



NEWS RELEASE

# FDA Approves Updated Indication for Merck's KEYTRUDA® (pembrolizumab) for Treatment of Certain Patients With Urothelial Carcinoma (Bladder Cancer)

8/31/2021

## KEYTRUDA Approved for Treatment of Patients With Locally Advanced or Metastatic Urothelial Carcinoma Who Are Not Eligible for Any Platinum-Containing Chemotherapy

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced a label update for KEYTRUDA, Merck's anti-PD-1 therapy, for its indication in first-line advanced urothelial carcinoma (bladder cancer) in the U.S. The U.S. Food and Drug Administration (FDA) has converted this indication from an accelerated to a full (regular) approval. In addition, as part of the label update, this indication has been revised to be for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for any platinum-containing chemotherapy.

Previously, KEYTRUDA was indicated for the treatment of patients with locally advanced or mUC who were not eligible for cisplatin-containing chemotherapy and whose tumors expressed PD-L1 (Combined Positive Score [CPS]  $\geq 10$ ), as determined by an FDA-approved test, or in patients who were not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication was approved under accelerated approval based on tumor response rate and duration of response. Continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. The subsequent Phase 3 trial KEYNOTE-361, evaluating KEYTRUDA as monotherapy and in combination with chemotherapy for the first-line treatment of patients with advanced or mUC who were eligible for platinum-containing chemotherapy, did not meet its pre-specified dual



primary endpoints of overall survival or progression-free survival, compared with standard of care chemotherapy.

This label update follows the FDA's Oncologic Drugs Advisory Committee (ODAC) meetings held earlier this year as part of an industry-wide evaluation of indications based on accelerated approvals that have not met their post-marketing requirements. As previously **announced**, members voted (5-3) in favor of maintaining the accelerated approval of KEYTRUDA for its first-line bladder indication.

"While the treatment landscape has evolved, an unmet need remains for appropriate patients newly diagnosed with certain types of advanced urothelial carcinoma who are not eligible for platinum-containing chemotherapy," said Dr. Scot Ebbinghaus, vice president, clinical research, Merck Research Laboratories. "We are confident in the role KEYTRUDA will continue to play for these patients who have few other treatment options and are working with urgency to advance studies to help more patients living with bladder and other types of cancer."

In addition to this first-line indication, KEYTRUDA is approved for the treatment of patients with locally advanced or 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 also approved for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Merck has an extensive clinical development program in bladder cancer and is advancing multiple studies evaluating KEYTRUDA as monotherapy and in combination with other anti-cancer therapies across multiple lines of therapy.

About KEYTRUDA® (pembrolizumab) Injection, 100 mg

KEYTRUDA is an anti-programmed death receptor-1 (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 1,500 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 benefitting from treatment with KEYTRUDA, including exploring several different biomarkers.

Selected KEYTRUDA® (pembrolizumab) Indications in the U.S.

## 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)  $\geq 1\%$ ] 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  $\geq 1\%$ ) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

## 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  $\geq 1$ )] as determined by an FDA-approved test.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with

disease progression on or after platinum-containing chemotherapy.

### Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

### 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. 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 any platinum-containing chemotherapy, or
- 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-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

### Microsatellite Instability-High or Mismatch Repair Deficient 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.

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.

#### Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

#### Gastric Cancer

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. 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 locally advanced or metastatic esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA-approved test.

#### 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  $\geq 1$ ) 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 adult patients with advanced renal cell carcinoma.

#### Tumor Mutational Burden-High Cancer

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] 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) or locally advanced cSCC that is not curable by surgery or radiation.

#### Triple-Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA-approved test.

## Selected Important Safety Information for KEYTRUDA

### Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the PD-1 or the PD-L1, blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. For patients with TNBC treated with KEYTRUDA in the neoadjuvant setting, monitor blood cortisol at baseline, prior to surgery, and as clinically indicated. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

#### Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Pneumonitis occurred in 8% (31/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grades 3-4 in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range:

2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 5.4% (21) of patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

### Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 69% (33/48); additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients.

### Hepatotoxicity and Immune-Mediated Hepatitis

#### KEYTRUDA as a Single Agent

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients.

#### KEYTRUDA with Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider monitoring more frequently 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. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased alanine aminotransferase (20%) and increased aspartate aminotransferase (13%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT  $\geq 3$  times upper limit of normal (ULN) (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT  $\geq 3$  times ULN was observed in 1 patient



receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT  $\geq$ 3 ULN subsequently recovered from the event.

### Immune-Mediated Endocrinopathies

#### Adrenal Insufficiency

KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

#### Hypophysitis

KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

#### Thyroid Disorders

KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8%

(237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 adult patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

#### Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 89% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

#### Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with anti-PD-1/PD-L1 treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38 patients.

#### Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other anti-PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. Cardiac/Vascular: Myocarditis, pericarditis, vasculitis; Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis; Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; Endocrine: Hypoparathyroidism; Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

## Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 reactions. For Grade 3 or Grade 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

## Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti-PD-1/PD-L1 treatment. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti-PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

## 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 an anti-PD-1/PD-L1 treatment 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 ( $\geq 20\%$ ) 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 ( $\geq 1\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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-204, KEYTRUDA was discontinued due to adverse reactions in 14% of 148 patients with cHL. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA; those  $\geq 1\%$  were pneumonitis, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from causes other than disease progression: 2 from complications after allogeneic HSCT and 1 from unknown cause. The most common adverse reactions ( $\geq 20\%$ ) were upper respiratory tract infection (41%), musculoskeletal pain (32%), diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

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  $\geq 1\%$  were 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 ( $\geq 20\%$ ) 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 ( $\geq 20\%$ ) 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 mUC. Serious adverse reactions occurred in 42% of patients; those  $\geq 2\%$  were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions ( $\geq 20\%$ ) 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 mUC. 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  $\geq 2\%$  were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions ( $\geq 20\%$ ) 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  $\geq 2\%$  were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions ( $\geq 20\%$ ) 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.

In KEYNOTE-811, when KEYTRUDA was administered in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 6% of 217 patients with locally advanced unresectable or metastatic HER2+ gastric or GEJ adenocarcinoma. The most common adverse

reaction resulting in permanent discontinuation was pneumonitis (1.4%). In the KEYTRUDA arm versus placebo, there was a difference of  $\geq 5\%$  incidence between patients treated with KEYTRUDA versus standard of care for diarrhea (53% vs 44%) and nausea (49% vs 44%).

The most common adverse reactions (reported in  $\geq 20\%$ ) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, and insomnia.

In KEYNOTE-590, when KEYTRUDA was administered with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation, KEYTRUDA was discontinued due to adverse reactions in 15% of 370 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ( $\geq 1\%$ ) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). The most common adverse reactions ( $\geq 20\%$ ) with KEYTRUDA in combination with chemotherapy were nausea (67%), fatigue (57%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

Adverse reactions occurring in patients with esophageal cancer who received KEYTRUDA as a monotherapy 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 ( $\geq 20\%$ ) 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 ( $\geq 1\%$ ) 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/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). The most common adverse reactions ( $\geq 20\%$ ) 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 recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-522, when KEYTRUDA was administered with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent (n=778) to patients with newly diagnosed, previously untreated, high-risk early-stage TNBC, fatal adverse reactions occurred in 0.9% of patients, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA; those  $\geq 2\%$  were febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%). KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions ( $\geq 1\%$ ) resulting in permanent discontinuation were increased ALT (2.7%), increased AST (1.5%), and rash (1%). The most common adverse reactions ( $\geq 20\%$ ) in patients receiving KEYTRUDA were fatigue (70%), nausea (67%), alopecia (61%), rash (52%), constipation (42%), diarrhea and peripheral neuropathy (41% each), stomatitis (34%), vomiting (31%), headache (30%), arthralgia (29%), pyrexia (28%), cough (26%), abdominal pain (24%), decreased appetite (23%), insomnia (21%), and myalgia (20%).

In KEYNOTE-355, when KEYTRUDA and chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) were administered to patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting (n=596), fatal adverse reactions occurred in 2.5% of patients, including cardio-respiratory arrest (0.7%) and septic shock (0.3%). Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemotherapy; the serious reactions in  $\geq 2\%$  were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%). KEYTRUDA was discontinued in 11% of



patients due to adverse reactions. The most common reactions resulting in permanent discontinuation ( $\geq 1\%$ ) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions ( $\geq 20\%$ ) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue (48%), nausea (44%), alopecia (34%), diarrhea and constipation (28% each), vomiting and rash (26% each), cough (23%), decreased appetite (21%), and headache (20%).

## 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

In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99 pediatric patients aged 12 years to 17 years) were administered KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months).

Adverse reactions that occurred at a  $\geq 10\%$  higher rate in pediatric patients when compared to adults were pyrexia (33%), vomiting (30%), leukopenia (30%), upper respiratory tract infection (29%), neutropenia (26%), headache (25%), and Grade 3 anemia (17%).

## 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 Merck

For over 130 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](http://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 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 2020 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site ([www.sec.gov](http://www.sec.gov)).

Please see Prescribing Information for KEYTRUDA (pembrolizumab) at [http://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf) and Medication Guide for KEYTRUDA at [http://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_mg.pdf](http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf).

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