



NEWS RELEASE

FDA Approves Merck's KEYTRUDA® (pembrolizumab) in Combination With Padcev® (enfortumab vedotin-ejfv) for First-Line Treatment of Certain Patients With Locally Advanced or Metastatic Urothelial Cancer

4/3/2023

First approved therapeutic regimen that combines an anti-PD-1 and an antibody-drug conjugate in the US in these patients

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA, Merck's anti-PD-1 therapy, in combination with Padcev (enfortumab vedotin-ejfv) for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (la/mUC) who are not eligible for cisplatin-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. This marks the first time an anti-PD-1 therapy has been approved in combination with an antibody-drug conjugate in the U.S. in these patients.

The approval is based on data from the KEYNOTE-869 trial (also known as EV-103) dose escalation cohort, Cohort A and Cohort K, which was conducted in collaboration with Seagen and Astellas. The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range, 0.7 to 52.4 months) and for Cohort K was 14.8 months (range, 0.6 to 26.2 months). In the combined efficacy analysis of the dose escalation cohort, Cohort A and Cohort K (n=121), KEYTRUDA in combination with enfortumab vedotin demonstrated an objective response rate (ORR) of 68% (95% CI: 58.7, 76.0), with complete and partial response rates of 12% and 55%, respectively. The median



duration of response (DOR) for the dose escalation cohort + Cohort A was 22.1 months (range, 1.0+ to 46.3+ months) and for Cohort K was not reached (range, 1.2 to 24.1+ months).

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time during or after treatment with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or permanently 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 is a major milestone in the treatment of patients with locally advanced or metastatic urothelial carcinoma because it is the first approved combination of an immunotherapy and an antibody-drug conjugate for these patients,” said Dr. Eliav Barr, senior vice president, head of global clinical development and chief medical officer, Merck Research Laboratories. “This expands the use of KEYTRUDA-based regimens to more patients with advanced urothelial carcinoma and demonstrates the value of collaboration in creating new combination approaches for patients in need of more options.”

Results from Cohort K were presented in a late-breaking session at the 2022 European Society for Medical Oncology Congress, and earlier results from dose escalation and Cohort A were published in the Journal of Clinical Oncology. The combination therapy was granted Breakthrough Therapy designation by the FDA in February 2020. The accelerated approval designation granted today is part of the FDA's Accelerated Approval Program, which allows earlier approval of a medicine based on a surrogate endpoint if the medicine fills an unmet medical need for a serious condition. The ongoing Phase 3 EV-302/KEYNOTE-A39 trial evaluating the clinical benefit of KEYTRUDA in combination with enfortumab vedotin in patients with previously untreated advanced urothelial cancer is intended to serve as the U.S. confirmatory trial for the accelerated approval. It will also serve as the basis for global registration.

Study design and additional data supporting the approval

The approval is based on data from KEYNOTE-869 (ClinicalTrials.gov, **NCT03288545**), an open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) study in patients with Ia/mUC who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease.

Patients with active central nervous system metastases, ongoing sensory or motor neuropathy Grade ≥ 2 or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) $\geq 8\%$ or HbA1c $\geq 7\%$ with associated diabetes symptoms were excluded from participating in this study.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received enfortumab vedotin 1.25 mg/kg as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by KEYTRUDA 200 mg as an IV infusion on Day 1 of a 21-day cycle approximately 30 minutes after enfortumab vedotin. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received KEYTRUDA in combination with enfortumab vedotin. The median age was 71 years (range, 51 to 91); 74% were male; 85% were White, 5% were Black, 4% were Asian, and 6% were other, unknown or not reported. Ten percent of patients were Hispanic or Latino. Forty-five percent of patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 and 15% had an ECOG performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of $< 5.7\%$. Reasons for cisplatin-ineligibility included: 60% with baseline creatinine clearance of 30-59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline, including 22% with liver metastases. Thirty-nine percent of patients had transitional cell carcinoma (TCC) histology, 13% had TCC with squamous differentiation and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DOR as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

In KEYNOTE-869, the safety of KEYTRUDA in combination with enfortumab vedotin was investigated in patients with locally advanced or metastatic urothelial carcinoma and who are not eligible for cisplatin-based chemotherapy. A total of 121 patients received KEYTRUDA 200 mg on Day 1, and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle. The median duration of exposure to KEYTRUDA was 6.9 months (range, 1 day to 29.6 months). Fatal adverse reactions occurred in 5% of patients treated with KEYTRUDA in combination with enfortumab vedotin, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis (0.8%). Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin; the serious adverse reactions in $\geq 2\%$ of patients were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), hematuria (3.3%), pneumonia (3.3%), pneumonitis (3.3%), sepsis (3.3%), anemia (2.5%), diarrhea (2.5%), hypotension (2.5%), myasthenia gravis (2.5%), myositis (2.5%), and urinary retention (2.5%). Permanent

discontinuation of KEYTRUDA occurred in 32% of patients. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of KEYTRUDA were pneumonitis (5%), peripheral neuropathy (5%), rash (3.3%), and myasthenia gravis (2.5%). The most common adverse reactions ($\geq 20\%$) occurring in patients treated with KEYTRUDA in combination with enfortumab vedotin were rash (71%), peripheral neuropathy (65%), fatigue (60%), alopecia (52%), weight loss (48%), diarrhea (45%), pruritus (40%), decreased appetite (38%), nausea (36%), dysgeusia (35%), urinary tract infection (30%), constipation (27%), peripheral edema (26%), dry eye (25%), dizziness (23%), arthralgia (23%), and dry skin (21%). Clinically relevant adverse reactions ($< 20\%$) include vomiting (19.8%), fever (18%), hypothyroidism (11%), pneumonitis (9%), myositis (3.3%), myasthenia gravis (2.5%), and infusion site extravasation (0.8%).

About bladder and urothelial cancer

It is estimated that approximately 82,290 people in the U.S. will be diagnosed with bladder cancer in 2023. Urothelial cancer accounts for about 90% of all bladder cancers and can also be found in the renal pelvis, ureters and urethra. Approximately 12% of cases are Ia/mUC at diagnosis, and some patients with metastatic disease may be ineligible for cisplatin-based chemotherapy due to certain factors such as medical comorbidities and performance status.

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 1,600 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.

Urothelial Carcinoma

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for cisplatin-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA, as a single agent, 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, as a single agent, 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.

See additional selected indications for KEYTRUDA in the U.S. after the Selected Important Safety Information.

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.

Pneumonitis occurred in 7% (41/580) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of KEYTRUDA in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% 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 (ALT) (20%) and increased aspartate aminotransferase (AST) (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 ≥ 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 ≥ 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 ≥ 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. The incidence of new or worsening hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving KEYTRUDA as a single agent as adjuvant treatment, including Grade 3 (0.2%) hyperthyroidism. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) 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 treatments. 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, when KEYTRUDA was administered as a single agent to patients with stage III melanoma, 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-716, when KEYTRUDA was administered as a single agent to patients with stage IIB or IIC melanoma, adverse reactions occurring in patients with stage IIB or IIC melanoma were similar to those occurring in 1011 patients with stage III melanoma from KEYNOTE-054.

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%).

Adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

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-869, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or mUC and who are not eligible for cisplatin-based chemotherapy (n=121), fatal adverse reactions occurred in 5% of patients, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis (0.8%). Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin; the serious adverse reactions in $\geq 2\%$ of patients were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), hematuria (3.3%), pneumonia (3.3%), pneumonitis (3.3%), sepsis (3.3%), anemia (2.5%), diarrhea (2.5%), hypotension (2.5%), myasthenia gravis (2.5%), myositis (2.5%), and urinary retention (2.5%). Permanent discontinuation of KEYTRUDA occurred in 32% of patients. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of KEYTRUDA were pneumonitis (5%), peripheral neuropathy (5%), rash (3.3%), and myasthenia gravis (2.5%). The most common adverse reactions ($\geq 20\%$) occurring in patients treated with KEYTRUDA in combination with enfortumab vedotin were rash (71%), peripheral neuropathy (65%), fatigue (60%), alopecia (52%), weight loss (48%), diarrhea (45%), pruritus (40%), decreased appetite (38%), nausea (36%), dysgeusia (35%), urinary tract infection (30%), constipation (27%), peripheral edema (26%), dry eye (25%), dizziness (23%), arthralgia (23%), and dry skin (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-158 and KEYNOTE-164, adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

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-826, when KEYTRUDA was administered in combination with paclitaxel and cisplatin or paclitaxel and

carboplatin, with or without bevacizumab (n=307), to patients with persistent, recurrent, or first-line metastatic cervical cancer regardless of tumor PD-L1 expression who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent, fatal adverse reactions occurred in 4.6% of patients, including 3 cases of hemorrhage, 2 cases each of sepsis and due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection. Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab; those $\geq 3\%$ were febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury and sepsis (3.3% each).

KEYTRUDA was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation ($\geq 1\%$) was colitis (1%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common adverse reactions ($\geq 20\%$) were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea and neutropenia (41% each), diarrhea (39%), hypertension and thrombocytopenia (35% each), constipation and arthralgia (31% each), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

For patients treated with KEYTRUDA in combination with chemotherapy with or without bevacizumab, the most common adverse reactions ($\geq 20\%$) were peripheral neuropathy (58%), alopecia (56%), fatigue (47%), nausea (40%), diarrhea (36%), constipation (28%), arthralgia (27%), vomiting (26%), hypertension and urinary tract infection (24% each), and rash (22%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with previously treated 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%).

In KEYNOTE-564, when KEYTRUDA was administered as a single agent for the adjuvant treatment of renal cell carcinoma, serious adverse reactions occurred in 20% of patients receiving KEYTRUDA; the serious adverse reactions ($\geq 1\%$) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% including 1 case of pneumonia. Discontinuation of KEYTRUDA due to adverse reactions occurred in 21% of 488 patients; the most common ($\geq 1\%$) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%). The most common adverse reactions ($\geq 20\%$) were musculoskeletal pain (41%), fatigue (40%), rash (30%), diarrhea (27%), pruritus (23%), and hypothyroidism (21%).

Adverse reactions occurring in patients with MSI-H or dMMR endometrial carcinoma who received KEYTRUDA as a single agent were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a single agent.

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 last dose.

Pediatric Use

In KEYNOTE-051, 173 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 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 25 months).

Adverse reactions that occurred at a $\geq 10\%$ higher rate in pediatric patients when compared to adults were pyrexia (33%), leukopenia (31%), vomiting (30%), neutropenia (29%), headache (25%), abdominal pain (23%), thrombocytopenia (22%), anemia (17%), decreased lymphocyte count (13%), and decreased white blood cell count (11%).

Additional Indications for KEYTRUDA 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 adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma 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.

KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.

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 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.

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, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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) as determined by an FDA-approved test.

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 gastroesophageal junction (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 ≥ 10) as determined by an FDA-approved test.

Cervical Cancer

KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (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 cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

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 (RCC).

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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) [≥ 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 ≥ 10) as determined by an FDA-approved test.

About the Astellas, Seagen and Merck collaboration

Astellas and Seagen entered a clinical collaboration agreement with Merck to evaluate the combination of Astellas' and Seagen's Padcev (enfortumab vedotin-ejfv) and Merck's KEYTRUDA® (pembrolizumab) in patients with previously untreated metastatic urothelial cancer. KEYTRUDA is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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 <https://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.

Merck's focus on cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of

research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. 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., Rahway, N.J., USA

This news release of Merck & Co., Inc., Rahway, 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 candidates that the candidates 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 Annual Report on Form 10-K for the year ended December 31, 2022 and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

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

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