Preliminary Data Demonstrate that 40 mg Daily Dose of Cabozantinib Yields a High Rate of Bone Scan Response in mCRPC

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- Encouraging signs of activity also observed in NSCLC at 40 mg daily dose -

SOUTH SAN FRANCISCO, Calif., Nov 12, 2011 (BUSINESS WIRE) -- Exelixis, Inc. (NASDAQ:EXEL) reported data from two ongoing clinical trials exploring lower starting doses of cabozantinib in cancer patients, including a phase 1 investigator-sponsored trial (IST) designed to assess the lowest effective dose of cabozantinib for treatment of metastatic bone lesions in patients with metastatic castration-resistant prostate cancer (CRPC) as assessed by post-treatment changes in bone scans. Preliminary data from the ongoing IST demonstrate that a daily starting dose of 40 mg resulted in high rates of bone scan response assessed by computer-aided detection (CAD) by an independent radiology facility (IRF) in men with CRPC and bone metastases. The 40 mg dose was also associated with improved tolerability compared with the 100 mg daily dose used in the ongoing phase 2 randomized discontinuation trial of cabozantinib. Richard J. Lee, M.D., Instructor in Medicine at the Massachusetts General Hospital Cancer Center, will present the data from the IST tomorrow in a poster session at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in San Francisco (Abstract A90). The poster will be available at http://www.exelixis.com/resources/presentations.

Bone Scan Results

The study enrolled 23 patients as of the 1 October 2011 cut-off. Bone scan response at week 6 is the primary endpoint of this study and is defined as a greater-than or equal to 30% reduction in the bone scan lesion area on the week 6 bone scan relative to baseline as assessed by a CAD system at an IRF.

Twelve patients were enrolled in the 40 mg cohort. One of the these patients discontinued the study at Week 2 due to worsening of pre-existing anorexia and fatigue, and another patient discontinued at Week 6 after experiencing a pathologic hip fracture. Eleven patients were evaluable at Week 6, of which 10 had bone scan responses. The median decrease in bone scan lesion area was 61.5%. Eight of the 10 responding patients had a confirmation of the bone scan response at week 12 and continue on treatment with a median duration of treatment of 19 weeks.

Based on the bone scan findings of the 40 mg cohort, a second cohort of 11 patients was enrolled and is receiving cabozantinib at a dose of 20 mg daily. Nine of these patients were evaluable at 6 weeks, of which two had a bone scan response. Six other patients had stable disease (SD) by bone scan (<30% decrease to <30% increase in bone scan lesion area), and one patient had progressive disease by bone scan (greater-than or equal to 30% increase in bone scan lesion area). Based on the results to date in the 20 mg and 40 mg cohorts, an expanded cohort of 13 patients at the 40 mg daily dose is expected to open shortly. Additional imaging, circulating tumor cell, and bone biomarker data are planned to be collected in the expanded cohort.

Safety and Tolerability Results

Daily cabozantinib at 40 mg or below was well tolerated. There were no dose reductions or interruptions during the first 12 weeks for the 40 mg cohort and during the first 6 weeks in the 20 mg cohort. A single patient in the 40 mg cohort experienced greater-than or equal to Grade 3 (G3) drug-related adverse events of worsening of pre-existing anorexia (G3) and fatigue (G3) and discontinued study treatment at week 2.

"The 100 mg starting dose of cabozantinib has shown important signs of clinical benefit in men with CRPC, including tumor shrinkage, extension of progression-free survival and resolution of metastatic bone lesions by bone scans," said Matthew Smith M.D., Ph.D., Professor of Medicine and Director of the Genitourinary Malignancies Program at the Massachusetts General Hospital Cancer Center. "The preliminary results from the ongoing dose ranging study clearly demonstrate that a 40 mg dose yields high rates of bone scan response with improved tolerability. I believe these data support continued evaluation of lower doses as both treatment and potential prevention of bone metastases in men with CRPC."

Trial Design

The phase 1 IST uses an adaptive design to determine the lowest effective dose of cabozantinib that yields a high rate of bone scan response in men with CRPC and bone metastases. Bone scan response at week 6 is the primary endpoint of this study and is defined as a greater-than or equal to 30% reduction in the bone scan lesion area on the week 6 bone scan relative to baseline as assessed by a CAD system at an IRF. Cohorts of 11 patients are enrolled, starting with 40 mg daily cabozantinib as the first cohort. In the second cohort, daily dosing is decreased to 20 mg if at least 8 patients in the first cohort have bone scan responses, and increased to 60 mg if fewer than 8 patients have a bone scan response. Based on the observed bone scan response rate in the second cohort of 11 patients, a dose level is selected for expansion to treat an additional 13 patients.

Low-Dose Data from Phase 1 Study in Japanese Patients

Preliminary data from a phase 1 clinical trial of cabozantinib in Japanese patients with advanced solid tumors, which will be the subject of a poster presentation at the conference on November 15 (Abstract C26), also support the potential utility of a 40 mg daily dose of cabozantinib in treating soft tissue and visceral tumors. In the phase 1 trial (N=6), two patients with non-small cell lung cancer (NSCLC) in the 40 mg arm had confirmed partial responses with target lesion shrinkage of 38% and 41%; three patients had stable disease, and one patient had disease progression. No dose-limiting toxicities, serious adverse events, or Grade 4 or 5 adverse events have been reported to date in this trial. The only Grade 3 adverse events reported were neutropenia in one patient and increased lipase in one patient, both at the 40 mg dose level. Additional safety and efficacy data from this trial will be presented on November 15. The poster will be available at http://www.exelixis.com/resources/presentations.

"The high rates of bone scan response at the 40 mg starting dose level suggest that this lower starting dose could be effective in CRPC with improved tolerability, as demonstrated by the reported absence of dose interruptions and reductions," said Michael M. Morrissey, Ph.D., president and chief

executive officer of Exelixis. "Additionally, data from a phase 1 trial of cabozantinib in Japanese patients, which will be presented later this week, show that two patients with NSCLC achieved partial responses with the 40 mg daily dose of cabozantinib, suggesting that this lower dose may also provide clinical benefit in the treatment of malignancies primarily metastasizing to or residing in soft tissue. These data support the emerging clinical differentiation for cabozantinib from the perspective of both broad clinical activity and improved tolerability in patients with cancer."

Additional cabozantinib data will also be presented at the conference, including results of a pain study in CRPC patients with bone metastases (Abstract B57) and results of a CAD imaging study in CRPC patients with bone metastases (Abstract B114), each of which will be the subject of poster presentations on November 14.

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 therapeutics for the treatment of cancer. Exelixis is focusing its proprietary resources and development efforts exclusively on cabozantinib, its most advanced solely-owned 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, 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. For more information, please visit the company's web site at http://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 potential clinical benefit of cabozantinib to patients with CRPC, including tumor shrinkage, extension of progression-free survival and resolution of metastatic bone lesions by bone scans; the potential effectiveness of a 40 mg daily dose of cabozantinib in causing resolution of metastatic bone lesions by bone scans with higher tolerability in CRPC patients with bone metastases; the opening of an expansion cohort of 13 patients in the IST at the 40 mg daily dose; the continued evaluation of lower doses of cabozantinib as both treatment and potential prevention of bone metastases in patients with CRPC; the potential utility of a 40 mg daily dose of cabozantinib in treating soft tissue and visceral tumors, including non-small cell lung cancer; the emerging clinical differentiation for cabozantinib from the perspective of both broad clinical activity and improved tolerability in patients with cancer; and additional future cabozantinib data presentations. Words such as "demonstrate," "encouraging," "expected," "planned," "believe," "support," "potential," "will," "suggest," "show," "may," 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 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' quarterly report on Form 10-Q for the quarter ended September 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.

SOURCE: Exelixis, Inc.

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