Clinical Data Suggest Potential Versatility of ALIMTA(R) (Pemetrexed for Injection)-Based Regimens in Lung Cancer

Study Highlights Quality-of-Life Data

CHICAGO, June 2, 2007 /PRNewswire-FirstCall via COMTEX News Network/ -- ALIMTA(R) (pemetrexed for injection) showed additional utility in the treatment of the most diagnosed type of cancer(i), according to data presented today at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Results from a Phase III study suggest that a first-line ALIMTA-based regimen may deliver less toxicity than a commonly used therapy in advanced non-small cell lung cancer (NSCLC). ALIMTA is manufactured and marketed by Eli Lilly and Company.

A prospective, randomized, multicenter Phase III study was conducted to compare ALIMTA plus carboplatin with the commonly used regimen of GEMZAR(R) (gemcitabine HC1 for injection) plus carboplatin (ASCO Abstract # 7517(ii)). The study, conducted by the Norwegian Lung Cancer Group, enrolled 446 chemonaive patients with either stage IIIB or IV NSCLC. The primary purpose of the study was to evaluate if the ALIMTA-carboplatin combination provided increased quality-of-life benefits while offering comparable survival data. As such, the primary endpoint was quality of life (defined in the study as nausea/vomiting; dyspnea or a difficulty in breathing, and; fatigue) and the secondary endpoint was overall survival.

Thus far, 384 patients have been analyzed for toxicity and there were fewer patients in the ALIMTA arm who experienced Grade 3/4 thrombocytopenia or a low platelet level (48 vs. 107, $p < .001$); leukopenia or a lowering of leukocyte white blood cells (44 vs. 89, $p < .001$), and; granulocytopenia or a lowering of granulocyte white blood cells (78 vs. 98, $p=.02$). More patients in the GEMZAR arm received transfusion of platelets (5 vs. 19, $p=.02$). At this point, no difference in survival has been observed.

"The patients in this study received a comparable quality-of-life benefit whether they received ALIMTA and carboplatin or GEMZAR and carboplatin," said Bjorn Henning Gronberg, M.D. of St. Olavs University Hospital in Norway and the study's principal investigator. "Patients on the ALIMTA arm also appeared to benefit from a lower toxicity profile."

Additional data to be presented on Sunday, June 3rd at ASCO from a Phase II, open-label, non-randomized trial will report on an International Oncology Network Study evaluating the safety of a triplet therapy in which bevacizumab (Avastin(R)) was added to the combination of ALIMTA plus oxaliplatin (Eloxatin(R)) in patients with advanced NSCLC (Abstract # 7700(iii)). Previous research has indicated that oxaliplatin and ALIMTA, as single agents, have shown activity in NSCLC, and ALIMTA has shown synergistic effects when combined with platinum-based drugs.(iv,v) This preliminary study was conducted to evaluate the efficacy and safety of the combination as first-line treatment for NSCLC.

"We are pleased to see that ALIMTA has a synergistic effect with platinum agents like carboplatin," said Richard Gaynor, M.D., vice president, cancer research and global oncology platform leader for Lilly. "We look forward to continued research on ALIMTA as a chemotherapeutic foundation with targeted therapies and other anti-cancer agents for the treatment of lung cancer.

"Lilly is aggressively investigating potential novel therapies in other tumor types, as we are committed to providing patients with therapeutic options that fight the cancer but do not compromise quality of life."

Lilly also has studied ALIMTA plus cisplatin for the first-line treatment of NSCLC. In the first quarter of 2007, a study of ALIMTA plus cisplatin versus GEMZAR plus cisplatin met its primary endpoint of non-inferiority relative to overall survival. Utilizing these data, Lilly plans to submit ALIMTA for an indication for the first-line treatment of NSCLC to the European Medicines Agency (EMEA) later this year.

At ASCO, researchers will also present data that show ALIMTA as a chemotherapeutic foundation to a variety of approved and investigational targeted anti-cancer agents, including bevacizumab (Avastin(R)), erlotinib (Tarceva(R)), cetuximab (Erbitux(R)) and vandetanib (Zactima(TM)).

ALIMTA is an antifolate which interferes with a crucial process that allows cancer cells to reproduce and spread. The most common side effects when ALIMTA is used as monotherapy are disorders of the blood and lymphatic system, gastrointestinal disorders, fatigue, rash and desquamation or flaking of skin in scales. Myelosuppression is usually the dose-limiting toxicity with

ALIMTA therapy.

About Non-Small Cell Lung Cancer

NSCLC is the most common type of lung cancer and represents 75-80 percent of all lung cancers. NSCLC has five-tier staging, starting at 0 and rising to the severity of stage IV. NSCLC can spread through the lymphatic system, penetrating the chest lining, ribs, and the nerves and blood vessels that lead to the arm. The liver, bones and brain are potential targets if the cancerous cells enter the blood stream.

ALIMTA

Indications

ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

ALIMTA as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. The effectiveness of ALIMTA in second-line NSCLC was based on the surrogate endpoint, response rate. There are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement of disease-related symptoms.

Important Safety Information

Myelosuppression is usually the dose-limiting toxicity with ALIMTA therapy.

Contraindication

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed or to any other ingredient used in the formulation.

Warnings

ALIMTA should not be administered to patients with a creatinine clearance < 45 mL/min. One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B12 died of drug-related toxicity following administration of ALIMTA alone.

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia).

Patients must be instructed to take folic acid and vitamin B12 with ALIMTA as a prophylaxis to reduce treatment-related hematologic and GI toxicities.

Pregnancy Category D-ALIMTA may cause fetal harm when administered to a pregnant woman.

Precautions

Complete blood cell counts, including platelet counts and periodic chemistry tests, should be performed on all patients receiving ALIMTA.

Patients should not begin a new cycle of treatment unless the ANC is 1500 cells/mm3, the platelet count is > 100,000 cells/mm3 and creatinine clearance greater than or equal to 45 mL/min.

Pretreatment with dexamethasone or its equivalent has been reported to reduce the incidence and severity of skin rash.

The effect of third space fluid, such as pleural effusion and Ascites on ALIMTA is unknown.

In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to ALIMTA administration.

Caution should be used when administering ibuprofen concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA.

In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal and gastrointestinal toxicities.

Concomitant administration of nephrotoxic drugs or substances that are tubularly secreted could result in delayed clearance of ALIMTA.

It is recommended that nursing be discontinued if the mother is being treated with ALIMTA.

ALIMTA should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents.

Dose adjustments may be necessary in patients with hepatic insufficiency.

Dosing and Modification Guidelines

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Modify or suspend therapy according to the Dosage Reduction Guidelines in the full Prescribing Information.

Adverse Events

The most common adverse events (grades 3/4) with ALIMTA in combination with cisplatin for the treatment of patients with MPM were neutropenia (24%); leukopenia (16%); anemia (6%); thrombocytopenia (5%); infection without neutropenia (2%); fatigue (17%); thrombsis/embolism (6%); nausea (12%); vomiting (11%); dyspnea (11%); and chest pain (9%). The most common clinically relevant adverse events (all grades) were fatigue (80%); thrombosis/embolism (7%); nausea (84%); vomiting (58%); constipation (44%); anorexia (35%); stomatitis/pharyngitis (28%); diarrhea (26%); dyspnea (66%); chest pain (40%); and rash (22%).

The most common adverse events (grades 3/4) with ALIMTA for the treatment of patients with NSCLC were anemia (8%); leukopenia (5%); neutropenia (5%); thrombocytopenia (2%); infection without neutropenia (6%); fatigue (16%); thrombosis/embolism (3%); cardiac ischemia (3%);anorexia (5%); dyspnea (18%); and chest pain (7%). The most common clinically relevant adverse events (all grades) were fatigue (87%); anorexia (62%); nausea (39%); constipation (30%); vomiting (25%); diarrhea (21%); stomatitis/pharyngitis (20%); dyspnea (72%); chest pain (38%); neuropathy/sensory (29%); infection without neutropenia (23%); and rash (17%).

See complete Warnings, Precautions, Adverse Reactions, and Dosage and Administration sections in the accompanying full Prescribing Information for safety and dosing guidelines.

GEMZAR

Indications

GEMZAR in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

GEMZAR is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (stage IIIA or IIIB), or metastatic (stage IV) non-small cell lung cancer.

GEMZAR is indicated as first-line treatment for patients with locally advanced (nonresectable stage II or stage III) or metastatic (stage IV)adenocarcinoma of the pancreas. GEMZAR is indicated for patients previously treated with 5-FU.

GEMZAR in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

Important Safety Information for GEMZAR

Myelosuppression is usually the dose-limiting toxicity with GEMZAR therapy.

Contraindication

Known hypersensitivity to GEMZAR. Anaphylactoid reaction has been reported rarely.

Warnings

Infusion times of GEMZAR longer than 60 minutes and more frequent than weekly dosing have been shown to increase toxicity.

Pulmonary toxicity has been reported with the use of GEMZAR. In cases of severe lung toxicity, GEMZAR therapy should be discontinued immediately and appropriate supportive care measures instituted.

Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of GEMZAR. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving GEMZAR alone or in combination with other potentially hepatotoxic drugs.

GEMZAR is Pregnancy Category D. GEMZAR can cause fetal harm when administered to a pregnant woman.

Precautions

Use caution in patients with pre-existing renal impairment or hepatic insufficiency. Administration of GEMZAR may exacerbate underlying hepatic insufficiency.

The optimum regimen for safe administration of GEMZAR with therapeutic doses of radiation has not yet been determined in all tumor types. GEMZAR has radiosensitizing activity and radiation recall reactions have been reported.

It is not known whether GEMZAR or its metabolites are excreted in human milk.

The effectiveness of GEMZAR in pediatric patients has not been demonstrated.

The toxicities of GEMZAR observed in pediatric patients were similar to those reported in adults.

GEMZAR clearance is affected by age as well as gender.

Patients receiving therapy with GEMZAR should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents.

Monitoring and Dosage Modifications

Dosage adjustments for hematologic toxicity may be required.

Serum creatinine, potassium, calcium, and magnesium should be monitored during combination therapy with cisplatin.

Patients should be assessed with a CBC, including differential and platelet count, prior to each dose of GEMZAR. Modify or suspend therapy according to the Dosage Reduction Guidelines in the full Prescribing Information.

Hepatic and renal function (including transaminases and serum creatinine) should be evaluated prior to therapy with GEMZAR and periodically thereafter.

Adverse Events

The most severe adverse events (grades 3/4) with GEMZAR plus paclitaxel for the treatment of patients with MBC were neutropenia (48%); alopecia (18%); leukopenia (11%); anemia (7%); fatigue (7%); thrombocytopenia (6%); ALT elevation (6%); and neuropathy-sensory (6%). The most common adverse events (all grades) were nausea (50%); fatigue (40%); myalgia (33%); and vomiting (29%).

The most severe adverse events (grades 3/4) with GEMZAR for the first-line treatment of patients with pancreatic cancer were neutropenia (24%-26%); alkaline phosphatase elevation (16%-20%); AST elevation (12%-17%); nausea/vomiting (12%-13%); ALT elevation (10%-11%); anemia (10%); leukopenia (9%-10%); thrombocytopenia (8%-10%); bilirubin elevation (4%-8%); and pain (2%-7%). The most common adverse events (all grades) were AST (72%-78%); alkaline phosphatase (71%-77%); anemia (65%-73%); ALT (72%); leukopenia (64%- 71%); nausea and vomiting (64%-71%); neutropenia (61%-62%); thrombocytopenia (36%-47%); pain (10%-42%); fever (30%-38%); proteinuria (10%-32%); constipation (10%-31%); diarrhea (24%-30%); rash (24%-28%); and bilirubin (16%-26%).

The most severe adverse events (grades 3/4) with GEMZAR plus cisplatin for the first-line treatment of patients with NSCLC were neutropenia (57%-64%); thrombocytopenia (50%-55%); leukopenia (29%-46%); anemia (22%-25%); nausea (27%); vomiting (23%); nausea/vomiting (39%); neuromotor (12%); hypomagnesemia (7%); neurohearing (6%); creatinine elevation (5%); alopecia (1%-13%); and dyspnea (1%-7%). The most common adverse events (all grades) were paresthesias (38%); hyperglycemia (30%); infection (18%-28%); and constipation (17%-28%).

The most severe adverse events (grades 3/4) with GEMZAR plus carboplatin for the treatment of patients with advanced ovarian cancer were neutropenia (71%), thrombocytopenia (35%), leukopenia (53%), anemia (28%), nausea (6%), vomiting (6%), and constipation (7%). The most common adverse events (all grades) were RBC transfusion (38%), alopecia (49%), neuropathy/sensory (29%), nausea (69%), fatigue (40%), vomiting (46%), diarrhea (25%), and constipation (42%).

See complete Warnings, Precautions, Adverse Reactions, and Dosage and Administration sections in the accompanying full Prescribing Information for safety and dosing guidelines.

About Lilly Oncology, a Division of Eli Lilly and Company

For more than four decades, Lilly Oncology has been collaborating with cancer researchers to deliver innovative treatment choices and valuable programs to patients and their physicians. Inspired by courageous patients living with cancer, Lilly Oncology is providing treatments that are considered global standards of care and developing a broad portfolio of novel targeted therapies to accelerate the pace and progress of cancer care. 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 first-in-class and best-in-class 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.

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ALIMTA(R) (pemetrexed for injection), Lilly
GEMZAR(R) (gemcitabine HCl for injection), Lilly
bevacizumab (Avastin(R)), Genentech
oxaliplatin (Eloxatin(R)), Sanofi Aventis
erlotinib (Tarceva(R)), Genentech, OSI Pharmaceuticals
cetuximab (Erbitux(R)), Bristol-Myers Squibb, ImClone, Merck
vandetanib (Zactima(TM)), AstraZeneca
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This press release contains forward-looking statements about the potential of ALIMTA and GEMZAR for the treatment of non-small cell lung cancer and reflects Lilly's current beliefs. However, as with any pharmaceutical products under development, there are substantial risks and uncertainties in the process of development, commercialization, and regulatory review. There is no guarantee that the products will receive additional regulatory approvals. There is also no guarantee that the products will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filing with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.


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