Exelixis' Cabozantinib Phase 2 Data Demonstrate Encouraging Clinical Activity in Patients with Metastatic Castration-Resistant Prostate Cancer

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Bone scan resolution associated with clinical benefit including improvement in bone pain, reduction in narcotic use, and regression of visceral and lymph node metastases

SOUTH SAN FRANCISCO, Calif., Jun 06, 2011 (BUSINESS WIRE) -- Exelixis, Inc. (NASDAQ:EXEL) today reported updated interim data from the fully enrolled cohort of patients with metastatic castration-resistant prostate cancer (CRPC) treated with cabozantinib (XL184) in a phase 2 adaptive randomized discontinuation trial (RDT). The data provide additional patient experience and longer-term follow-up showing that cabozantinib results in resolution or stabilization of metastatic bone lesions on bone scan in the majority of patients evaluable by this method. Additionally, cabozantinib treatment relieved or eliminated bone pain in the majority of patients, thus allowing for most who require narcotic analgesic medication to either reduce or eliminate the use of these medicines. Patients with partial or complete resolution of metastatic bone lesions by bone scan were more likely to remain free of disease progression at month 6, experience pain relief, reduce or eliminate their use of narcotic analgesics, achieve tumor regression, and experience marked declines in markers of bone turnover when compared to those who did not achieve bone scan resolution.

Updated progression-free survival (PFS) data show that cabozantinib results in median PFS that appears to be similar in docetaxel-naïve and pretreated patients, and compares favorably to population matched historical controls. In the randomized discontinuation phase of this study, significant improvement in median PFS was observed in patients randomized to cabozantinib. Despite only 31 patients randomized at week 12, the results were highly statistically significant, suggestive of a sizable treatment effect over placebo. Durable increases in hemoglobin levels in anemic patients were also observed.

Maha Hussain, M.D., Associate Director for Clinical Research at the University of Michigan Comprehensive Cancer Center, presented the data today in an oral session at the American Society of Clinical Oncology's 2011 Annual Meeting (Abstract #4516) in Chicago.

As of the February 11, 2011 cut-off date, accrual in this cohort was complete at 171 patients. Randomization was halted, and randomized patients were un-blinded based on an observed high rate of clinical activity. Unlike most clinical trials in CRPC, which is a bone-predominant malignancy, all 171 patients enrolled in this trial had measurable soft tissue disease per mRECIST, of which 37% had evidence of disease in liver or lung. The bone scan evaluable population includes 108 patients with evidence of bone metastasis, a baseline bone scan, and at least 1 post-baseline bone scan assessment. Prior therapies included docetaxel (43%), abiraterone/MDV3100 (9%), and other cytotoxic and/or experimental agents (22%).

Cabozantinib Improves Progression-Free Survival

In the randomized discontinuation phase, a total of 31 patients with stable disease (SD) at week 12 were randomized to either placebo or cabozantinib. From week 12 onward, the investigator-assessed median PFS is 6 weeks (95% Confidence Interval [CI]: 5, 12 weeks) for the placebo group (n=17), and 21 weeks (95% CI: 11 weeks, upper limit not yet reached) for the cabozantinib group (n=14). The hazard ratio of 0.13 (95% CI 0.03, 0.50) strongly favored the cabozantinib arm and corresponds to an 87% reduction in the risk of progression for patients treated with cabozantinib compared with placebo. These results were statistically significant (p=0.0007).

Excluding those randomized to placebo, the median PFS was 29 weeks for the overall population (n=154). Median PFS in the subsets of docetaxel-naïve and -pretreated patients was 24 weeks (95% CI 24, upper limit not yet reached) and 29 weeks (95% CI 18, 33), respectively. These data indicate that cabozantinib treatment results in durable disease control in both docetaxel-naïve and pretreated populations.

High Rates of Complete or Partial Bone Scan Resolution Observed with Cabozantinib

Effects on bone scan were further assessed by an independent reviewer in a larger subset (n=108) of patients with bone metastases. Partial or complete resolution of bone scan was observed in 82 (76%) patients. Twenty-three patients (21%) had SD on bone scan, and only three patients (3%) had progressive disease in bone as their best assessment.

Partial or Complete Resolution on Bone Scan is Associated with Clinical Benefit

Based on a post hoc analysis, patients with bone scan resolution (either complete or partial) were more likely to be free of disease progression at month 6 (61% vs. 35%), experience pain relief (83% vs. 43%), reduce or eliminate their need for narcotic analgesics (68% vs. 33%), achieve tumor regression (78% vs. 58%), and experience substantial declines in markers of bone turnover (60% vs. 43%), as compared to those who did not achieve bone scan resolution (stable or progressing bone scan).

"Cabozantinib continues to show a unique and differentiated profile compared to other prostate cancer agents. Data presented today demonstrate that the majority of patients achieve complete or partial resolution of metastatic bone lesions by bone scan. Reductions in pain, narcotic utilization, soft tissue lesions, and bone biomarkers were found to be associated with bone scan resolution. Treatment with cabozantinib resulted in a statistically significant progression-free survival benefit in the randomized portion of the trial," said Michael M. Morrissey, Ph.D, president and chief executive officer of Exelixis. "As part of our comprehensive development program and regulatory strategy for cabozantinib in prostate cancer, we plan to pursue our first pivotal trial in CRPC with cabozantinib using a combined endpoint of pain reduction and bone scan response. Our initial interaction with the FDA on key components of the phase 3 trial design was highly informative and productive. We plan to work closely with the agency and key investigators to secure a special protocol assessment and initiate the trial by year end 2011."

Improvement in Symptomatic Bone Pain

The majority of patients treated with cabozantinib reported reduced bone pain and reduced reliance upon narcotic pain medication. A total of 83 patients had bone metastases and bone pain reported at baseline, and at least one post-baseline assessment of pain status. Of these patients, 56 (68%) had pain improvement at either Week 6 or 12. Narcotic analgesic medication was required at baseline for control of bone pain in 67 patients assessable for post-baseline review of narcotic consumption. Of these 67 patients, 47 (70%) were able to decrease or discontinue narcotic medication for bone pain. Data on bone pain and narcotic use, as assessed by the investigator, were collected retrospectively.

Of 55 patients who had baseline bone pain, 42 had complete (n=10) or partial (n=32) resolution and 13 had stabilization of disease by bone scan evaluation. Of these patients, 80%, 84%, and 38%, respectively, reported improvements in bone pain. These findings are the first to show an association between changes in bone scan imaging and improvement in clinical symptoms of disease.

"Today's presentation encompasses the largest data set for cabozantinib in CRPC released to date, and the results continue to support cabozantinib as a novel and unique approach to addressing the unmet medical needs of patients with this disease," said Matthew R. Smith, MD, PhD, director of the Genitourinary Oncology Program at Massachusetts General Hospital Cancer Center and a professor of medicine at Harvard Medical School. "In a substantially larger group of patients than seen before, the compound's activity continues to demonstrate that it may provide important clinical benefit to patients with metastatic CRPC, reducing both bone and soft tissue lesions. I am particularly encouraged by the continued benefit observed in the bone-related aspects of this disease, including resolution or stabilization of disease as determined by bone scan and improvements in investigator-reported bone pain and narcotic usage. Metastatic bone lesions remain a key driver of morbidity and mortality in CRPC, and our ability to improve patient outcomes would be advanced by an agent that could address bone disease."

Effects on Markers of Bone Formation and Resorption

Alkaline phosphatase (ALP) and cross-linked C-telopeptides of type I collagen (CTx) which are markers of osteoblast (bone formation) and osteoclast (bone resorption) activity, respectively, are often elevated in patients with bone metastases. Reductions in levels of CTx and ALP have been correlated in the past with a reduced risk of skeletal-related events and mortality. Of 28 CRPC patients treated with cabozantinib who had ALP levels at least twice the upper limit of normal, and at least 12 weeks of follow-up, 25 had decreases in ALP. Similarly, the vast majority of the 118 patients with plasma CTx values showed a decrease in CTx at Week 6 or Week 12. Reductions in either CTx or ALP occurred regardless of prior bisphosphonate treatment. ALP and CTx levels decreased from baseline by approximately 60% on average at Weeks 12 and 24, respectively.

Reduction and Stabilization of Soft Tissue Lesions in Majority of Patients

All 171 patients who participated in the Lead-In phase of the trial were evaluable by mRECIST. Seven patients (4%) had partial responses (PRs), and 3 additional PRs (2%) were observed beyond the Lead-In phase. SD was reported in 136 patients (80%). The Week 12 disease control rate (PR + SD) was 68%. Tumor regression was observed in 74% of 151 patients with measurable soft-tissue metastatic lesions and at least one post-baseline scan. Consistent with prior data, changes in prostate-specific antigen appear to be independent of radiographic changes.

Safety and Tolerability Consistent with Previous Experience

Safety data are available for the 171 patients in the Lead-In phase of the study. The most common grade 3 or 4 adverse events (AEs), regardless of causality, were fatigue (16%), PPE syndrome (6%), hypertension (6%), decreased appetite (5%), nausea (4%), vomiting (4%), dyspnea (2%), rash (2%), diarrhea (2%), and mucosal inflammation (1%). One patient (1%) experienced a grade 5 event of unexplained death at Week 33. At least one dose reduction was reported in 51% of patients. Less frequent important medical events, regardless of causality, were hemorrhage (13% all grades, 2% grade 3 or 4), venous thrombosis (8%, 7%), gastrointestinal perforation (2%, 1%), and arterial thrombosis (1%, 1%).

To access the clinical data poster mentioned in this press release, please visit www.exelixis.com/sites/default/files/pdf/ASCO_2011-XL184-CRPC.pdf.

Cabozantinib Targets Key Pathways That Contribute to Prostate Cancer

Cabozantinib, an inhibitor of tumor growth, metastasis and angiogenesis, simultaneously targets MET and VEGFR2, key kinases involved in the development and progression of many cancers. Prominent expression of MET has been observed in primary and metastatic prostate carcinomas, with evidence for higher levels of expression in bone metastases. Overexpression of hepatocyte growth factor (HGF), the ligand for MET, has also been observed in prostate carcinoma, and increased plasma levels of HGF are associated with decreased overall survival in CRPC. Data from preclinical studies also suggest that both HGF and MET are regulated by the androgen signaling pathway in prostate cancer, where upregulation of MET signaling is associated with the transition to androgen-independent tumor growth. Additionally, both the MET and VEGFR signaling pathways also appear to play important roles in the function of osteoblasts and osteoclasts -- cells in the bone microenvironment that are often dysregulated during the establishment and progression of bone metastases.

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.

Conference Call and Webcast

An investor briefing webcast will be held in conjunction with the 2011 ASCO Annual Meeting on Monday, June 6, 2011, from 6:00-8:00 p.m. Central Daylight Time. The webcast may be accessed by visiting the Event Calendar page under Investors at www.exelixis.com. An archived replay will be available on the Event Calendar page under Investors at www.exelixis.com and via phone until 11:59 p.m. EDT/8:59 p.m. PDT on July 6, 2011. Access numbers for the replay are: 1-888-286-8010 (domestic) and 1-617-801-6888 (international). The replay passcode is 15003148.

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 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 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 cabozantinib; the suggestion that cabozantinib had a sizable treatment effective over placebo in the randomized discontinuation phase of the CRPC cohort in the RDT; Exelixis' plan to pursue its first pivotal trial in CRPC with cabozantinib using a combined endpoint of pain reduction and bone scan response; Exelixis' plan to work closely with the FDA and key investigators to secure a special protocol assessment and initiate the first pivotal trial in CRPC by year-end 2011; the belief that the results continue to support cabozantinib as a unique and novel approach to addressing the unmet medical needs of patients with CRPC, reducing both bone and soft tissue lesions; the belief that cabozantinib may provide important clinical benefit to patients with metastatic CRPC; and the belief that the ability to improve patient outcomes would be advanced by an agent that could address bone disease. Words such as "encouraging," "suggestive," "demonstrate," "plan," "initiate," "continue," "support," "may," "would," "believes," "potential," 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' quarterly report on Form 10-Q for the quarter ended April 1, 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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