Exelixis' Cabozantinib Demonstrates Broad Clinical Activity in Multiple Tumor Types

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Resolution of metastatic soft tissue, visceral, and bone lesions observed in randomized discontinuation trial

SOUTH SAN FRANCISCO, Calif., Jun 05, 2011 (BUSINESS WIRE) -- Exelixis, Inc. (NASDAQ:EXEL) today reported updated interim data from an ongoing phase 2 adaptive randomized discontinuation trial (RDT) of cabozantinib in patients with advanced solid tumors. Of the 9 tumor types included in the RDT, a Week 12 disease control rate (DCR, partial response [PR] + stable disease [SD] at Week 12 divided by the number of evaluable patients) of 40% or higher was observed in the melanoma, hepatocellular cancer (HCC), breast, prostate, ovarian, and non-small cell lung cancer (NSCLC) cohorts. Soft tissue and visceral tumor regression and resolution of bone lesions on bone scan were seen across multiple tumor types.

Michael Gordon, M.D., medical oncologist at Pinnacle Oncology Hematology and an Associate Professor of Clinical Medicine at the University of Arizona College of Medicine, presented the data today in an oral session at the American Society of Clinical Oncology's 2011 Annual Meeting (Abstract #3010) in Chicago. The presentation included updated interim data on the melanoma, breast, HCC and NSCLC cohorts. Updated data for the ovarian cohort were presented in a separate oral presentation on Saturday, June 4 (Abstract #5008), and updated data from the cohort of patients with castration-resistant prostate cancer (CRPC) are scheduled for presentation in an oral session on Monday, June 6 (Abstract #4516).

Overall Results

As of the February 11, 2011 cut-off date, 490 patients had been enrolled in the RDT. Evidence of soft tissue tumor regression was observed in all tumor types. Rates of overall disease control at Week 12 of 40% or higher were observed in HCC (73%), CRPC (68%), ovarian cancer (53%), melanoma (47%), breast cancer (45%), and NSCLC (40%). Lower rates of disease control at week 12 were observed in small cell lung cancer (SCLC; 38%), pancreatic adenocarcinoma (35%) and gastric/GEJ cancer (33%), and these tumor cohorts will not be studied further in the RDT. Confirmed tumor responses (partial or complete) per mRECIST criteria over the first 12 weeks of the study have been observed in 40 of the 490 patients. Tumor responses in the Lead-in phase of the trial have been observed in HCC (3), CRPC (7), ovarian (17), melanoma (4), breast (2), NSCLC (6), and SCLC (1). Additional responses occurred in the later phase of the trial in HCC (1), CRPC (3), and gastric/GEJ cancer (1). Bone scan resolution also was observed in multiple cohorts including CRPC, melanoma, and breast cancer.

"The overall RDT results provide further evidence that cabozantinib has broad utility in a variety of advanced solid tumors, and validate our strategy for pursuing a robust clinical development program for this promising compound. Across all studies, we have observed objective tumor responses in 12 of 13 separate tumor types tested, and we've seen dramatic resolution of metastatic bone lesions by bone scan in 5 tumor types," said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. "Based on these results we have already converted the CRPC and ovarian cohorts into non-randomized extension cohorts and expect to initiate a phase 3 pivotal trial in CRPC by the end of the year. The totality of the data presented for cabozantinib demonstrate its broad potential in multiple cancers."

Breast Cancer Results

Twenty patients were enrolled in the breast cancer cohort, of which 15 (79%) were ER+/PR+ and 3 (15%) were HER2+. The majority of patients (85%) had 3 or more lines of therapy, and 40% had been treated previously with anti-VEGF pathway therapy. Despite the heavily pre-treated nature of the cohort, tumor regression was observed in 15 of 16 (94%) evaluable patients. Two of 3 patients with bone metastases followed by bone scan experienced partial resolution on bone scan accompanied by symptomatic pain relief.

HCC Results

Thirty patients were enrolled in the HCC cohort. All 30 (100%) were Child-Pugh Class A, and 19 (63%) had evidence of extrahepatic spread. The majority of patients (93%) had 0-1 line of prior therapy and 7% had 2 or more lines of therapy. Nearly half (47%) of patients had been treated previously with sorafenib. Of 27 patients evaluable for tumor response, 22 patients (81%) had objective tumor regression with 4 (15%) achieving PRs, including patients with and without prior sorafenib therapy. Nine of 16 (56%) patients who had AFP levels greater-than or equal to 20 ng/mL at baseline experienced greater-than or equal to 50% reduction in AFP. Of the 30 patients in the cohort, 47% remained on study greater than 6 months.

Melanoma Results

Seventy-seven patients were enrolled in the melanoma cohort, of which 54 (70%) had cutaneous/mucosal disease and 23 (30%) had primary ocular disease. BRAF mutation was detected in 17 (32%) patients. The majority of patients (87%) had 0-2 lines of prior therapy and 13% had 3 or more lines of therapy. Prior therapies of interest included BRAF inhibitors (6%), MEK inhibitors (4%), and ipilimumab (4%). Objective tumor regression was observed in 39 of 65 (60%) patients with at least one post-baseline tumor assessment, and 2 of 2 patients with bone metastases followed by bone scan experienced partial resolution of bone lesions. A patient with symptomatic bone metastases following treatment with ipilimumab experienced relief of bone pain on cabozantinib and remains on study with stable disease for more than 6 months. Of the 77 patients in the cohort, including those potentially randomized to placebo, 27% remained on study at 6 months.

NSCLC Results

Sixty patients were enrolled in the NSCLC cohort, the majority of which (93%) had stage IV disease at diagnosis, and 7% had stage III disease. Seventeen (28%) patients had squamous cell cancer, and 43 (72%) had adenocarcinoma or other histologic subtypes. Half of the patients had 0-2 lines of prior therapy, and the other half had 3 or more lines of prior therapy. Prior therapies included anti-VEGF pathway therapy (32%) and anti-EGFR therapy (42%). Of the 60 patients in the cohort, 47 were evaluable for tumor response. Six patients (13%) had confirmed PRs. Objective tumor regression appeared to occur regardless of either EGFR or KRAS mutational status. Forty percent of patients in the cohort remained on study greater than 3 months.

"These data are very encouraging, not only because they demonstrate that cabozantinib has activity in a variety of solid tumors but also because they show clinical benefit in patient populations that are often difficult to treat. This study suggests that cabozantinib is a targeted agent with true potential for broad applicability across multiple cancers," said Dr. Gordon. "Heavily pre-treated patients typically have poor prognoses, so a disease control rate of 40% to 73% in these populations is somewhat unexpected. Additionally, these disease control rates were achieved in several tumor types that have had a low rate of response to tyrosine kinase inhibitor therapy, such as ovarian cancer and hepatoma. Additional studies of cabozantinib are warranted in order to understand its full potential in treating a variety of cancers."

Safety and Tolerability Results

Safety data are available for all 490 patients enrolled in the study. The most common grade 3 or 4 adverse events (AEs), regardless of causality, were fatigue (13%), PPE syndrome (7%), diarrhea (5%), hypertension (5%), decreased appetite, nausea, vomiting, abdominal pain, dyspnea (each 3%), rash, hemorrhage, increased transaminase (each 2%), and mucosal inflammation, constipation, and stomatitis (each 1%). There were 6 (1%) cabozantinib-related grade 5 events, all of which were reported after the Lead-In phase of the trial: respiratory compromise (breast cancer), hemorrhage (NSCLC), enterocutaneous perforation (ovarian cancer), intestinal perforation (ovarian cancer), gastrointestinal hemorrhage (pancreatic cancer), and death (CRPC). At least one dose reduction was reported in 40% of patients. Less frequent important medical events, regardless of causality, were venous thrombosis (6% all grades, 5% grade 3 or 4), gastrointestinal perforation (3%, 1%), and arterial thrombosis (1%, 1%).

Adaptive Randomized Discontinuation Trial Design

In the RDT design, patients initially receive open label cabozantinib at 100 mg daily (free base equivalents, corresponding to 125 mg salt form) during a 12-week Lead-In phase, which evaluates the effects of uninterrupted cabozantinib administration. Patients achieving a PR per RECIST criteria during this phase are eligible for continued open label treatment with cabozantinib, and patients with progressive disease discontinue treatment. Patients with SD enter the randomized discontinuation phase, which assesses the progression free survival of these patients after random allocation to blinded placebo vs. cabozantinib. Patients progressing on placebo have the option of receiving salvage therapy with cabozantinib.

Patients were enrolled into 9 disease-specific cohorts: HCC, melanoma, CRPC, ovarian, breast, pancreatic, gastric/GEJ, NSCLC, or SCLC. The Study Oversight Committee (SOC) reviewed response data for the cohorts as they achieved the initial accrual goal of 20 patients each. Of the 9 tumor types initially enrolled, the SOC selected responsive tumor cohorts for expanded enrollment based on the preliminary clinical activity in the first 20 patients upon completion of the Lead-In phase. Cohorts with a Week-12 DCR of at least 40% were expanded to include additional patients.

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

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; cabozantinib's broad utility in a variety of advanced solid tumors; the belief that the overall RDT results validate Exelixis' strategy for pursuing a robust clinical development program for cabozantinib; the expected initiation of a phase 3 pivotal trial of cabozantinib in CRPC by the end of the year; the belief that cabozantinib is a targeted agent with true potential for broad applicability across multiple cancers; and the belief that additional studies of cabozantinib are warranted. Words such as "encouraging," "evidence," "strategy," "promising," "expect," "demonstrate," "suggests," "potential," "may," "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 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.

SOURCE: Exelixis, Inc.

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