FDA Expands Lilly's ALIMTA® (pemetrexed) Label with Combination of KEYTRUDA® (pembrolizumab) and Platinum Chemotherapy for the First-Line Treatment of Metastatic Nonsquamous Non-Small Cell Lung Cancer

January 31, 2019

New approval based on Phase 3 KEYNOTE-189 results

INDIANAPOLIS, Jan. 31, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that the U.S. Food and Drug Administration (FDA) has granted approval for a new indication for ALIMTA® (pemetrexed for injection) in combination with KEYTRUDA® (pembrolizumab), developed and marketed by Merck (known as MSD outside the U.S. and Canada), and platinum chemotherapy for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. This indication is approved based on data from Merck's Phase 3 KEYNOTE-189 trial, which enrolled patients regardless of PD-L1 expression and had dual primary endpoints of overall survival (OS) and progression-free survival (PFS).

ALIMTA in combination with pembrolizumab and carboplatin was first approved in June 2018 under the FDA's accelerated approval process for the first-line treatment of patients with metastatic nonsquamous NSCLC, based on tumor response rates and PFS data from the Phase 2 study KEYNOTE-021 (Cohort G1). In accordance with the accelerated approval process, continued approval was contingent upon verification and description of clinical benefit, which has now been demonstrated in the KEYNOTE-189 trial and has resulted in the FDA converting the accelerated approval to full (regular) approval.

"KEYNOTE-189 demonstrated an exceptional effect of the ALIMTA-pembrolizumab-platinum chemotherapy combination in the first-line setting, offering significantly improved survival in patients with metastatic nonsquamous non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations," said Anne White, president, Lilly Oncology. "This new indication reinforces Lilly's continued commitment to providing practice-changing treatment options that can make a meaningful difference for people living with lung cancer."

ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed. See additional Important Safety Information below.

KEYNOTE-189 Trial Results

On August 20, 2018, Merck's pembrolizumab was approved by the FDA for this indication, based on data from the KEYNOTE-189 study, which demonstrated that treatment with ALIMTA in combination with pembrolizumab plus platinum-based chemotherapy resulted in significantly longer OS and PFS than ALIMTA plus platinum chemotherapy with placebo.

Efficacy Results

Endpoint	ALIMTA Pembrolizumab Platinum Chemotherapy n=410	ALIMTA Placebo Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Median in months (95% CI)	NR (NR, NR)	11.3 (8.7, 15.1)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.0001	
PFS		

Number (%) of patients with event	244 (60%)	166 (81%)
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.0001	
ORR		
Overall response rate‡ (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

*Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Response: Best objective response as confirmed complete response or partial response

§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status

NR = not reached

In the KEYNOTE-189 study, safety was evaluated in 405 patients who received ALIMTA in combination with pembrolizumab and platinum chemotherapy and 202 patients who received placebo, ALIMTA and platinum chemotherapy. ALIMTA was discontinued for adverse reactions in 23 percent of patients in the ALIMTA-pembrolizumab-platinum chemotherapy arm. The most common adverse reactions resulting in discontinuation of ALIMTA in this arm were acute kidney injury (3%) and pneumonitis (2%). Adverse reactions leading to the interruption of ALIMTA occurred in 49 percent of patients in the ALIMTA-pembrolizumab-platinum chemotherapy arm; the most common adverse reactions or laboratory abnormalities leading to interruption of ALIMTA in this arm (≥2%) were neutropenia (12%), anemia (7%), asthenia (4%), pneumonia (4%), thrombocytopenia (4%), increased blood creatinine (3%), diarrhea (3%), and fatigue (3%). Adverse reactions of any grade occurring in ≥20 percent of patients receiving ALIMTA in combination with pembrolizumab and platinum chemotherapy were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%) and pyrexia (20%).

KEYNOTE-189 Trial Design

Conducted by Merck, the KEYNOTE-189 trial (ClinicalTrials.gov, NCT02578680), a randomized, double-blind, placebo-controlled, Phase 3 study, evaluated ALIMTA in combination with pembrolizumab and cisplatin or carboplatin compared with ALIMTA in combination with placebo and cisplatin or carboplatin, in 616 untreated patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression. Patients had no sensitizing EGFR or ALK genomic tumor aberrations, and had not previously received systemic therapy for advanced disease. This was a treat-to-progression protocol, with both ALIMTA and pembrolizumab being used until progression or unacceptable toxicity (or 35 cycles for pembrolizumab)[1], and had dual primary endpoints of OS and PFS [assessed by blinded independent central review (BICR) per RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)]; secondary endpoints include overall response rate (ORR) and duration of response (DOR). Patients were randomized 2:1 to one of two treatment groups, as follows:

- ALIMTA (500 mg/m^2) (with vitamin supplementation) plus pembrolizumab (200 mg fixed dose every three weeks) plus cisplatin (75 mg/m^2) or carboplatin AUC 5 mg/mL/min on day one every three weeks (Q3W) for four cycles, followed by ALIMTA (500 mg/m^2) plus pembrolizumab 200 mg Q3W; or
- ALIMTA (500 mg/m^2) (with vitamin supplementation) plus saline placebo plus cisplatin (75 mg/m^2) or carboplatin AUC 5 mg/mL/min on day one every three weeks (Q3W) for four cycles, followed by ALIMTA (500 mg/m^2) plus placebo Q3W.

Patients on the control arm who experienced disease progression, verified by central independent review, were permitted to undergo treatment assignment unblinding and crossover to receive open-label pembrolizumab. The KEYNOTE-189 study was conducted in collaboration with Lilly.

About Lung Cancer

Lung cancer is the leading cause of cancer death in the U.S. and most other countries, killing nearly 1.7 million people worldwide each year.[2] In the U.S., lung cancer is responsible for approximately 25 percent of all cancer deaths, more than those from breast, colon and prostate cancers combined.[3] Stage IV non-small cell lung cancer (NSCLC) is a very difficult-to-treat cancer and the prognosis is poor for metastatic NSCLC.[4] NSCLC is much more common than other types of lung cancer and accounts for about 80 to 85 percent of all lung cancer cases.[5] For those people afflicted with NSCLC, about 70 percent have nonsquamous cell carcinoma, while about 30 percent have squamous cell carcinoma.[5]

About ALIMTA® (pemetrexed for injection)

ALIMTA is indicated in combination with pembrolizumab and platinum chemotherapy for the initial treatment of patients with metastatic nonsquamous non-small cell lung cancer, with no EGFR or ALK genomic tumor aberrations. For all FDA-approved indications for ALIMTA, please see full Prescribing Information.

IMPORTANT SAFETY INFORMATION FOR ALIMTA® (pemetrexed for injection)

CONTRAINDICATION

- ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed.

WARNINGS AND PRECAUTIONS

Myelosuppression and Increased Risk of Myelosuppression Without Vitamin Supplementation

- ALIMTA can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic

infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation.

- Prior to treatment with ALIMTA, patients must be instructed to initiate supplementation with oral folic acid. Intramuscular injections of vitamin B_{12} are also required prior to ALIMTA treatment. Folic acid and vitamin B_{12} supplementation should be continued during treatment and for 21 days after the last dose of ALIMTA as they may reduce the severity of treatment-related hematologic and gastrointestinal toxicities. Obtain a complete blood count at the beginning of each cycle. Do not administer ALIMTA until the ANC is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3. Permanently reduce ALIMTA in patients with an ANC of less than 500 cells/mm^3 or platelet count of less than 50,000 cells/mm^3 in previous cycles.
- In Studies JMDB and JMCH, among patients who received vitamin supplementation, incidence of Grade 3-4 neutropenia was 15% and 23%, the incidence of Grade 3-4 anemia was 6% and 4%, and incidence of Grade 3-4 thrombocytopenia was 4% and 5%, respectively. In Study JMCH, 18% of patients in the ALIMTA arm required red blood cell transfusions compared to 7% of patients in the cisplatin arm. In Studies JMEN, PARAMOUNT, and JMEI, where all patients received vitamin supplementation, incidence of Grade 3-4 neutropenia ranged from 3% to 5%, and incidence of Grade 3-4 anemia ranged from 3% to 5%.

Renal Failure

- ALIMTA can cause severe, and sometimes fatal, renal toxicity. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with ALIMTA.
- The incidences of renal failure in clinical studies in which patients received ALIMTA with cisplatin were 2.1% in Study JMDB and 2.2% in Study JMCH. The incidence of renal failure in clinical studies in which patients received ALIMTA as a single agent ranged from 0.4% to 0.6% (Studies JMEN, PARAMOUNT, and JMEI).
- Withhold ALIMTA in patients with a creatinine clearance of less than 45 mL/min.

Bullous and Exfoliative Skin Toxicity

- Serious and sometimes fatal, bullous, blistering, and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson Syndrome/toxic epidermal necrolysis, can occur with ALIMTA. Permanently discontinue ALIMTA for severe and life-threatening bullous, blistering, or exfoliating skin toxicity.

Interstitial Pneumonitis

- Serious interstitial pneumonitis, including fatal cases, can occur with ALIMTA treatment. Withhold ALIMTA for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, or fever pending diagnostic evaluation. If pneumonitis is confirmed, permanently discontinue ALIMTA.

Radiation Recall

- Radiation recall can occur with ALIMTA in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue ALIMTA for signs of radiation recall.

Increased Risk of Toxicity With Ibuprofen in Patients With Renal Impairment

- Exposure to ALIMTA is increased in patients with mild to moderate renal impairment who take concomitant ibuprofen, increasing the risks of adverse reactions of ALIMTA. In patients with creatinine clearances between 45 mL/min and 79 mL/min, avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA. If concomitant ibuprofen use cannot be avoided, monitor patients more frequently for ALIMTA adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity.

Embryo-Fetal Toxicity

- Based on findings from animal studies and its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and increased malformations at doses lower than the recommended human dose of 500 mg/m^2. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ALIMTA and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALIMTA and for 3 months after the final dose.

DRUG INTERACTIONS

- Ibuprofen increases exposure (AUC) of pemetrexed. In patients with creatinine clearance between 45 mL/min and 79 mL/min:

- Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA.
- Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

ADVERSE REACTIONS

- Severe adverse reactions (Grade 3-4) occurring in ≥20% of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) receiving ALIMTA in combination with pembrolizumab and platinum chemotherapy (carboplatin or cisplatin) versus ALIMTA with platinum chemotherapy + placebo for initial treatment (KEYNOTE-189), respectively, were fatigue (12% vs 6%); diarrhea (5% vs 3%); dyspnea (3.7% vs 5%); vomiting (3.7% vs 3%); nausea (3.5% vs 3.5%); rash (2% vs 2.5%); decreased appetite (1.5% vs 0.5%); constipation (1% vs 0.5%); and pyrexia (0.2% vs 0%).
- Common adverse reactions (all grades) occurring in ≥20% of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) receiving ALIMTA in combination with pembrolizumab and platinum chemotherapy (carboplatin or cisplatin) versus ALIMTA with platinum chemotherapy + placebo for initial treatment (KEYNOTE-189), respectively, were nausea (56% vs 52%); fatigue (56% vs 58%); constipation (35% vs 32%); diarrhea (31% vs 21%); decreased appetite (28% vs 30%); rash (25% vs 17%); vomiting (24% vs 23%); cough (21% vs 28%); dyspnea (21% vs 26%); and pyrexia (20% vs 15%).

USE IN SPECIFIC PATIENT POPULATIONS

- **Lactation**: There is no information regarding the presence of pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from ALIMTA, advise women not to breastfeed during treatment with ALIMTA and for one week after the last dose.
- **Males of Reproductive Potential**: ALIMTA may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible.
- **Pediatric Use**: The safety and effectiveness of ALIMTA in pediatric patients have not been established. Adverse reactions observed in pediatric patients studied were similar to those observed in adults.
- **Patients with Renal Impairment**: ALIMTA is primarily excreted by the kidneys. Decreased renal function results in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function. No dose is recommended for patients with creatinine clearance less than 45 mL/min.
- **Geriatric**: The incidences of Grade 3-4 anemia, fatigue, thrombocytopenia, hypertension, and neutropenia were higher in patients 65 years of age and older as compared to younger patients: in at least one of five randomized clinical trials.

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For safety and dosing guidelines for ALIMTA, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the full Prescribing Information and Patient Prescribing 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 create medicines that 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 http://newsroom.lilly.com/social-channels. P-LLY

Lilly Forward-Looking Statement
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about ALIMTA as a treatment for patients with nonsquamous 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 and commercialization. Among other things, there can be no guarantee that ALIMTA will receive additional regulatory approvals or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

[1] Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med. 2018;378:2078-2092.

[2] International Agency for Research on Cancer. 2018 Lung Cancer Fact Sheet. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-

fact-sheet.pdf. Accessed January 14, 2019.

3 American Cancer Society. Cancer Facts and Figures 2018. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed January 14, 2019.

4 American Cancer Society. Non-Small Cell Lung Cancer Survival Rates, by Stage. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed January 14, 2019.

5 American Cancer Society. What is non-small cell lung cancer? Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer. Accessed January 14, 2019.

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