Preclinical Data Presented at AACR Describe a Mechanism of Action of Cabozantinib in a Prostate Cancer Bone Metastasis Model

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SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Apr. 9, 2013-- Exelixis, Inc. (NASDAQ: EXEL) announced the presentation of preclinical data that provide insight into the mechanism of action of its lead compound, cabozantinib, with respect to its activity against prostate cancer tumors that have metastasized to the bone. Timothy Graham, a researcher at The Institute of Cancer Research in London, UK, presented the data (abstract #3924) today in a poster presentation session at the American Association for Cancer Research (AACR) Annual Meeting 2013, which is being held April 6-10, 2013, in Washington, D.C.

Previously reported clinical findings with cabozantinib in castration-resistant prostate cancer (CRPC) patients with bone metastases have included a 67% rate of bone scan response, reduced ^{99}Tc-MDP uptake, and reductions in plasma markers of osteoclast activity. In addition, an increase in tumor apparent diffusion coefficient (ADC) measured using diffusion-weighted MRI was reported in a cabozantinib-treated CRPC patient with a bone scan response. Based on these observations, studies of cabozantinib in preclinical models of prostate cancer bone metastases were undertaken to understand the mechanism(s) of action underlying these effects.

In the poster presented today, the investigators reported on a refined prostate cancer bone metastasis model that develops many of the features associated with bone metastases in CRPC patients. In this model, injection of VCaP prostate cancer cells expressing luciferase (to allow bioluminescent imaging of tumors) into the tibiae of mice induced aberrant bone remodeling and development of tumor bone lesions. Both histological analysis of tissue sections and radiological imaging showed the development of extensive osteosclerosis, with abnormal new bone protruding from the tibiae as well as osteolysis resulting in destruction of normal bone structures. This was accompanied by increased numbers of osteoclasts at the sites of bone remodeling. A large increase in ^{99}Tc-methylene diphosphonate (MDP) uptake was observed at the site of the bone lesions as measured by single photon emission computed tomography (SPECT) imaging. ^{99}Tc-MDP bone scans are routinely employed in clinical practice to detect bone metastases in CRPC patients.

Treatment of tumor-bearing animals with cabozantinib resulted in rapid and substantial inhibition of tumor growth evident by both bioluminescent and magnetic resonance imaging (MRI) techniques. Monitoring tumors in cabozantinib-treated animals using diffusion-weighted MRI showed a significant increase in the apparent diffusion coefficient (ADC) compared to tumors in vehicle-treated animals. Increases in ADC are the result of increased mobility of water molecules in the tumor, and have been shown to correlate with tumor cell death. Consistent with these findings, histological examination of tumors from cabozantinib-treated animals showed substantial tumor cell death, further validating the link between increases in tumor ADC and anti-tumor activity.

Cabozantinib treatment also resulted in a rapid and sustained reduction of ^{99}Tc-MDP uptake at the site of bone metastasis. Furthermore, radiological imaging showed a normalization of bone architecture, with a significant reduction in sclerotic bone growth and increased trabecular bone growth. Histological analysis showed that this was accompanied by a greatly decreased number of tibial osteoclasts. These preclinical data provide support for the use of ^{99}Tc-MDP bone scan and diffusion weighted MRI as methods for monitoring treatment response to cabozantinib in the clinic.

“In this preclinical study, we investigated cabozantinib’s activity in an animal model of prostate cancer bone metastasis with many of the same features associated with bone metastases in CRPC patients,” said Dr. Simon Robinson, Team Leader for Pre-Clinical Imaging within the Division of Radiotherapy and Imaging at The Institute of Cancer Research in London, UK, and the senior author of the study. “Treatment with cabozantinib resulted in tumor cell death, increases in ADC, and normalization of bone architecture, which was accompanied by reduced uptake of ^{99}Tc-MDP. These results suggest the compound’s effect upon bone metastases is significant and comprised of multiple mechanisms.”

“These preclinical data provide important new insights into the potential impact of cabozantinib on tumors that have metastasized to the bone, and on pathological bone remodeling,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “We are encouraged that these preclinical results highlight the direct anti-tumor activity of cabozantinib against tumors metastatic to bone. We look forward to further characterizing cabozantinib’s activity through our development program in prostate cancer and other tumor types in which bone metastases are prevalent.”

About Cabozantinib

Cabozantinib inhibits the activity of tyrosine kinases including RET, MET and VEGFR2. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

About Exelixis

Exelixis is a biotechnology company committed to developing small molecule therapies for the treatment of cancer. Exelixis is focusing its proprietary resources and development efforts exclusively on COMETRIQ™ (cabozantinib)Exelixis has also established a portfolio of other novel compounds that it believes have the potential to address serious unmet medical needs, many of which are being advanced by partners as part of collaborations. For more information, please visit the company's web site at www.exelixis.com.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the clinical and therapeutic potential of cabozantinib; the potential for cabozantinib to inhibit the growth of prostate cancer tumors that have metastasized to the bone; the link between increases in tumor ADC and anti-tumor activity; the relevance of the referenced preclinical data, including the suggestion that cabozantinib's effect upon bone metastases is significant and comprised of multiple mechanisms; the belief that the referenced preclinical data provide support for the use of ^{99}Tc-MDP bone scan and diffusion weighted MRI as methods for monitoring treatment response to cabozantinib in the clinic; and further characterization of cabozantinib's activity through Exelixis' development program in prostate cancer and other tumor types in which bone metastases are prevalent. Words such as "demonstrating," "provide," "further," "evidence," "validating," "suggest," "support," "new," "insights," "encouraged," "look forward," and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Exelixis' current plans, assumptions, beliefs and expectations. Forward-looking statements involve risks and uncertainties. Exelixis' actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation: risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; the availability of data at the expected times; the uncertain timing and level of expenses associated with the development of cabozantinib; the sufficiency of Exelixis' capital and other resources; the uncertainty of the regulatory approval processes; market competition; and changes in economic and business conditions. These and other risk factors are discussed under "Risk Factors" and elsewhere in Exelixis' annual report on Form 10-K for the fiscal year ended December 28, 2012, filed with the Securities and Exchange Commission (SEC) on February 21, 2013, and Exelixis' other filings with the SEC. Exelixis expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Exelixis' expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

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