



Study Showed ALIMTA(R) (pemetrexed for injection) Improved Survival in Certain Types of Non-Small Cell Lung Cancer

Patients with Adenocarcinoma or Large Cell Carcinoma Histologies Achieved Improvement in Overall Survival when Treated with ALIMTA-based Regimen

INDIANAPOLIS, May 28, 2008 /PRNewswire-FirstCall via COMTEX News Network/ -- The type of non-small cell lung cancer (NSCLC) patients have may now influence their treatment regimen and, in turn, survival outcome according to the results of a major study published online in the Journal of Clinical Oncology. Publication of the study was announced by Eli Lilly and Company.

The 1,725-patient study, the largest Phase III clinical trial in the first-line NSCLC setting, evaluated ALIMTA(R) (pemetrexed for injection) plus cisplatin versus GEMZAR(R) (gemcitabine HCl for injection) plus cisplatin, a standard of treatment in this setting. The trial met its primary endpoint of non-inferiority relative to overall survival.

Additionally, in a pre-planned histological analysis, patients with either adenocarcinoma or large-cell carcinoma had a statistically superior and clinically relevant improvement in overall survival when treated with the pemetrexed regimen in the first-line setting.

In comparison, patients with squamous cell histology were found to have a more favorable overall survival when treated with the gemcitabine regimen.

"While non-small cell lung cancer has typically been treated as one disease, this study confirms that histology, or tumor type, can provide a clue as to which treatment regimen works best for a particular tumor type," said the study's lead author, Giorgio Scagliotti, M.D., Department of Clinical and Biological Sciences Thoracic Oncology Unit, University of Torino, Orbassano, Italy. "If we can tailor the therapy for better results, we are closer to improving outcomes for this terrible disease."

The overall survival of patients treated with either the pemetrexed regimen or gemcitabine regimen was found to be non-inferior, with a median survival of 10.3 months. However, when researchers reviewed survival rates according to histological analysis, it was found that patients with adenocarcinoma achieved 12.6 months of overall median survival when treated with the pemetrexed regimen compared to 10.9 months for those treated with the gemcitabine regimen. Patients with large cell carcinoma who were treated with the pemetrexed regimen achieved 10.4 months of overall median survival versus 6.7 months for those treated with the gemcitabine regimen. Both findings are statistically significant.

Comparatively, patients with squamous cell histology were found to have a more favorable rate of survival when treated with the gemcitabine regimen, achieving 10.8 months of median survival, compared to the 9.4 months for those treated with the pemetrexed regimen. This finding also was statistically significant.

The Phase III, randomized study compared the overall survival between pemetrexed+cisplatin versus gemcitabine+cisplatin in 1,725 chemo-naïve patients with stage IIIB or IV NSCLC who also exhibited a performance status of 0-1. Patients on the pemetrexed arm (n = 862) were treated with pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) on day one every three weeks for up to six cycles. Patients on the gemcitabine arm (n = 863) were treated with cisplatin (75 mg/m²) on day one and gemcitabine (1250 mg/m²) on days one and eight every three weeks for up to six cycles.

Hematologic grade 3/4 drug-related toxicities - neutropenia, anemia and thrombocytopenia - were significantly lower for patients on the pemetrexed arm (p less than or equal to 0.001). Drug-related grade 3/4 febrile neutropenia (p = 0.002) and alopecia (all grades; p < 0.001) were also significantly less on the pemetrexed arm. However, drug-related grade 3/4 nausea (p = 0.004) was more common in patients treated with pemetrexed. Safety data by histology was generally consistent with the overall safety results.

"In research, we're always looking for a new door to open - a different way of looking at the problem, in the hope of finding a better solution. That's why this study is so important. It has opened a door that points to histology as a way of helping physicians decide which lung cancer treatment may work best for a particular patient," said Richard Gaynor, M.D., vice president of cancer research and global oncology platform leader at Lilly.

Notes to Editor

About Non-Small Cell Lung Cancer (NSCLC)

NSCLC is the most common type of lung cancer and represents 85 to 90 percent of all lung cancers.(1) NSCLC has five-tier staging, starting at 0 and rising to the severity of stage IV.(2) 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 bloodstream.

According to the World Health Organization (WHO) Cancer Report, lung cancer is the world's most common cancer and the leading cause of cancer death for both men and women. More than 1 million people die from lung cancer each year.(3)

NSCLC is defined as a group of histologies, that is, tumor types differentiated by cellular structure. The most common NSCLC histology types are squamous (or epidermoid) carcinoma, adenocarcinoma, and large cell carcinoma. These histologies are often classified together because, to date, approaches to diagnosis, staging, prognosis, and treatment have been similar.(4)

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.

(1) American Cancer Society, "What Is Non-Small Cell Lung Cancer?," October 15, 2007, American Cancer Society, http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Is_Non-Small_Cell_Lung_Cancer.asp?nav=cri, (February 21, 2008).

(2) American Cancer Society, "How Is Non-Small Cell Lung Cancer Staged?" October 15, 2007, American Cancer Society, www.cancer.org/docroot/CRI/content/CRI_2_4_3x_How_Is_Non-Small_Cell_Lung_Cancer_Staged.asp?nav=cri, (February 21, 2008).

(3) World Health Organization, Gender in Lung Cancer and Smoking Research, Department of Gender, Women and Health, 2003, <http://www.who.int/gender/documents/en/lungcancerlow.pdf>.

(4) National Cancer Institute, "Non-Small Cell Lung Cancer Treatment (PDQ(R)) Health Professional Version," December 14, 2007, National Cancer Institute, www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/HealthProfessional/page2, (February 14, 2008).

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.

P-LLY

ALIMTA(R) (pemetrexed for injection), Lilly

GEMZAR(R) (gemcitabine HCl for injection), Lilly

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 product 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 filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

Important Safety Information for ALIMTA

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 greater than or equal to 1500 cells/mm³ and the platelet count is greater than or equal to 100,000 cells/mm³ and creatinine clearance is 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.

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

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.

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.

Abbreviated Adverse Events (% incidence)

The most common adverse events (grades 3/4) with ALIMTA versus docetaxel, respectively, for the treatment of patients with NSCLC were anemia (8 vs 7); leukopenia (5 vs 28); neutropenia (5 vs 40); thrombocytopenia (2 vs 1); ALT elevation (3 vs 1); febrile neutropenia (2 vs 13); infection without neutropenia (6 vs 4); infection/febrile neutropenia - other (2 vs 1); fatigue (16 vs

17); thrombosis/embolism (3 vs 3); cardiac ischemia (3 vs 1); anorexia (5 vs 8); dyspnea (18 vs 26); and chest pain (7 vs 8). The most common clinically relevant adverse events (all grades) with ALIMTA versus docetaxel, respectively, were fatigue (87 vs 81); anorexia (62 vs 58); nausea (39 vs 25); constipation (30 vs 23); vomiting (25 vs 19); diarrhea (21 vs 34); stomatitis/pharyngitis (20 vs 23); edema (19 vs 24); dyspnea (72 vs 74); chest pain (38 vs 32); neuropathy/sensory (29 vs 32); infection without neutropenia (23 vs 17); anemia (33 vs 33); fever (26 vs 19); and rash (17 vs 9).

The most common adverse events (grades 3/4) with ALIMTA in combination with cisplatin versus cisplatin alone, respectively, for the treatment of patients with MPM were neutropenia (24 vs 4); leukopenia (16 vs 1); anemia (6 vs 0); thrombocytopenia (5 vs 0); infection without neutropenia (2 vs 0); infection with grade 3/4 neutropenia (1 vs 0); infection/febrile neutropenia - other (1 vs 0); febrile neutropenia (1 vs 0); fatigue (17 vs 13); thrombosis/embolism (6 vs 4); nausea (12 vs 6); vomiting (11 vs 5); dyspnea (11 vs 7); and chest pain (9 vs 6). The most common clinically relevant adverse events (all grades) with ALIMTA in combination with cisplatin versus cisplatin alone, respectively, were neutropenia (58 vs 16); leukopenia (55 vs 20); anemia (33 vs 14); thrombocytopenia (27 vs 10); fatigue (80 vs 74); thrombosis/embolism (7 vs 4); nausea (84 vs 79); vomiting (58 vs 52); constipation (44 vs 39); anorexia (35 vs 25); stomatitis/pharyngitis (28 vs 9); diarrhea (26 vs 16); dyspnea (66 vs 62); chest pain (40 vs 30); and rash (22 vs 9).

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

Important Safety Information for GEMZAR

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

Contraindication

Known hypersensitivity to GEMZAR.

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. 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.

Abbreviated Adverse Events (% incidence)

The most severe adverse events (grades 3/4) with GEMZAR plus cisplatin for the first-line treatment of patients with NSCLC in comparative trials of a 28-day regimen (GEMZAR plus cisplatin versus cisplatin alone) and a 21-day regimen (GEMZAR plus cisplatin versus etoposide plus cisplatin), respectively, were neutropenia (57 vs 4, 64 vs 76); thrombocytopenia (50 vs 4, 55 vs 13); leukopenia (46 vs 3, 29 vs 43); anemia (25 vs 7, 22 vs 15); nausea 28d (27 vs 21); vomiting 28d (23 vs 19); nausea/vomiting 21d (39 vs 26); neuromotor 28d (12 vs 3); hypomagnesemia 28d (7 vs 2); neurohearing 28d (6 vs 6); creatinine elevation 28d (5 vs 3); and dyspnea (7 vs 5, 1 vs 0). The most common adverse events (all grades) of the 28-day regimen (GEMZAR plus cisplatin versus cisplatin alone) and the 21-day regimen (GEMZAR plus cisplatin versus etoposide plus cisplatin), respectively, were anemia (89 vs 67, 88 vs 77); leukopenia (82 vs 25, 86 vs 87); neutropenia (79 vs 20, 88 vs 87), thrombocytopenia (85 vs 13, 81 vs 45), lymphocytopenia 28d (75 vs 51); hematuria (15 vs 13, 22 vs 10); creatinine 28d (38 vs 31), hyperglycemia 28d (30 vs 23); hypomagnesemia 28d (30 vs 17); nausea 28d (93 vs 87); vomiting 28d (78 vs 71); nausea and vomiting 21d (96 vs 86); alopecia (53 vs 33, 77 vs 92); neuromotor 28d (35 vs 15); constipation (28 vs 21, 17 vs 15); neurohearing 28d (25 vs 21); paresthesias 21d (38 vs 16); and infection (18 vs 12, 28 vs 21).

The most severe adverse events (grades 3/4) with GEMZAR plus carboplatin versus carboplatin, respectively, for the treatment of patients with advanced ovarian cancer were neutropenia (71 vs 12), thrombocytopenia (35 vs 11), leukopenia (53 vs 7), anemia (28 vs 11), nausea (6 vs 3), vomiting (6 vs 3), and constipation (7 vs 3). The most common adverse events (all grades) were neutropenia (90 vs 58); leukopenia (86 vs 70); anemia (86 vs 75); and thrombocytopenia (78 vs 57); RBC transfusion (38 vs 15), alopecia (49 vs 17), neuropathy/sensory (29 vs 27), nausea (69 vs 61), fatigue (40 vs 32), vomiting (46 vs 36), diarrhea (25 vs 14), and constipation (42 vs 37).

The most severe adverse events (grades 3/4) with GEMZAR plus paclitaxel versus paclitaxel, respectively, for the treatment of patients with MBC were neutropenia (48 vs 11); alopecia (18 vs 22); leukopenia (11 vs 2); anemia (7 vs 4); fatigue (7 vs 2); thrombocytopenia (6 vs 2); ALT elevation (6 vs 1); and neuropathy-sensory (6 vs 3). The most common adverse events (all grades) were alopecia (90 vs 92); anemia (69 vs 51); neutropenia (69 vs 31); neuropathy-sensory (64 vs 58); nausea (50 vs 31); fatigue (40 vs 28); myalgia (33 vs 33); vomiting (29 vs 15); and thrombocytopenia (26 vs 7).

The most severe adverse events (grades 3/4) with GEMZAR versus 5-FU for the first-line treatment of patients with pancreatic cancer and data reported from a single agent safety database, respectively, were neutropenia (26 vs 5, 24); alkaline phosphatase elevation (16 vs 17, 20); AST elevation (12 vs 2, 17); nausea/vomiting (13 vs 5, 12); ALT elevation (10 vs 0, 11); anemia (10 vs 0, 10); leukopenia (10 vs 2, 9); thrombocytopenia (10 vs 2, 8); bilirubin elevation (4 vs 9, 8); and pain (2 vs 0, 7). The most common adverse events (all grades), defined as reported in > 25% of patients, were AST elevation (72 vs 52, 78); alkaline phosphatase elevation (71 vs 64, 77); anemia (65 vs 45, 73); ALT elevation (72 vs 38, 72); leukopenia (71 vs 15, 64); nausea and vomiting (64 vs 58, 71); neutropenia (62 vs 18, 61); thrombocytopenia (47 vs 15, 36); pain (10 vs 7, 42); fever (30 vs 16, 38); proteinuria (10 vs 2, 32); constipation (10 vs 11, 31); diarrhea (24 vs 31, 30); rash (24 vs 13, 28); and bilirubin elevation (16 vs 25, 26).

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

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