Exelixis Reports Positive Phase 1 Data for PI3K/mTOR Inhibitor XL765 at EORTC-NCI-AACR Symposium

October 22, 2008

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

GENEVA--(BUSINESS WIRE)--

Exelixis, Inc. (Nasdaq:EXEL) today reported interim data from a phase 1 dose-escalation trial of XL765, a novel small molecule inhibitor of 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. Dr. Ben Markman, Medical Oncologist, Vall D'Hebron University Hospital, Barcelona, Spain, and a lead investigator in the trial, presented the data in a poster session (Abstract #216) at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, which is being held October 21-24 in Geneva, Switzerland. The poster will be available today on the Exelixis web site.

"The robust pharmacodynamic results in this trial clearly demonstrate that XL765 inhibits the PI3K/mTOR pathway in patients at doses that are well tolerated," said Michael M. Morrissey, PhD, President of Research and Development at Exelixis. "We believe these data support the development of this compound both as a single agent and in combination with other anti-cancer agents. Our work with XL765 is one of several approaches we are taking toward PI3K pathway inhibition. We are also developing XL147, which selectively targets just PI3K. We believe that pursuing multiple approaches to targeting this important signaling pathway is warranted given the diverse genotypes and cancers that involve activation of the pathway."

In the trial, XL765 is orally administered on 28-day cycles at dose levels of 15, 30, 50, 60, and 120 mg twice a day (BID) and 100 mg once a day (QD). There were 29 patients available for safety, pharmacokinetic, and tumor response analyses as of October 1, 2008. Five of 28 evaluable patients with various cancers had achieved stable disease (greater than 3 months), including 2 patients (appendiceal carcinoma and mesothelioma) with stable disease lasting 7 months or longer.

Results from pharmacodynamic 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 BID dose level. Reductions in the phosphorylation of these pathway components in surrogate tissues, including hair, skin, and peripheral blood mononuclear cells, were observed at doses as low as 15 mg BID. 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. Some of the pharmacodynamic effects occurred in an exposure-dependent fashion, and comparable PI3K pathway inhibition was observed in both the 100 mg QD and 60 mg BID cohorts.

"These positive data may serve as the basis for future major advances toward the development of treatments for the many different cancers that involve the PI3K pathway," said Kyriakos Papadopoulos, MD, Clinical Investigator at South Texas Accelerated Research Therapeutics (START) and a lead investigator in the trial. "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."

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.

XL765 was generally well tolerated at 30 mg BID, with the most common adverse events (AEs) being gastrointestinal-related toxicities. Four dose-limiting toxicities have occurred at higher doses: one event of hypophoshatemia and anorexia at the maximum administered dose (MAD) of 120 mg BID, and one event each of Grade 2 nausea/vomiting, Grade 2 diffuse rash, and Grade 2 ALT increase at 60 mg BID. At 100 mg QD, one event of non-specific neurologic complaints occurred. Serious adverse events (SAEs) have been reported for 5 subjects, with one Grade 4 increase in hepatic transaminases being considered study-related. Two study drug-related events of Grade 3 elevated hepatic transaminases have been reported at 120 mg BID. The most common study drug-related AEs were Grade 1 or 2 nausea, diarrhea, and increase in ALT/AST. The maximum tolerated dose (MTD) has not yet been established and dose ranging is ongoing to establish the MTD for both BID and QD dosing regimens.

Phase 1b clinical trials of XL765 in combination with other targeted agents or cytotoxic chemotherapy have been initiated.

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. Thus, 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 3, 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 path for XL765 as both a single agent and in combination with other anti-cancer agents; and data from XL765 studies serving as the basis for future advances toward the development of treatments for cancers involving the PI3K pathway. Words such as "believe," "may," "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: the potential failure of XL765 to demonstrate safety and efficacy in clinical testing; the therapeutic and commercial value of XL765; the ability to conduct XL765 clinical trials sufficient to achieve a positive completion; and the uncertainty of the U.S. Food and Drug Administration approval process. These and other risk factors are discussed under "Risk Factors" and elsewhere in Exelixis' quarterly report on Form 10-Q for the quarter ended June 27, 2008, and 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.