Cabozantinib Demonstrates Durable Effects in Bone and Soft Tissue in Advanced Prostate Cancer

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-- Improved Bone Scans, Reduced Pain & Narcotic Requirements

-- Decreased Circulating Tumor Cells and Bone Biomarkers Also Seen

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jun. 5, 2012-- Exelixis, Inc. (NASDAQ:EXEL) today reported positive updated interim data from an ongoing phase 2 trial of cabozantinib in men with metastatic castration-resistant prostate cancer (CRPC) and bone metastases. These data confirm cabozantinib's effects on metastatic bone lesions and soft tissue disease, and demonstrate a positive impact on bone related pain and narcotic use, as well as biomarkers of bone formation and resorption. Matthew R. Smith, M.D., Ph.D., Director of the Genitourinary Malignancies Program at the Massachusetts General Hospital Cancer Center and an investigator on the trial, presented the data today in an oral session at the American Society of Clinical Oncology 2012 Annual Meeting (Abstract #4513), which is taking place in Chicago, Illinois. In addition, preliminary results from an ongoing phase 1 investigator-sponsored trial (IST) designed to determine the lowest effective dose of cabozantinib for the treatment of men with CRPC and bone metastases were also presented at the conference. Richard J. Lee, M.D., Ph.D., Assistant Physician in the Department of Medicine at Massachusetts General Hospital Cancer Center, and an investigator on the study, presented the data yesterday in a poster discussion session (Abstract #4566).

Both presentations are available at http://www.exelixis.com/resources/events/asco-2012.

Cabozantinib in Chemotherapy-Pretreated Metastatic CRPC: Interim Results from a Phase 2 Non-Randomized Expansion Cohort

The interim results reported today include data from 93 men enrolled in the ongoing non-randomized expansion (NRE) 100 mg cohort of the company's phase 2 randomized discontinuation trial. All patients had bone metastases on bone scan and 46% had measurable soft tissue disease. All patients had received prior docetaxel, 35% had prior abiraterone or MDV3100, and 24% had received prior cabazitaxel. Bone directed therapies such as zoledronic acid, denosumab and alpharadin were used in 57%, 14% and 1% of patients, respectively. Seventy-three percent of patients had received at least 2 prior lines of therapy for CRPC. Clinically significant pain, defined as baseline pain score by Brief Pain Inventory (BPI) ≥4, was present in 44% of patients, with the majority requiring chronic narcotic administration.

Bone Scan Response (BSR). Computer-assisted evaluation of bone scan lesion area (BSLA) was determined by an Independent Radiology Committee (IRC) and showed an overall BSR rate (complete response + partial response) of 67%. Another 16% of patients had stable disease and 8% had a best response of progressive disease. Median best BSLA change was a reduction of 60%, and reductions were observed in patients with prior abiraterone, MDV3100, cabazitaxel, and/or radionuclide therapy. The median duration of bone scan response was 5.4 months (range 5.0 – 6.9 months).

Pain Palliation. In 39 patients with clinically significant baseline pain, the median maximal reduction in pain from baseline was 46%. A clinically significant reduction of pain, defined as a ≥30% decrease in pain score, was observed in 25 patients (64%). Fifty-six percent of patients decreased their use of narcotics, including 31% who discontinued narcotics. These improvements were observed in patients with a variety of prior therapies.

Circulating Tumor Cells. Robust reductions in circulating tumor cells (CTCs) were observed regardless of prior therapy in 62 patients with baseline CTC counts ≥5/7.5 mL of blood and a week 6 and/or week 12 assessment. Fifty-seven patients (92%) had ≥30% decrease in their CTC count. Thirty-nine percent of evaluable patients converted to <5 CTCs at week 6.

Progression-Free Survival (PFS). Analyses of progression free survival based on radiographic progression per IRC in soft tissue and/or bone included either the total population (N=93) or only patients who had received prior docetaxel and abiraterone (n= 29). Median progression-free survival was 4.2 months (95% CI 4.1, 6.6) for the total population, and 4.6 months (95% CI 2.9, 8.3) for patients who had previously received docetaxel and abiraterone.

Bone Biomarkers. Substantial decreases were seen in serum levels of cross-linked C-terminal telopeptides of type 1 collagen (CTx) and bone-specific alkaline phosphatase (BSAP), which are biomarkers of bone metabolism. Reductions occurred in patients previously treated with bone directed therapy such as zoledronic acid or denosumab.

Safety Results. The most frequently reported adverse events (AEs) of grade 3 or higher, regardless of causality, were: fatigue (28%), diarrhea (11%), nausea (10%), hypertension (9%), back pain (7%), decreased appetite (6%), venous thrombosis (6%), hand-foot syndrome (5%), dyspnea (5%), vomiting (4%), and decreased weight (3%). A single related grade 5 event was observed in a patient with extensive liver metastases and abnormal liver function tests at baseline who went on to experience portal vein thrombosis and subsequent liver failure.

"The effects of cabozantinib on bone metastases, soft-tissue metastases, and pain are compelling. In men with bone-predominant disease, the most common phenotype in metastatic CRPC, the impact was particularly profound," said Dr. Smith. "The scope of activity of cabozantinib as a single agent is unique relative to approved agents or agents in development. The compound's ability to positively impact PFS, bone scan response, circulating tumor cells, pain, and bone turnover markers demonstrates its potential as an important new agent in CRPC."

Trial Results of Low-Dose Cabozantinib in Treating Bone Metastases in CRPC

This dose-ranging study used an adaptive design. Dose levels of 20 and 40 mg daily cabozantinib were explored, with BSR as the primary endpoint. Additionally, CTCs and safety were assessed.

In Cohort 1 (40 mg daily cabozantinib), 10 of 11 evaluable patients (91%) had a BSR at week 6, comprising 1 complete response (CR) and 9 partial

responses (PRs). A lower BSR rate (10%) was observed in Cohort 2, with 10 evaluable patients receiving 20 mg. Therefore, an expansion cohort of 13 patients was enrolled at 40 mg. The week 6 BSR rate among all 24 patients who received a 40 mg daily dose of cabozantinib was 67%.

Patients receiving 40 mg of cabozantinib were included in the CTC assessment. Twelve of 21 evaluable patients had baseline CTCs ≥5/7.5 mL of blood. Eleven of these 12 patients (92%) demonstrated best CTC decrease ≥30%, and 7 patients (58%) converted to <5 CTCs.

None of the patients receiving cabozantinib at either 20 or 40 mg daily required dose reductions or interruptions during the first 12 weeks of treatment. A patient in Cohort 1 discontinued treatment at week 2 for worsening of preexisting fatigue, weight loss, and anorexia. In Cohort 2 and the expansion cohort, a total of three patients discontinued treatment due to a venous thromboembolic event.

“These new data reinforce cabozantinib’s differentiated clinical profile and potential utility for the treatment of men with metastatic CRPC,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “The durable improvements in bone scans and bone pain, the high rate of tumor regression, and other indicators of clinical activity observed in these trials support using overall survival and bone pain response as the endpoints for our two recently initiated prostate cancer phase 3 pivotal trials, COMET-1 and COMET-2, respectively. We believe these two pivotal trials provide us the best opportunity to maximize the clinical and commercial potential of cabozantinib in CRPC.”

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 BSAP 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 targeted therapy that inhibits 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 potential of cabozantinib as an important new agent in CRPC; the belief that the referenced data support using overall survival and bone pain response as the endpoints for Exelixis’ two recently initiated prostate cancer phase 3 pivotal trials, COMET-1 and COMET-2; and the belief that the COMET-1 and COMET-2 trials provide Exelixis with the best opportunity to maximize the clinical and commercial potential of cabozantinib in CRPC. Words such as “demonstrates,” “potential,” “support,” “opportunity,” “believe,” 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; timely receipt of potential reimbursements, milestones, royalties and profits under Exelixis’ collaborative agreements; Exelixis’ ability to enter into new collaborations; 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 March 30, 2012 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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