Lilly and Innovent Announce Global Expansion of TYVYT Licensing Agreement

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INDIANAPOLIS and SUZHOU, China, Aug. 18, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Innovent Biologics, Inc. (HKEX: 01801) today announced a global expansion of their strategic alliance for TYVYT® (sintilimab injection), an anti-PD-1 monoclonal antibody immuno-oncology medicine that was co-developed by Innovent and Lilly in China.

In 2019, Lilly and Innovent began commercializing TYVYT in China after being granted marketing approval for relapsed or refractory classic Hodgkin's lymphoma after at least two lines of systemic chemotherapy. TYVYT is the only PD-1 inhibitor to be included in China's National Reimbursement Drug List (NRDL) and is included in the 2019 Guidelines of Chinese Society of Clinical Oncology for Lymphoid Malignancies.

Lilly and Innovent currently co-commercialize TYVYT in China. Under the terms of the expanded license agreement, Lilly will obtain an exclusive license for TYVYT for geographies outside of China and plans to pursue registration of TYVYT in the U.S. and other markets. In return, Innovent will receive an upfront payment of $200 million and will be eligible for up to $825 million in potential development and commercial milestones, as well as tiered double-digit royalties on net sales. Both companies will also retain the right to study TYVYT in combination with other medicines as part of their own clinical programs.

The two companies are also studying TYVYT as a potential therapy in non-squamous non-small cell lung cancer (NSCLC) and several other types of cancer. Earlier this month, the two companies released encouraging interim analysis data from ORIENT-11 at the IASLC World Conference on Lung Cancer 2020 Virtual Presidential Symposium. ORIENT-11 is a randomized, double-blind, Phase 3 clinical trial evaluating TYVYT or placebo in combination with Alimta® (pemetrexed for injection) and platinum chemotherapy as a first-line treatment for advanced or recurrent non-squamous NSCLC without sensitizing EGFR mutations or ALK rearrangements. Based on the interim analysis conducted by the Independent Data Monitoring Committee, TYVYT in combination with Alimta and platinum chemotherapy demonstrated a statistically significant improvement in progression-free survival compared with placebo in combination with Alimta and platinum chemotherapy, which met the pre-defined efficacy criteria. A supplemental New Drug Application (sNDA) for this indication is under regulatory review in China. The companies look forward to future submissions with the U.S. Food and Drug Administration and other regulatory agencies for this and other indications.

"We are thrilled to expand on our successful China TYVYT collaboration with Lilly to now include markets outside of China. This agreement also marks the first solid step in getting Innovent's innovative portfolio into the global market," said Michael Yu, Ph.D., Founder, Chairman and CEO of Innovent. "We are confident that pairing Lilly's global commercial expertise with TYVYT's clinical profile will further accelerate our mission, benefitting patients globally."

"Lilly Oncology is dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them," said Anne White, president of Lilly Oncology. "Our alliance with Innovent successfully brought TYVYT to market in China. Through this expansion of our collaboration, we hope to make TYVYT accessible to patients globally. We believe TYVYT could deliver significant value to people living with cancer around the world and we intend to continue to study its potential across tumor types."

This transaction is subject to customary closing conditions, including clearance under the Hart-Scott-Rodino Antitrust Improvements Act. The transaction will be reflected in Lilly's reported results and financial guidance according to Generally Accepted Accounting Principles (GAAP). There will be no change to Lilly's 2020 non-GAAP earnings per share guidance as a result of this transaction.

About TYVYT (Sintilimab Injection)
TYVYT (sintilimab injection) is an innovative drug with global quality standards jointly developed by Innovent and Lilly in China. TYVYT has been granted marketing approval by the NMPA for the treatment of relapsed or refractory classic Hodgkin's lymphoma after at least two lines of systemic chemotherapy and was included in the 2019 Guidelines of Chinese Society of Clinical Oncology for Lymphoid Malignancies.

In April 2020, the NMPA accepted the supplemental new drug application for TYVYT in combination with ALIMTA (pemetrexed for injection) and platinum as first-line therapy in advanced or recurrent non-squamous non-small cell lung cancer (NSCLC). In May 2020, TYVYT combined with gemcitabine and platinum chemotherapy met the predefined primary endpoint in the Phase 3 ORIENT-12 study as first-line therapy in patients with locally advanced or metastatic squamous NSCLC. TYVYT monotherapy met the primary endpoint in the ORIENT-2 study as second-line therapy in patients with advanced or metastatic esophageal squamous cell carcinoma as well. In August 2020, the NMPA accepted the sNDA for TYVYT in combination with gemcitabine and platinum chemotherapy as first-line therapy in patients with locally advanced or metastatic squamous NSCLC.

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 with TYVYT to evaluate its safety and efficacy in a wide variety of cancer indications, including more than 10 registrational 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 B12 are also required prior to ALIMTA treatment. Folic acid and vitamin B12 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/mm3 and platelet count is at least 100,000 cells/mm3. Permanently reduce ALIMTA in patients with an ANC of less than 500 cells/mm3 or platelet count of less than 50,000 cells/mm3 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/m2. 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 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.

About Innovent Biologics' strategic cooperation with Eli Lilly and Company
Innovent entered into a strategic collaboration with Lilly focusing on biological medicine in March 2015 – a groundbreaking partnership between a Chinese pharmaceutical company and a multinational pharmaceutical company. Under the agreement, Innovent and Lilly are co-developing and commercializing oncology medicines, including TYVYT (sintilimab injection) 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. In August 2019, Innovent entered into an additional licensing agreement with Lilly to develop and commercialize a potentially global best-in-class diabetes medicine in China. In August

2020, Innovent and Lilly announced an expansion of their strategic alliance for TYVYT. Its collaboration with Lilly indicates that Innovent has established a comprehensive level of cooperation between China's innovative pharmaceuticals sector and the international pharmaceuticals sector in areas such as R&D, CMC, clinical development and commercialization.

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 cancer, metabolic, autoimmune 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 its inception, Innovent has developed a fully-integrated multi-functional 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 23 valuable assets in the fields of cancer, metabolic, autoimmune diseases and other major therapeutic areas, with 19 in clinical development, 5 in Phase 3 or pivotal clinical trials, 2 under NDA reviews with priority review status by the NMPA, while 2 products, TYVYT® (sintilimab injection) and BYVASDA® (bevacizumab injection), officially approved for marketing in China. TYVYT® has been the only PD-1 inhibitor included in the NRDL since 2019.

Innovent has built an international team expereinced in cutting-edge biological drug development and commercialization, including many overseas experts. The company has also entered into strategic collaborations with Eli Lilly, Adimab, Incyte, Alector, MD Anderson Cancer Center, Hanmi and other international partners. For more information, please visit: www.innoventbio.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. C-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 benefits of a license agreement between Lilly and Innovent, and reflects Lilly's current beliefs. However, as with any such undertaking, there are substantial risks and uncertainties in the process of drug development and commercialization. Among other things, there can be no guarantee that Lilly will realize the expected benefits of the agreement, or that TYVYT will continue to be commercially successful in China or receive regulatory approvals or achieve commercial success elsewhere in the world. For a further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see Lilly's most recent Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

Alimta® (pemetrexed for injection, Lilly)
TYVYT® (sintilimab injection, Innovent)

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