Dual Inhibition of MET and VEGF Signaling With Cabozantinib Blocks Tumor Invasiveness and Metastasis

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-- Preclinical data published in *Cancer Discovery* support clinical development program evaluating cabozantinib's potential in multiple oncology indications

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Feb. 24, 2012-- Exelixis, Inc. (NASDAQ:EXEL) today announced the company's lead compound, cabozantinib, is highlighted in a new peer-reviewed publication demonstrating that simultaneous inhibition of MET and VEGF signaling reduces tumor invasiveness and metastasis in preclinical models of pancreatic cancer. The research, led by Dr. Donald M. McDonald at the University of California, San Francisco (UCSF), showed that selective inhibition of VEGF signaling with a neutralizing antibody against VEGF or with a small molecule kinase inhibitor resulted in more invasive and metastatic tumors than from placebo-treated mice. Importantly, this effect was accompanied by increased expression of MET. The researchers went on to show that treatment with cabozantinib (which targets both MET and VEGF signaling), or with a combination of selective inhibitors targeting both pathways, reduced these malignant processes. The researchers also reported that cabozantinib prolonged survival compared with all other treatment combinations examined.

The preclinical data will be published in the March 1, 2012 issue of *Cancer Discovery* and are also discussed in a press release issued by the American Association for Cancer Research, the journal's publisher. Starting today, the article will be available at http://cancerdiscovery.aacrjournals.org. Researchers at Exelixis collaborated on the studies with UCSF.

"These data provide important insights into the potential clinical benefits of simultaneously inhibiting the MET and VEGF signaling pathways with cabozantinib, and add to the scientific rationale for our ongoing clinical investigation of the compound," said Michael M. Morrissey, Ph.D., president and chief executive officer at Exelixis. "To date, cabozantinib has shown activity in 12 of 13 tumor types studied, including particularly encouraging interim results in castration-resistant prostate, medullary thyroid, renal, liver, ovarian, non-small cell lung, and breast cancers, as well as melanoma. These results suggest that, in many types of tumors, cabozantinib may have a potentially differentiated activity profile as compared to compounds that inhibit only VEGF or MET."

In the research described in *Cancer Discovery,* tumor-bearing mice were treated with an anti-VEGF antibody or with sunitinib, which inhibits multiple tyrosine kinases including VEGF receptors. These treatments were tested alone or in combination with an inhibitor of MET. Separate groups of animals were treated with cabozantinib. Key findings include:

- Cabozantinib reduced tumor invasiveness compared with VEGF inhibition alone, through a mechanism consistent with MET inhibition.
- Liver metastases were completely absent in animals treated with cabozantinib.
- Overall survival was longest in cabozantinib-treated animals. All animals treated with cabozantinib survived until the end of the study, whereas most or all animals in all other treatment groups did not survive until the end of the study.

"Inhibition of VEGF signaling has become a mainstay of cancer therapy, and its ability to delay disease progression and prolong survival in certain cancers has been extensively documented. However, there is a growing body of evidence suggesting that VEGF inhibition on its own can lead to increased tumor aggressiveness in some preclinical models and in at least one human cancer," said Donald M. McDonald, M.D., Ph.D., a member of the Helen Diller Comprehensive Cancer Center and the Cardiovascular Research Institute and professor of anatomy at UCSF. "These new preclinical findings suggest that upregulation of MET contributes to the evasive response of tumors to anti-VEGF therapy, and that simultaneous inhibition of MET and VEGF signaling can confer the benefits associated with VEGF inhibition while significantly reducing, and in some cases reversing, invasion and metastasis. Additional preclinical and clinical evaluation of combined MET and VEGF inhibition are clearly warranted."

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 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 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 the referenced research and data support the cabozantinib clinical development program; the belief that interim results in various cancers are encouraging and suggest that cabozantinib may have a potentially differentiated activity profile compared to compounds that inhibit only VEGF or MET; the potential benefits of simultaneous inhibition of MET and VEGF; and the belief that additional preclinical and clinical evaluation of combined MET and VEGF inhibition are clearly warranted. Words such as “support,” “potential,” “ongoing,” “encouraging,” “suggest,” “may,” “can,” “warranted,” “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; market competition; and changes in economic and business conditions. These and other risk factors are discussed under "Risk Factors" and elsewhere in Exelixis' annual report on Form 10-K for the fiscal year ended December 30, 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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Exelixis, Inc.
Charles Butler, 650-837-7277
Vice President
Investor Relations and Corporate Communications
cbutler@exelixis.com