Cabozantinib Meets Primary Endpoint of Progression Free Survival in Phase 3 Pivotal Trial in Medullary Thyroid Cancer

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-- Nearly three-fold increase in median progression-free survival --

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jun. 4, 2012-- Exelixis, Inc. (NASDAQ:EXEL) today reported data from the phase 3 pivotal trial of cabozantinib in patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). The trial, known as EXAM, met its primary endpoint of improving progression-free survival (PFS), with patients in the cabozantinib arm achieving a median PFS of 11.2 months compared with 4.0 months for patients in the placebo arm. Overall response rate (ORR), a secondary endpoint, was 28% in the cabozantinib arm and 0% in the placebo arm. Estimated PFS at one year was 47.3% with cabozantinib vs. only 7.2% with placebo. Data for overall survival (OS), another secondary endpoint, are not yet mature. Patients on the cabozantinib arm of the trial received a dose of 140 mg (free base equivalent). Adverse events were generally manageable allowing for treatment with cabozantinib for prolonged periods of time. Exelixis recently submitted a New Drug Application (NDA) for cabozantinib in MTC to the U.S. Food and Drug Administration (FDA).

Dr. Patrick Schöffski, professor at the Department of General Medical Oncology at the University Hospitals of Leuven, Catholic University Leuven, Belgium, presented the data (Abstract #5508) today in an oral session at the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois. The slides from the presentation are available at http://www.exelixis.com/resources/events/asco-2012.

“As the first phase 3 trial to enroll patients with independently confirmed radiographic progressing medullary thyroid cancer, EXAM represents an important milestone for this orphan disease in which there have been very few rigorous prospective clinical trials,” said Dr. Schöffski. “The data presented today are highly compelling and demonstrate that cabozantinib can provide a significant benefit to patients with advanced MTC. Taken as a whole, the results clearly show that cabozantinib is an important advance in the treatment of MTC and has the potential to improve the care and outcomes for MTC patients.”

Efficacy Results

All 330 patients were included in the efficacy analysis. Cabozantinib met the primary endpoint of the trial, with a median PFS of 11.2 months vs. 4.0 months for placebo [HR 0.28, $p<0.0001$] based on the independent radiology committee (IRC) evaluation. The Kaplan Meier estimate for the proportion of patients alive and progression-free at 1 year was 47.3% in the cabozantinib arm and 7.2% in the placebo arm. Other sensitivity analyses (investigator assessment, uniform date, and per protocol assessment) were consistent with the primary analysis. Cabozantinib’s benefit on PFS was seen across a number of pre-specified subgroups including RET mutational status or prior tyrosine kinase inhibitor (TKI) therapy. With respect to secondary endpoints, the ORR, per RECIST evaluated by the IRC, was 28% in the cabozantinib arm and 0% in the placebo group. Median duration of response was 14.6 months. At the time of the June 2011 data cut-off, 44% of the events required for the OS analysis had occurred, making data on overall survival immature. At the time of the interim analysis, no difference in OS was observed between treatment arms. A final OS analysis will be conducted after 217 events have occurred.

“As seen in the initial topline results, and again today at the ASCO Annual Meeting, cabozantinib delivered a nearly three-fold increase in median PFS in the EXAM trial,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “The trial was conducted under a Special Protocol Assessment with the FDA, with progression-free survival as the primary endpoint, and we completed the submission of our NDA for MTC at the end of May. Beyond MTC, we are also excited about the encouraging interim cabozantinib data that have been generated in a variety of other tumor indications, including hepatocellular carcinoma, renal cell carcinoma and castration-resistant prostate cancer, which are the subjects of oral presentations at this year’s ASCO Annual Meeting. In particular, the prostate cancer data formed the basis for advancing cabozantinib into two recently initiated phase 3 pivotal trials, COMET-1 and COMET-2.”

Patient Demographics

The trial enrolled 330 patients with locally advanced or metastatic MTC that had progressed per RECIST within 14 months of screening. Patients were randomized 2:1 to cabozantinib (N=219) or placebo (N=111). Median age in both arms was 54 years, and almost all patients had ECOG performance status of 0-1 (95% and 90% in the cabozantinib and placebo arms, respectively). Prior TKI exposure (20%, 22%), measurable disease (95%, 94%), and bone metastases at baseline (each 51%) were also balanced between the cabozantinib and placebo arms, respectively. RET mutations were seen at a similar rate between arms (46%, 52%).

As of the June 15, 2011 data cut off date, 45% of cabozantinib-treated and 13% of placebo-treated patients were still receiving study treatment. 60% of placebo-treated patients discontinued treatment for progressive disease, compared with 26% of cabozantinib-treated patients. 16% of patients on the cabozantinib arm had discontinued treatment for an AE compared to 8% of patients on the placebo arm. 5% of patients on both arms discontinued for death. 12% of patients on the placebo arm discontinued study treatment because of subject request compared to 4% on the cabozantinib-treated arm.

Safety Results

The safety analysis included the 323 patients in both arms of the trial who had received at least one dose of study treatment (214 in the cabozantinib arm and 109 in the placebo arm). Consistent with the much longer PFS, the median duration of exposure was twice as long in the cabozantinib arm (6.7 months) versus the placebo arm (3.4 months).

Overall AE results for the trial are consistent with a long duration of exposure to an active agent in a patient population with advanced disease. The most frequent adverse events (AEs) of grade ≥ 3 with greater than 2% incidence in the cabozantinib arm were: diarrhea (16%), palmar-plantar

erythrodysesthesia (13%), fatigue (9%), hypertension (8%), decreased weight (5%), decreased appetite (5%), and stomatitis (2%). The most frequent adverse events (AEs) of grade ≥ 3 with greater than 2% incidence in the placebo arm were: diarrhea (2%) and fatigue (2%). Diarrhea and decreased weight are commonly associated with advanced and progressive MTC.

Cabozantinib is a potent inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2), and investigators reported infrequent adverse events that have previously been associated with VEGF-pathway inhibition. Grade ≥ 3 adverse events in the cabozantinib arm that are generally associated with VEGF-pathway inhibition were: hypertension (8%), venous thrombosis (4%), hemorrhage (3%), GI perforation (3%), and non-GI fistula (2%). In some cases, these events may also be the result of an anti-tumor effect. For example, two patients who experienced non-GI fistulas had involvement of the lungs or bronchus and had partial responses.

Deaths were generally balanced between treatment arms, and most were due to progressive disease. Deaths for reasons other than progressive disease and within 30 days of treatment cessation occurred in 5.6% of patients on the cabozantinib arm and in 2.8% of patients on the placebo arm. The difference is largely accounted for by 1.9% of the total number of deaths in the cabozantinib arm that were due to events commonly associated with VEGF-pathway inhibition.

Biochemical Response Results

Biochemical responses assessed as additional secondary endpoints were consistent with the observed anti-tumor activity of cabozantinib. Calcitonin levels dropped by 45% in the cabozantinib arm, but rose by 57% in the placebo arm during the first three months on study. Similar effects were seen with CEA.

EXAM Trial Design

EXAM is an international, randomized, placebo-controlled, double-blinded study of cabozantinib in patients with progressive, unresectable, locally advanced, or metastatic MTC. The study enrolled 330 patients who were randomized in a 2:1 ratio to receive cabozantinib (N=219) or placebo (N=111) administered at a daily dose of 140 mg (free base equivalent). The study did not allow for crossover from the placebo arm to cabozantinib. The first patient was randomized in October 2008 and the last patient was randomized in February 2011. The trial provided 90% power to detect a 75% increase in PFS, the primary endpoint of the study. Additionally, the study is designed to assess OS once the appropriate number of events have occurred, and has 80% to detect a 50% improvement in survival compared with placebo. Exelixis conducted this trial under a SPA from the FDA, which allows for full approval on the basis of PFS if the data are supportive.

About Cabozantinib

Cabozantinib is a potent targeted therapy that inhibits MET, VEGFR2, and RET, all of which play an important role in the biology of medullary thyroid cancer. 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 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 belief that EXAM represents an important milestone and advance for the treatment of MTC; the belief that the referenced data are highly compelling and demonstrate that cabozantinib can provide a significant clinical benefit to patients with advanced MTC; the belief that MTC has the potential to improve the care and outcomes for MTC patients; potential approval by the FDA of the referenced NDA; and encouraging cabozantinib data generated in other tumor indications. Words such as “milestone,” “compelling,” “demonstrate,” “can,” “advance,” “potential,” “encouraging,” “believes,” 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; 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.

Source: Exelixis, Inc.

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