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Lilly Debuts Early Oncology Pipeline Data At AACR Annual Meeting

Diverse pipeline reflected in four molecules targeting key cancer pathways

WASHINGTON, April 10, 2013 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) unveiled data from four key molecules that represent the next generation of its oncology pipeline at the American Association for Cancer Research (AACR) Annual Meeting held in Washington, D.C. from April 6-10. The data reflect Lilly's diverse oncology pipeline via molecules that target several pathways that are among the most common and difficult-to-treat in cancer.

Each of the four molecules—a CDK4/6 inhibitor, MET antibody, MET small molecule and TGF-beta inhibitor—are being evaluated as both single agent tailored therapies and as combination therapies.

"Strong preclinical research presented at AACR lifts the curtain on our next generation of potential cancer medicines from Lilly," said Richard Gaynor, M.D., vice president of product development and medical affairs for Lilly Oncology. "Our studies are looking at medicines with novel methods of action that target key cancer pathways and identify important biomarkers. We believe that our research is going to position Lilly at the forefront of the next decade of cancer research."

Abstract # LB-122: LY2835219, a selective inhibitor of CDK4 and CDK6, inhibits growth in preclinical models of human cancer

LY2835219 has been shown *in vitro* to inhibit the cyclin-dependent kinases 4 and 6 (CDK4/6) and thereby induce G1 cell cycle arrest. Mutation and amplification of the genes encoding CDK4/6 are associated with cell cycle deregulation in certain types of human cancers.

This preclinical study evaluated the activity of LY2835219 in models of non-small cell lung cancer (NSCLC), melanoma, mantle cell lymphoma (MCL), and ovarian cancer. The study also investigated potential predictive biomarkers for response to LY2835219.

For NSCLC, increased sensitivity to LY2835219 is associated both *in vitro* and *in vivo* with KRAS mutations. For melanoma, similar levels of *in vitro* sensitivity were observed in different genetic subtypes with LY2835219 showing single-agent activity in the A375 BRAF mutant melanoma xenograft model with daily oral dosing at 45 or 90 mg/kg. For MCL, LY2835219 demonstrated durable growth inhibition of subcutaneously implanted xenografts with daily oral dosing at 50 mg/kg. For ovarian cancer, LY2835219 inhibited tumor growth and increased survival in an intra-peritoneal mouse model that recapitulates key features of human ovarian cancer.

These studies suggest that LY2835219 may have potential therapeutic application in the treatment of human cancers where the CDK4/6 pathway is key to regulating cancer cell growth (such as genetic subtypes of NSCLC, melanoma, MCL, and ovarian cancer).

Abstract # 5465: LY2875358, a bivalent MET antibody with anti-tumor activity through blocking HGF as well as inducing degradation of MET, differentiates from a one-armed 5D5 MET antibody

LY2875358 is a humanized IgG4 monoclonal antibody directed against 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.

Normally, c-MET signaling is activated when its only known ligand—the hepatic growth factor (HGF)—binds to the c-MET receptor. This 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 (or the formation of new blood vessels from existing blood vessels), invasion, metastasis and drug resistance. LY2875358 has demonstrated an ability to inhibit HGF-dependent and HGF-independent MET pathway activation and tumor growth, and in an animal model to which human gastric tumors were grafted, resembled activities of a humanized one-armed 5D5 MET antibody.

In the preclinical HGF-dependent model, LY2875358 induced internalization and degradation of MET, resulting in decreased pMET and total MET, an inhibition of cell proliferation of tumor growth in specific gastric tumor lines (MKN45 and SNU5) and NSCLC tumor lines (EBC-1 and H1993). LY2875358 also enhanced anti-tumor activity in combination with cisplatin or 5-FU *in*

vitro and *in vivo* MET amplified tumor cells. In contrast, the similar 5D5 antibody did not have anti-tumor activities in the same ligand-independent conditions. When HGF was added to high MET gene amplified tumor cells, LY2875358 decreased cell proliferation while the 5D5 antibody did not.

In various HGF responsive cells, LY2875358 had no or otherwise negligible agonist activity and did not stimulate biological activities such as cell proliferation, scattering, invasion, tubulogenesis (or the formation of small tubes in the epithelial or endothelial cells), apoptosis protection (or the defense from programmed cell death) or angiogenesis.

These findings indicate that LY2875358 has a different mechanism of action from the 5D5 MET antibody and may be a promising therapy for treatment of patients whose tumors are driven by HGF-dependent and HGF-independent MET activation.

Abstract # 2339: Prevalence of MET expression, activating mutations of KRAS and IDH1/2, and ROS1 fusions in cholangiocarcinoma patient tumor samples

Exploring the c-MET pathway from a different direction is LY2801653, a small molecule, reversible oral ATP-competitive c-MET inhibitor. In addition to targeting MET, LY2801653 has been shown to inhibit the activity of ROS1 fusion proteins and MNK1 and MNK2, two signaling proteins downstream of KRAS. The study evaluated LY2801653 as a potential treatment of cholangiocarcinoma, a rare cancer that originates in the biliary tract epithelium and has a typically poor prognosis.

The study examined the prevalence of MET overexpression, activating single point mutations of KRAS and IDH1/2, and ROS1 gene fusions in intrahepatic and extrahepatic cholangiocarcinoma tumor tissues obtained from non-Asian (n=40) and Asian (n=60) patients. The majority of cholangiocarcinoma tumors expressed MET with approximately 50 percent of cases having strong staining (IHC score of 2+ or 3+). Overall, 25 percent of analyzed samples were positive for KRAS mutation, and mutations were more frequent in Asian patients. At approximately 60 percent of samples, G12D was the predominant mutation. For IDH1, the frequency of mutation was less than 10 percent overall, with R132C as the predominant mutation. IDH mutations were more frequent in non-Asian patients. There is no apparent correlation of MET expression with either KRAS or IDH1 mutations. IDH2 and ROS1 analyses are ongoing. The data suggest that inhibitors of receptor tyrosine kinases and their signaling pathways—such as LY2801653—may merit clinical evaluation in patients with cholangiocarcinoma.

Abstract # 2094: Effects of TGF-beta signaling inhibition with LY2157299 in hepatocarcinoma models and in ex vivo whole tumor tissue samples from patient specimen

LY2157299 is a small-molecule kinase inhibitor that was designed to selectively block TGF-beta signaling, the overexpression of which can enhance tumor growth and exacerbate invasive and metastatic tumor cell behavior.

The study aimed to explore the effects of LY2157299 in hepatocellular carcinoma cell lines and patient samples with various AFP expression levels. LY2157299 was evaluated against a variety of hepatocellular carcinoma cells (HEPG2, HEP3B and SK-HEP1), as well as SK-HEP1 derived cells tolerant to tyrosine kinase inhibitors sorafenib and sunitinib. In stimulation of all hepatocellular carcinoma cell lines with TGF-beta yielded downstream activation of p-Smad2 and p-Smad3 that was potently inhibited with LY2157299 treatment at micromolar concentrations. Low concentrations of LY2157299 displayed anti-proliferative effects in HEPG2 cells when stimulated by TGF-beta, but not in SK-HEP1, SK-Sora, SK-Suni and HEP3B cells.

LY2157299 also yielded anti-migratory and anti-invasive properties in invasive SK-HEP1, SK-Suni and SK-Sora cells. Tumor slices from surgically resected tumor samples from three patients with advanced disease were exposed *ex vivo* to LY2157299 (1 micrometer and 10 micrometers) or sorafenib (5 micrometers).

The study finds that using LY2157299 inhibits TGF-beta dependent cell signaling in hepatocellular carcinoma cell lines with either anti-proliferative or anti-invasive effects. In tumor samples taken directly from patients, the inhibition of TGF-beta signaling was associated with decreased AFP levels, inhibition of proliferation and apoptosis induction. The results suggest that LY2157299 may merit clinical evaluation in hepatocellular carcinoma.

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.

This press release contains forward-looking statements about the potential of LY2835219, LY2875358, LY2801653 and LY2157299 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.

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