June 3, 2013

PRONOUNCE Study Does Not Achieve Primary Superiority Endpoint for ALIMTA® (pemetrexed for injection), Similar PFS and OS Results Were Observed Between the Two Drug and the Three Drug Regimens in the Treatment of NSCLC

CHICAGO, June 3, 2013 /PRNewswire/ -- Eli Lilly and Company (NYSE:LLY) announced results from its PRONOUNCE trial of ALIMTA® (pemetrexed for injection) for treatment of nonsquamous non-small cell lung cancer (NSCLC) that was presented today at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago, Ill.

The PRONOUNCE trial compared an ALIMTA (pemetrexed), carboplatin doublet regimen to a paclitaxel, carboplatin and bevacizumab triplet regimen.

The study did not achieve its primary superiority endpoint of improved progression-free survival without grade four adverse events (G4PFS). No significant difference was observed between the treatment arms for secondary endpoints of progression-free survival (PFS), overall survival, overall response rate and disease control rate. Toxicity profiles observed in the trial were consistent with the known safety profiles of each therapy.

"The history of ALIMTA clinical evaluation — from histology to its use in the maintenance therapy paradigm — encourages us to explore new avenues to determine if we can improve patient outcomes," said Richard Gaynor, M.D., vice president of product development and medical affairs for Lilly Oncology. "These data give us additional insights that further inform the vast body of ALIMTA clinical data."

The safety and efficacy profile for ALIMTA has been the subject of Lilly-sponsored studies involving an estimated 32,500 patients over the span of almost 20 years[1].

About PRONOUNCE (Abstract #LBA8003)
PRONOUNCE is a randomized, open-label Phase III superiority study of first-line chemotherapy pemetrexed plus carboplatin (PemC regimen) followed by maintenance pemetrexed, compared to paclitaxel plus carboplatin plus bevacizumab (PacCBev regimen) followed by maintenance bevacizumab in patients with advanced nonsquamous NSCLC conducted in the U.S.

Patients were randomized (1:1) to the PemC regimen (n=182) or PacCBev regimen (n=179). Patients received four cycles of induction PemC regimen: pemetrexed, 500 mg/m^2 and carboplatin, AUC=6; PacCBev regimen: paclitaxel, 200 mg/m^2, carboplatin, AUC=6 and bevacizumab, 15 mg/kg followed by pemetrexed (PemC regimen) or bevacizumab (PacCBev regimen) maintenance therapy in the absence of progressive disease or discontinuation. The primary endpoint, G4PFS was measured by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[2] Secondary endpoints were PFS, overall survival (OS), overall response rate (ORR), and disease control rate (DCR). The study was powered for G4PFS. Assuming a hazard ratio (HR) of 0.75, there was 80 percent power to detect superiority of the PemC regimen over the PacCBev regimen with a two-sided type one error of 0.10.

The median G4PFS was 3.91 months on the PemC regimen vs. 2.86 months on the PacCBev regimen (HR=0.85, 90% CI 0.7, 1.04, p=0.176). PFS and OS had HR=1.06 (95% CI 0.84, 1.35), p=0.610, and HR=1.07 (95% CI 0.83, 1.36), p=0.615, respectively. The ORR was 23.6% (PemC regimen) and 27.4% (PacCBev regimen) and the DCR was 59.9% (PemC regimen) and 57.0% (PacCBev regimen).

There were no unexpected toxicities in either regimen in the PRONOUNCE trial. Results from the PemC arm saw significantly more drug-related Grade 3/4 anemia, or low red blood cells, (18.7% vs. 5.4%), and thrombocytopenia, which is a decrease in blood platelets (24.0% vs. 9.6%). Results from the PacCBev arm saw significantly more Grade 3/4 neutropenia, which is low white blood cell count (48.8% vs. 24.6%), grade 1-3 sensory neuropathy, which is sensory alteration in nerves that ranges from mild tingling to impaired functioning and pain (32.5% vs. 8.2%), and grade 1/2 alopecia or hair loss (28.3% vs. 8.2%). No difference in grade 3/4 fatigue was seen between the treatment arms in this trial (6.4% in the PemC arm vs. 5.4% in the PacCBev arm). Toxicity profiles were otherwise consistent with the known safety profiles of each therapy.

U.S. ALIMTA Approvals
In 2004, ALIMTA received consecutive approvals: it was the first agent to be approved in combination with cisplatin as a treatment for patients with malignant pleural mesothelioma, whose disease is unresectable or who are otherwise not candidates

for curative surgery, and then as a single agent for the second-line treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy treatment.

In 2008, ALIMTA, in combination with cisplatin, was approved as a first-line treatment for locally advanced or metastatic NSCLC for patients with nonsquamous histology. At the time of the first-line approval, the FDA also approved a change to the second-line indication. ALIMTA is now indicated as a single agent for the treatment of patients with locally advanced or metastatic, nonsquamous NSCLC after prior chemotherapy.

In 2009, ALIMTA was approved as a maintenance therapy for locally advanced or metastatic NSCLC, specifically for patients with a nonsquamous histology whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

In 2012, ALIMTA was approved by the FDA as a continuation maintenance therapy for locally-advanced or metastatic NSCLC, following first-line therapy with ALIMTA plus cisplatin in patients with a nonsquamous histology.

ALIMTA is not indicated for treatment of patients with squamous cell NSCLC. Myelosuppression is usually the dose-limiting toxicity with ALIMTA therapy.

About Non-Small Cell Lung Cancer (NSCLC)
Lung cancer has long been the most common cancer in the world, representing nearly 13 percent of all new cancers and causing nearly 1.4 million deaths annually. About 85 percent of all lung cancers are NSCLC. The liver, bones and brain are potential targets if the cancerous cells spread to other areas in the body.

NSCLC comprises a group of histologies or tumor types differentiated by cellular structure. Nonsquamous histology includes adenocarcinoma and large cell carcinoma, which account for more than half of all NSCLC diagnoses, as well as histologies classified as "other."

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.

Important Safety Information for ALIMTA® (pemetrexed for injection)

What is the most important information that I should know about ALIMTA?
ALIMTA can suppress bone marrow function, which may cause low blood cell counts.

ALIMTA may not be appropriate for some patients.

If you are allergic to ALIMTA, tell your doctor because you should not receive it.

If you have liver or kidney problems, be sure to tell your doctor. Your dose of ALIMTA may have to be changed, or ALIMTA may not be right for you.

It is very important to take the following medications prior to and during your treatment with ALIMTA to lower your chances of harmful side effects:

- *You must take folic acid every day by mouth beginning 7 days before your first dose of ALIMTA. You must keep taking folic acid every day during the time you are being treated with ALIMTA, and every day for 21 days after you receive your last dose of ALIMTA.*
- *Your doctor will give you vitamin B_{12} injections while you are getting treatment with ALIMTA. You will get your first vitamin B_{12} injection one week before your first dose of ALIMTA, and then about every 9 weeks during treatment.*
- *Your doctor will prescribe a medicine called a "corticosteroid" that you must take the day before, the day of, and the day after each treatment with ALIMTA to reduce rash.*

You will have regular blood tests before and during your treatment with ALIMTA. Your doctor may adjust your dose of ALIMTA or delay your treatment based on the results of your blood test and on your general condition.

What should I tell my doctor before receiving ALIMTA?
If you think you are pregnant, are planning to become pregnant, or are nursing, please tell your healthcare team. ALIMTA may harm your unborn or nursing baby. Your physician may advise you to use effective contraception (birth control) to prevent pregnancy while you are being treated with ALIMTA.

Tell your doctor if you are taking other medicines, including prescription and nonprescription medicines, vitamins, and herbal supplements. ALIMTA and other medicines may affect each other, causing serious side effects. Especially, tell your doctor if you are taking medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs) for pain or swelling.

What are the possible side effects of ALIMTA?
Most patients taking ALIMTA will have side effects. Sometimes it is not always possible to tell whether ALIMTA, another medicine, or the cancer itself is causing these side effects.

***Call your doctor right away if you have a fever, chills, diarrhea, or mouth sores.** These symptoms could mean you have an infection, which may be severe and could lead to death.*

The most common side effects of ALIMTA when given alone or in combination with cisplatin are:

- ***Stomach upset, including nausea, vomiting, diarrhea, or constipation.** You can obtain medicines to help control some of these symptoms. Call your doctor if you get any of these symptoms.*

- ***Low blood cell counts:***
  - ***Low red blood cells.** Low red blood cells may make you feel tired, get tired easily, appear pale, and become short of breath.*
  - ***Low white blood cells.** Low white blood cells may give you a greater chance for infection. If you have a fever (temperature above 100.4°F) or other signs of infection, call your doctor right away.*
  - ***Low platelets.** Low platelets give you a greater chance for bleeding. Your doctor will do blood tests to check your blood counts before and during treatment with ALIMTA.*

- ***Tiredness.** You may feel tired or weak for a few days after your ALIMTA treatments. If you have severe weakness or tiredness, call your doctor.*

- ***Redness or sores in your mouth, throat, on your lips, or in the tube that connects your throat and stomach (esophagus).** You may get redness or sores in your mouth, throat, on your lips, or in your esophagus (stomatitis, pharyngitis, esophagitis) or you may feel pain or have difficulty when drinking or swallowing food. These symptoms may happen a few days after ALIMTA treatment. Talk with your doctor if you get any of these symptoms.*

- ***Loss of appetite.** You may lose your appetite and lose weight during your treatment. Talk to your doctor if this is a problem for you.*

- ***Rash.** You may get a rash or itching during treatment. These reactions usually appear between treatments with ALIMTA and usually go away before the next treatment. Skin reactions or rashes that include blistering or peeling may be severe and could lead to death. Call your doctor if you have any of these symptoms.*

Talk with your doctor, nurse, or pharmacist about any side effect that bothers you or that doesn't go away.

These are not all the side effects of ALIMTA. For more information, ask your doctor, nurse, or pharmacist.

How is ALIMTA given?
ALIMTA is slowly infused (injected) into a vein. The injection or infusion will last about 10 minutes. You will usually receive ALIMTA once every 21 days (3 weeks).

For more information about all of the side effects of ALIMTA, please talk with your healthcare team, see the Patient Prescribing Information and full Prescribing Information accompanying this booklet, visit www.ALIMTA.com, or call 1-800-545-5979.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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This press release contains forward-looking statements about the potential of ALIMTA for the treatment of non-small cell lung cancer and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development, commercialization, and regulatory review. There is no guarantee that the product will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

[1] Data on file, March 2013

[2] The G4PFS (grade 4 progression-free survival) is a composite endpoint. This endpoint is defined as the first occurrence of any of the following: Grade 4 adverse event or progression-free survival (which is disease progression or death).

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