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Lilly Releases Early-Stage Pipeline Data at AACR Annual Meeting 2015

Diverse pipeline compounds target key cancer pathways

INDIANAPOLIS, April 20, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) will present early stage data from several targeted cancer therapies, reflecting Lilly's diverse oncology pipeline, during the American Association for Cancer Research (AACR) Annual Meeting 2015, held April 18-22 in Philadelphia, Pa.

"Bringing Cancer Discoveries to Patients" is the theme of this year's AACR meeting and one that is mirrored through Lilly's commitment to broadening its portfolio of therapies that accelerate the pace and progress of cancer care. Lilly research to be presented at AACR represents findings from several of its oncology pipeline compounds in various stages of development.

"The research we present at AACR will set the stage for the next generation of therapies from Lilly," said Richard Gaynor, M.D., senior vice president of product development and medical affairs for Lilly Oncology. "Each step we take in the course of our research—both in the lab and in clinical trials—leads us toward the same overall goal: to increase the number of life-changing medicines and innovative solutions available to patients."

Abstract #3101: In-vitro characterization of abemaciclib pharmacology in ER+ breast cancer cell lines
Presentation date: April 21, 2015, 8:00 AM - 12:00 PM
Authors: Lallena, M.J.; Torres, R.; et.al.
Cyclin-dependent kinases play a key role in regulating cell-cycle progression. In many cancers, there is a loss of control in regulating the cell cycle in response to increased signaling from CDK4/6. As a result there is uncontrolled growth of cancer cells. Lilly's abemaciclib (LY2835219) is a cell-cycle inhibitor, designed to block the growth of cancer cells by specifically inhibiting CDK 4 and 6. Preclinical and early-stage clinical evaluation indicates that Lilly's abemaciclib may have potential therapeutic application for the treatment of human cancers—including breast cancer—in which an aberrant CDK4/6 pathway enhances cancer cell growth.

Lilly researchers have thoroughly investigated the mechanism of action of abemaciclib in estrogen receptor positive (ER+) luminal breast cancer cells. A diversity of breast cancer cell lines showed marked sensitivity to treatment with abemaciclib. Phenotypic and cell-fate characterization was conducted by monitoring proliferation, cell-cycle arrest, retinoblastoma (Rb) phosphorylation, senescence response (the loss of a cell's ability to divide), apoptosis (programmed cell death) and cell metabolism profile. The study identified three distinct mechanisms of action when luminal ER+ breast cancer cells are treated with abemaciclib at relevant pharmacological concentrations: potent cell-cycle arrest, efficient senescence response and induction of metabolic alterations.

Abemaciclib has now entered Phase III development in hormone receptor positive breast cancer patients.

Abstract #CT240: Checkpoint Kinase (CHK) 1/2 Inhibitor LY2606368 in a Phase I Dose-Expansion Study in Patients with Squamous Cell Carcinoma of the Head and Neck
Presentation date: April 20, 2015, 4:30 - 4:50 PM
Authors: Bendell, J.; Grant, S.; Janku F.; et.al.
Checkpoint kinase 1 (CHK1) regulates DNA damage checkpoints, and also plays a central role in normal DNA replication, mitosis (when a cell divides into an identical, replicated cell) and cytokinesis (the process by which a cell divides). Inhibition of CHK1 can cause impaired DNA replication, loss of DNA damage checkpoints, a cell's premature entry into mitosis, mitotic catastrophe and cell death. LY2606368 is a small molecule that has been observed, *in vitro*, to preferentially bind to and inhibit CHK1 and, to a lesser extent, CHK2, thus inducing DNA double-strand breaks, a loss in DNA checkpoint function and cell death.

LY2606368 was evaluated in this Phase I, multicenter, non-randomized, open-label study in patients with advanced cancer. For this cohort, based on results from the dose-escalation phase, patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) were treated with single-agent LY2606368 (105 mg/m^2) on day one of a 14-day cycle.

The trial enrollment included 57 patients with recurrent or metastatic SCCHN with more than half of those receiving at least two prior lines of treatment (median of three cycles; range 1-5) in the recurrent/metastatic setting. Twenty-five patients (44%) achieved stable disease and three patients (5%) achieved a partial response for at least three treatment cycles. The duration

of patient response ranged from 4.8-7.8 months and the median progression-free survival (PFS) was 1.6 months (90% CI: 1.4, 2.8). Pretreatment biopsy samples from 34 patients were evaluated for pharmacogenomic analysis, including human papillomavirus (HPV) status. Patients who were HPV positive (n=15) achieved 4.5 months of median PFS while HPV-negative patients (n=19) achieved 1.4 months median PFS.

The most frequently reported adverse event was a transient decrease in neutrophil/leukocyte count (91%). Grade 4 neutropenia occurred in 63 percent of patients, but was transient (typically less than five days). Febrile neutropenia was identified in 10 patients (18%). Other treatment-related adverse events occurring in greater than 10 percent of patients included thrombocytopenia (44%), anemia (25%), fatigue (23%) and headache (14%). The majority of non-hematologic adverse events were identified as grades 1 or 2.

LY2606368 is now entering Phase II development.

Abstract #2142: Novel Oncogenic BRaf Deletions Functioning as BRaf Homodimer and Sensitive to Inhibition by LY3009120, a Pan Raf and Raf Dimer Inhibitor
Presentation date: April 20, 2015, 1:00 - 5:00 PM
Authors: Chen, S.; Buchanan, S.; Zhang, Y.; et.al.
BRAF genetic mutations have been identified in many cancer types with BRAF V600E, a specific potent oncogene that activates the MAPK pathway and functions as a BRAF monomer. Several BRAF selective inhibitors have demonstrated efficacy in the inhibition of the BRAF monomer kinase activity, but no compound to date has demonstrated efficacy on non-BRAF V600E mutations, which generally function as a RAF dimer.

This study identified and characterized novel BRAF variants, which have in-frame deletions within or adjacent to the L485-P490 region in patient samples and/or cell lines of lung, pancreatic and ovarian cancers. These BRAF in-frame deletions function as a BRAF homodimer. Tumor cells with these BRAF deletions are resistant to BRAF monomer inhibitors. However, preclinical evaluation has shown Lilly's pan-RAF and RAF dimer inhibitor, LY3009120, to be active to these cells. In the study, lung and pancreatic cancer xenograft models developed with BRAF deletion tumor cells demonstrated significant tumor growth inhibition and regression when treated with LY3009120.

These findings, and other preclinical research, have advanced LY3009120 to Phase I of clinical development.

About Lilly Oncology
For more than fifty years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly's commitment to people with cancer, please visit www.LillyOncology.com.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and newsroom.lilly.com/social-channels.

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This press release contains forward-looking statements about the potential of abemaciclib, LY2606368 and LY3009120 as potential treatments for several types of cancer and reflects Lilly's current beliefs. However, as with any pharmaceutical products, there are substantial risks and uncertainties in the process of development and commercialization. There can be no guarantee that future study results and patient experience will be consistent with the study findings to date. There can also be no guarantee that these compounds will receive regulatory approval for any future indications or that they will prove to be commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see the company's latest Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements.

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