



NEWS RELEASE

# European Commission Approves KEYTRUDA® (pembrolizumab) for First-Line Treatment of Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Whose Tumors Have High PD-L1 Expression with No EGFR or ALK Positive Tumor Mutations

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Approval Based on Data Showing Improved Overall Survival and Progression-Free Survival with KEYTRUDA Compared to Chemotherapy

First Anti-PD-1 Therapy Approved in Europe for Previously Untreated Patients with Metastatic NSCLC

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the European Commission has approved KEYTRUDA® (pembrolizumab), the company's anti-PD-1 therapy, for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumors have high PD-L1 expression (tumor proportion score [TPS] of 50 percent or more) with no EGFR or ALK positive tumor mutations.

"The approval of KEYTRUDA as a first treatment instead of chemotherapy for patients who express high levels of PD-L1 has the potential to transform the way metastatic non-small cell lung cancer is treated," said Dr. Roy Baynes, senior vice president, head of clinical development, and chief medical officer, Merck Research Laboratories. "We are committed to ensuring that patients in Europe – who are in need of new treatment options – are able to quickly gain access to KEYTRUDA."

The approval is based on phase 3 data which demonstrated superior overall survival (OS) and progression-free survival (PFS) with KEYTRUDA compared to chemotherapy, the current standard of care for advanced NSCLC. The approval allows marketing of KEYTRUDA in all 28 EU member states plus Iceland, Lichtenstein and Norway, at the approved dose of 200 mg every three weeks until disease progression or unacceptable toxicity. In August 2016, KEYTRUDA (pembrolizumab) (2 mg/kg every three weeks) was approved in Europe for previously-treated patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 (TPS of 1 percent or more) and who have received at least one prior chemotherapy regimen.

“The data demonstrate that KEYTRUDA provided meaningful improvements in survival versus the current standard of care in patients whose tumors express high levels of PD-L1,” said Dr. Luis Paz-Ares, chair of the medical oncology department, Hospital Universitario Doce de Octubre, Madrid, Spain. “These findings supporting the approval also provide further rationale for biomarker testing in order to identify those patients more likely to benefit the most from treatment with KEYTRUDA.”

## About KEYNOTE-024

The European Commission’s approval is based on data from KEYNOTE-024, a randomized, open-label, phase 3 study evaluating KEYTRUDA monotherapy at a fixed dose of 200 mg compared to standard of care platinum-containing chemotherapy (pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin) for the treatment of patients with both squamous and non-squamous metastatic NSCLC. The study enrolled 305 patients who had not received prior systemic chemotherapy treatment for their metastatic disease and whose tumors had high PD-L1 expression with no EGFR or ALK aberrations. The primary endpoint was PFS; additional efficacy outcome measures were OS and objective response rate (ORR).

In the study, KEYTRUDA reduced the risk of disease progression or death by 50 percent compared to chemotherapy (HR, 0.50 [95% CI, 0.37, 0.68];  $p < 0.001$ ). The median PFS for KEYTRUDA was 10.3 months (95% CI, 6.7-not reached) compared to 6.0 months for chemotherapy (95% CI, 4.2-6.2). At six months and 12 months, respectively, 62 percent and 48 percent of patients treated with KEYTRUDA were alive and had no disease progression compared to 50 percent and 15 percent of those receiving chemotherapy.

Additionally, KEYTRUDA resulted in a 40 percent reduction in the risk of death compared to chemotherapy (HR, 0.60 [95% CI, 0.41, 0.89];  $p = 0.005$ ); this finding includes the 66 patients (43.7%) on the chemotherapy arm who crossed over in-study to receive KEYTRUDA once their cancer had progressed; median OS was not reached in either group. The OS rate at six months and 12 months, respectively, was 80 percent and 70 percent in patients treated with KEYTRUDA compared to 72 percent and 54 percent in those receiving chemotherapy.

Further, ORR was 45 percent for patients receiving KEYTRUDA (pembrolizumab) (95% CI, 37-53), including six complete responses, compared to 28 percent with chemotherapy (95% CI, 21-36), including one complete response.

The safety analysis supporting the European approval of KEYTRUDA was based on 2,953 patients with advanced melanoma or NSCLC across four doses (2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks) in studies KEYNOTE-001, KEYNOTE-002, KEYNOTE-010 and KEYNOTE-024 combined. The most common adverse reactions ( $\geq 10\%$ ) with KEYTRUDA were fatigue (24%), rash (19%), pruritus (17%), diarrhea (12%), nausea (11%) and arthralgia (10%). The majority of adverse reactions reported were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions.

## 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 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 use vial.

## KEYTRUDA Indications and Dosing in the U.S.

### 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 (pembrolizumab).

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 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.

## 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.

KEYTRUDA (pembrolizumab) 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 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.

KEYTRUDA (pembrolizumab) 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.

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.

KEYTRUDA 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 was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common ( $\geq 1\%$ ) 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%).

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.

## About Lung Cancer

Lung cancer, which forms in the tissues of the lungs, usually within cells lining the air passages, is the leading cause of cancer death worldwide. Each year, more people die of lung cancer than die of colon, breast, and prostate cancers combined. The two main types of lung cancer are non-small cell and small cell. NSCLC is the most common type of lung cancer, accounting for about 85 percent of all cases. The five-year survival rate for patients suffering from highly advanced, metastatic (Stage IV) lung cancers is estimated to be two percent.

## 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 2015 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 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) .

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