Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

# Press Release

## Updated Phase 1 Data for Daiichi Sankyo's U3-1402 in Patients with EGFR Mutated NSCLC Presented at 2019 World Conference on Lung Cancer

- Late-breaking results presented for U3-1402, a HER3 targeting ADC, in patients with metastatic EGFR mutated, TKI resistant NSCLC
- Manageable safety profile reported for U3-1402 with six confirmed partial responses and a reduction in tumor size in 22 of 26 evaluable patients across all doses
- Partial responses and tumor shrinkage observed in patients with diverse mechanisms of resistance
- Study to advance into dose expansion including additional cohort of patients with previously treated metastatic squamous or non-squamous NSCLC without EGFR mutation

**Tokyo, Munich, and Basking Ridge, NJ – (September 10, 2019)** – Daiichi Sankyo Company, Limited (hereafter, Daiichi Sankyo) announced the presentation of updated phase 1 data for U3-1402, an investigational HER3 targeting antibody drug conjugate (ADC), in 30 patients with metastatic EGFR mutated, TKI resistant non-small cell lung cancer (NSCLC). The late-breaking data were featured today in a Mini Oral Session at the IASLC 2019 World Conference on Lung Cancer (#WCLC19) in Barcelona, Spain (#MA21.06, Abstract #1720).

Updated efficacy results for 26 patients who received U3-1402 in one of four dose cohorts, and had baseline and at least one post-baseline tumor assessment, showed six confirmed partial responses across three dose levels. A reduction in tumor size was observed in 22 patients across all doses, with median best percentage change of -25.7 percent [range -82.6 percent to 13.3 percent]. Responses were reported in patients with and without a history of CNS metastases. All 30 patients in the trial had received prior treatment with an EGFR tyrosine kinase inhibitor (TKI) including 28 (93 percent) with osimertinib. Fifteen patients (50 percent) had also received prior chemotherapy. The median follow-up time was 4.5 months. At the time of data cut-off on May 3, 2019, a total of 17 patients remained on treatment.

Next-generation sequencing (NGS) and cfDNA analysis determined the presence of multiple resistance mechanisms to prior EGFR TKI therapies in patients who experienced partial responses and tumor reduction while being treated with U3-1402. Three patients with confirmed partial response harbored the EGFR resistance mutations T790M, which is the target of osimertinib, and C797S, which is associated with resistance to osimertinib. Additionally, all evaluable tumors demonstrated HER3 expression at various levels in retrospective immunohistochemistry (IHC) analysis (n=25).

"As more patients are treated on study, the findings continue to demonstrate activity with U3-1402, including ongoing confirmed partial responses, in patients with EGFR-mutant metastatic non-small cell lung cancer that is no longer responding to EGFR TKI therapy," said Helena Yu, MD, Medical

Oncologist, Memorial Sloan Kettering Cancer Center, and a trial investigator. “These data suggest that targeting HER3 with U3-1402 may be an effective treatment strategy irrespective of mechanism of resistance identified in the setting of EGFR TKI resistance, where new precision treatments are needed.”

Preliminary safety data for 30 patients who received U3-1402 in one of four doses indicated a manageable safety profile for U3-1402 at a median treatment exposure of 3.2 months. The recommended dose for expansion has been established at 5.6 mg/kg. The most common treatment-emergent adverse events (TEAEs) of any grade, occurring in ≥30 percent of patients, included nausea (63.3 percent), fatigue (43.3 percent), vomiting (36.7 percent) and platelet count decrease (30 percent). One TEAE grade ≥3 occurred in more than 10 percent of patients (platelet count decrease, 20 percent). The following dose-limiting toxicities were observed in four patients: four grade 4 platelet count decrease and one grade 3 febrile neutropenia. One patient experienced a TEAE associated with treatment discontinuation (3.3 percent). Nine patients (30 percent) experienced treatment-emergent serious adverse events regardless of causality. Four patients (13.3 percent) experienced treatment-emergent serious adverse events that were drug-related.

“HER3 is frequently overexpressed in non-small cell lung cancers as well as other types of solid tumors, but no HER3 targeting therapies are approved for NSCLC or any cancer,” said Dalila Sellami, MD, Vice President, U3-1402 Global Team Leader, Global Oncology Research and Development, Daiichi Sankyo. “U3-1402 is a potential first-in-class ADC designed to target and deliver treatment directly to HER3 expressing tumors, and based on these results, we will advance to dose expansion and broaden the scope of the trial to include patients with squamous or non-squamous NSCLC.”

**About the Study**

The global, phase 1, open label, two-part study is enrolling patients with metastatic or unresectable EGFR mutated NSCLC whose disease has progressed while taking an EGFR TKI. The first part of the study includes patients who either experienced disease progression on erlotinib, gefitinib, dacomitinib or afatinib and tested negative for the T790M mutation or who experienced disease progression on osimertinib regardless of T790M status. The primary objectives of the study are to assess the safety and tolerability of U3-1402. Secondary study objectives are to evaluate preliminary efficacy by measuring antitumor activity of U3-1402 and to characterize the pharmacokinetics of U3-1402. Part one (dose escalation) assesses U3-1402 at four doses (3.2 mg/kg to 6.4 mg/kg) to determine a recommended dose for expansion. Part two (dose expansion) will evaluate U3-1402 at the recommended dose for expansion of 5.6 mg/kg and include an additional cohort of patients with metastatic squamous or non-squamous NSCLC without EGFR mutation whose disease has progressed after chemotherapy and anti-PD-L1 regimens. The study is expected to enroll more than 100 patients at approximately 17 sites globally. For more information, visit ClinicalTrials.gov.

**About U3-1402**

Part of the investigational ADC Franchise of the Daiichi Sankyo Cancer Enterprise, U3-1402 is an investigational and potential first-in-class HER3 targeting ADC. ADCs are targeted cancer medicines that deliver cytotoxic chemotherapy ("payload") to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Designed using Daiichi Sankyo's proprietary DXd ADC technology, U3-1402 is comprised of a human anti-HER3 antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide-based linker. It is designed to target and deliver chemotherapy inside cancer cells and reduce systemic exposure to the cytotoxic payload (or chemotherapy) compared to the way chemotherapy is commonly delivered.

U3-1402 is one of three Daiichi Sankyo ADCs in clinical development for NSCLC in addition to DS-1062 and [fam-] trastuzumab deruxtecan (DS-8201), which is being co-developed and co-commercialized globally in collaboration with AstraZeneca. U3-1402 is also being evaluated in a phase 1/2 study in patients with HER3 positive metastatic breast cancer.

U3-1402, DS-1062 and DS-8201 are investigational agents that have not been approved for any indication in any country. Safety and efficacy have not been established.

**Unmet Need in Non-Small Cell Lung Cancer (NSCLC)**

Lung cancer is the most common cancer and the leading cause of cancer mortality worldwide; there were an estimated 2.1 million new cases of lung cancer in 2018 and 1.8 million deaths.[1] Most lung cancers are diagnosed at an advanced or metastatic stage.[2] Non-small cell lung cancer (NSCLC) accounts for 80 to 85 percent of all lung cancers.[3] The introduction of targeted therapies and checkpoint inhibitors in the past decade has improved the treatment landscape for patients with advanced or metastatic NSCLC; however, for those who are not eligible for current treatments, or whose cancer continues to progress, new therapeutic approaches are needed.[4]

EGFR mutation is a well-established oncogenic target for management of advanced stage NSCLC.[5] For patients with advanced EGFR mutated NSCLC, targeted therapy with EGFR TKIs offers higher response rates and progression-free survival compared to chemotherapy.[5] However, most patients eventually develop resistance to the drugs, at which point treatment options become more limited.[6] Clinical resistance to EGFR TKIs has been linked to multiple gene-based mechanisms, and in many cases, the underlying cause remains unknown.[7,8,9] At the same time, a majority of EGFR mutant NSCLCs show some level of HER3 expression.[10,11]

HER3 is a member of the human epidermal growth factor receptor (EGFR) family of tyrosine kinase receptors, which are associated with aberrant cell growth.[12] HER3 expression has been associated with increased metastases and reduced survival in patients with non-small cell lung cancer, where frequency

has been reported as high as 75 percent.[13] HER3 is overexpressed in several types of cancers.[14] In recent years, researchers have recognized potential for HER3 as a therapeutic target.[12] Currently, no HER3 targeting agents are approved for NSCLC or any cancer.

**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. 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.

**Media Contacts:**

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

**EU**
Lydia Worms
Daiichi Sankyo Europe
lydia.worms@daiichi-sankyo.eu
+49 (89) 7808751(office)
+49 176 11780861 (mobile)

**Japan:**
Koji Ogiwara
Daiichi Sankyo, Co., Ltd
ogiwara.koji.ay@daiichisankyo.co.jp
+81 3 6225 1126 (office)

**Investor Relations Contact:**
DaiichiSankyoIR@daiichisankyo.co.jp

References

[1] Bray F, et al. *CA: Cancer J. Clin* 2018;68:394-424. Global Cancer Statistics 2018.
[2] American Cancer Society. Lung Cancer Prevention and Early Detection. 2019.
[3] American Cancer Society. Types of Non-Small Cell Lung Cancer. 2019.
[4] Economopoulou and Mountzios. *Ann Transl Med* 2018 Apr; 6(8):138
[5] Planchard D, et al. Metastatic NSCLC. ESMO CPGs. *Ann of Onc* 29(Supp4): iv192–237 2018. updated Jan2019.
[6] Morgillo F, Della Corte CM, Fasano M, et al. *ESMO Open* 2016; 1:e000060.
[7] Wu, et al. *Mol Cancer.* 2018;17:38.
[8] Papadimitrakopoulou, et al. *Ann Oncol*. 2018;29.
[9] Ramalingam, et al. *Ann Oncol*. 2018;29.
[10] Yi, et al. *Mod Pathol*. 1997;10:142-148.
[11] Kawano, et al. *J Surg Res*. 2008;146:43-48.
[12] Mishra R, et al. *Oncology Reviews* 2018;12:355.
[13] Muller-Tidow C, et al. *Cancer Res* 2005; 65:1778-1772.
[14] Mujoo K, et al. *OncoTarget* 2014; 5:21 10222-10236.