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Daiichi-Sankyo

Press Release

Daiichi Sankyo Initiates Phase 1 Study of AXL Inhibitor DS-1205 in Patients with EGFR-Mutated Metastatic Non-Small Cell Lung Cancer

- First-in-human phase 1 study to assess the safety and tolerability of DS-1205, a highly selective investigational AXL inhibitor, in combination with gefitinib in patients with metastatic or unresectable EGFR-mutated non-small cell lung cancer (NSCLC)
- Study to build upon preclinical research indicating that the addition of DS-1205 at beginning of treatment with tyrosine kinase inhibitors (TKIs) might delay onset of resistance to gefitinib and other TKI therapies[1,2]
- DS-1205 is the fourth compound in the oncology pipeline of Daiichi Sankyo being developed as a potential targeted therapy for metastatic NSCLC, demonstrating commitment to researching innovative treatment approaches for patients with lung cancer

Tokyo, Munich and Basking Ridge, NJ – (October 18, 2018) – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced that the first patient has been dosed in a first-in-human phase 1 study assessing the safety and tolerability of DS-1205, a highly selective investigational AXL inhibitor, in combination with gefitinib in patients with metastatic or unresectable epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who have progressed on therapy with tyrosine kinase inhibitors (TKIs).

For patients with metastatic EGFR-mutated NSCLC, targeted EGFR TKI therapies such as gefitinib, erlotinib, afatinib or osimertinib represent the first-line treatment of choice.[3,4,5,6] However, patients eventually develop resistance to these treatments, typically experiencing disease progression within a year.[3,4,5,6] Once a patient is resistant to all possible EGFR TKIs, there are limited treatment options, including chemotherapy, immunotherapy or investigational agents.[3,6] Research suggests that inhibition of AXL, a receptor tyrosine kinase, may help delay or overcome the onset of resistance to the TKIs.[1,2]

“This first-in-human trial will build upon preclinical research to evaluate the potential of our AXL inhibitor, DS-1205, in combination with gefitinib in EGFR-mutated NSCLC that has progressed on TKI therapy,” said Eric Slosberg, PhD, Head, Oncology Translational Development, Oncology Research and Development, Daiichi Sankyo. “We are evaluating for the first time in a clinical setting whether inhibition of the AXL pathway with DS-1205 may help prevent, delay or overcome the onset of resistance to EGFR TKIs, as we continue to research and develop new targeted therapy approaches for patients with metastatic NSCLC.”

About the DS-1205 and Gefitinib Combination Study

The multicenter phase 1, open-label, two-part study will enroll patients with metastatic or unresectable EGFR-mutated NSCLC who have T790M mutation-negative tumors and have experienced disease progression during treatment with erlotinib, gefitinib or afatinib, or developed disease progression while

on osimertinib. The first part of the study (dose escalation) will assess the safety, tolerability, pharmacokinetics and efficacy of DS-1205 in combination with gefitinib to determine the recommended dose for expansion. The second part of the study (dose expansion) will evaluate the safety, tolerability, pharmacokinetics and efficacy of the combination therapy. Study endpoints include safety, pharmacokinetics, objective response rate, duration of response, disease control rate, time to response, progression-free survival, overall survival and exploratory biomarker analyses. The study is expected to enroll approximately 60 patients at approximately 20 sites in Japan and other countries. For more information on the clinical trial, visit ClinicalTrials.gov.

Unmet Need in EGFR-Mutated Metastatic NSCLC

Lung cancer is the most common cancer in the world and the leading cause of cancer deaths.[7, 8] There were approximately 1.8 million new cases of lung cancer reported globally and 1.69 million deaths from lung cancer in 2012.[8] NSCLC is the most common form of lung cancer, accounting for approximately 80 to 85 percent of all cases. It is difficult to treat, particularly in advanced disease, and the five-year survival rate for metastatic NSCLC is only one percent.[9]

In the past decade, significant improvements in treatment have occurred due to the development of targeted therapies, such as EGFR TKIs, for advanced NSCLC.[3] EGFR mutations have been reported in a wide range of NSCLC patients (from 10 to 50 percent), and frequency may vary based on ethnicity and other factors.[3,10]

While the majority of patients with EGFR-mutated tumors respond to EGFR TKIs, resistance eventually develops in more than half of these patients, and they typically experience disease progression within a year.[11] Resistance may be acquired or intrinsic.[3] The most common mechanism for acquired resistance to gefitinib, erlotinib or afatinib involves a secondary EGFR mutation called T790M, which may be treated with the EGFR TKI osimertinib.[3,4,5,6] However, patients who experience disease progression following treatment with gefitinib, erlotinib or afatinib and whose tumors lack the T790M mutation, and patients who experience disease progression following osimertinib treatment have limited options such as chemotherapy, immunotherapy or investigational treatments.[5,6]

Researchers are exploring specific therapeutic strategies to overcome acquired resistance to EGFR TKIs.[3] Studies have demonstrated that up-regulation of AXL, a receptor tyrosine kinase, may develop in some patients with EGFR-mutated NSCLC who experience disease progression on TKI therapy, and this up-regulation might be a mechanism of resistance to EGFR TKI treatment.[11,12,13] Accordingly, inhibition of AXL might restore sensitivity to EGFR TKI treatment.[11] While preclinical research has demonstrated that inhibition of AXL by DS-1205 restored sensitivity to erlotinib and the addition of DS-1205 to TKI therapy at the beginning of treatment delayed the onset of resistance to gefitinib, erlotinib or osimertinib, it is as yet to be confirmed that DS-1205 will work similarly in humans.[1,2]

Abnormal expression and activation of AXL have been correlated with poor prognosis, increased growth and metastasis, and drug resistance in many cancers including NSCLC.[12,13]

About DS-1205

Part of the investigational Breakthrough Science pipeline of Daiichi Sankyo Cancer Enterprise, DS-1205 is an investigational highly selective AXL inhibitor currently being evaluated in a phase 1 clinical study in combination with gefitinib for metastatic or unresectable EGFR-mutated NSCLC. DS-1205 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 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.

Contact
Jennifer Brennan
Daiichi Sankyo, Inc.
jbrennan2@dsi.com
+1 908 992 6631 (office)
+1 201 709 9309 (mobile)

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