FDA Approves Merck’s KEYTRUDA® (pembrolizumab) for First-Line Treatment of Patients With Unresectable or Metastatic MSI-H or dMMR Colorectal Cancer

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KEYTRUDA Is the First Single-Agent, Anti-PD-1 Therapy Approved for the First-Line Treatment of These Patients

Approval Received Less Than One Month Following Submission of sBLA Application Based on Results of KEYNOTE-177

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, as monotherapy for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer. The approval is based on results from the Phase 3 KEYNOTE-177 trial, in which KEYTRUDA significantly reduced the risk of disease progression or death by 40% (HR=0.60 [95% CI, 0.45-0.80; p=0.0004]) compared with chemotherapy, the current standard of care. In the study, treatment with KEYTRUDA also more than doubled median progression-free survival (PFS) compared with chemotherapy (16.5 months [95% CI, 5.4-32.4] versus 8.2 months [95% CI, 6.1-10.2]).

“Today’s approval has the potential to change the treatment paradigm for the first-line treatment of patients with MSI-H colorectal cancer, based on the important findings from KEYNOTE-177 that showed KEYTRUDA monotherapy demonstrated superior progression-free survival compared to standard of care chemotherapy,” said Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research

Laboratories. “Our commitment to pursuing biomarker research continues to help us bring new treatments to patients, particularly for those who have few available options.”

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.

This approval was granted less than one month following the submission of a new supplemental Biologics License Application (sBLA), which was reviewed under the FDA’s Real-Time Oncology Review (RTOR) pilot program. This review also was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence that provides a framework for concurrent submission and review of oncology drugs among its international partners. For this application, a modified Project Orbis was undertaken, and the FDA is collaborating with the Australian Therapeutic Goods Administration, Health Canada and Swissmedic on their ongoing review of the application.

“Patients with unresectable or metastatic MSI-H colorectal cancer have historically faced poor outcomes, and until today, chemotherapy-containing regimens were the only FDA-approved first-line treatment options,” said Luis A. Diaz, M.D., head of the division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center. “In patients who were treated with KEYTRUDA and responded (n=67) in the KEYNOTE-177 trial, 43% of patients experienced a duration of response lasting two years or longer. This approval helps address the unmet need to provide a new monotherapy treatment option for patients.”

Data Supporting the Approval

The approval was based on data from KEYNOTE-177 (NCT02563002), a multi-center, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR colorectal cancer. Microsatellite instability (MSI) or mismatch repair (MMR) tumor status was determined locally using polymerase chain reaction or immunohistochemistry, respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized 1:1 to receive KEYTRUDA 200 mg intravenously every three weeks or investigator’s choice of the following chemotherapy regimens given intravenously every two weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and fluorouracil) or mFOLFOX6 in combination with either bevacizumab or
cetuximab: oxaliplatin 85 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and fluorouracil 400 mg/m² bolus on Day 1, then fluorouracil 2,400 mg/m² over 46-48 hours; plus bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.

- FOLFIRI (irinotecan, leucovorin, and fluorouracil) or FOLFIRI in combination with either bevacizumab or cetuximab: irinotecan 180 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and fluorouracil 400 mg/m² bolus on Day 1, then fluorouracil 2,400 mg/m² over 46-48 hours; plus bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.

Treatment with KEYTRUDA or chemotherapy continued until Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every nine weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The main efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ, and overall survival (OS). Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DOR).

Patients were enrolled and randomized to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range, 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, and 48% had an ECOG PS of 1; and 27% received prior adjuvant or neoadjuvant chemotherapy. Among the 154 patients randomized to receive chemotherapy, 143 received chemotherapy per the protocol. Of these 143 patients, 56% received mFOLFOX6, 44% received FOLFIRI, 70% received bevacizumab plus mFOLFOX6 or FOLFIRI, and 11% received cetuximab plus mFOLFOX6 or FOLFIRI. The median follow-up time was 27.6 months (range, 0.2 to 48.3 months).

In this study, KEYTRUDA monotherapy significantly reduced the risk of disease progression or death by 40% (HR=0.60 [95% CI, 0.45-0.80; p=0.0004]) and showed a median PFS of 16.5 months (95% CI, 5.4-32.4) compared with 8.2 months (95% CI, 6.1-10.2) for patients treated with chemotherapy. For PFS, in the KEYTRUDA arm, there were 82 patients (54%) with an event versus 113 patients (73%) in the chemotherapy arm. At the time of the PFS analysis, the OS data were not mature (66% of the required number of events for the OS final analysis). For patients treated with KEYTRUDA, the ORR was 44% (95% CI, 35.8-52.0), with a complete response rate of 11% and a partial response rate of 33%, and for patients treated with chemotherapy, the ORR was 33% (95% CI, 25.8-41.1), with a complete response rate of 4% and a partial response rate of 29%. Median DOR was not reached (range, 2.3+ to 41.4+) with KEYTRUDA versus 10.6 months (range, 2.8 to 37.5+) with chemotherapy. Based on 67 patients with a response in the KEYTRUDA arm and 51 patients with a response in the chemotherapy arm, 75% in the KEYTRUDA arm had a duration of response greater than or equal to 12 months versus 37% in the chemotherapy arm, and 43% in the
KEYTRUDA arm had a duration of response greater than or equal to 24 months versus 18% in the chemotherapy arm.

Among the 153 patients with MSI-H or dMMR colorectal cancer treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months (range, 1 day to 30.6 months). Adverse reactions occurring in patients with MSI-H or dMMR colorectal cancer were similar to those occurring in 2,799 patients with melanoma or non-small cell lung cancer treated with KEYTRUDA as a single agent.

About KEYTRUDA® (pembrolizumab) Injection, 100 mg

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. 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 1,200 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.

Selected KEYTRUDA® (pembrolizumab) Indications

Melanoma

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

Non-Small Cell 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 NSCLC expressing PD-L1
[tumor proportion score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.

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.

Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least 1 other prior line 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.

Head and Neck Squamous Cell Cancer

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [combined positive score (CPS) ≥1] as determined by an FDA-approved test.

KEYTRUDA, as a single agent, 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.

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.

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 treatment of patients with PMBCL who require urgent cytoreductive therapy.

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 [combined positive score (CPS) ≥10], 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 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.

KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

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.
Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

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 on or 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.

Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

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.

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.

Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or
metastatic Merkel cell carcinoma (MCC). 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.

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

Tumor Mutational Burden-High (TMB-H)

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) \( \geq 10 \) mutations/megabase (mut/Mb)) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. 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 TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation.

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%). Pneumonitis occurred in 6% (18/300) of HNSCC patients receiving KEYTRUDA as a single agent, including Grades 3-5 in 1.6% of patients, and occurred in 5.4% (15/276) of patients receiving KEYTRUDA in combination with platinum and FU as first-line therapy for advanced disease, including Grades 3-5 in 1.5% of patients.
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 (KEYTRUDA) and Hepatotoxicity (KEYTRUDA 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 for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

**Hepatotoxicity in Combination With Axitinib**

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. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed.

**Immune-Mediated Endocrinopathies**

KEYTRUDA can cause adrenal insufficiency (primary and secondary), hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Adrenal insufficiency occurred in 0.8% (22/2799) of patients, including Grade 2 (0.3%), 3 (0.3%), and 4 (<0.1%). 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 1185 patients with HNSCC (16%) receiving KEYTRUDA, as a single
agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. 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 adrenal insuﬃciency, hypophysitis (including hypopituitarism), thyroid function (prior to and periodically during treatment), and hyperglycemia. For adrenal insuﬃciency or hypophysitis, administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2 adrenal insuﬃciency or hypophysitis and withhold or discontinue KEYTRUDA for Grade 3 or Grade 4 adrenal insuﬃciency or hypophysitis. Administer hormone replacement for hypothyroidism 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 classical Hodgkin lymphoma, 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-002, KEYTRUDA was permanently discontinued due to adverse reactions in 12% of 357 patients with advanced melanoma; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). The most common adverse reactions were fatigue (43%), pruritus (28%), rash (24%), constipation (22%), nausea (22%), diarrhea (20%), and decreased appetite (20%).

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 with advanced NSCLC; 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%).

Adverse reactions occurring in patients with SCLC were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse events in 12% of 300 patients with HNSCC; the most common adverse reactions leading to permanent discontinuation were sepsis (1.7%) and pneumonia (1.3%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 276 patients with HNSCC. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (49%), constipation (37%), vomiting (32%), mucosal inflammation (31%), diarrhea (29%), decreased appetite (29%), stomatitis (26%), and cough (22%).

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, confusional 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 arrhythmia (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%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Serious adverse reactions occurred in 28% of patients; those ≥2% were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (29%), diarrhea (24%), and rash (24%).

Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

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.

Adverse reactions occurring in patients with esophageal 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 hepatocellular carcinoma (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 (≥1%) were hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (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 were hepatotoxicity (13%), diarrhea/colicitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). 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%).

Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

Adverse reactions occurring in patients with cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.
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](http://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 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. More information is available by calling 855-257-3932 or visiting [www.merckaccessprogram-keytruda.com](http://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 support. For further
information and to sign up, eligible patients may call 85-KEYTRUDA (855-398-7832) or visit www.keytruda.com.

About Merck

For more than 125 years, Merck, 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 in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. 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 the recent global outbreak of novel coronavirus disease (COVID-19); 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 2019 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).

Dr. Diaz is an uncompensated consultant for Merck. Dr. Diaz is also an inventor on a patent related to MSI as a predictor of response to PD-1 blockade.


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