Exelixis Reports Positive Clinical Pharmacodynamics Data for PI3K/mTOR Inhibitor XL765 at ASCO

May 31, 2008

Robust Pathway Inhibition in Tumor and Surrogate Tissues at Well-Tolerated Doses

CHICAGO, May 31 /PRNewswire-FirstCall/ -- Exelixis, Inc. (Nasdaq: EXEL) reported interim data from a phase 1 dose-escalation trial of XL765, a novel small molecule inhibitor of phosphoinositide-3 kinase (PI3K) and mTOR, which are implicated in tumor cell proliferation, survival, and resistance to chemotherapy and radiotherapy. The trial is being carried out in patients with metastatic or unresectable solid tumors for which known effective measures do not exist or are no longer effective. Kyriakos Papadopoulos, MD, Clinical Investigator at South Texas Accelerated Research Therapeutics (START) and a lead investigator in the trial, presented the data in the PI-3 Kinase/mTOR Directed Agents oral abstract session (Abstract #3510) at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO).

There were 19 patients available for safety, pharmacokinetic, and tumor response analyses as of the May 1, 2008 cutoff. Results from pharmacodynamics analyses indicate that XL765 inhibits the PI3K/mTOR pathway in patients at well-tolerated doses. Reductions of 80-90% in the phosphorylation of pathway components including AKT, 4EBP1, and S6, and a reduction of 54% in cell proliferation (as assessed by Ki67 staining) were observed in tumor tissue from a patient with chondrosarcoma at the 60 mg twice-a-day (BID) dose level. Reductions in the phosphorylation of these pathway components were also observed at this dose level in surrogate patient tissues, including hair bulbs, skin, and peripheral blood cells. The pattern of inhibition of protein phosphorylation observed in these tissues is consistent with observations from preclinical studies, and suggests that XL765 inhibits PI3K and both mTOR/raptor and mTOR/rictor in patients.

XL765 administration also resulted in the augmentation of food-induced changes in plasma insulin in an exposure-dependent fashion, but generally had no effect on plasma glucose levels. PI3K is known to play a key role in insulin signaling, and PI3K inhibition has been shown to increase insulin levels in preclinical models.

Five patients with various cancers have experienced stable disease for at least three months, including two patients (colon adenocarcinoma and mesothelioma) with stable disease lasting six months or longer.

Administration of XL765 at doses up to 60 mg BID has been generally well-tolerated, with no dose-limiting toxicities reported. At the maximum administered dose of 120 mg BID, dose-limiting toxicities included anorexia, hypophosphatemia, and reversible increases in liver enzyme levels. The preliminary maximum tolerated dose (MTD) is 60 mg BID, and dose ranging is ongoing to establish the MTD for both twice-daily and once-daily dosing regimens.

"The encouraging pharmacodynamic results in this trial are consistent with the target profile of XL765, and clearly demonstrate that XL765 inhibits both PI3K and mTOR in patients at doses that are well-tolerated," said Michael M. Morrissey, PhD, President of Research and Development at Exelixis. "We are very encouraged by these data, and believe they support the development of this compound both as a single agent and in combination with other anti-cancer agents."

"These positive data set the stage for possibly major advances toward the development of treatments for the many different cancers that involve the PI3K pathway," said Dr. Papadopoulos. "For perhaps the first time, we have seen inhibition of the PI3K pathway in humans, with good tolerability. The data suggest that XL765 has potential both alone and in combination with other therapies."

Phase 1b/2 clinical trials of XL765 as a single agent and in combination with other targeted agents or cytotoxic chemotherapy are planned to initiate later this year.

Investor and Analyst Briefing at ASCO, Monday, June 2, 6 p.m.

Exelixis will host an investor and analyst briefing on Monday, June 2, at 6:00 p.m. at the Hyatt McCormick Place (Regency C&D - 2nd Floor). At this event, Exelixis will provide a review of its data presented at ASCO and describe additional data on XL147, a PI3K inhibitor, and XL281, an inhibitor of RAF. The event will be webcast and may be accessed in the Event Calendar page under Investors at www.exelixis.com. An archived replay of this webcast will be available until 9:00 p.m. PT/12:00 a.m. ET on July 2, 2008. Access numbers for this replay are: 1-888-286-8010 (domestic) and +1-617-801-6888 (international); the replay passcode is: 42662164.

About XL765

XL765 targets both PI3K and mTOR, key kinases in the PI3K signaling pathway. PI3K is a lipid kinase that plays a pivotal role in transmitting pro-mitotic and pro-survival signals in cells, and mTOR is a serine/threonine kinase that controls the protein translation machinery and hence, cell growth. PI3K is activated in human cancers by elevated receptor tyrosine kinase activity, by deletion of the tumor suppressor PTEN, or by mutation of its catalytic domain. mTOR is activated by growth factors via PI3K and AKT, but is also activated in a PI3K-independent fashion in response to nutrient and energy levels. Hence, targeting both PI3K and mTOR may provide additional benefit in some tumors compared with selectively targeting PI3K. In preclinical studies, XL765 has shown attractive pharmacokinetic and pharmacodynamic properties, and compelling efficacy in xenograft models, both as a single agent and in combination with other therapies.

About Exelixis

Exelixis, Inc. is a development-stage biotechnology company dedicated to the discovery and development of novel small molecule therapeutics for the treatment of cancer and other serious diseases. The company is leveraging its fully integrated drug discovery platform to fuel the growth of its development pipeline, which is primarily focused on cancer. Currently, Exelixis' broad product pipeline includes investigational compounds in phase 2 and phase 1 clinical development. Exelixis has established strategic corporate alliances with major pharmaceutical and biotechnology companies, including GlaxoSmithKline, Bristol-Myers Squibb, Genentech, Wyeth Pharmaceuticals, and Daiichi-Sankyo. 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 future development and potential efficacy of XL765 and the timing of the initiation of clinical trials for XL765. Words such as "plan," "believe," and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon our current plans, assumptions, beliefs and expectations. Forward-looking statements involve risks and uncertainties. Our 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 XL765 to demonstrate safety and efficacy in clinical testing, our ability to initiate and complete pivotal trials for XL765 at the referenced times; the timing and level of expenses associated with the growth of proprietary programs and other collaborations; the therapeutic and commercial value of XL765 and our other compounds; our relationship with our partners; and our ability to enter into new collaborations, continue existing collaborations and receive milestones and royalties under our collaborative agreements. These and other risk factors are discussed under "Risk Factors" and elsewhere in our quarterly report on Form 10-Q for the quarter ended March 28, 2008, and other filings with the Securities and Exchange Commission. We expressly disclaim any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in our 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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