



November 19, 2015

Lilly and Merck Expand Immuno-oncology Collaboration with Phase III Nonsquamous Non-Small Cell Lung Cancer Trial

INDIANAPOLIS and KENILWORTH, N.J., Nov. 19, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced the extension of an existing collaboration to evaluate the safety and efficacy of the combination of Lilly's ALIMTA® (pemetrexed for injection) and Merck's KEYTRUDA® (pembrolizumab) in a pivotal Phase III study in first-line nonsquamous non-small cell lung cancer (NSCLC). The study will be sponsored by Merck and will be open to patients with NSCLC in the first-line setting, regardless of PD-L1 status. Financial details of the collaboration were not disclosed.

The expansion of this oncology clinical trial collaboration comes following the release of encouraging data from a Phase I study, presented earlier this year at the 16th World Congress on Lung Cancer, which evaluated pemetrexed, carboplatin and pembrolizumab in first-line nonsquamous NSCLC.

Pemetrexed is a leading therapeutic option used in combination with platinum-based therapies in this setting, making it an ideal candidate for combination studies with immunotherapy treatments. Pembrolizumab 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 - and is currently approved as a single-agent therapy for certain types of NSCLC.

"The extension of our immuno-oncology collaboration with Merck reinforces our combination-focused strategy, which we believe has the potential to help this patient population where there is a significant unmet need," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "Building upon this scientific partnership represents our shared, strong commitment to improve the lives of those living with cancer."

"Based on the data for ALIMTA, we believe this collaboration with Lilly has great potential to help even more patients," said Roger Dansey, M.D., therapeutic area head and senior vice president, oncology late stage development, Merck Research Laboratories. "We look forward to continuing our collaboration with Lilly across all of these trials - including the registrational Phase III all-comers trial for NSCLC."

In addition to the studies of pemetrexed and pembrolizumab in first-line nonsquamous NSCLC, other ongoing trials from the [original agreement](#) between Lilly and Merck, through a subsidiary, include:

- A Phase I/II study examining the combination of ramucirumab with pembrolizumab in multiple tumors.
- A Phase I/II study examining the combination of necitumumab with pembrolizumab in NSCLC.

NOTES TO EDITORS

About KEYTRUDA® (pembrolizumab) Injection 100 mg

KEYTRUDA is indicated in the United States at a dose of 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. KEYTRUDA is also indicated at the same dosing for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. These indications are approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Selected Important Safety Information for KEYTRUDA® (pembrolizumab)

Pneumonitis, including fatal cases, occurred in patients receiving KEYTRUDA. Pneumonitis occurred in 12 (2.9%) of 411 melanoma patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA. Pneumonitis occurred in 19 (3.5%) of 550 patients with NSCLC, including Grade 2 (1.1%), 3 (1.3%), 4 (0.4%), or 5 (0.2%) pneumonitis in patients, receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected

pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients with melanoma, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving KEYTRUDA.

Colitis occurred in 4 (0.7 %) of 550 patients with NSCLC, including Grade 2 (0.2%) or 3 (0.4%) colitis in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

Hepatitis occurred in patients receiving KEYTRUDA. Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients with melanoma, including a Grade 4 case in 1 (0.2%) patient, receiving KEYTRUDA. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Hypophysitis occurred in 2 (0.5%) of 411 patients with melanoma, including a Grade 2 case in 1 and a Grade 4 case in 1 (0.2% each) patient, receiving KEYTRUDA. Hypophysitis occurred in 1 (0.2 %) of 550 patients with NSCLC, which was Grade 3 in severity. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as indicated. Withhold KEYTRUDA for Grade 2 and withhold or discontinue for Grade 3 or Grade 4 hypophysitis.

Hyperthyroidism occurred in 5 (1.2%) of 411 patients with melanoma, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving KEYTRUDA. Hypothyroidism occurred in 34 (8.3%) of 411 patients with melanoma, including a Grade 3 case in 1 (0.2%) patient, receiving KEYTRUDA. Hyperthyroidism occurred in 10 (1.8%) of 550 patients with NSCLC, including Grade 2 (0.7%) or 3 (0.3%). Hypothyroidism occurred in 38 (6.9%) of 550 patients with NSCLC, including Grade 2 (5.5%) or 3 (0.2%). Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or Grade 4 hyperthyroidism.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has occurred in patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia.

Nephritis occurred in patients receiving KEYTRUDA. Nephritis occurred in 3 (0.7%) patients with melanoma, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 nephritis.

Other clinically important immune-mediated adverse reactions can occur. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement of the adverse reaction to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following steroid taper. Permanently discontinue KEYTRUDA for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Across clinical studies with KEYTRUDA, the following clinically significant, immune-mediated adverse reactions have occurred: bullous pemphigoid and Guillain-Barré syndrome. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients with melanoma treated with KEYTRUDA: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 550 patients with NSCLC treated with KEYTRUDA: rash, vasculitis, hemolytic anemia, serum sickness, and myasthenia gravis.

Infusion-related reactions, including severe and life-threatening reactions, have occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For severe or life-threatening reactions, stop infusion and permanently discontinue KEYTRUDA.

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of KEYTRUDA.

Among the 411 patients with metastatic melanoma, KEYTRUDA was discontinued for adverse reactions in 9% of 411 patients. Adverse reactions, reported in at least two patients, that led to discontinuation of KEYTRUDA were: pneumonitis, renal failure, and pain. Serious adverse reactions occurred in 36% of patients. The most frequent serious adverse reactions, reported in 2% or more of patients, were renal failure, dyspnea, pneumonia, and cellulitis. The most common adverse reactions (reported in at least 20% of patients) were fatigue (47%), cough (30%), nausea (30%), pruritus (30%), rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%), and diarrhea (20%).

Among the 550 patients with metastatic NSCLC, KEYTRUDA was discontinued due to adverse reactions in 14% of patients. Serious adverse reactions occurred in 38% of patients. The most frequent serious adverse reactions reported in 2% or more of patients were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis. The most common adverse reactions (reported in at least 20% of patients) were fatigue (44%), decreased appetite (25%), dyspnea (23%), and cough (29%).

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA.

It is not known whether KEYTRUDA is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

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 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 ALIMTA plus cisplatin 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.

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 B₁₂ injections while you are getting treatment with ALIMTA. You will get your first vitamin B₁₂ 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" which 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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About Lilly Oncology

For more than fifty 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)

Merck's Focus on Cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck Oncology, helping people fight cancer is our passion and supporting accessibility to our cancer medicines is our commitment. Our focus is on pursuing research in immuno-oncology and we are accelerating every step in the journey - from lab to clinic - to potentially bring new hope to people with cancer. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

Today's Merck is a global health care leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on [Twitter](#), [Facebook](#), [YouTube](#) and [LinkedIn](#).

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 the research collaboration between Lilly and Merck evaluating pemetrexed and pembrolizumab. This press release 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.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2014 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see Prescribing Information for KEYTRUDA (pembrolizumab) at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf and the Medication Guide for KEYTRUDA at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf

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