropic virus type 1 (HTLV-1).[7]

PTCL tends to be aggressive and prognosis is generally poor, with five-year overall survival at 32% in two common PTCLs (PTCL-NOS and AITL) and at 14% for ATL.[7] Initial treatment for PTCL is typically a multi-drug chemotherapy-based regimen, and a majority of patients progress with median overall survival of 5.8 months from time of relapse.[4] Development of more effective medicines for PTCL and ATL continues to

be an unmet clinical need, and one newer area of research and development includes therapeutic targeting of epigenetic changes that contribute to lymphomagenesis.[8]

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] These enzymes are thought to contribute to silencing of genes that suppress tumor cell growth and proliferation.[10] EZH1 and EZH2 are recurrently highly expressed or mutated in many hematologic malignancies.[10] Research shows that both EZH1 and EZH2 enzymes have a role in hematologic cancer progression and that simultaneous inhibition would be effective in targeting the cancers.[1] There are no dual EZH1/2 directed therapies approved for cancer treatment.

About Valemetostat

Valemetostat (DS-3201) is a potential first-in-class, potent and selective small molecule EZH1/2 dual inhibitor currently in clinical development in the Alpha portfolio of Daiichi Sankyo. Valemetostat targets epigenetic regulation by inhibiting both the EZH1 and EZH2 enzymes.

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; a phase 1 study in patients with relapsed/refractory NHL in the U.S. and Japan; and, a phase 1 study in patients with acute lymphocytic leukemia and acute myeloid leukemia in the U.S.

In April 2019, valemetostat received SAKIGAKE Designation for the treatment of adult patients with relapsed or refractory PTCL by the Japan Ministry of Health, Labour and Welfare (MHLW).

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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