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Press Release

Phase 1/2 Trial Initiated for Daiichi Sankyo's Menin Inhibitor DS-1594 in Patients with Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia

Tokyo, Basking Ridge, N.J., Munich – (April 7, 2021) – Daiichi Sankyo Company, Limited (hereafter Daiichi Sankyo) today announced the first patient has been dosed in the first-in-human phase 1/2 study of DS-1594, a selective small-molecule menin inhibitor, in adults with relapsed/refractory acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). The trial is being conducted by The University of Texas MD Anderson Cancer Center under an existing strategic research collaboration.

Inhibition of the menin protein is being studied as a novel treatment approach for acute leukemias with MLL rearrangement (MLLr) or NPM1 mutation (NPM1m), two gene alterations that drive cancer development and growth.[1] MLLr occurs in approximately 5 to 10% of acute leukemia patients and is associated with aggressive disease, reduced treatment response and poor prognosis.[2] NPM1m occurs in about 30% of patients with AML.[3] There are currently no medicines specifically approved for MLLr or NPM1m leukemias and no approved menin inhibitors.

"Research has shown that the menin protein, which binds to MLL, plays a critical role in the development and growth of leukemias with MLL rearrangement," said Arnaud Lesegretain, Vice President, Oncology R&D and Head, Alpha Portfolio, Daiichi Sankyo. "Our scientists designed DS-1594 to inhibit the menin-MLL interaction and disrupt the intracellular activity implicated in leukemogenesis. Together with MD Anderson, we will evaluate DS-1594 as a potential therapeutic option for patients with AML or ALL who have exhausted standard treatments."

The collaboration with MD Anderson is focused on accelerating development of Daiichi Sankyo pipeline therapies for AML, including phase 1 and 2 clinical trials to evaluate single and combination regimens, translational research to explore novel biomarkers, and pre-clinical studies aimed at identifying resistance mechanisms.

About the Study

MD Anderson will sponsor and lead an open-label, non-randomized, multi-arm phase 1/2 study to evaluate DS-1594 in single and combination regimens for patients with relapsed/refractory AML and ALL.

The primary objective of the phase 1 part of the study is to determine the maximum tolerated dose and recommended phase 2 dose of DS-1594 in up to 54 patients with AML or ALL regardless of mutation status. Primary endpoints include dose-limiting toxicities, recommended phase 2 dose and safety profile. Secondary endpoints include complete remission rate (CR) and CR with partial hematologic recovery rate (CRh).

In the phase 2 part of the study, DS-1594 will be further evaluated at the established dose in four expansion cohorts of patients with specific genetic markers. Patients with relapsed/refractory AML with MLLr or NPM1m will receive DS-1594 as monotherapy (Cohorts A and B) or in combination with azacitidine and venetoclax (Cohort C), and patients with ALL with MLLr will receive DS-1594 in combination with a mini-HCVD regimen (Cohort D). The primary endpoints are safety, CR/CRh rates for the AML cohorts, and CR/CR with incomplete hematologic recovery rates (CRi) for patients in the ALL cohort.

A number of secondary efficacy and pharmacokinetic endpoints along with exploratory pharmacodynamic and biomarker endpoints will also be evaluated. Up to 170 patients will be enrolled in the study, which will initially be conducted only at MD Anderson with global expansion planned for phase 2. For more information, visit Clinicaltrials.gov.

About Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia

More than 474,500 new cases of leukemia were reported globally in 2020 with more than 311,500 deaths.[4] In the U.S., there were approximately 60,530 new cases of leukemia and 23,100 deaths in 2020.[5]

AML is the most common form of acute leukemia in adults, accounting for about 33% of all new cases.[6] An aggressive and heterogenous cancer originating in bone marrow, AML is characterized by a five-year survival rate of 28.7%, the lowest by far among the major leukemia subtypes.[7] Standard chemotherapy remains the main treatment option for most patients with AML with or without targeted therapy. Newer treatments for genetically defined AML subtypes have increased options and improved response rates and outcomes for some patients, but primary and secondary resistance remain a challenge and new types of therapies continue to be researched.[8]

ALL is a less common form of leukemia with 6,150 new cases estimated in the U.S. in 2020.[9] The overall five-year survival rate for ALL is 68.8% among patients of all ages but significantly lower for adults.[10] ALL is typically treated with standard chemotherapy-based regimens with or without targeted therapy.[9]

About MLL, NPM1 and Menin

The MLL (mixed-lineage leukemia) gene, also known as KMT2A, is important in sustaining hematopoietic stem cells and is known to undergo chromosomal translocations or epigenetic changes resulting in the expression of MLL fusion proteins that ultimately drive formation and growth of leukemia.[11] Approximately 5 to 10% of acute leukemias harbor the MLL rearrangement, with a five-year overall survival rate of about 35%.[11]

The NPM1 (nucleophosmin 1) mutation causes aberrant expression of the NPM1 protein, which is involved in functions, including cell proliferation. NPM1m is observed in approximately 30% of AML patients with a five-year overall survival rate of about 50%.[3]

Menin is a scaffold protein that interacts with a multitude of other proteins to regulate gene expression and cell signaling.[11] The interaction between menin and MLL proteins is critical to the leukemogenic activity in MLLr leukemia and is also reported to play a key role in development of NPM1m leukemia.[1] Scientific evidence supports inhibition of the menin-MLL interaction as a therapeutic approach for acute leukemias.[11] There are currently no medicines specifically approved for MLLr or NPM1m leukemias and no approved menin inhibitors.

About DS-1594

DS-1594 is a potent and selective small molecule menin inhibitor in clinical development in the Alpha portfolio of Daiichi Sankyo. DS-1594 was designed to target and disrupt the protein-protein interaction of menin and MLL to inhibit leukemic cell growth and proliferation. In preclinical studies, DS-1594 displayed selective growth inhibition against AML and ALL cells with MLLr and demonstrated robust and durable anti-tumor activity in AML models with an acceptable safety profile.[12] DS-1594 is an investigational agent that has not been approved for any indication in any country. Safety and efficacy have not been established.

About Daiichi Sankyo Cancer Enterprise

The mission of Daiichi Sankyo Cancer Enterprise is to leverage our world-class, innovative science and push beyond traditional thinking to create meaningful treatments for patients with cancer. We are dedicated to transforming science into value for patients, and this sense of obligation informs everything we do. Anchored by our DXd antibody drug conjugate (ADC) technology, our powerful 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 Berkeley, CA. For more information, please visit: www.DSCancerEnterprise.com.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical therapies to improve standards of care and address diversified, unmet medical needs of people globally by leveraging our world-class science and technology. With more than 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 15,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to a strong portfolio of medicines for cardiovascular diseases, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo is primarily focused on providing novel therapies in oncology, as well as other research areas centered around rare diseases and immune disorders. For more information, please visit: www.daiichisankyo.com.

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References:
[1] Kuhn MW et al. *Cancer Discov*. 2016;6: 1166-1181.
[2] Britten O et al. *Cells* 2019, 8, 1341.
[3] Klossowski et al. *J Clin Invest*. 2020;130(2):981–997.
[4] Global Cancer Observatory. Population Fact Sheet: World. Updated November 2020.
[5] Leukemia & Lymphoma Society. Leukemia Facts and Statistics. 2019-2020.
[6] SEER Cancer Stat Facts. Acute Myeloid Leukemia. Estimated New Cases 2020.
[7] SEER Cancer Stat Facts. Acute Myeloid Leukemia. Data from SEER 18 2010–2016.
[8] Short et al. *Cancer Discov* 2020;10:506–25.
[9] Leukemia & Lymphoma Society. Facts 2019-2020. Acute Lymphocytic Leukemia.
[10] SEER Cancer Stat Facts. Acute Lymphocytic Leukemia. Data from SEER 18 2010-2016.
[11] Borkin et al. *Cancer Cell*. 2015 April 13; 27(4): 589–602.
[12] Numata M et al. AACR Annual Meeting 2021 April 10-15. Abstract #1132; and Daiichi Sankyo in-house data.