FDA Approves Merck’s KEYTRUDA® (pembrolizumab) in Combination With Inlyta® (axitinib) as First-Line Treatment for Patients With Advanced Renal Cell Carcinoma (RCC)

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Approval Based on Results of KEYNOTE-426, Where KEYTRUDA in Combination With Axitinib Reduced the Risk of Death by Nearly Half Compared to Sunitinib

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, Merck's anti-PD-1 therapy, in combination with Inlyta (axitinib), a tyrosine kinase inhibitor, for the first-line treatment of patients with advanced renal cell carcinoma (RCC). The approval is based on findings from the pivotal Phase 3 KEYNOTE-426 trial, which demonstrated significant improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) for KEYTRUDA in combination with axitinib (KEYTRUDA-axitinib combination) compared to sunitinib. Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status. For the main efficacy outcome measures of OS and PFS, the KEYTRUDA-axitinib combination reduced the risk of death by 47% compared to sunitinib (HR=0.53 [95% CI, 0.38-0.74]; p<0.0001); for PFS, the KEYTRUDA-axitinib combination showed a reduction in the risk of progression of disease or death of 31% compared to sunitinib (HR=0.69 [95% CI, 0.57-0.84]; p=0.0001). The ORR, an additional efficacy outcome measure, was 59% for patients who received the KEYTRUDA-axitinib combination (95% CI, 54-64) and 36% for those who received sunitinib (95% CI, 31-40) (p<0.0001). This is the first indication for KEYTRUDA in advanced RCC, the most common type of kidney cancer, and the first anti-PD-1 therapy FDA-approved as part of a combination regimen that significantly improved OS, PFS, and ORR versus sunitinib in patients with advanced RCC.

“Today's approval reflects Merck’s commitment to patients with cancer and further supports the use of KEYTRUDA to help improve survival outcomes for patients with advanced renal cell carcinoma,” said Dr. Scot Ebbinghaus, vice president, clinical research, Merck Research Laboratories. “This represents a new treatment option for patients with advanced renal cell carcinoma, who will now have access to KEYTRUDA as part of a first-line combination regimen.”

Immune-mediated adverse reactions, which may be severe or fatal, can occur with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, severe skin reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation (HSCT). Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate. KEYTRUDA can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. For more information, see “Selected Important Safety Information” below.

Given the aggressive nature of the disease, many patients with advanced renal cell carcinoma need additional treatment options that can help improve survival outcomes,” said Dr. Brian Rini, medical oncologist at Cleveland Clinic Cancer Center and professor of medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. “Pembrolizumab in combination with axitinib offers an important new therapeutic option for physicians to consider when approaching initial treatment for patients newly diagnosed with advanced renal cell carcinoma.” Dr. Rini reports consulting and research funding from Merck.

About KEYNOTE-426

The approval was based on data from the pre-specified interim analysis of the Phase 3 KEYNOTE-426 trial, a randomized, multi-center, open-label trial conducted in 861 patients who had not received systemic therapy for advanced RCC. Patients were enrolled regardless of PD-L1 tumor expression status. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”). Patients with active autoimmune disease requiring systemic immunosuppression within the last two years were ineligible.
Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every three weeks up to 24 months in combination with axitinib 5 mg orally, twice daily (n=432).
- Sunitinib 50 mg orally, once daily for four weeks and then off treatment for two weeks (n=429).

Among the 861 patients, the study population characteristics were: median age of 62 years (range, 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 19% and 80% of patients had a baseline Karnofsky Performance Status (KPS) of 70 to 80 and 90 to 100, respectively; and patient distribution by MDACC risk categories was 31% favorable, 56% intermediate, and 13% poor.

Treatment with the KEYTRUDA-axitinib combination continued until RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined progression of disease or unacceptable toxicity. The main efficacy outcome measures were OS and PFS as assessed by BICR according to modified RECIST v1.1. Additional efficacy outcome measures included ORR, as assessed by BICR.

The trial demonstrated statistically significant improvements in OS, PFS, and ORR in patients randomized to receive the KEYTRUDA-axitinib combination compared to sunitinib.

With a median follow-up time of 12.8 months (range, 0.1 to 22 months), OS was significantly improved in patients who received the KEYTRUDA-axitinib combination compared to sunitinib (HR=0.53 [95% CI, 0.38-0.74]; p<0.0001). Estimated 12-month OS rates were 90% (95% CI, 86-92) with the KEYTRUDA-axitinib combination versus 78% (95% CI, 74-82) with sunitinib. Median OS was not reached with either treatment regimen. Progression-free survival was also significantly improved with the KEYTRUDA-axitinib combination compared to sunitinib (HR=0.69 [95% CI, 0.57-0.84]; p=0.0001). Median PFS was 15.1 months (95% CI, 12.6-17.7) in patients receiving the KEYTRUDA-axitinib combination versus 11.1 months (95% CI, 8.7-12.5) with sunitinib. In the study, the ORR was 59% for patients who received the KEYTRUDA-axitinib combination (95% CI, 54-64) and 36% for those who received sunitinib (95% CI, 31-40) (p<0.0001), with a complete response rate of 6% and 2% and a partial response rate of 53% and 34%, for patients receiving the KEYTRUDA-axitinib combination versus sunitinib, respectively.

In KEYNOTE-426, the safety of KEYTRUDA in combination with axitinib was investigated in patients with previously untreated, advanced RCC. The median duration of exposure to the combination therapy of KEYTRUDA and axitinib was 10.4 months (range, 1 day to 21.2 months). Fatal adverse reactions occurred in 3.3% of patients receiving KEYTRUDA in combination with axitinib. Serious adverse reactions occurred in 40% of patients receiving KEYTRUDA in combination with axitinib. Serious adverse reactions in ≥1% of patients receiving KEYTRUDA in combination with axitinib included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%). Permanent discontinuation due to an adverse reaction of either KEYTRUDA or axitinib occurred in 31% of patients; 13% KEYTRUDA only, 13% axitinib only, and 8% both drugs. The most common adverse reaction (>1%) resulting in permanent discontinuation of KEYTRUDA, axitinib or the combination was hepatotoxicity (13%), diarrhea/coilitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). The most common adverse reactions (≥20%) in patients receiving in patients receiving KEYTRUDA and axitinib were diarrhea (56%), fatigue/asthenia (52%), hypertension (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia (28%), nausea (28%), stomatitis/mucosal inflammation (27%), dysphonia (25%), rash (25%), cough (21%), and constipation (21%).

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

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of T lymphocytes to attack tumors. 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.

Merck has the industry’s largest immuno-oncology clinical research program. There are currently more than 950 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to understand the role of KEYTRUDA across cancers and the factors that may predict a patient’s likelihood of benefiting from treatment with KEYTRUDA, including exploring several different biomarkers.

**KEYTRUDA® (pembrolizumab) Indications and Dosing**

**Melanoma**

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma. The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease recurrence, unacceptable toxicity, or for up to 12 months in patients without disease recurrence.

**Lung Cancer**

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (tumor proportion...
KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥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 NSCLC, the recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

When administering KEYTRUDA in combination with chemotherapy, KEYTRUDA should be administered prior to chemotherapy when given on the same day. See also the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, as appropriate.

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 200 mg is administered as an intravenous infusion over 30 minutes 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 3 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. KEYTRUDA is not recommended for the treatment of patients with cHL who require urgent cytoreductive therapy.

In adults with cHL, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with cHL, KEYTRUDA is administered as an intravenous infusion over 30 minutes 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.

Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 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 confirmatory trials. KEYTRUDA is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy.

In adults with PMBCL, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with PMBCL, KEYTRUDA is administered as an intravenous infusion over 30 minutes 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.

Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

In locally advanced or metastatic urothelial carcinoma, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Microsatellite Instability-High (MSI-H) Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

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. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.
In adult patients with MSI-H cancer, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with MSI-H cancer, KEYTRUDA is administered as an intravenous infusion over 30 minutes 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.

**Gastric Cancer**

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test, with disease progression or on after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted 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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

**Cervical Cancer**

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. 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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

**Hepatocellular Carcinoma**

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. 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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

**Merkel Cell Carcinoma**

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. 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. The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

**Renal Cell Carcinoma**

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma. In renal cell carcinoma, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every 3 weeks in combination with 5 mg axitinib orally twice daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression. When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer. See also the Prescribing Information for recommended axitinib dosing information.

**Selected Important Safety Information for KEYTRUDA**

**Immune-Mediated Pneumonitis**

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 3.4% (94/2799) of patients with various cancers receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%). Pneumonitis occurred in 8.2% (65/790) of NSCLC patients receiving KEYTRUDA as a single agent, including Grades 3-4 in 3.2% of patients, and occurred more frequently in patients with a history of prior thoracic radiation (17%) compared to those without (7.7%).

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.

**Immune-Mediated Colitis**

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

**Immune-Mediated Hepatitis**

KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%). Monitor patients for changes in liver function. Administer corticosteroids
KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Grades 3 and 4 increased ALT and AST were seen in 20% and 13% of patients, respectively. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed.

Immune-Mediated Endocrinopathies

KEYTRUDA can cause hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Hypophysitis occurred in 0.6% (17/2799) of patients, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%). Hypothyroidism occurred in 8.5% (237/2799) of patients, including Grade 2 (6.2%) and 3 (0.1%). The incidence of new or worsening hypothyroidism was higher in patients with HNSCC, occurring in 15% (28/192) of patients. Hyperthyroidism occurred in 3.4% (96/2799) of patients, including Grade 2 (0.8%) and 3 (0.1%), and thyroiditis occurred in 0.6% (16/2799) of patients, including Grade 2 (0.3%). Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 0.2% (6/2799) of patients.

Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency), thyroid function (prior to and periodically during treatment), and hyperglycemia. For hypophysitis, administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2 and withhold or discontinue for Grade 3 or 4 hypophysitis. Administer hormone replacement for hypophysitis and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism. Administer insulin for type 1 diabetes and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

Immune-Mediated Nephritis and Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. Nephritis occurred in 1.7% (7/405) of patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue for Grade 3 or 4 nephritis.

Immune-Mediated Skin Reactions

Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

Other Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA and may also occur after discontinuation of treatment. 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%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including chL and postmarketing use.

Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment vs the risk of possible organ rejection in these patients.

Infusion-Related Reactions

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic HSCT after treatment with KEYTRUDA. Of 23 patients with chL who proceeded to allogeneic HSCT after KEYTRUDA, 6 (26%) developed graft-versus-host disease (GVHD) (1 fatal case) and 2 (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning (1 fatal case). 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. Follow patients closely for early evidence of transplant-related complications such as hyperacute graft-versus-host disease (GVHD), Grade 3 to 4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions.

In patients with a history of allogeneic HSCT, acute GVHD (including fatal GVHD) has been reported after treatment with
KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after KEYTRUDA. Consider the benefit of KEYTRUDA vs the risk of GVHD in these patients.

Increased Mortality in Patients With Multiple Myeloma

In trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with a PD-1 or PD-L1 blocking antibody in this combination is not recommended outside of controlled trials.

Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-054, KEYTRUDA was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. The most common adverse reaction (≥20%) with KEYTRUDA was diarrhea (28%).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and either paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 15% of 101 patients. The most frequent serious adverse reactions reported in at least 2% of patients were febrile neutropenia, pneumonia, and urinary tract infection. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs 36%) and peripheral neuropathy (31% vs 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients; the most common were pneumonitis (3%), death due to unknown cause (1.6%), and pneumonia (1.4%). The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-010, KEYTRUDA monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC; the most common was pneumonitis (1.8%). The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

In KEYNOTE-012, 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, state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions (≥20%) 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 who received KEYTRUDA as a monotherapy, with the exception of increased incidences of facial edema and new or worsening hypothyroidism.

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL. Serious adverse reactions occurred in 16% of patients; those ≥1% included pneumonia, pneumonitis, pyrexia, dyspnea, GVHD, and herpes zoster. Two patients died from causes other than disease progression: 1 from GVHD after subsequent allogeneic HSCT and 1 from septic shock. The most common adverse reactions (≥20%) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

In KEYNOTE-170, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with PMBCL. Serious adverse reactions occurred in 26% of patients and included arthralgia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (23%), and dyspnea (21%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with locally advanced or metastatic urothelial carcinoma. Serious adverse reactions occurred in 42% of patients; those ≥2% were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%).

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%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients; those ≥2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased appetite (21%), nausea (21%), and rash (20%).
Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA; the most frequent included anemia (7%), fistula, hemorrhage, and infections [except urinary tract infections] (4.1% each). The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%).

Adverse reactions occurring in patients with HCC were generally similar to those in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

Among the 50 patients with MCC enrolled in study KEYNOTE-017, adverse reactions occurring in patients with MCC were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (11%) and hyperglycemia (19%).

In KEYNOTE-426, when KEYTRUDA was administered in combination with axitinib, fatal adverse reactions occurred in 3.3% of 429 patients. Serious adverse reactions occurred in 40% of patients, the most frequent of which (≥1%) included hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonia (1%). Permanent discontinuation due to an adverse reaction occurred in 31% of patients; KEYTRUDA only (13%), axitinib only (13%), and the combination (8%). The most common adverse reactions (≥1%) resulting in permanent discontinuation of KEYTRUDA, axitinib or the combination were hepatotoxicity (13%), diarrhea/collitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). When KEYTRUDA was used in combination with axitinib, the most common adverse reactions (≥20%) were diarrhea (56%), fatigue/asthenia (52%), hypertension (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia (28%), nausea (28%), stomatitis/mucosal inflammation (27%), dysphonia (25%), rash (25%), cough (21%), and constipation (21%).

Lactation
Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the final dose.

Pediatric Use
There is limited experience in pediatric patients. In a trial, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with various cancers, including unapproved usages, were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1–17 doses), with 34 patients (85%) receiving 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults; adverse reactions 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%), increased transaminases (28%), and hyponatremia (18%).

Merck’s Focus on Cancer
Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology 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 the Merck Access Program for KEYTRUDA
At Merck, we are committed to supporting accessibility to our cancer medicines. Merck provides multiple programs to help ensure that appropriate patients who are prescribed KEYTRUDA have access to our anti-PD-1 therapy. The Merck Access Program provides reimbursement support for patients receiving KEYTRUDA, including information to help with out-of-pocket costs and co-pay assistance for eligible patients. Merck also offers free product through our patient assistance program to eligible patients, primarily the uninsured, who, without our assistance, could not afford their medicine. More information is available by calling 855-257-3932 or visiting www.merckaccessprogram-keytruda.com.

About Merck’s Patient Support Program for KEYTRUDA
Merck is committed to helping provide patients and their caregivers support throughout their treatment with KEYTRUDA. The KEY+YOU Patient Support Program provides a range of resources and services. For further information and to sign up, patients and physicians may call 855-KEYTRUDA (855-398-7832) or visit www.keytruda.com.

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 2018 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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