



NEWS RELEASE

# Merck Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for KEYTRUDA® (pembrolizumab) in Advanced Colorectal Cancer

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Designation Based on Results in Patients with Metastatic Colorectal Cancer with High Levels of Microsatellite Instability

Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation to KEYTRUDA® (pembrolizumab), the company's anti-PD-1 therapy, for the treatment of patients with microsatellite instability high (MSI-H) metastatic colorectal cancer. This is the third Breakthrough Therapy Designation granted for KEYTRUDA.

"We are committed to understanding the full potential of KEYTRUDA to help patients with a broad range of difficult-to-treat cancers," said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. "The data investigating the use of KEYTRUDA in patients with advanced colorectal cancer whose tumors have substantial evidence of mismatch DNA repair defects have been encouraging, and we appreciate the opportunity that this FDA Breakthrough Therapy Designation provides us to accelerate our effort to bring KEYTRUDA to these patients."

The FDA's Breakthrough Therapy Designation is intended to expedite the development and review of a candidate that is planned for use, alone or in combination, to treat a serious or life-threatening disease or condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. KEYTRUDA was previously granted breakthrough status for advanced melanoma and advanced non-small cell lung cancer (NSCLC).

The Breakthrough Therapy Designation in advanced colorectal cancer is based on data from a Phase 2 study evaluating the activity of KEYTRUDA in cancers with microsatellite instability, a well-established feature seen in cells with certain types of DNA repair defects. Findings from the study, led by researchers from Johns Hopkins Kimmel Cancer Center, were presented at the 2015 American Society of Clinical Oncology (ASCO) annual meeting and were published simultaneously in the New England Journal of Medicine.

Testing tumors for microsatellite instability can identify patients with defective DNA mismatch repair (MMR) systems. DNA MMR is a process that permits cells to recognize and repair genetic mismatches generated during DNA replication. A defective MMR system allows mismatch mutations to persist. The average tumor has dozens of mutations; however tumors with DNA MMR deficiency may harbor thousands, especially in regions of repetitive DNA known as microsatellites. Tumors that are found to have mutations in select microsatellite sequences, called microsatellite instability (MSI), are considered DNA MMR-deficient. These tumors are referred to as being “MSI high.” Overall, DNA MMR-deficiency is present in approximately 15-20 percent in Stage II disease, 10 percent in Stage III disease and approximately 5 percent or less in Stage IV disease. In colorectal cancers, MMR-deficiency is seen in approximately 15-20 percent of non-hereditary colorectal cancers and in most hereditary colorectal cancers associated with Lynch Syndrome.

Merck is conducting a Phase 2 registration study (KEYNOTE-164) to evaluate the efficacy and safety of KEYTRUDA based on microsatellite instability status in patients with previously treated advanced colorectal cancers, and is also planning a Phase 3 study (KEYNOTE-177) in a treatment naïve patient population.

The KEYTRUDA clinical development program includes patients with more than 30 tumor types in more than 160 clinical trials, including more than 80 trials that combine KEYTRUDA with other cancer treatments. Registration-enabling trials of KEYTRUDA are currently enrolling patients in melanoma, NSCLC, head and neck cancer, bladder cancer, gastric cancer, colorectal cancer, esophageal cancer, breast cancer, Hodgkin lymphoma, multiple myeloma and other tumors, with further trials in planning for other cancers.

## **About KEYTRUDA® (pembrolizumab) Injection 100 mg**

KEYTRUDA is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA 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.

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.

## Our 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](http://www.merck.com/clinicaltrials).

## About Merck

Today's Merck is a global healthcare 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 healthcare through far-reaching policies, programs and partnerships. For more information, visit [www.merck.com](http://www.merck.com) and connect with us on **Twitter**, **Facebook**, and **YouTube**.

## 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 United States 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](http://www.sec.gov)).

Please see Prescribing Information for KEYTRUDA (pembrolizumab) at [http://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](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](http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf)

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