



Lilly Targets Faulty c-MET Receptor in Cancer Research Studies Presented Today at AACR Meeting

Studies provided basis for ongoing Phase I, II studies in gastric, other cancers

CHICAGO, April 2, 2012 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results of three preclinical studies focused on c-MET, a receptor tyrosine kinase that, when it functions normally, plays a key role in transmitting signals within a cell. Abnormalities in c-MET function and signaling have been found in many types of cancer including lung, breast, prostate, gastric, esophageal and renal cancers.

Two of the abstracts (#2734 and #2738) assess the anti-cancer activity of Lilly's LY2875358, a humanized IgG4 monoclonal antibody directed against c-MET currently in Phase II clinical development, while the third (#1738) looks at a Lilly assay for detecting c-MET expression levels in circulating tumor cells (CTCs) that are shed into the bloodstream. The data were presented today during the American Association for Cancer Research (AACR) 103rd Annual Meeting in Chicago, Ill.

"Our c-MET program includes two different potential medicines in Phase I and II development—a monoclonal antibody and a small molecule inhibitor—that both target a receptor believed to play a critical role in the development of some cancers," said Richard Gaynor, M.D., vice president of product development and medical affairs at Lilly Oncology. "Our job now is to discover if these potential medicines will inhibit the growth of certain cancers, and identify which patients would specifically benefit for treatments such as these."

Identifying and Exploring c-MET

Normally, c-MET signaling is activated when its only known ligand—the hepatic growth factor (HGF)—binds to the c-MET receptor. c-MET signaling is necessary for normal embryonic development, particularly of the liver, as well as for liver regeneration and wound healing. Dysregulated c-MET signaling can cause cell proliferation, increased cell survival, angiogenesis, invasion, metastasis and drug resistance.

In cancer cells, c-MET signaling can become active in two ways: either by binding of its ligand HGF (i.e., ligand-dependent mechanisms) or by ligand-independent mechanisms, such as gene amplification or activating mutations. The c-MET antibody LY2875358 is capable of blocking both ligand-dependent and ligand-independent c-MET activations. LY2875358 binds to c-MET, which prevents the c-MET ligand HGF from binding, but also induces internalization and degradation of c-MET, thereby blocking ligand-independent c-MET signaling caused by overexpression, amplification or mutation of c-MET. Because LY2875358 affects both ligand-dependent and ligand-independent mechanisms, binding of this antibody to c-MET-expressing tumor cells has the potential to inhibit c-MET-driven tumor proliferation.

Abstract #2734: c-MET antibody LY2875358 (LA480) has enhanced efficacy with gastric cancer standard-of-care in vitro and in vivo

One of the ligand-independent causes of aberrant c-MET signaling—amplification of the c-MET gene—has been observed in 10 percent to 20 percent of gastric tumors. Gene overexpression due to these extra copies of the c-MET gene is associated with poor prognosis in gastric cancer patients.

In vitro, this study found that LY2875358 successfully reduced cell proliferation in gastric cancer cell lines in which c-MET activation was caused by c-MET overexpression. LY2875358 appeared to deplete the c-MET molecules from the surface of the cancer cells. In vivo, in an animal model to which human gastric tumors were grafted, LY2875358 alone showed marked antitumor activity.

The combination of LY2875358 therapy and standard chemotherapy was more effective than either treatment alone both in vitro and in vivo, suggesting that combining LY2875358 with standard chemotherapy may be a promising approach for treating gastric cancer.

Abstract #2738: c-MET antibody LY2875358 (LA480) shows differential antitumor effects in non-small cell lung cancer

Aberrant c-Met expression occurs in 41 percent to 72 percent of cases of non-small cell lung cancer (NSCLC); amplification of the c-MET gene is present in 5 percent to 10 percent of cases.

This study found that LY2875358, either alone or combined with standard chemotherapy, inhibits cell proliferation and

migration, as well as signal transduction in NSCLC cells in which the c-MET gene was amplified, mutated or overexpressed.

In vitro, LY2875358 induces c-MET degradation in both wild type and mutant c-MET cells. In vivo, in an animal model bearing human NSCLC tumors produced by c-MET amplification, LY2875358 alone showed marked antitumor activity. The combination of LY2875358 with standard chemotherapy produced better efficacy than either treatment alone, both in vitro and in vivo.

Abstract #1738: Assay development for detecting c-MET expression in circulating tumor cells (CTC), a potential patient tailoring marker for evaluation of c-MET inhibitors

Patients with cancers in which the c-MET gene is amplified or overexpressed typically have a poor prognosis. Lilly scientists hypothesized that such patients would be especially likely to benefit from experimental therapies such as LY2875358, which target c-MET. What was needed was a noninvasive technique for monitoring the effectiveness of c-MET inhibitors over the course of treatment.

One noninvasive alternative to the standard biopsy is to count the CTCs present in a patient's blood sample. These cells, which are shed by tumors, appear representative of cells migrating from primary tumors to form distant metastases. The greater the number of CTCs found in a blood sample, the worse the patient's prognosis.

Lilly scientists evaluated the development of an assay that counts the number of CTCs in a blood sample and measures their c-MET expression to potentially determine which patients may respond better to agents such as LY2875358 that target c-MET. Scientists first collected cells from several cultured cell lines that were derived from solid epithelial tumors and had different c-MET expression levels. Initially, mouse blood was spiked with the cells from the various cell lines. Those results were later successfully reproduced using human whole blood from healthy subjects, to which tumor cells were added.

After the mouse and human blood was spiked with tumor cells, the CTCs were collected and counted. A Lilly proprietary c-MET antibody, optD11, was then used to determine the c-MET expression levels of the collected cells.

The optD11 antibody was used in this assay for several reasons. It could detect different c-MET expression levels among several cell lines in which c-MET was expressed at high levels, and it could successfully identify a different cell line as not having aberrant c-MET gene expression. Equally important, the optD11 antibody could function in the presence of the Lilly therapeutic antibody LY2875358. This means that the Lilly assay can monitor c-MET gene expression levels in patients being treated with LY2875358.

This Lilly assay for measuring c-MET expression levels in CTCs—and a different Lilly assay that measures c-MET gene amplification in CTCs—are now being used in early phase clinical studies evaluating additional c-MET inhibitors being developed in Lilly laboratories.

For more information on Lilly's c-MET antibody, please visit www.lillyoncologynewsroom.com.

About Lilly Oncology

For more than four decades, Lilly Oncology, a division of Eli Lilly and Company, has been dedicated to delivering innovative solutions that improve the care of people living with cancer. Because no two cancer patients are alike, Lilly Oncology is committed to developing novel treatment approaches. To learn more about Lilly's commitment to cancer, please visit www.LillyOncology.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers — through medicines and information — for some of the world's most urgent medical needs.

P-LLY

This press release contains forward-looking statements about the potential of LY2875358 and LY2801653 as treatments for various cancers and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that these products will be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

(Logo: <http://photos.prnewswire.com/prnh/20031219/LLYLOGO>)

