FDA Grants Priority Review to Merck’s Supplemental Biologics License Application (sBLA) for KEYTRUDA® (pembrolizumab) for Treatment of Recurrent or Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

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Data Supporting Application to Be Presented at 2017 ASCO Annual Meeting

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that the U.S. Food and Drug Administration (FDA) has accepted for review a supplemental Biologics License Application (sBLA) for KEYTRUDA® (pembrolizumab), the company’s anti-PD-1 therapy, seeking approval for treatment of patients with recurrent or advanced gastric or gastroesophageal junction adenocarcinoma who have already received two or more lines of chemotherapy. The FDA granted Priority Review with a PDUFA, or target action, date of Sept. 22, 2017.

“An estimated nearly one-hundred-thousand people are living with gastric cancer in the U.S., yet little progress has been made in bringing forward new treatment options to these patients for whom chemotherapy has long been the standard of care,” said Dr. Roger Dansey, senior vice president and therapeutic area head, oncology late-stage development, Merck Research Laboratories. “We look forward to working with the FDA to bring KEYTRUDA to people with gastric cancer who have progressed after receiving chemotherapy and are in urgent need of another option.”

The application submitted to the FDA is seeking approval for KEYTRUDA monotherapy in previously treated patients at a fixed dose of 200 mg administered intravenously every three weeks. The application is based on data from cohort one of the phase 2 KEYNOTE-059 trial investigating KEYTRUDA in heavily pretreated patients with recurrent or advanced gastric or gastroesophageal junction adenocarcinoma that has progressed after two or more lines of chemotherapy. Data from cohort one of KEYNOTE-059 will be presented at the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, June 2 – 6, 2017 during an oral session on Sunday, June 4 at 9:00 a.m. - 9:12 a.m. CDT (Location: Hall D2).

Merck is committed to investigating new approaches across the spectrum of cancers with more than 500 clinical trials evaluating KEYTRUDA (pembrolizumab) in more than 30 tumor types, including multiple gastrointestinal cancers like gastric cancer. Specific to gastric cancer, Merck’s broad clinical development program encompasses all stages of advanced disease and is investigating KEYTRUDA as monotherapy and in combination with other cancer treatments across multiple lines of therapy. To date, the program includes four gastric cancer registration-enabling studies and numerous other gastrointestinal cancer studies are underway.

About Gastric Cancer

Gastric cancer, also called stomach cancer, is a type of cancer that begins in the stomach and tends to develop slowly over many years. Most gastric cancers are adenocarcinomas, which develop from the cells of the innermost lining (mucosa) of the stomach. Risk factors for gastric cancer include gender, age, ethnicity, geography and infection with Helicobacter pylori. Worldwide, gastric cancer is the fifth most common type of cancer and the third leading cause of cancer death. Each year there are approximately 952,000 newly diagnosed cases of gastric cancer resulting in approximately 723,000 deaths worldwide. It is estimated that in 2017, more than 10,000 people will die from gastric cancer in the U.S. alone.

About KEYTRUDA® (pembrolizumab) Injection

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body’s immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that 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.

Studies of KEYTRUDA – from the largest immuno-oncology program in the industry with more than 500 trials – include a wide
KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA (pembrolizumab) for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including
Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%) colitis. 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.

KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%) hepatitis. 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.

KEYTRUDA can cause hypophysitis. Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%) hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2; withhold or discontinue for Grade 3 or 4 hypophysitis.

KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis. Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and 3 (0.1%) hyperthyroidism. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and 3 (0.1%) hypothyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. 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 4 hyperthyroidism.

KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

KEYTRUDA (pembrolizumab) can cause immune-mediated nephritis. Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. 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.

KEYTRUDA can cause other clinically important immune-mediated adverse reactions. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology and exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), exfoliative dermatitis, bullous pemphigoid, rash (1.4%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocarditis were reported in other clinical trials, including classical Hodgkin lymphoma, and postmarketing use.

Solid organ transplant rejection has been reported in postmarketing use of KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider benefit of treatment with KEYTRUDA vs the risk of possible organ rejection in these patients.

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For Grade 3 or 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with chl who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Based on its mechanism of action, KEYTRUDA (pembrolizumab) 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.

In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polynephropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA (pembrolizumab) occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions with KEYTRUDA vs ipilimumab were fatigue (28% vs 28%), diarrhea (26% with KEYTRUDA), rash (24% vs 23%), and nausea (21% with KEYTRUDA). Corresponding incidence rates are listed for ipilimumab only for those adverse reactions that occurred at the same or lower rate than with KEYTRUDA.
In KEYNOTE-002, KEYTRUDA was discontinued due to adverse reactions in 12% of 357 patients with advanced melanoma; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculopapular rash (1%). The most common adverse reactions with KEYTRUDA vs chemotherapy were fatigue (43% with KEYTRUDA), pruritus (28% vs 8%), rash (24% vs 8%), constipation (22% vs 20%), nausea (22% with KEYTRUDA), diarrhea (20% vs 20%), and decreased appetite (20% with KEYTRUDA). Corresponding incidence rates are listed for chemotherapy only for those adverse reactions that occurred at the same or lower rate than with KEYTRUDA.

KEYTRUDA monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC. The most common adverse event resulting in permanent discontinuation of KEYTRUDA (pembrolizumab) was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). The most common adverse reactions (occurring in at least 20% of patients and at a higher incidence than with docetaxel) were decreased appetite (25% vs 23%), dyspnea (23% vs 20%), and nausea (20% vs 18%).

When KEYTRUDA was administered in combination with pemetrexed and carboplatin, KEYTRUDA was discontinued in 10% of 59 patients. The most common adverse reaction resulting in discontinuation of KEYTRUDA (≥2%) was acute kidney injury (3.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 39% of patients; the most common (≥2%) were fatigue (8%), neutrophil count decreased (8%), anemia (5%), dyspnea (3.4%), and pneumonitis (3.4%). The most common adverse reactions (≥20%) with KEYTRUDA compared to carbo/pem alone were fatigue (71% vs 50%), nausea (68% vs 56%), constipation (51% vs 37%), rash (42% vs 21%), vomiting (39% vs 27%), dyspnea (39% vs 21%), diarrhea (37% vs 23%), decreased appetite (31% vs. 23%), headache (31% vs 16%), cough (24% vs 18%), dizziness (24% vs 16%), insomnia (24% vs 15%), pruritus (24% vs 4.8%), peripheral edema (22% vs 18%), dysgeusia (20% vs 11%), alopecia (20% vs 3.2%), upper respiratory tract infection (20% vs 3.2%), and arthralgia (15% vs 24%). The study was not designed to demonstrate a statistically significant difference in adverse reaction rates for KEYTRUDA plus chemotherapy, as compared to chemotherapy alone, for any specified adverse reaction.

KEYTRUDA was discontinued due to adverse reactions in 17% of 192 patients with HNSCC. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusion, pleural effusion, and respiratory failure. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3 or 4) and new or worsening hypothyroidism.

KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL, and treatment was interrupted due to adverse reactions in 26% of patients. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, GVHD, and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock. The most common adverse reactions (occurring in ≥20% of patients) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

In KEYNOTE-052, KEYTRUDA (pembrolizumab) was discontinued due to adverse reactions in 11% of 370 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20% of patients) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%). Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and 3 patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurring in 42% of patients, the most frequent (≥2%) of which were urinal tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinal tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (≥20%) in patients who received KEYTRUDA vs those who received chemotherapy were fatigue (38% vs 56%), musculoskeletal pain (32% vs 27%), pruritus (23% vs 6%), decreased appetite (21% vs 21%), nausea (21% vs 29%), and rash (20% vs 13%). Serious adverse reactions occurring in 39% of KEYTRUDA-treated patients, the most frequent (≥2%) of which were urinal tract infection, pneumonia, anemia, and pneumonitis.

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.

There is limited experience in pediatric patients. In a study of 40 pediatric patients with advanced melanoma, PD-L1-positive advanced, relapsed, or refractory solid tumors or lymphoma, patients were treated with KEYTRUDA for a median of 43 days (range 1 to 414 days), with 24 patients (60%) receiving treatment for 42 days or more. The safety profile in pediatric patients was similar to that seen in adults treated with KEYTRUDA. Toxicities that occurred at a higher rate (≥15% difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%), and hyponatremia (18%).

**Our Focus on Cancer**

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, 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.
As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the fastest-growing development programs in the industry. We are currently executing an expansive research program that includes more than 500 clinical trials evaluating our anti-PD-1 therapy across more than 30 tumor types. We also continue to strengthen our immuno-oncology portfolio through strategic acquisitions and are prioritizing the development of several promising immunotherapeutic candidates with the potential to improve the treatment of advanced cancers.

For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. 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. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer’s disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

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 2016 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).


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