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Press Release

Daiichi Sankyo Initiates First Novel-Novel Combination Study of Two Investigational Agents within its AML Franchise in Patients with AML

- Phase 1 study initiated to evaluate the combination of a FLT3 inhibitor, quizartinib, and an MDM2 inhibitor, milademetan (DS-3032), in patients with relapsed/refractory *FLT3*-ITD AML or newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy
- Expansion of an ongoing phase 1 study to evaluate the combination of milademetan and 5-azacitidine, an inhibitor of DNA methylation, is also underway in AML and high-risk MDS
- The AML Franchise of Daiichi Sankyo is evaluating multiple investigational agents as single agents and in combination to further advance the treatment of patients with AML

Tokyo, Munich and Basking Ridge, NJ – (December 19, 2018) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced that the first patient has been dosed in the first novel-novel combination study evaluating two investigational agents within its AML Franchise. The phase 1 study will evaluate the safety and activity of the combination of a FLT3 inhibitor, quizartinib, and an MDM2 inhibitor, milademetan (DS-3032), in patients with relapsed/refractory *FLT3*-ITD acute myeloid leukemia (AML) or newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy, a very aggressive form of the disease associated with poor prognosis.

"We have initiated this combination study of quizartinib and milademetan in order to determine the safety and tolerability of the combination and if the addition of the MDM2 inhibitor milademetan may potentially further improve the outcomes of patients with relapsed/refractory *FLT3*-ITD AML beyond what has been previously reported with single agent quizartinib," said Arnaud Lesegretain, Vice President, Oncology R&D and Head, AML Franchise, Daiichi Sankyo. "In this study, we also are exploring the potential of the combination of quizartinib and milademetan in patients with newly-diagnosed *FLT3*-ITD AML who are unfit for intensive chemotherapy. This study is the first of several planned studies that will evaluate the potential of novel combinations within our investigational AML Franchise, as we are committed to continuously improving the standard of care for patients with AML."

Quizartinib is the first FLT3 inhibitor to demonstrate a survival benefit as an oral, single agent compared to chemotherapy in a randomized, phase 3 study (QuANTUM-R) in patients with *FLT3*-ITD AML, which was refractory or relapsed within six months of first remission, and single agent milademetan has demonstrated preliminary clinical activity in AML and myelodysplastic syndrome (MDS) in a phase 1

study.[1,2] Additionally, preclinical research has shown that the combination of quizartinib and mademetan has greater activity in *FLT3*-ITD AML cells compared to the respective single agent treatments.[3]

In the QuANTUM-R study, the median treatment duration with quizartinib was 4 cycles of 28 days each versus 1 cycle in the salvage chemotherapy arm. Incidence of treatment-emergent adverse events was comparable between patients who received single agent quizartinib and those who received salvage chemotherapy. The most common adverse drug reactions (>30 percent, any Grade) in patients treated with quizartinib included infections, bleeding, nausea, asthenic conditions, pyrexia, febrile neutropenia and vomiting, and the most common Grade ≥ 3 adverse drug reactions (>20 percent) were infection and febrile neutropenia. The most common laboratory adverse reactions (incidence >50 percent) were decreased white blood cell count, decreased lymphocyte count, decreased hemoglobin, decreased neutrophil count and decreased platelet count. The safety profile observed in QuANTUM-R appears consistent with that observed at similar doses in the quizartinib clinical development program.

In addition to the quizartinib and mademetan combination study, an ongoing phase 1 study of mademetan has been expanded to include evaluation of mademetan in combination with the hypomethylating agent 5-azacitidine, an inhibitor of DNA methylation, in patients with newly-diagnosed AML unfit for intensive chemotherapy, relapsed/refractory AML or high-risk MDS.

About the Quizartinib/Mademetan Combination Study

The multi-center, non-randomized, phase 1, open-label, two-part study is investigating the safety and efficacy of the combination of quizartinib and mademetan in patients with relapsed/refractory *FLT3*-ITD AML or newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy. The first part of the study (dose escalation) will assess the safety and tolerability of the combination to determine the dosing schedule, maximum tolerated dose and recommended dose for expansion. The second part of the study (dose expansion) will confirm the safety and tolerability at the recommended dose for expansion of the combination and will identify a recommended phase 2 dose. The primary objective of the study is safety. Secondary objectives include evaluation of pharmacokinetics and preliminary efficacy. The study is expected to enroll approximately 110 patients in the U.S., EU and Japan. For more information about the study, visit ClinicalTrials.gov.

About the Mademetan/5-Azacitidine Combination Study

The multi-center, non-randomized, phase 1, open-label, two-part study is investigating the safety and efficacy of mademetan as a single agent and in combination with the hypomethylating agent 5-azacitidine. The first part of the study (dose escalation) will evaluate the safety and tolerability and

identify the maximum tolerated dose and recommended dose for expansion of milademetan as a single agent and in combination with 5-azacitidine in patients with relapsed/refractory AML or high-risk MDS. The second part of the study (dose expansion) will confirm the safety and tolerability at the recommended dose of milademetan in combination with 5-azacitidine and will identify a recommended phase 2 dose in patients with relapsed/refractory AML, newly-diagnosed AML unfit for intensive chemotherapy or high-risk MDS. The primary objectives of the study are safety and tolerability, maximum tolerated dose, recommended dose for expansion and response to treatment. Key secondary objectives include evaluation of pharmacokinetics and pharmacodynamic effects. The study is expected to enroll up to 200 patients in the U.S. For more information about the study, visit ClinicalTrials.gov.

About Acute Myeloid Leukemia and Myelodysplastic Syndrome

AML is an aggressive blood and bone marrow cancer that causes uncontrolled growth and accumulation of malignant white blood cells that fail to function normally and interfere with the production of normal blood cells.[4] In the U.S. this year, it is estimated that there will be more than 19,000 new diagnoses of AML and more than 10,000 deaths from AML.[5] The five-year survival rate of AML reported from 2007 to 2013 was approximately 27 percent, which was the lowest of all leukemias.[4]

FLT3 gene mutations are one of the most common genetic abnormalities in AML.[6] *FLT3*-ITD is the most common *FLT3* mutation, affecting approximately one in four patients with AML.[7,8,9,10] *FLT3*-ITD is a driver mutation that presents with high leukemic burden and has poor prognosis and a significant impact on disease management for patients with AML.[8,11] Patients with *FLT3*-ITD AML have a worse overall prognosis, including an increased incidence of relapse, an increased risk of death following relapse and a higher likelihood of relapse following hematopoietic stem cell transplantation as compared to those without this mutation.[12,13]

MDS is a type of cancer that can occur when blood-forming cells in the bone marrow become abnormal.[14] There were over 14,000 new cases of MDS diagnosed each year from 2010 to 2014.[4] In about one in three patients, MDS progresses to AML.[14]

About Quizartinib

Quizartinib, the lead investigational agent in the AML Franchise of the Daiichi Sankyo Cancer Enterprise, is an oral selective type II FLT3 inhibitor currently in phase 3 development for relapsed/refractory *FLT3*-ITD AML (QuANTUM-R) in the U.S. and EU; phase 3 development for newly-diagnosed *FLT3*-ITD AML (QuANTUM-First) in the U.S., EU and Japan; phase 2 development for relapsed/refractory *FLT3*-ITD AML in Japan; and phase 1 development in combination with an investigational agent, milademetan,

for relapsed/refractory *FLT3*-ITD AML and newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy in the U.S., EU and Japan.

Quizartinib has been granted Priority Review and Breakthrough Therapy designation for the treatment of adult patients with relapsed/refractory *FLT3*-ITD AML, and Fast Track designation for the treatment of relapsed/refractory AML by the U.S. Food and Drug Administration (FDA). Quizartinib also has been granted accelerated assessment by the European Medicines Agency (EMA) for the treatment of adults with relapsed or refractory AML, which is *FLT3*-ITD positive, and granted Orphan Drug designation by both the FDA and the European Commission (EC) for the treatment of AML and by the Japan Ministry of Health, Labour and Welfare (MHLW) for the treatment of *FLT3*-mutated AML.

About Milademetan

Milademetan (DS-3032) is an oral selective MDM2 inhibitor currently in phase 1 clinical development for solid and hematologic malignancies, including a combination study with quizartinib in relapsed/refractory *FLT3*-ITD AML or newly-diagnosed *FLT3*-ITD AML unfit for intensive chemotherapy in the U.S., EU and Japan; a single agent and combination study with 5-azacitidine in newly-diagnosed AML unfit for intensive chemotherapy, relapsed/refractory AML or high-risk MDS in the U.S.; and two single agent studies in lymphomas and solid tumors in the U.S. and Japan.

Quizartinib and milademetan are investigational agents that have not been approved for any indication in any country. Safety and efficacy of these investigational agents 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 three pillars including our investigational Antibody Drug Conjugate Franchise, Acute Myeloid Leukemia Franchise and Breakthrough Science, we aim to deliver seven distinct new molecular entities over eight years during 2018 to 2025. Our powerful research engines include two laboratories for biologic/immuno-oncology and small molecules in Japan, and Plexxikon Inc., our small molecule structure-guided R&D center in Berkeley, CA. Compounds in pivotal stage development include: [fam-] trastuzumab deruxtecan, an antibody drug conjugate (ADC) for HER2 expressing breast, gastric and other cancers; quizartinib, an oral selective FLT3 inhibitor, for newly-diagnosed and

relapsed/refractory *FLT3*-ITD acute myeloid leukemia (AML); and pexidartinib, an oral CSF1R inhibitor, for tenosynovial giant cell tumor (TGCT). For more information, please visit: www.DSCancerEnterprise.com.

About Daiichi Sankyo

Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address diversified, unmet medical needs of patients in both mature and emerging markets. With over 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 hypertension and thrombotic disorders, under the Group's 2025 Vision to become a "Global Pharma Innovator with Competitive Advantage in Oncology," Daiichi Sankyo research and development is primarily focused on bringing forth novel therapies in oncology, including immuno-oncology, with additional focus on new horizon areas, such as pain management, neurodegenerative diseases, heart and kidney diseases, and other rare diseases. For more information, please visit: www.daiichisankyo.com. Daiichi Sankyo, Inc., headquartered in Basking Ridge, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit: www.dsi.com.

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References

1. Cortes J, et al. 2018 EHA Annual Congress Oral Presentation. Abstract #LB2600.
2. DiNardo C, et al. 2016 ASH Annual Meeting Oral Presentation. Abstract #593.
3. Andreeff M, et al. 2018 EHA Annual Congress Poster Presentation. Abstract #PF219.
4. Leukemia & Lymphoma Society. Facts 2017-2018. 2018.
5. American Cancer Society. Key Statistics for AML. 2018.
6. Small D. Am Soc Hematol Educ Program. 2006;178-184.
7. Schneider F, et al. Ann Hematol. 2012;91:9-18.
8. Santos FPS, et al. Cancer. 2011;117(10):2145-2155.
9. Kainz B, et al. Hematol J. 2002;3:283-289.
10. Kottaridis PD, et al. Blood. 2001;98(6):1752-1759.
11. Zarrinkar P, et al. Blood. 2009;114(14):2984-2992.
12. Wagner K, et al. Haematol. 2011;96(5):681-686.
13. Brunet S, et al. J Clin Onc. 2012;30(7):735-741.
14. American Cancer Society. MDS Overview. 2018.