



## News Release

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### FOR IMMEDIATE RELEASE

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### **FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Adult and Pediatric Patients with Classical Hodgkin Lymphoma (cHL) Refractory to Treatment, or Who Have Relapsed After Three or More Prior Lines of Therapy**

#### **Only Anti-PD-1 Therapy Approved for the Treatment of Patients with Difficult-to-Treat cHL Regardless of Prior Stem Cell Transplantation or Use of Brentuximab Vedotin**

KENILWORTH, N.J., March 14, 2017 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA® (pembrolizumab), the company's anti-PD-1 (programmed death receptor-1) therapy, for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy. Under the FDA's accelerated approval regulations, this indication is approved 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. In refractory or relapsed cHL, KEYTRUDA is approved for use in adult patients at a fixed dose of 200 mg and in pediatric patients at a dose of 2 mg/kg (up to a maximum of 200 mg). KEYTRUDA is administered intravenously every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Immune-mediated adverse reactions occurred with KEYTRUDA including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered when appropriate. Immune-mediated complications, including fatal events, occurred in patients with cHL who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Follow patients closely for early evidence of transplant-related complications, and intervene promptly. KEYTRUDA can also cause severe or life-threatening

infusion-related reactions. Monitor patients for signs and symptoms of infusion-related reactions; for Grade 3 or 4 reactions, stop infusion and permanently discontinue KEYTRUDA (pembrolizumab). Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus. For more information regarding immune-mediated and infusion-related adverse reactions and use in pregnancy, see “Selected Important Safety Information” below.

The approval is based on data in 210 patients from the KEYNOTE-087 trial, which demonstrated an overall response rate (ORR) with KEYTRUDA (200 mg every three weeks) of 69 percent (95% CI: 62, 75) with a complete remission rate (CRR) of 22 percent and a partial remission rate (PRR) of 47 percent. The median follow-up time was 9.4 months. Among the 145 responding patients, the median duration of response was 11.1 months (range 0.0+ to 11.1 months).

“The results from KEYNOTE-087 showed that most patients with relapsed or refractory classical Hodgkin lymphoma responded to treatment with KEYTRUDA, and 22 percent experienced complete remission,” said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. “Today’s approval – the first for KEYTRUDA in a hematologic malignancy – reinforces the hope that immunotherapy will prove useful in a wide variety of cancers.”

“For the patients with classical Hodgkin lymphoma who are not cured with existing treatments, there are limited options, and treating their disease becomes more challenging,” said Dr. Craig Moskowitz, clinical director, division of hematologic oncology, Memorial Sloan Kettering Cancer Center. “This approval is an important step forward in treating these patients, who are generally young and have a particularly poor prognosis, and gives us the opportunity to help patients in their fight against this devastating disease.”

### **Data Supporting the Approval**

The accelerated FDA approval was based on data in 210 patients with relapsed or refractory cHL enrolled in the multicenter, nonrandomized, open-label KEYNOTE-087 study. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past five years (or greater than five years but with symptoms of GVHD [graft-versus-host disease]), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA at a dose of 200 mg every three weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients who did not progress. The major efficacy

outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Fifty-eight percent (58%) of patients were refractory to the last prior therapy, including 35 percent with primary refractory disease and 14 percent whose disease was chemo-refractory to all prior regimens. Additionally, 61 percent of patients had undergone prior auto-HSCT, 17 percent had no prior brentuximab use, and 36 percent had prior radiation therapy.

Efficacy analysis showed an ORR of 69 percent (95% CI: 62, 75) with a CRR of 22 percent and a PRR of 47 percent. The median follow-up time was 9.4 months. Among the 145 responding patients, the median duration of response was 11.1 months (range 0.0+ to 11.1 months).

KEYTRUDA (pembrolizumab) was discontinued due to adverse reactions in five percent of 210 patients with cHL and treatment was interrupted due to adverse reactions in 26 percent of patients. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16 percent of patients. The most frequent serious adverse reactions ( $\geq 1\%$ ) 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  $\geq 20\%$  of patients) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

There is limited experience in pediatric patients. Efficacy for pediatric patients was extrapolated from the results in the adult cHL population. 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 1-414 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 ( $\geq 15\%$  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%).

### **About KEYTRUDA® (pembrolizumab)**

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 (pembrolizumab) is administered as an intravenous infusion over 30 minutes every three weeks for the approved indications. KEYTRUDA for injection is supplied in a 100 mg single-dose vial.

## **KEYTRUDA Indications and Dosing**

### *Melanoma*

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma at a dose of 2 mg/kg every three weeks until disease progression or unacceptable toxicity.

### *Lung Cancer*

KEYTRUDA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [tumor proportion score (TPS)  $\geq 50\%$ ] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA is also indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS  $\geq 1\%$ ) 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.

In metastatic NSCLC, KEYTRUDA is administered at a fixed dose of 200 mg every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

### *Head and Neck Cancer*

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. 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. In

HNSCC, KEYTRUDA (pembrolizumab) is administered at a fixed dose of 200 mg every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

### *Classical Hodgkin Lymphoma*

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy. 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. In adults with cHL, KEYTRUDA is administered at a fixed dose of 200 mg every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with cHL, KEYTRUDA is administered at a dose of 2 mg/kg (up to a maximum of 200 mg) every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

### **Selected Important Safety Information for KEYTRUDA® (pembrolizumab)**

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 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 (pembrolizumab).

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 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 or 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 (pembrolizumab) 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 cHL, and postmarketing use.

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

KEYTRUDA can cause severe or life-threatening infusion-related reactions, 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 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 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 (pembrolizumab).

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 ( $\geq 1\%$ ) 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  $\geq 20\%$  of patients) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

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 1-414 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 ( $\geq 15\%$  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 400 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](http://www.merck.com/clinicaltrials).

## **About Merck**

For over a century, Merck has been a global health care 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 health care 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](#), [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](http://www.sec.gov)).

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**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  
Patient Information/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).**