



NEWS RELEASE

Merck Receives Two Positive EU CHMP Opinions for KEYTRUDA® (pembrolizumab), for Subcutaneous (SC) Administration and for New Indication for Earlier-Stage Head and Neck Cancer

2025-09-19

Positive opinion granted for SC administration of KEYTRUDA for all adult indications approved in the European Union for KEYTRUDA

Positive opinion also granted for KEYTRUDA as part of a perioperative regimen for the treatment of certain adult patients with resectable locally advanced head and neck squamous cell carcinoma (LA-HNSCC) based on results of Phase 3 KEYNOTE-689 trial

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted two positive opinions for KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy. One recommends approval of a new subcutaneous (SC) route of administration and a new pharmaceutical form (solution for injection) for KEYTRUDA® (pembrolizumab), which if approved would be marketed in the European Union (EU) as KEYTRUDA SC™. The other positive opinion recommends approval of a new indication in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). The CHMP recommendations will now be reviewed by the European Commission (EC) for marketing authorization in the EU, Iceland, Liechtenstein and Norway, and final decisions are expected in the fourth quarter of 2025.

"Building on the legacy of KEYTRUDA, we are committed to driving innovation in cancer care with new routes of administration and indications in difficult-to-treat and earlier stages of cancer," said Dr. Marjorie Green, senior vice

president and head of oncology, global clinical development, Merck Research Laboratories. “This is a significant step forward in our pursuit of bringing this therapy to more patients. If approved, we believe KEYTRUDA SC has the potential to provide meaningful benefits to patients and providers in Europe because it can offer a shorter administration time compared to KEYTRUDA and the option to receive treatment in additional health care settings.”

The first CHMP opinion recommends approval of KEYTRUDA SC as a subcutaneous, or under the skin, injection administered by a health care provider. If approved, KEYTRUDA SC could be administered in one minute every three weeks (395 mg) or in two minutes every six weeks (790 mg). As a subcutaneous injection, a health care provider would be able to administer KEYTRUDA SC in multiple settings, providing more options where patients can receive their treatment. The CHMP’s positive opinion applies to all KEYTRUDA indications for adult patients in Europe. KEYTRUDA SC contains pembrolizumab and berahyaluronidase alfa, a variant of human hyaluronidase, developed and manufactured by Alteogen Inc.

The marketing authorization application for KEYTRUDA SC is based on results from the pivotal 3475A-D77 trial comparing KEYTRUDA SC and KEYTRUDA administered every six weeks, each with chemotherapy, studied in patients with treatment naïve metastatic non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 genomic tumor aberrations. This trial demonstrated comparable pharmacokinetic exposure levels between KEYTRUDA SC and KEYTRUDA. The secondary efficacy endpoints of objective response rate (ORR) and progression-free survival (PFS), which were descriptive analyses, were consistent for KEYTRUDA SC with chemotherapy compared to KEYTRUDA with chemotherapy. The ORR in the KEYTRUDA SC with chemotherapy arm was 45.4% (95% CI, 39.1-51.8) and 42.1% (95% CI, 33.3-51.2) in the KEYTRUDA with chemotherapy arm.

Results from the trial were **presented** at the European Lung Cancer Congress (ELCC) 2025 in March and **published** simultaneously in Annals of Oncology. A Biologics License Application (BLA) seeking approval of subcutaneous pembrolizumab for use in adults across all previously approved solid tumor indications for KEYTRUDA is currently under review in the U.S. with a Prescription Drug User Fee Act (PDUFA), or target action, date of Sept. 23, 2025.

The second CHMP opinion recommends approval of KEYTRUDA as monotherapy for the treatment of resectable locally advanced head and neck squamous cell carcinoma (LA-HNSCC) as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumors express PD-L1 with a Combined Positive Score (CPS) ≥ 1 . This treatment regimen would be the first perioperative anti-PD-1 treatment option for certain patients with resectable LA-HNSCC in the EU.

The recommendation for resectable LA-HNSCC is based on results from the pivotal Phase 3 KEYNOTE-689 trial. At the trial’s first pre-specified interim analysis, the KEYTRUDA-based perioperative regimen demonstrated a

statistically significant and clinically meaningful improvement in event-free survival (EFS), the study's primary endpoint, compared to adjuvant radiotherapy (RT) (with or without cisplatin) alone in patients with tumors expressing PD-L1 (CPS ≥ 1). Results from the trial were **presented** at the American Association for Cancer Research (AACR) Annual Meeting in April 2025 and also **published** in The New England Journal of Medicine in June 2025. In **June 2025**, KEYTRUDA was approved in the U.S. for the treatment of adult patients with resectable LA-HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by a Food and Drug Administration (FDA)-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin and then as a single agent.

About Subcutaneous Administration

Subcutaneous administration is a method of delivering medications under the skin. As an alternative to intravenous infusion, subcutaneous administration potentially offers more options where patients can receive their treatment because it can be administered by healthcare providers in multiple settings from an infusion center to a doctor's office or a local community-based clinic. For patients who do not require a port or whose veins are difficult to access, subcutaneous administration may simplify treatment administration.

About head and neck cancer

Head and neck cancer describes a number of different tumors that develop in or around the throat, larynx, nose, sinuses and mouth. It is estimated there were more than 947,200 new cases of head and neck cancer diagnosed and more than 482,400 deaths from the disease in 2022 globally. In Europe, it is estimated there were approximately 161,900 new cases of head and neck cancer and more than 72,500 deaths from the disease in 2022. These data include cancers of the oral cavity, pharynx and larynx. Most head and neck cancers are squamous cell carcinomas, which begin in the flat, squamous cells that make up the thin mucosal lining of the head and neck. Locally advanced head and neck squamous cell carcinoma is cancer that has spread from where it started to nearby tissue or lymph nodes but has not yet spread to distant parts of the body. There are several factors that greatly increase the risk of developing head and neck cancer, including tobacco and alcohol use and human papillomavirus.

About Merck's early-stage cancer clinical program

Finding cancer at an earlier stage may give patients a greater chance of long-term survival. Many cancers are considered most treatable and potentially curable in their earliest stage of disease. Building on the strong understanding of the role of KEYTRUDA in later-stage cancers, Merck is evaluating our portfolio of medicines and pipeline candidates in earlier disease states, with approximately 30 ongoing registrational studies across multiple types of cancer.

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.

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 is indicated for the treatment of patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in

combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

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

Malignant Pleural Mesothelioma

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and Neck Squamous Cell Cancer

KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 [Combined Positive Score (CPS) $\geq$ 1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent 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 (CPS $\geq$ 1) as determined by an FDA-approved test.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma

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

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

Primary Mediastinal Large B-Cell Lymphoma

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

Urothelial Cancer

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:

- 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.

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 adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA approved test.

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 for patients with tumors that express PD-L1 (CPS ≥ 1), 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 chemoradiotherapy (CRT), is indicated for the treatment of patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).

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) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

Biliary Tract Cancer

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

Merkel Cell Carcinoma

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

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, in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

KEYTRUDA, as a single agent, is indicated for the treatment of adult 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.

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.

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 programmed death receptor-1 (PD-1) or the programmed death ligand 1 (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, other transplant (including corneal graft) 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 treatments 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%).

In KEYNOTE-671, adverse reactions occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as single-agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

The most common adverse reactions (reported in $\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy or chemoradiotherapy 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, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, hypothyroidism, radiation skin injury, dysphagia, dry mouth, and musculoskeletal pain.

In the neoadjuvant phase of KEYNOTE-671, when KEYTRUDA was administered in combination with platinum-containing chemotherapy as neoadjuvant treatment, serious adverse reactions occurred in 34% of 396 patients. The most frequent ($\geq 2\%$) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%). Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy; the most frequent adverse reactions ($\geq 1\%$) that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the KEYTRUDA-treated patients who received neoadjuvant treatment, 6% of 396 patients did not receive surgery due to adverse reactions. The most frequent ($\geq 1\%$) adverse reaction that led to cancellation of surgery in the KEYTRUDA arm was interstitial lung disease (1%).

In the adjuvant phase of KEYNOTE-671, when KEYTRUDA was administered as a single agent as adjuvant treatment, serious adverse reactions occurred in 14% of 290 patients. The most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 12% of patients who received KEYTRUDA as a single agent, given as adjuvant treatment; the most frequent adverse reactions ($\geq 1\%$) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1%), and musculoskeletal pain (1%).

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.

Adverse reactions observed in KEYNOTE-483 were generally similar to those occurring in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

In KEYNOTE-689, the most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), dry mouth (22%), diarrhea (22%), and musculoskeletal pain (22%).

In the neoadjuvant phase of KEYNOTE-689, of the 361 patients who received at least one dose of single agent

KEYTRUDA, 11% experienced serious adverse reactions. Serious adverse reactions that occurred in more than one patient were pneumonia (1.4%), tumor hemorrhage (0.8%), dysphagia (0.6%), immune-mediated hepatitis (0.6%), cellulitis (0.6%), and dyspnea (0.6%). Fatal adverse reactions occurred in 1.1% of patients, including respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each). Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 2.8% of patients who received KEYTRUDA as neoadjuvant treatment. The most frequent adverse reaction which resulted in permanent discontinuation of neoadjuvant KEYTRUDA in more than one patient was arthralgia (0.6%).

Of the 361 patients who received KEYTRUDA as neoadjuvant treatment, 11% did not receive surgery. Surgical cancellation on the KEYTRUDA arm was due to disease progression in 4%, patient decision in 3%, adverse reactions in 1.4%, physician's decision in 1.1%, unresectable tumor in 0.6%, loss of follow up in 0.3%, and use of non-study anti-cancer therapy in 0.3%.

Of the 323 KEYTRUDA-treated patients who received surgery following the neoadjuvant phase, 1.2% experienced delay of surgery (defined as on-study surgery occurring ≥ 9 weeks after initiation of neoadjuvant KEYTRUDA) due to adverse reactions, and 2.8% did not receive adjuvant treatment due to adverse reactions.

In the adjuvant phase of KEYNOTE-689, of the 255 patients who received at least one dose of KEYTRUDA, 38% experienced serious adverse reactions. The most frequent serious adverse reactions reported in $\geq 1\%$ of KEYTRUDA-treated patients were pneumonia (2.7%), pyrexia (2.4%), stomatitis (2.4%), acute kidney injury (2.0%), pneumonitis (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhea (1.2%), dysphagia (1.2%), gastrostomy tube site complication (1.2%), and immune-mediated hepatitis (1.2%). Fatal adverse reactions occurred in 5% of patients, including death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%), and gastrointestinal hemorrhage (0.4%). Permanent discontinuation of adjuvant KEYTRUDA due to an adverse reaction occurred in 17% of patients. The most frequent ($\geq 1\%$) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were pneumonitis, colitis, immune-mediated hepatitis, and death not otherwise specified.

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-A39, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer (n=440), fatal adverse reactions occurred in 3.9% of patients, including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%). 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 rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection

(3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%). Permanent discontinuation of KEYTRUDA occurred in 27% of patients. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of KEYTRUDA were pneumonitis/ILD (4.8%) and rash (3.4%). The most common adverse reactions ($\geq 20\%$) occurring in patients treated with KEYTRUDA in combination with enfortumab vedotin were rash (68%), peripheral neuropathy (67%), fatigue (51%), pruritus (41%), diarrhea (38%), alopecia (35%), weight loss (33%), decreased appetite (33%), nausea (26%), constipation (26%), dry eye (24%), dysgeusia (21%), and urinary tract infection (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%).

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, fatal adverse reactions occurred in 3 patients who received KEYTRUDA in combination with trastuzumab and CAPOX (capecitabine plus oxaliplatin) or FP (5-FU plus cisplatin) and included pneumonitis in 2 patients and hepatitis in 1 patient. KEYTRUDA was discontinued due to adverse reactions in 13% of 350 patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma. Adverse reactions

resulting in permanent discontinuation of KEYTRUDA in $\geq 1\%$ of patients were pneumonitis (2.0%) and pneumonia (1.1%). In the KEYTRUDA arm vs placebo, there was a difference of $\geq 5\%$ incidence between patients treated with KEYTRUDA vs standard of care for diarrhea (53% vs 47%), rash (35% vs 28%), hypothyroidism (11% vs 5%), and pneumonia (11% vs 5%).

In KEYNOTE-859, when KEYTRUDA was administered in combination with fluoropyrimidine- and platinum-containing chemotherapy, serious adverse reactions occurred in 45% of 785 patients. Serious adverse reactions in $>2\%$ of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%). Fatal adverse reactions occurred in 8% of patients who received KEYTRUDA, including infection (2.3%) and thromboembolism (1.3%). KEYTRUDA was permanently discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) were infections (1.8%) and diarrhea (1.0%). The most common adverse reactions (reported in $\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were peripheral neuropathy (47%), nausea (46%), fatigue (40%), diarrhea (36%), vomiting (34%), decreased appetite (29%), abdominal pain (26%), palmar-plantar erythrodysesthesia syndrome (25%), constipation (22%), and weight loss (20%).

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-A18, when KEYTRUDA was administered with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) to patients with FIGO 2014 Stage III-IVA cervical cancer, fatal adverse reactions occurred in 1.4% of 294 patients, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage. Serious adverse reactions occurred in 34% of patients; those $\geq 1\%$ included urinary tract infection (3.1%), urosepsis (1.4%), and sepsis (1%). KEYTRUDA was discontinued for adverse reactions in 9% of patients. The most common adverse reaction ($\geq 1\%$) resulting in permanent discontinuation was diarrhea (1%). For patients treated with KEYTRUDA in combination with CRT, the most common adverse reactions ($\geq 10\%$) were nausea (56%), diarrhea (51%), urinary tract infection (35%), vomiting (34%), fatigue (28%), hypothyroidism (23%),

constipation (20%), weight loss (19%), decreased appetite (18%), pyrexia (14%), abdominal pain and hyperthyroidism (13% each), dysuria and rash (12% each), back and pelvic pain (11% each), and COVID-19 (10%).

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%).

In KEYNOTE-394, KEYTRUDA was discontinued due to adverse reactions in 13% of 299 patients with previously treated hepatocellular carcinoma. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was ascites (2.3%). The most common adverse reactions in patients receiving KEYTRUDA ($\geq 10\%$) were

pyrexia (18%), rash (18%), diarrhea (16%), decreased appetite (15%), pruritus (12%), upper respiratory tract infection (11%), cough (11%), and hypothyroidism (10%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of 529 patients with locally advanced unresectable or metastatic biliary tract cancer. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) was pneumonitis (1.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ($\geq 2\%$) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood cell count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In KEYNOTE-017 and KEYNOTE-913, adverse reactions occurring in patients with MCC (n=105) were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a single agent.

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%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma (n=382), serious adverse reactions occurred in 35% of patients receiving KEYTRUDA in combination with chemotherapy, compared to 19% of patients receiving placebo in combination with chemotherapy (n=377). Fatal adverse reactions occurred in 1.6% of patients receiving

KEYTRUDA in combination with chemotherapy, including COVID-19 (0.5%) and cardiac arrest (0.3%). KEYTRUDA was discontinued for an adverse reaction in 14% of patients. Adverse reactions occurring in patients treated with KEYTRUDA and chemotherapy were generally similar to those observed with KEYTRUDA alone or chemotherapy alone, with the exception of rash (33% all Grades; 2.9% Grades 3-4).

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 (including 108 pediatric patients aged 12 years to 17 years) were administered intravenous pembrolizumab 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 (30%), vomiting (29%), neutropenia (28%), headache (25%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (17%), decreased lymphocyte count (13%), and decreased white blood cell count (11%).

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with melanoma, cHL, PMBCL, MCC, and MSI-H or dMMR cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

The safety and effectiveness of KEYTRUDA in pediatric patients have not been established in the other approved indications shown.

Geriatric Use

Of the 564 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in combination with enfortumab vedotin, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with KEYTRUDA in combination with enfortumab vedotin experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Merck's focus on cancer

Every day, we follow the science as we work to discover innovations that can help patients, no matter what stage of

cancer they have. As a leading oncology company, we are pursuing research where scientific opportunity and medical need converge, underpinned by our diverse pipeline of more than 25 novel mechanisms. With one of the largest clinical development programs across more than 30 tumor types, we strive to advance breakthrough science that will shape the future of oncology. By addressing barriers to clinical trial participation, screening and treatment, we work with urgency to reduce disparities and help ensure patients have access to high-quality cancer care. Our unwavering commitment is what will bring us closer to our goal of bringing life to more patients with cancer. For more information, visit <http://www.merck.com/research/oncology>.

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 **X (formerly 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 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, 2024 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.

Media Contacts:

Julie Cunningham
(617) 519-6264

Diane Foley
(862) 260-0060

Verena Vorwald
(862) 783-6546

Investor Contacts:

Peter Dannenbaum
(732) 594-1579

Steven Graziano
(732) 594-1583

Source: Merck & Co., Inc.