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FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma with Disease Progression on or After Platinum-Containing Chemotherapy

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KENILWORTH, N.J.--(BUSINESS WIRE)--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, at a fixed dose of 200 mg every three weeks, 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. Under the FDA's accelerated approval regulations, this indication for KEYTRUDA 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. For HNSCC patients, PD-L1 testing is not needed prior to use of KEYTRUDA.

The approval is based on data from the KEYNOTE-012 study, which included patients with recurrent or metastatic HNSCC who had disease progression on or after platinum-containing chemotherapy or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy and ECOG performance status (PS) of zero or one. The data showed an objective response rate (ORR) of 16 percent (95% CI: 11, 22), complete response rate of five percent, with responses of six months or longer observed in 82 percent (n=23/28) of the responding patients. ORR and duration of response were similar regardless of human papilloma virus (HPV) status.

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. 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 adverse reactions and use in pregnancy, see "Selected Important Safety Information" below.

"Today's approval represents a meaningful advance for the oncology community, as well as for our head and neck cancer clinical program," said Dr. Roger M. Perlmutter, president, Merck Research Laboratories. "Together with prior approvals in the treatment of other tumor types, today's action by the FDA underscores our tireless commitment to addressing the unmet needs of patients suffering from a broad range of cancers."

KEYNOTE-012 was the first clinical study to investigate the role of a PD-1 inhibitor in patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. Merck currently has the largest immuno-oncology clinical development program, including multiple registration-enabling studies in head and neck cancer, and is conducting research investigating KEYTRUDA (pembrolizumab) as a monotherapy, as well as in combination with chemotherapy compared to the current standard of care.

"Head and neck cancer is a complex disease that historically has been associated with high recurrence rates and poor long-term outcomes, highlighting the critical need for new treatment options," said Dr. Tanguy Seiwert, associate director of the Head and Neck Cancer Program and assistant professor of medicine at The University of Chicago. "The approval of KEYTRUDA for previously treated patients with recurrent or metastatic head and neck squamous cell carcinoma is an important step forward in treating this disease."

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.

"Head and neck squamous cell carcinoma presents unique challenges including limited treatment options, especially for patients with recurrent or metastatic disease," said Holly Boykin, executive director, Head and Neck Cancer Alliance. "We welcome the approval of KEYTRUDA as a new treatment option for people whose lives are impacted by this devastating disease."

Data Supporting the Approval

The accelerated FDA approval was based on a multicenter, nonrandomized, open-label, multi-cohort phase 1b study, KEYNOTE-012, that evaluated safety in 192 patients with recurrent or metastatic HNSCC and ECOG PS of zero or one; efficacy was evaluated in 174 of these patients who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy. Patients were enrolled regardless of tumor HPV status (33% were HPV-positive).

The median number of prior lines of therapy administered for the treatment of HNSCC was two. Nearly all (95%) of the patients enrolled had prior radiation therapy. Patients received KEYTRUDA (pembrolizumab) at a dose of 10 mg/kg every two weeks (n=53) or a 200 mg fixed dose every three weeks (n=121) until unacceptable toxicity or disease progression. Patients without disease progression were treated for up to 24 months. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to one additional year. The primary efficacy outcome measures were ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, as assessed by blinded independent central review (BICR), and duration of response.

Efficacy analysis showed an ORR of 16 percent (95% CI: 11, 22) with a complete response rate of five percent. The median follow-up time was 8.9 months. Among the 28 responding patients, the median duration of response had not been reached (range 2.4+ to 27.7+ months), with 23 patients having responses of six months or longer. The ORR and duration of response were similar irrespective of dosage regimen (10 mg/kg every 2 weeks or 200 mg every 3 weeks) or HPV status.

In HNSCC, serious adverse reactions occurred in 45 percent of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least two percent of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks). The most common adverse reactions (reported in at least 20% of patients) were fatigue (46%), decreased appetite (22%), and dyspnea (20%). Adverse reactions in patients with HNSCC were generally similar to those occurring in patients with melanoma and non-small cell lung cancer (NSCLC), with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism.

About KEYTRUDA ® (pembrolizumab)

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

Melanoma

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

Lung Cancer

KEYTRUDA is indicated 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, at a dose of 2 mg/kg every three weeks. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA (pembrolizumab). This indication is 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 this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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 at a fixed dose of 200 mg every three weeks. 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.

Selected Important Safety Information for KEYTRUDA ® (pembrolizumab)

Immune-mediated pneumonitis, including fatal cases, occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging and 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.

Immune-mediated colitis occurred 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.

Immune-mediated hepatitis occurred in patients 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 patients receiving KEYTRUDA. 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.

New or worsening hypothyroidism occurred in 28 (14.6%) of 192 patients, including Grade 3 (0.5%) hypothyroidism. 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 (pembrolizumab) for Grade 3 or 4 hyperthyroidism.

Type 1 diabetes mellitus, including diabetic ketoacidosis, 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.

Immune-mediated nephritis occurred in patients receiving KEYTRUDA. 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 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.

Severe and life-threatening infusion-related reactions have been reported in 3 (0.1%) of 2117 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 (pembrolizumab) was discontinued due to adverse reactions in 17 percent of 192 patients. Serious adverse reactions occurred in 45 percent of patients. The most frequent serious adverse reactions reported in at least 2 percent of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions (reported in at least 20% of patients) were fatigue (46%), decreased appetite (22%), and dyspnea (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.

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.

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 300 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 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 125 years, 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 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).

Please see Prescribing Information for KEYTRUDA (pembrolizumab) at 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 .

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