Exelixis Announces Initiation of Investigator-Sponsored Clinical Trial Combining Cabozantinib and Abiraterone in Men With Castration-Resistant Prostate Cancer

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SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Mar. 5, 2012-- Exelixis Inc. (NASDAQ:EXEL) today announced the initiation of a phase 1 dose-finding trial of cabozantinib in combination with abiraterone in men with metastatic castration-resistant prostate cancer (CRPC) who have disease progression following treatment with up to two prior chemotherapy regimens. The study is designed to define the maximum tolerated dose (MTD) of cabozantinib in combination with abiraterone and prednisone. Abiraterone was approved by the FDA in April 2011 and is indicated in combination with prednisone for the second-line treatment of CRPC in men who have received prior chemotherapy containing docetaxel. The study is being led by Dr. Chris Sweeney at the Dana-Farber Cancer Institute. The Massachusetts General Hospital and Beth Israel Deaconess Medical Center will also participate in accrual to the study.

“The Exelixis clinical development strategy for cabozantinib in CRPC is designed to rationally exploit the compound’s unique activity profile as both a single-agent and in combination with other therapies,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “This investigator-sponsored trial is designed to provide important insight into the potential clinical utility of a combination of cabozantinib and abiraterone as a second-line regimen. Based on the extensive preclinical and clinical data generated to date for both compounds, we believe that a combination regimen of cabozantinib and abiraterone may provide CRPC patients with improved outcomes. Additional cabozantinib combination studies with other therapies are planned for the near future.”

Rationale for Combination Approach

Clinical and preclinical evidence suggest that inhibition of androgen receptor signaling (a consequence of treatment with androgen synthesis inhibitors such as abiraterone) leads to upregulation of MET signaling, which may contribute to the survival and invasiveness of prostate cancer cells. Cabozantinib is a potent inhibitor of MET, and may therefore enhance the activity of abiraterone by blocking this putative resistance mechanism. Additionally, the high level of activity that cabozantinib has demonstrated against both soft tissue and bone lesions in men with CRPC may complement the clinical activity of abiraterone.

“Based on our increasing understanding of the biology and pathogenesis of CRPC, we now have the opportunity to impact the course of disease in this debilitating and deadly cancer. We are hopeful that the combination of two active agents with different mechanisms of action may meaningfully improve the outcome for men with metastatic prostate cancer,” said Philip Kantoff, M.D., Chief Clinical Research Officer and Director of the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute and Professor of Medicine, Harvard Medical School.

“Although the recent approval of several new agents for the treatment of metastatic CRPC has helped to improve the treatment and outcomes for men with this disease, this is an indication that still has significant unmet medical need,” said Christopher Sweeney, M.D., Clinical Director of the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute and Associate Professor of Medicine, Harvard Medical School, and principal investigator of the trial. “Bone metastases occur in approximately 90% of CRPC patients, and these lesions are the primary cause of morbidity and mortality in this patient population. The combination of cabozantinib and abiraterone may improve control of both soft tissue and bone lesions. Data from this study will provide a foundation on which to explore the clinical benefit this combination regimen may provide to men with CRPC.”

Trial Design

The study will enroll men with progressive metastatic CRPC who have received up to two prior chemotherapy regimens; patients who have received prior MET or VEGFR inhibitors or prior CYP17A1 inhibitor therapy are not eligible to participate (although prior ketoconazole therapy is allowed if treatment was completed more than 120 days prior to study entry). The study will be conducted in two parts. Part A is a dose-escalation study in which patients will receive cabozantinib (20 mg, 40 mg, or 60 mg) in combination with 1000 mg of abiraterone daily and 5 mg of prednisone twice daily. This part of the study is a standard “3 plus 3” dose-escalation design in which 3 patients are initially accrued at each dose level. If none of the patients experiences a dose-limiting toxicity (DLT) in the first 4 weeks of treatment, dose escalation will proceed to the next dose level. If 1 patient experiences a DLT, 3 additional patients will be accrued at that dose. If 2 or more patients experience a DLT, that dose will be considered as exceeding the MTD. In Part B of the study, the dose levels identified as safe and tolerable in Part A will be expanded to include up to 12 patients.

The primary endpoint is the rate of dose limiting toxicity (DLT) in the first 4 weeks of therapy when abiraterone is combined with escalating doses of cabozantinib. The secondary objective is to define a dosing regimen of abiraterone and cabozantinib suitable for further evaluation based on long-term toxicity and efficacy data. This objective comprises several secondary endpoints, including DLT incidence, impact on soft tissue disease per RECIST, time to disease progression, time to skeletal-related events, impact on bone scan, and changes in a variety of biomarkers.

The Significance of Bone Metastases in CRPC

The primary cause of morbidity and mortality in patients with CRPC is metastasis to the bone, which occurs in about 90% of cases. Bone metastases cause local disruption of normal bone remodeling, with lesions generally showing a propensity for an osteoblastic (bone-forming) phenotype on imaging. These lesions often lead to increased skeletal fractures, spinal cord compression, and severe bone pain. Osteoblastic lesions are typically visualized in CRPC patients by bone scan, which detects rapid incorporation of 99mTc-labeled methylene-diphosphonate radiotracer into newly forming bone. In addition, increased blood levels of ALP and CTx, markers for osteoblast and osteoclast activity, respectively, are often observed in CRPC patients with bone metastases, and are associated with shorter overall survival.

About Cabozantinib

Cabozantinib is a potent, dual inhibitor of MET and VEGFR2. Cabozantinib is an investigational agent that provides coordinated inhibition of metastasis and angiogenesis to kill tumor cells while blocking their escape pathways. The therapeutic role of cabozantinib is currently being investigated across several tumor types. MET is upregulated in many tumor types, thus facilitating tumor cell escape by promoting the formation of more aggressive phenotypes, resulting in metastasis. MET-driven metastasis may be further stimulated by hypoxic conditions in the tumor environment, which are often exacerbated by selective VEGF-pathway inhibitors. In preclinical studies, cabozantinib has shown powerful tumoricidal, antimetastatic and antiangiogenic effects, including:

- Extensive apoptosis of malignant cells

- Decreased tumor invasiveness and metastasis

- Decreased tumor and endothelial cell proliferation

- Blockade of metastatic bone lesion progression

- Disruption of tumor vasculature

About Exelixis

Exelixis, Inc. 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 cabozantinib (XL184), its most advanced product candidate, in order to maximize the therapeutic and commercial potential of this compound. Exelixis believes cabozantinib has the potential to be a high-quality, broadly-active, differentiated pharmaceutical product that can make a meaningful difference in the lives of patients. 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 continued development and clinical, therapeutic and commercial potential of, and opportunities for, cabozantinib; the design, conduct, goals and expected benefits and outcome of the referenced clinical trial combining cabozantinib and abiraterone; the potential utility of, and clinical benefit provided by, a combination of cabozantinib and abiraterone as a treatment for CRPC patients; additional planned cabozantinib combination studies with other therapies; and the belief that the activity demonstrated by cabozantinib against both soft tissue and bone lesions in men with CRPC may complement the clinical activity of abiraterone. Words such as “designed,” “will,” “potential,” “believe,” “may,” “planned,” “suggest,” “opportunity,” “hopeful,” 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 referenced times; the sufficiency of Exelixis' capital and other resources; the uncertain timing and level of expenses associated with the development of cabozantinib; the uncertainty of the FDA approval process; 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 30, 2011 and Exelixis' other filings with the Securities and Exchange Commission. 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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