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Daiichi-Sankyo Plexxikon

Press Release

Daiichi Sankyo and Plexxikon Announce Study Published in NEJM Demonstrates PLX3397 Induced Prolonged Tumor Regression in Tenosynovial Giant Cell Tumor (TGCT) in Most Patients

- *Fifty-two percent of patients achieved a partial response and 30 percent of patients had stable disease following treatment with PLX3397, an investigational CSF-1R inhibitor*
- *A rare tumor of the joint or tendon sheath, TGCT can lead to significant pain, stiffness, loss of mobility and joint destruction; currently no systemic therapy is approved for TGCT*
- *Pivotal phase 3 ENLIVEN study currently enrolling patients with locally advanced TGCT to further evaluate efficacy and safety of PLX3397*

Parsippany, NJ and Berkeley, CA – (July 29, 2015) – Daiichi Sankyo, Inc. and Plexxikon Inc., a member of the Daiichi Sankyo Group, announced today that *The New England Journal of Medicine (NEJM)* published clinical trial results demonstrating that the investigational drug, PLX3397, an oral targeted CSF-1R inhibitor, induced prolonged tumor regressions in most patients with tenosynovial giant cell tumor (TGCT), a rare, locally aggressive neoplasm of the joint or tendon sheath.

Following phase 1 dose-escalation, which evaluated the safety and pharmacokinetics of PLX3397 in solid tumors, 23 patients with advanced TGCT were dosed in a single-arm, multi-center, extension cohort to evaluate the safety and efficacy of PLX3397 at 1,000 mg/day. In an intention-to-treat analysis of response by RECIST 1.1 criteria, 12 out of 23 patients achieved a partial response with PLX3397 for an overall response rate of 52 percent [95 percent CI: 32 - 73 percent], and an additional seven patients had stable disease, providing a disease control rate of 83 percent [95 percent CI: 67 - 98 percent]. Responses to PLX3397 usually occurred within four months of treatment and the median duration of response exceeded eight months. Median progression-free survival has not yet been reached in this study.

“TGCT can be a very difficult disease to manage, with treatment options largely limited to surgery to remove as much of the tumor as possible. Despite the best surgical intervention, recurrence of diffuse TGCT is high and the disease may advance to the point where surgery is no longer an option,” said William D. Tap, MD, lead author of the study and Chief of the Sarcoma Medical Oncology Service at Memorial Sloan Kettering Cancer Center. “These preliminary results demonstrate that by targeting

CSF-1R, PLX3397 may inhibit tumor growth in some patients with TGCT, potentially offering those patients an alternative non-surgical treatment option."

"The patient responses highlighted in the NEJM publication are very encouraging and underscore our rationale for initiating a global, phase 3 study of PLX3397 in TGCT," said Paul S. Lin, MD, MBA, Chief Operating Officer of Plexxikon. "Our TGCT trial offers important preliminary proof-of-concept on the efficacy of selective CSF-1R inhibition. The targeted molecular design of PLX3397, like vemurafenib, is another hallmark of our efforts to bring new targeted therapies to patients who need them."

About the Study

Patients enrolled in this phase 1 single-arm, multi-center, extension cohort study included those with a histologically confirmed diagnosis of TGCT with demonstrated tumor progression within the past year that was recurrent, inoperable or resectable but requiring extensive surgery. Following baseline assessment, the efficacy of PLX3397 was assessed radiologically every two months utilizing RECIST 1.1 criteria and tumor volume score (TVS), a novel scoring method developed specifically for TGCT. Patients remained on treatment until disease progression or drug intolerance.

Analysis of efficacy by TVS was available for 14 patients who had a baseline and at least one post-baseline MRI. By TVS response assessment, 11 of 14 patients achieved a partial response (79 percent) and an additional three patients had stable disease, providing a disease control rate of 100 percent. As with the RECIST assessment, patients generally experienced a large decrease in tumor burden by TVS within the first four months that persisted over time. Mean TVS reduction was 61percent [95 percent CI: 45 - 76 percent].

The most common treatment-related adverse events seen in the study included fatigue, hair color changes, nausea, dysgeusia (abnormal taste), and periorbital edema (swelling around the eyes), which rarely led to drug discontinuation. Treatment-related severe adverse events included fatigue, diarrhea, anemia, hyponatremia, elevated liver enzymes and neutropenia.

About TGCT

Tenosynovial giant cell tumor (TGCT) – a group of neoplasms including pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS) – is a rare, usually non-metastatic tumor that affects the synovium-lined joints, bursae, and tendon sheaths, resulting in swelling, pain, stiffness and reduced mobility in the affected joint or limb.[1] It is estimated that TGCT has an annual incidence of 11 cases per million.[2] Patients are commonly diagnosed in their 20s to 50s,[3] and depending on the type of TGCT, women can be up to twice as likely to develop a tumor as men.[4]

Primary treatment of TGCT includes surgery to remove the tumor, but in patients with a diffuse form where it can wrap around bone, tendons, ligaments and other parts of the joint, the tumor is more difficult to remove and may require multiple surgeries or joint replacements, eventually advancing to the point where surgery is no longer an option and amputation may be considered. It is estimated that the rate of recurrence in the diffuse form of the disease can be 45 percent or higher in some case series.[5] New, effective, non-surgical treatment options are greatly needed for the treatment of TGCT.

About PLX3397

PLX3397 is an investigational novel, oral small molecule that potently and selectively inhibits CSF-1R (colony stimulating factor-1 receptor), which is a primary growth driver of abnormal cells in the synovium that causes TGCT. PLX3397 has not been approved by the U.S. Food and Drug Administration (FDA) or any other regulatory authority for uses under investigation.

A pivotal, phase 3 study of PLX3397 called ENLIVEN is currently enrolling patients with symptomatic TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity. Approximately 126 patients are planned to be enrolled into the study at approximately 45 study sites in the U.S., Canada, EU, and Australia. For more information about ENLIVEN, please visit the study link at https://www.clinicaltrials.gov/ct2/show/NCT02371369.

PLX3397 has been granted Orphan Drug Designation by the U.S. Food and Drug Administration (FDA) for the treatment of PVNS and GCT-TS and received Orphan Designation from the European Commission for the treatment of TGCT.

In addition to TGCT, PLX3397 is being evaluated in several other potential clinical indications including glioblastoma, melanoma and breast cancer as well as in combination with anti-PD-1 therapy, pembrolizumab, for advanced melanoma and other multiple solid tumors. PLX3397 also has been selected for the I-SPY 2 TRIAL, a collaborative research effort studying the benefits of adding specific investigational drugs to standard chemotherapy prior to surgery in women with newly diagnosed, locally advanced breast cancer.

About Plexxikon

Plexxikon, a member of the Daiichi Sankyo Group since April 2011, is a leader in the structure-guided discovery and development of novel small molecule pharmaceuticals to treat human disease. The company's drug Zelboraf® (vemurafenib/PLX4032) was approved by the FDA in 2011, and is being co-promoted in the U.S. by Daiichi Sankyo Inc. and Genentech. Plexxikon is developing a portfolio of preclinical and clinical stage compounds to address significant unmet medical needs in oncology and

other therapeutic areas. Plexxikon's Scaffold-Based Drug Discovery™ platform integrates multiple state-of-the-art technologies, including structural screening as a key component that provides a significant advantage over other drug discovery approaches.

About Daiichi Sankyo, Inc.

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 17,000 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 its strong portfolio of medicines for hypertension, dyslipidemia, bacterial infections, and thrombotic disorders, the Group's research and development is focused on bringing forth novel therapies in cardiovascular-metabolic diseases, pain management, and oncology, including biologics. For more information, please visit: www.daiichisankyo.com. Daiichi Sankyo, Inc., headquartered in Parsippany, 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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