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New Data on the Combination of Lilly's ALIMTA® (pemetrexed) and Merck's KEYTRUDA® (pembrolizumab) Show a Near-Doubling of Objective Response Rate Compared to Standard of Care Alone in First-Line Metastatic Non-Small Cell Lung Cancer

Patients Receiving ALIMTA-KEYTRUDA-Carboplatin Combination Demonstrate Response Rate of 55 Percent and Reduction in the Risk of Disease Progression or Death by 47 Percent, with a Median Progression-Free Survival of 13 Months

Trial Enrolled Patients Regardless of PD-L1 Expression

Results to Be Presented at ESMO 2016 Congress Presidential Session Today

INDIANAPOLIS, Oct. 9, 2016 /PRNewswire/ -- Important clinical study results from one of Eli Lilly and Company's (NYSE: LLY) ongoing immuno-oncology collaborations with Merck (known as MSD outside the U.S. and Canada) were announced today at the ESMO 2016 Congress, the annual meeting of the European Society for Medical Oncology. Specifically, data released from KEYNOTE-021, Cohort G, which evaluated ALIMTA® (pemetrexed) plus carboplatin in combination with Merck's KEYTRUDA® (pembrolizumab) in the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC), showed that the combination of ALIMTA, KEYTRUDA and carboplatin demonstrated superior efficacy compared to ALIMTA and carboplatin - standard of care - alone.

In KEYNOTE-021, Cohort G, which included patients with advanced nonsquamous NSCLC regardless of PD-L1 expression level, the combination of pemetrexed, pembrolizumab and carboplatin achieved a 55 percent objective response rate (ORR) compared to 29 percent for pemetrexed-plus-carboplatin alone, and reduced the risk of disease progression or death by 47 percent. Median progression-free survival (PFS) was 13.0 months with the pemetrexed-pembrolizumab-carboplatin combination. To date, this combination of pemetrexed-pembrolizumab-carboplatin is the only anti-PD-1-containing regimen to demonstrate superior efficacy compared to chemotherapy alone in NSCLC patients receiving first-line treatment.

"These randomized study data of ALIMTA and KEYTRUDA in first-line nonsquamous non-small cell lung cancer build on the early results we've seen in this combination and are very encouraging," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "To see a near-doubling in the number of patients responding to this combination gives us hope for what may be able to be achieved above and beyond what is seen with the ALIMTA-containing standard-of-care regimen. These types of clinical advancements are truly exciting as we continue our pursuit to bring meaningful benefits to patients facing cancer."

Dr. Gaynor added, "These data also reflect the progress that Lilly is making in its oncology R&D strategy to develop cancer treatments across three key areas of disease modification: tumor cell signaling, tumor microenvironment and immuno-oncology. This approach allows for testing of combinations of internally derived agents to address tumor heterogeneity and drug resistance, through our own efforts and research collaborations."

KEYNOTE-021, Cohort G, included 123 previously untreated patients with advanced nonsquamous NSCLC regardless of PD-L1 expression and whose tumors did not have EGFR mutations or ALK translocations. Patients were randomized to receive the pemetrexed-pembrolizumab-carboplatin combination (n=60) or pemetrexed-plus-carboplatin (n=63). Patients randomized to the pemetrexed-plus-carboplatin control arm had the option of crossing over to pembrolizumab monotherapy upon disease progression. The median follow-up was 10.6 months (range, 0.8-19.3).

The findings demonstrated that ORR nearly doubled with the pemetrexed-pembrolizumab-carboplatin combination, with an ORR of 55 percent (n=33/60), compared to 29 percent (n=18/63) for the control arm alone (treatment difference 26%, 95% CI, 9-42% p=0.0016); all responses were partial. Median duration of response was not reached in either group (range, 1.4+-13.0+ for the pemetrexed-pembrolizumab-carboplatin combination; 1.4+-15.2+ for the control arm). Responses in both groups were durable, with 88 percent (n=29/33) of responders in the pemetrexed-pembrolizumab-carboplatin combination group and 78 percent (n=14/18) of responders in the control arm group experiencing ongoing response at the time of data cut-off.

Additionally, the pemetrexed-pembrolizumab-carboplatin combination significantly reduced the risk of disease progression or death compared to the control arm (hazard ratio 0.53, 95% CI, 0.31-0.91, p=0.0102). Median PFS was 13.0 months with

the pemetrexed-pembrolizumab-carboplatin combination compared to 8.9 months in the control arm. Overall survival (OS) was similar between the two arms, with 92 percent survival at six months in both, and 75 percent and 72 percent survival at 12 months in the pemetrexed-pembrolizumab-carboplatin combination and control arm, respectively.

Of treated patients on the pemetrexed-pembrolizumab-carboplatin combination arm, 47 percent remained on treatment as of the cut-off date, compared to 31 percent on the control arm. Of the treated patients who discontinued treatment on the control arm, 52 percent (n=32/62) subsequently received anti-PD-L1 therapy, with 32 percent crossing over to pembrolizumab monotherapy as allowed by the study protocol and 19 percent receiving it outside of study crossover.

Additional Safety Information from KEYNOTE-021, Cohort G

The most common treatment-related adverse events (occurring in at least 15% of patients) for the pemetrexed-pembrolizumab-carboplatin combination were fatigue, nausea, anemia, rash, vomiting, diarrhea, increased AST, constipation, decreased appetite, increased ALT, dysgeusia, and decreased neutrophils. Grade 3-4 treatment-related adverse events in this arm included fatigue, nausea, anemia, rash, vomiting, increased AST, increased ALT, and decreased neutrophils. The most common immune-mediated adverse events in patients receiving the pemetrexed-pembrolizumab-carboplatin combination were hypothyroidism and hyperthyroidism. Additionally, pneumonitis, infusion reactions, and severe skin toxicity were noted. These immune-mediated adverse events occurred at similar rates to patients receiving pembrolizumab as a single agent. There was one treatment-related death from sepsis in a patient receiving the pemetrexed-pembrolizumab-carboplatin combination, and two (one from sepsis and one from pancytopenia) in patients on the control arm.

About KEYNOTE-021, Cohort G

Cohort G of the multicenter, open-label, phase 1/2 multi-cohort KEYNOTE-021 study evaluated the efficacy and safety of pembrolizumab in combination with pemetrexed and carboplatin compared with pemetrexed and carboplatin in patients with advanced, nonsquamous, EGFR- and ALK-negative NSCLC in the first-line treatment setting. Patients were randomized 1:1 to four cycles of pembrolizumab (200 mg) plus pemetrexed (500 mg/m² every three weeks) plus carboplatin AUC 5 (5 mg/mL/min), or pemetrexed plus carboplatin alone, followed by maintenance pemetrexed with or without pembrolizumab. Randomization was stratified by PD-L1 expression (positive expression defined as TPS of one percent or more; negative expression defined as TPS of less than one percent). Patients randomized to the control arm were allowed to cross over to pembrolizumab monotherapy if they experienced disease progression. Response was assessed by blinded, independent central review using RECIST 1.1 every six weeks for the first 18 weeks, every nine weeks through the first year, and every 12 weeks in the second year. The primary endpoint was ORR; secondary endpoints included PFS, duration of response, and OS.

About KEYNOTE-189, a Phase 3 Trial of Pemetrexed-Pembrolizumab-Platinum Combination

[KEYNOTE-189](#), a randomized Phase 3 study evaluating pemetrexed-plus-platinum chemotherapy (carboplatin or cisplatin) with and without pembrolizumab as initial therapy in NSCLC patients, is currently enrolling. The first results from this study could be available before the end of 2017.

Pemetrexed (marketed under the brand name ALIMTA[®]) is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. *In vitro* studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides.

Pembrolizumab (marketed under the brand name KEYTRUDA[®]) is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to help detect and fight tumor cells. Pembrolizumab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes, which may affect both tumor cells and healthy cells.

NOTES TO EDITORS

About ALIMTA[®] (pemetrexed)

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 treatment of patients with locally advanced or metastatic NSCLC after prior treatment.

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

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 initial chemotherapy.

In 2012, ALIMTA was approved by the FDA as maintenance therapy for locally-advanced or metastatic NSCLC, following initial ALIMTA-plus-cisplatin treatment for locally advanced or metastatic nonsquamous NSCLC.

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

Indications and Important Safety Information for ALIMTA[®] (pemetrexed for injection)

Indications

ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

ALIMTA is indicated for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

ALIMTA is indicated as a single agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy.

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

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.

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.

Warnings and Precautions

Prior to treatment with ALIMTA, patients must be instructed to initiate supplementation with oral folic acid. Additionally, intramuscular injections of vitamin B₁₂ are also required prior to ALIMTA treatment. Folic acid and vitamin B₁₂ supplementation should be continued throughout treatment as they may reduce the severity of treatment-related hematologic and GI toxicities.

Dexamethasone or its equivalent should be administered the day before, the day of, and the day after ALIMTA treatment.

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia). Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities.

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.

Caution should be used when administering NSAIDs 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 NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity. No dose adjustment of ALIMTA is needed with concomitant NSAIDs in patients with normal renal function.

Do not initiate a cycle of treatment in patients unless the ANC is ≥ 1500 cells/mm³, the platelet count is $\geq 100,000$ cells/mm³, and creatinine clearance is ≥ 45 mL/min.

Pregnancy Category D—ALIMTA may cause fetal harm when administered to a pregnant woman. Women should be apprised of the potential hazard to the fetus and should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA.

Drug Interactions

See Warnings and Precautions for specific information regarding NSAID administration in patients with renal insufficiency.

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

Use in Specific Patient Populations

It is recommended that nursing be discontinued if the mother is being treated with ALIMTA or discontinue the drug, taking into account the importance of the drug for the mother.

Efficacy of ALIMTA in pediatric patients has not been demonstrated. The most common toxicities reported in the studied pediatric patients were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

Dosage and Administration Guidelines

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

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 Reactions (% incidence) - 1st-line advanced nonsquamous non-small cell lung cancer (NS NSCLC)

The most severe adverse reactions (grades 3-4) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, for the 1st-line treatment of patients with advanced nonsquamous non-small cell lung cancer (NSCLC) were neutropenia (15% vs 27%); leukopenia (5% vs 8%); thrombocytopenia (4% vs 13%); anemia (6% vs 10%); fatigue (7% vs 5%); nausea (7% vs 4%); vomiting (6% vs 6%); anorexia (2% vs 1%); creatinine elevation (1% vs 1%); and diarrhea (1% vs 2%).

Common adverse reactions (all grades) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, were nausea (56% vs 53%); fatigue (43% vs 45%); vomiting (40% vs 36%); anemia (33% vs 46%); neutropenia (29% vs 38%); anorexia (27% vs 24%); constipation (21% vs 20%); leukopenia (18% vs 21%); stomatitis/pharyngitis (14% vs 12%); alopecia (12% vs 21%); diarrhea (12% vs 13%); thrombocytopenia (10% vs 27%); neuropathy/sensory (9% vs 12%); taste disturbance (8% vs 9%); rash/desquamation (7% vs 8%); dyspepsia/heartburn (5% vs 6%); and creatinine elevation (10% vs 7%).

Abbreviated Adverse Reactions (% incidence) - Maintenance in advanced NS NSCLC following non-ALIMTA containing, platinum-based induction therapy

The most severe adverse reactions (grades 3-4) with ALIMTA as a single agent versus placebo, respectively, for the maintenance treatment of patients with locally advanced nonsquamous non-small cell lung cancer (NS NSCLC) following non-ALIMTA containing platinum-based induction therapy were anemia (3% vs 1%); neutropenia (3% vs 0%); leukopenia (2% vs 1%); fatigue (5% vs 1%); nausea (1% vs 1%); anorexia (2% vs 0%); mucositis/stomatitis (1% vs 0%); diarrhea (1% vs 0%); infection (2% vs 0%); and neuropathy-sensory (1% vs 0%).

Common adverse reactions (all grades) with ALIMTA as a single agent versus placebo, respectively, after non-ALIMTA containing platinum-based induction therapy were anemia (15% vs 6%); neutropenia (6% vs 0%); leukopenia (6% vs 1%); increased ALT (10% vs 4%); increased AST (8% vs 4%); fatigue (25% vs 11%); nausea (19% vs 6%); anorexia (19% vs 5%); vomiting (9% vs 1%); mucositis/stomatitis (7% vs 2%); diarrhea (5% vs 3%); infection (5% vs 2%); neuropathy-sensory (9% vs 4%); and rash/desquamation (10% vs 3%).

Abbreviated Adverse Reactions (% incidence) - Maintenance in advanced NS NSCLC following ALIMTA plus cisplatin induction therapy

The most severe adverse reactions (grades 3-4) with ALIMTA as a single agent versus placebo, respectively, for the maintenance treatment of patients with locally advanced nonsquamous non-small cell lung cancer (NS NSCLC) following ALIMTA plus cisplatin induction therapy were anemia (4.8% vs 0.6%); neutropenia (3.9% vs 0%); and fatigue (4.5% vs 0.6%).

Common adverse reactions (all grades) with ALIMTA as a single agent versus placebo, respectively, following ALIMTA plus cisplatin induction therapy were anemia (15% vs 4.8%); neutropenia (9% vs 0.6%); fatigue (18% vs 11%); nausea (12% vs 2.4%); vomiting (6% vs 1.8%); mucositis/stomatitis (5% vs 2.4%); and edema (5% vs 3.6%).

Abbreviated Adverse Reactions (% incidence) - 2nd-line advanced NS NSCLC

The most severe adverse reactions (grades 3-4) with ALIMTA as a single agent versus docetaxel, respectively, for the 2nd-line treatment of patients with advanced non-small cell lung cancer (NSCLC) were neutropenia (5% vs 40%); leukopenia (4% vs 27%); thrombocytopenia (2% vs 0%); anemia (4% vs 4%); fatigue (5% vs 5%); nausea (3% vs 2%); anorexia (2% vs 3%); vomiting (2% vs 1%); increased ALT (2% vs 0%); increased AST (1% vs 0%); and stomatitis/pharyngitis (1% vs 1%).

Common adverse reactions (all grades) with ALIMTA as a single agent versus docetaxel, respectively, were fatigue (34% vs 36%); nausea (31% vs 17%); anorexia (22% vs 24%); anemia (19% vs 22%); vomiting (16% vs 12%); stomatitis/pharyngitis (15% vs 17%); rash (14% vs 6%); diarrhea (13% vs 24%); leukopenia (12% vs 34%); thrombocytopenia (8% vs 1%); increased ALT (8% vs 1%); increased AST (7% vs 1%); constipation (6% vs 4%); fever (8% vs 8%); pruritus (7% vs 2%); alopecia (6% vs 38%); and neutropenia (11% vs 45%).

Abbreviated Adverse Reactions (% incidence) - MPM

The most severe adverse reactions (grades 3-4) with ALIMTA in combination with cisplatin versus cisplatin alone, respectively, for the treatment of patients with malignant pleural mesothelioma (MPM) were neutropenia (23% vs 3%); leukopenia (15% vs 1%); thrombocytopenia (5% vs 0%); anemia (4% vs 0%); nausea (12% vs 6%); vomiting (11% vs 4%); fatigue (10% vs 9%); creatinine elevation (1% vs 1%); stomatitis/pharyngitis (3% vs 0%); anorexia (1% vs 1%); diarrhea (4% vs 0%); constipation (1% vs 1%); dyspepsia (1% vs 0%); dehydration (4% vs 1%); neuropathy-sensory (0% vs 1%); rash (1% vs 0%); and creatinine clearance decrease (1% vs 2%).

Common adverse reactions (all grades) with ALIMTA in combination with cisplatin versus cisplatin alone, respectively, were neutropenia (56% vs 13%); leukopenia (53% vs 17%); anemia (26% vs 10%); thrombocytopenia (23% vs 9%); nausea (82% vs 77%); vomiting (57% vs 50%); fatigue (48% vs 42%); creatinine elevation (11% vs 10%); creatinine clearance decreased (16% vs 18%); conjunctivitis (5% vs 1%); anorexia (20% vs 14%); diarrhea (17% vs 8%); constipation (12% vs 7%); dyspepsia (5% vs 1%); dehydration (7% vs 1%); neuropathy-sensory (10% vs 10%); taste disturbance (8% vs 6%); rash (16% vs 5%); alopecia (11% vs 6%); and stomatitis/pharyngitis (23% vs 6%).

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For more complete information for Alimta, please see full [Prescribing Information](#) and [Patient Information](#).

About Lilly Oncology

For more than 50 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. (P-LLY)

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KEYTRUDA[®] is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Lilly Forward-Looking Statement

This press release contains "forward-looking statements" (as that term is defined in the United States Private Securities Litigation Reform Act of 1995) regarding ALIMTA and Lilly's oncology research program, and reflects Lilly's current beliefs. However, there are substantial risks and uncertainties in the process of drug research, development and commercialization. Among other risks, there can be no guarantee that these investigational combination regimens will receive regulatory approval, or, if approved, will achieve intended benefits or become commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ materially 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 for events occurring after the date of this release.

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