



NEWS RELEASE

## FDA Approves New Monotherapy Indication for Merck's KEYTRUDA® (pembrolizumab)

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KEYTRUDA Now Approved for Recurrent Locally Advanced or Metastatic Squamous Cell Carcinoma of the Esophagus in Patients Whose Tumors Express PD-L1 (CPS  $\geq 10$ ) With Disease Progression After One or More Prior Lines of Systemic Therapy

KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved KEYTRUDA, Merck's anti-PD-1 therapy, as monotherapy for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (Combined Positive Score [CPS]  $\geq 10$ ) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

"Historically, patients with advanced esophageal cancer have had limited treatment options, particularly after their disease has progressed," said Dr. Jonathan Cheng, vice president, oncology clinical research, Merck Research Laboratories. "With this approval, KEYTRUDA is now the first anti-PD-1 therapy approved for the treatment of previously-treated patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS  $\geq 10$ ), providing an important new monotherapy option for physicians and patients in the United States."

Immune-mediated adverse reactions, which may be severe or fatal, can occur with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, severe skin reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation (HSCT). Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if

appropriate. KEYTRUDA can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. For more information, see “Selected Important Safety Information” below.

## About KEYNOTE-181 and KEYNOTE-180

The approval was based on data from KEYNOTE-181 (**NCT02564263**), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either KEYTRUDA 200 mg every three weeks or investigator’s choice of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m<sup>2</sup> on Days 1, 8, and 15 of every four-week cycle, docetaxel 75 mg/m<sup>2</sup> every three weeks, or irinotecan 180 mg/m<sup>2</sup> every two weeks. Randomization was stratified by tumor histology (esophageal squamous cell carcinoma [ESCC] vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least four weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every nine weeks. The major efficacy outcome measure was overall survival (OS) evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS  $\geq 10$ , and all randomized patients. Additional efficacy outcome measures were progression-free survival (PFS), objective response rate (ORR), and duration of response (DoR), according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ, as assessed by blinded independent central review (BICR).

The observed hazard ratios for OS were 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS  $\geq 10$ , and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination, in patients whose ESCC tumors expressed PD-L1 (CPS  $\geq 10$ ), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy.

In ESCC patients with PD-L1 expression (CPS  $\geq 10$ ), there were 68 events (80%) observed for patients receiving KEYTRUDA (n=85) and 72 events (88%) observed for patients receiving chemotherapy (n=82). There was a median OS in patients receiving KEYTRUDA of 10.3 months (95% CI: 7.0, 13.5) compared with 6.7 months in the chemotherapy arm (95% CI: 4.8, 8.6) (HR=0.64 [95% CI: 0.46, 0.90]). The median PFS was 3.2 months (range, 2.1, 4.4 months) for patients receiving KEYTRUDA and 2.3 months (range, 2.1, 3.4 months) for patients receiving chemotherapy (HR=0.66 [95% CI: 0.48, 0.92]). The ORR was 22% (95% CI: 14.0, 33.0) in patients receiving KEYTRUDA, with a complete response rate (CRR) of 5% (n=4) and partial response rate of 18% (n=15). In the chemotherapy arm, the ORR was 7% (95% CI: 3.0, 15.0), with a CRR of 1% (n=1) and partial response rate of 6% (n=5). The median duration of response was 9.3 months (range, 2.1+, 18.8+) in patients receiving KEYTRUDA and 7.7 months (range, 4.3, 16.8+) in the chemotherapy arm.

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range, 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2,799 patients with melanoma or non-small cell lung cancer (NSCLC) treated with KEYTRUDA as a single agent.

This indication was also based on data from KEYNOTE-180 (**NCT02559687**), a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least two prior systemic treatments for advanced disease. With the exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181.

The major efficacy outcome measures were ORR and DoR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ, as assessed by BICR.

The ORR in the 35 patients with ESCC expressing PD-L1 (CPS  $\geq 10$ ) was 20% (95% CI: 8.0, 37.0). Among the seven responding patients, the DoR ranged from 4.2 to 25.1+ months, with five patients (71%) having responses of six months or longer and three patients (57%) having responses of 12 months or longer.

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

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck has the industry's largest immuno-oncology clinical research program. There are currently more than 1,000 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.

## KEYTRUDA® (pembrolizumab) Indications and Dosing

### Melanoma

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma. The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months in patients without disease recurrence.

### 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.

In NSCLC, the recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without

disease progression.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

### Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. In SCLC, the recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

### Head and Neck 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.

In HNSCC, the recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

### Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. In adults with cHL, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. In pediatric patients with cHL, KEYTRUDA is administered as an intravenous infusion over 30 minutes at a dose of 2 mg/kg (up to a maximum of 200 mg) every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

#### Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. KEYTRUDA is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy.

In adults with PMBCL, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

#### Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [CPS  $\geq 10$ ] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

In locally advanced or metastatic urothelial carcinoma, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

### Microsatellite Instability-High (MSI-H) Cancer

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

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

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

In adult patients with MSI-H cancer, KEYTRUDA 200 mg is administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

### Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS  $\geq 1$ ) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

### Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell

carcinoma of the esophagus whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

In patients with esophageal cancer, the recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

### Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS  $\geq 1$ ) 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. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

### Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The recommended dose of KEYTRUDA is 200 mg as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

### Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.



## Renal Cell Carcinoma

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

## Selected Important Safety Information for KEYTRUDA

### Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 3.4% (94/2799) of patients with various cancers receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%). Pneumonitis occurred in 8.2% (65/790) of NSCLC patients receiving KEYTRUDA as a single agent, including Grades 3-4 in 3.2% of patients, and occurred more frequently in patients with a history of prior thoracic radiation (17%) compared to those without (7.7%). Pneumonitis occurred in 6% (18/300) of HNSCC patients receiving KEYTRUDA as a single agent, including Grades 3-5 in 1.6% of patients, and occurred in 5.4% (15/276) of patients receiving KEYTRUDA in combination with platinum and FU as first-line therapy for advanced disease, including Grade 3-5 in 1.5% of patients.

Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

### Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%). Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

### Immune-Mediated Hepatitis (KEYTRUDA) and Hepatotoxicity (KEYTRUDA in Combination with Axitinib)

## Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%). Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

## Hepatotoxicity in Combination with Axitinib

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

## Immune-Mediated Endocrinopathies

KEYTRUDA can cause hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Hypophysitis occurred in 0.6% (17/2799) of patients, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%). Hypothyroidism occurred in 8.5% (237/2799) of patients, including Grade 2 (6.2%) and 3 (0.1%). The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC (16%), receiving KEYTRUDA, as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. Hyperthyroidism occurred in 3.4% (96/2799) of patients, including Grade 2 (0.8%) and 3 (0.1%), and thyroiditis occurred in 0.6% (16/2799) of patients, including Grade 2 (0.3%). Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 0.2% (6/2799) of patients.

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

## Immune-Mediated Nephritis and Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Nephritis occurred in 0.3% (9/2799) of patients receiving

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

## Immune-Mediated Skin Reactions

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

## Other Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA and may also occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including cHL, and postmarketing use.

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

## Infusion-Related Reactions

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

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

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

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

## Increased Mortality in Patients With Multiple Myeloma

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

## Embryofetal Toxicity

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

## Adverse Reactions

In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). The most common adverse reactions ( $\geq 20\%$ ) 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; 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 occurring in patients with SCLC were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse events in 12% of 300 patients with HNSCC; the most common adverse reactions leading to permanent discontinuation were sepsis (1.7%) and pneumonia (1.3%). The most common adverse reactions ( $\geq 20\%$ ) 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-087, KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL. Serious adverse reactions occurred in 16% of patients; those  $\geq 1\%$  included pneumonia, pneumonitis, pyrexia, dyspnea, GVHD, and herpes zoster. Two patients died from causes other than disease progression; 1 from GVHD after subsequent allogeneic HSCT and 1 from septic shock. The most common adverse reactions ( $\geq 20\%$ ) 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 metastatic urothelial carcinoma. 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 metastatic urothelial carcinoma. The most common adverse reaction resulting in permanent discontinuation of

KEYTRUDA was pneumonitis (1.9%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients; those  $\geq 2\%$  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%).

Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA; the most frequent included anemia (7%), fistula, hemorrhage, and infections [except urinary tract infections] (4.1% each). The most common adverse reactions ( $\geq 20\%$ ) 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 of which ( $\geq 1\%$ ) included 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 adverse reactions ( $>1\%$ ) resulting in permanent discontinuation of KEYTRUDA, axitinib or the combination were hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). When KEYTRUDA was used in combination with axitinib, the most common adverse reactions ( $\geq 20\%$ ) 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%).

## Lactation

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

## Pediatric Use

There is limited experience in pediatric patients. In a trial, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with various cancers, including unapproved usages, were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1–17 doses), with 34 patients (85%) receiving 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults; adverse reactions that occurred at a higher rate ( $\geq 15\%$  difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), increased transaminases (28%), and hyponatremia (18%).

## Merck's Focus on Cancer

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

## About the Merck Access Program for KEYTRUDA

At Merck, we are committed to supporting accessibility to our cancer medicines. Merck provides multiple programs to help appropriate patients who are prescribed KEYTRUDA have access to our anti-PD-1 therapy. The Merck Access Program provides reimbursement support for patients receiving KEYTRUDA, including information to help with out-of-pocket costs and co-pay assistance for eligible patients. More information is available by calling 855-257-3932 or visiting [www.merckaccessprogram-keytruda.com](http://www.merckaccessprogram-keytruda.com).

## About Merck's Patient Support Program for KEYTRUDA



Merck is committed to helping provide patients and their caregivers support throughout their treatment with KEYTRUDA. The KEY+YOU Patient Support Program provides a range of resources and support. For further information and to sign up, eligible patients may call 85-KEYTRUDA (855-398-7832) or visit [www.keytruda.com](http://www.keytruda.com).

## About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit [www.merck.com](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 pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from

those described in the forward-looking statements can be found in the company's 2018 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site ([www.sec.gov](http://www.sec.gov)).

Please see Prescribing Information for KEYTRUDA 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).

Media Contacts:

Pamela Eisele  
(267) 305-3558

Justine Moore  
(347) 281-3754

Investor Contacts:

Teri Loxam  
(908) 740-1986

Michael DeCarbo  
(908) 740-1807