January 13, 2015

Bristol-Myers Squibb and Lilly Enter Clinical Collaboration Agreement to Evaluate Opdivo (nivolumab) in Combination with Galunisertib in Advanced Solid Tumors

NEW YORK & INDIANAPOLIS--(BUSINESS WIRE)-- Bristol-Myers Squibb Company (NYSE:BMY) and Eli Lilly and Company (NYSE:LLY) announced today a clinical trial collaboration to evaluate the safety, tolerability and preliminary efficacy of Bristol-Myers Squibb's immunotherapy *Opdivo* (nivolumab) in combination with Lilly's galunisertib (LY2157299). The Phase 1/2 trial will evaluate the investigational combination of *Opdivo* and galunisertib as a potential treatment option for patients with advanced (metastatic and/or unresectable) glioblastoma, hepatocellular carcinoma and non-small cell lung cancer.

Opdivo is a human programmed death receptor-1 (PD-1) blocking antibody that binds to the PD-1 receptor expressed on activated T-cells. Galunisertib (pronounced gal ue" ni ser'tib) is a TGF beta R1 kinase inhibitor that *in vitro* selectively blocks TGF beta signaling. TGF beta promotes tumor growth, suppresses the immune system and increases the ability of tumors to spread in the body. This collaboration will address the hypothesis that co-inhibition of PD-1 and TGF beta negative signals may lead to enhanced anti-tumor immune responses than inhibition of either pathway alone.

"Advanced solid tumors represent a serious unmet medical need among patients with cancer," said Michael Giordano, senior vice president, Head of Development, Oncology, Bristol-Myers Squibb. "Our clinical collaboration with Lilly underscores Bristol-Myers Squibb's continued commitment to explore combination regimens from our immuno-oncology portfolio with other mechanisms of action that may accelerate the development of new treatment options for patients."

"Combination therapies will be key to addressing tumor heterogeneity and the inevitable resistance that is likely to develop to even the most promising new tailored therapies," said Richard Gaynor, M.D., senior vice president, Product Development and Medical Affairs, Lilly Oncology. "To that end, having multiple cancer pathways and technology platforms will be critical in an era of combinations to ensure sustainability beyond any single asset."

The study will be conducted by Lilly. Additional details of the collaboration were not disclosed.

About *Opdivo* (nivolumab)

The U.S. Food and Drug Administration (FDA) approved *Opdivo* (nivolumab) injection, for intravenous use. *Opdivo* is a PD-1 blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following *Yervoy* (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Bristol-Myers Squibb has a broad, global development program to study *Opdivo* in multiple tumor types consisting of more than 50 trials - as monotherapy or in combination with other therapies - in which more than 7,000 patients have been enrolled worldwide.

About Galunisertib

Galunisertib (pronounced gal ue" ni ser'tib) is Lilly's TGF beta R1 kinase inhibitor that *in vitro* selectively blocks TGF beta signaling. TGF beta promotes tumors growth, suppresses the immune system, and increases the ability of tumors to spread in the body.

Immune function is suppressed in cancer patients, and TGF beta worsens immunosuppression by enhancing the activity of immune cells called T regulatory cells. TGF beta also reduces immune proteins, further decreasing immune activity in patients

Galunisertib is currently under investigation as an oral treatment for advanced/metastatic malignancies, including Phase 2 evaluation in hepatocellular carcinoma, myelodysplastic syndromes (MDS), glioblastoma, and pancreatic cancer.

OPDIVO IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis

- Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 574 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.9% (5/574) of patients

receiving OPDIVO; no cases occurred in Trial 1. In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis occurred in 2.2% (6/268) of patients receiving OPDIVO; one with Grade 3 and five with Grade 2. Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue OPDIVO for Grade 3 or 4 and withhold OPDIVO until resolution for Grade 2.

Immune-Mediated Colitis

- In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis occurred in 2.2% (6/268) of patients receiving OPDIVO; five with Grade 3 and one with Grade 2. Monitor patients for immune-mediated colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO for Grade 2 or 3. Permanently discontinue OPDIVO for Grade 4 colitis or recurrent colitis upon restarting OPDIVO.

Immune-Mediated Hepatitis

- In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs 12%), alkaline phosphatase (22% vs 13%), ALT (16% vs 5%), and total bilirubin (9% vs 0). Immune-mediated hepatitis occurred in 1.1% (3/268) of patients receiving OPDIVO; two with Grade 3 and one with Grade 2. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4 immune-mediated hepatitis.

Immune-Mediated Nephritis and Renal Dysfunction

- In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients. Monitor patients for elevated serum creatinine prior to and periodically during treatment. For Grade 2 or 3 serum creatinine elevation, withhold OPDIVO and administer corticosteroids; if worsening or no improvement occurs, permanently discontinue OPDIVO. Administer corticosteroids for Grade 4 serum creatinine elevation and permanently discontinue OPDIVO.

Immune-Mediated Hypothyroidism and Hyperthyroidism

- In Trial 1, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism.

Other Immune-Mediated Adverse Reactions

- In Trial 1, the following clinically significant, immune-mediated adverse reactions occurred in less than 1% of OPDIVO-treated patients: pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis. Across clinical trials of OPDIVO administered at doses 3 mg/kg and 10 mg/kg, additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillian-Barré syndrome, and myasthenic syndrome. Based on the severity of adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy.

Embryofetal Toxicity

- Based on its mechanism of action, OPDIVO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO.

Lactation

- It is not known whether OPDIVO is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO, advise women to discontinue breastfeeding during treatment.

Serious Adverse Reactions

- Serious adverse reactions occurred in 41% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in

42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to < 5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.

Common Adverse Reactions

The most common adverse reaction (≥20%) reported with OPDIVO was rash (21%).

Please see US Full Prescribing Information for OPDIVO.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

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 http://newsroom.lilly.com/social-channels.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that this investigational combination regimen will receive regulatory approval, or, if approved, that it will become a commercially successful product. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2013 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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 Bristol-Myers Squibb and Lilly. 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 this investigational combination regimen will receive regulatory approval, or, if approved, that it will achieve intended benefits or become a commercially successful product. 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.

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