Tyvyt (Sintilimab Injection) Combined with ALIMTA (Pemetrexed) and Platinum Met Predefined Primary Endpoint in Phase 3 ORIENT-11 Study as First-Line Therapy in Nonsquamous NSCLC

January 14, 2020

INDIANAPOLIS, Jan. 13, 2020 /PRNewswire/ -- Today, Eli Lilly and Company (NYSE: LLY) jointly announced with Innovent Biologics, Inc. the results of a Phase 3 study in China; the ORIENT-11 trial of Tyvyt® (sintilimab injection) in combination with ALIMTA® (pemetrexed) and platinum in first-line advanced or recurrent nonsquamous non-small cell lung cancer (nsqNSCLC), without sensitive EGFR mutation or ALK rearrangement, met the predefined primary endpoint of progression-free survival (PFS) in an interim analysis.

Based on the interim analysis conducted by the Independent Data Monitoring Committee (IDMC), sintilimab in combination with ALIMTA and platinum demonstrated a statistically significant improvement in PFS compared with placebo in combination with ALIMTA and platinum, which met the pre-defined efficacy criteria. The safety profile of sintilimab in this trial was consistent with previously reported studies, and no new safety signals were identified.

Relevant data will be presented at an upcoming medical conference. Based on the IDMC recommendations, Lilly and Innovent will initiate regulatory discussions for registration with the National Medical Products Administration (NMPA) in China in the near future.

Professor Li Zhang, Head of the Department of Internal Medicine, Sun Yat-sen University Cancer Center, stated: "In 2019, the National Cancer Center published Chinese data on lung cancer from 2015, showing an incidence of 20 percent and a mortality rate of about 27 percent, ranking it first among all cancer types. Patients who have nsqNSCLC without sensitive EGFR mutation or ALK rearrangement need more treatment options. Treatment with an anti-PD-1 monoclonal antibody in combination with chemotherapy may bring a greater survival benefit to this patient population. We are glad to see that these findings from this trial of sintilimab met the predefined primary endpoint in the interim analysis."

"We are excited about these results, which show Tyvyt plus ALIMTA and platinum significantly delayed disease progression in this patient population. This study is another example of the joint commitment from Lilly and Innovent to provide new treatment options to patients with lung cancer," said Dr. Wang Li, Senior Vice-President of Lilly China and Head of Lilly China Drug Development and Medical Affairs. "We would like to thank the patients, investigators and clinical trial sites that are participating in the study, and our colleagues from Innovent. We look forward to bringing this new treatment option to lung cancer patients in China."

Dr. Hui Zhou, Vice President and Head of Oncology Strategy and Medical Sciences, Innovent, said: "So far, Tyvyt is the only anti-PD-1 monoclonal antibody included in the New Catalogue of the National Reimbursement Drug List. It was officially approved by the NMPA on December 24, 2018 for the treatment of relapsed or refractory classic Hodgkin's lymphoma after at least second-line system chemotherapy. Currently, we have several ongoing Phase 3 randomized clinical trials in lung cancer. With the encouraging result of ORIENT-11 we anticipate that sintilimab has the potential to benefit more patients with lung cancer and provide them more time with their families."

About ORIENT-11 Trial
ORIENT-11 is a randomized, double-blind, Phase 3 clinical trial to evaluate the efficacy and safety of Tyvyt (sintilimab injection) or placebo in combination with ALIMTA and platinum as first-line therapy for advanced or recurrent nsqNSCLC without sensitive EGFR mutation or ALK rearrangement (ClinicalTrials.gov, NCT03607539). The primary endpoint is progression-free survival (PFS) assessed by the Independent Radiographic Review Committee (IRRC) based on RECIST v1.1. The other secondary endpoints include overall survival (OS) and safety profile.

A total of 397 subjects have been enrolled in the ORIENT-11 trial and randomized in a 2:1 ratio to receive either sintilimab 200mg or placebo in combination with ALIMTA and platinum every three weeks for up to four cycles, followed by either sintilimab or placebo plus ALIMTA maintenance therapy. The subjects will receive treatment until radiographic disease progression, unacceptable toxicity or any other conditions that require treatment discontinuation. Conditional crossover is permitted.

About nsqNSCLC
Lung cancer is a malignancy with the highest morbidity and mortality rates in China. NSCLC accounts for about 80 percent to 85 percent of lung cancers. Approximately 70 percent of NSCLC are locally advanced or metastatic at initial diagnosis, rendering the patients with no chance of radical resection. Meanwhile, even after radical surgery patients still have a high chance of recurrence and eventually die from disease progression. About 70 percent of NSCLC in China are nonsquamous subtype and 50 percent of nsqNSCLC are without sensitive EGFR mutation or ALK rearrangement. These patients do not respond well to targeted therapy and there are limited treatment options available to them.

About Tyvyt® (Sintilimab Injection)
Tyvyt® (sintilimab injection), an innovative drug jointly developed in China by Innovent and Lilly, has been granted marketing approval by the NMPA for relapsed or refractory classic Hodgkin's lymphoma after at least second-line system chemotherapy, and is included in the 2019 Guidelines of Chinese Society of Clinical Oncology for Lymphoid Malignancies. Tyvyt is the only PD-1 inhibitor with global quality that has been included in the new Catalogue of the National Reimbursement Drug List (NRDL) in November 2019.

Tyvyt is a type of immunoglobulin G4 monoclonal antibody, which binds to PD-1 molecules on the surface of T-cells, blocks the PD-1/ PD-Ligand 1 (PD-L1) pathway and reactivates T-cells to kill cancer cells. Innovent is currently conducting more than 20 clinical studies for sintilimab injection to

evaluate its safety and efficacy in a wide variety of cancer indications, including eight registration or pivotal clinical trials.

Tyvyt (sintilimab injection) is not an approved product in the United States. ALIMTA® (pemetrexed for injection) is not approved for use in combination with Tyvyt in the United States.

U.S. INDICATIONS FOR ALIMTA® (pemetrexed for injection)
ALIMTA is indicated:

- in combination with pembrolizumab and platinum chemotherapy for the initial treatment of patients with nonsquamous metastatic non-small cell lung cancer (mNSCLC) with no EGFR or ALK genomic tumor aberrations.
- in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC).
- as a single agent for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- as a single agent for the treatment of patients with recurrent metastatic nonsquamous non-small cell lung cancer (NSCLC) after prior chemotherapy. Limitation of Use: ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.
- in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma (MPM) whose disease is unresectable or who are otherwise not candidates for curative surgery.

U.S. 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.

For U.S. safety and dosing guidelines for ALIMTA, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the full U.S. Prescribing Information and Patient Prescribing Information.

ALIMTA® is a registered trademark owned by or licensed to Eli Lilly and Company, its subsidiaries, or affiliates.

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 health care 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 lilly.com and lilly.com/newsroom.

About Innovent
Inspired by the spirit of "Start with Integrity, Succeed through Action," Innovent's mission is to develop and commercialize high quality biopharmaceutical products that are affordable to ordinary people. Established in 2011, Innovent is committed to developing, manufacturing and commercializing high quality innovative medicines for the treatment of oncology, autoimmune, metabolic and other major diseases. On October 31, 2018, Innovent was listed on the Main Board of the Stock Exchange of Hong Kong Limited with the stock code: 01801.HK.

Since it was founded, Innovent has developed a fully-integrated platform which includes R&D, CMC (Chemistry, Manufacturing, and Controls), clinical development and commercialization capabilities. Leveraging the platform, the company has built a robust pipeline of 21 innovative assets in the fields of oncology, autoimmune, metabolic diseases and other major therapeutic areas, with sixteen in clinical development, five in Phase III clinical trials, three NDAs under review by NMPA with priority review status, while Tyvyt®, officially approved for marketing in China in 2018, has been the only PD-1 inhibitor included in the NRDL since 2019.

Innovent has built an international team of advanced talents in high-end biological drug development and commercialization, including many overseas experts. The company has also entered into strategic collaborations with Eli Lilly and Company, Adimab, Incyte, Hanmi and other international pharmaceutical companies. Innovent strives to work with all relevant parties to help advance China's biopharmaceutical industry, improve drug availability to ordinary people and enhance the quality of the patients' lives. For more information, please visit：www.innoventbio.com.

About Innovent Biologics' strategic cooperation with Eli Lilly and Company
Eli Lilly and Company launched a program focusing on biological medicine co-development with Innovent Biologics in March 2015 – a groundbreaking partnership between a Chinese pharmaceutical company and a multinational pharmaceutical company. Under the agreement, Lilly and Innovent Biologics will co-develop and commercialize oncology medicines, including Tyvyt in China. In October 2015, the two companies announced the extension of their existing collaboration to include co-development of three additional antibodies targeting oncology indications. Its collaboration with Lilly indicates that Innovent Biologics has established a comprehensive level of cooperation between China's innovative pharmaceuticals sector and the international pharmaceuticals sector in fields such as R&D, pipeline quality and commercial.

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 the ORIENT-11 trial and Tyvyt® (sintilimab injection) in combination with ALIMTA®(pemetrexed) and platinum in first-line advanced or recurrent 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 Tyvyt will receive regulatory approval for first-line advanced or recurrent nonsquamous non-small cell lung cancer or will 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.

Contact:

Media:
Innovent: pr@innoventbio.com; +86 512-6956 6088
Lilly: Carole Copeland; Carole_Copeland@Lilly.com; (317) 610-6196

Investors:
Innovent: ir@innoventbio.com; +86 512-6956 6088
Lilly: Kevin Hern; hern_kevin_r@lilly.com; (317) 277-1838

SOURCE Eli Lilly and Company

Related Links

http://www.lilly.com