KEYTRUDA® (pembrolizumab) Injection 100 mg



# A Key to More Possibilities for Treating Your Patients

KEYTRUDA is approved for 41 indications across 18 types of cancer

One indication is for the treatment of patients with resectable (tumors ≥4 cm or node positive) non–small cell lung cancer (NSCLC) in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

View Selected Indications

Scroll below to review Selected Safety Information

## Selected Safety Information

**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.

**Before prescribing KEYTRUDA, please read the additional Selected Safety Information on the following page and the accompanying Prescribing Information. The Medication Guide also is available.**

# Selected Indications

For KEYTRUDA® (pembrolizumab)

| | |
|---|---|
| **Advanced Melanoma or Adjuvant Therapy for Melanoma** | KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.<br>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. |
| **Advanced NSCLC, Adjuvant, or Neoadjuvant Therapy for Resectable Non-Small Cell Lung Cancer (NSCLC)** | 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.<br>KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC).<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) expressing programmed death ligand 1 (PD-L1) [tumor proportion score (TPS) ≥1%] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.<br>• Stage III where patients are not candidates for surgical resection or definitive chemoradiation, or<br>• Metastatic. |
| **Advanced Head and Neck Squamous Cell Cancer (HNSCC) or Neoadjuvant Followed by Adjuvant Therapy for Resectable Locally Advanced HNSCC** | KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or unresectable, recurrent head and neck squamous cell cancer (HNSCC).<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic or unresectable, recurrent head and neck squamous cell cancer (HNSCC) whose tumors express PD-L1 [CPS ≥1] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with resectable locally advanced head and neck squamous cell cancer (HNSCC) who are at high risk for recurrence. |
| **Relapsed or Refractory Classical Hodgkin Lymphoma (cHL)** | KEYTRUDA is indicated for the treatment of adult and pediatric patients with relapsed or refractory classical Hodgkin lymphoma (cHL) at 10 kg or greater, who have failed autologous HSCT and brentuximab vedotin or who are ineligible for autologous HSCT and have failed brentuximab vedotin. |
| **Refractory or Relapsed Primary Mediastinal Large B-Cell Lymphoma (PMBCL)** | 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 two or more prior lines of therapy. KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy. |
| **Locally Advanced or Metastatic Urothelial Cancer** | KEYTRUDA, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC).<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial cancer (mUC) who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [CPS ≥10] as determined by an FDA-approved test.<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial cancer (mUC) who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.<br>KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-containing chemotherapy for patients with ypT2-4 or ypN+ disease, and as monotherapy for patients with pT2-4 or pN+ disease who are not eligible for cisplatin-containing chemotherapy. |
| **High-Risk Non-muscle Invasive Bladder Cancer (NMIBC)** | KEYTRUDA, as a single agent, is indicated for the treatment of patients with Bacillus Calmette-Guérin (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. |
| **Advanced RCC in Combination** | 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) colorectal cancer (CRC) as determined by an FDA-approved test. |
| **Advanced RCC in Combination with Axitinib** | KEYTRUDA, in combination with pembrolizumab and axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC). |
| **Advanced RCC with Lenvatinib** | KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC). |
| **Advanced MSI-H/dMMR Colorectal Cancer (CRC)** | KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the first-line treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC) as determined by an FDA-approved test. |
| **Advanced MSI-H/dMMR Endometrial Cancer (EC)** | KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma (EC) that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), as determined by an FDA-approved test, who have disease progression during or following prior systemic therapy and are not candidates for curative surgery or radiation.<br>KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma (EC) that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), as determined by an FDA-approved test, who have disease progression during or following any prior systemic therapy and are not candidates for curative surgery or radiation. |
| **Advanced Esophageal or GEJ Carcinoma** | KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) adenocarcinoma expressing PD-L1 [combined positive score (CPS) ≥1] as determined by an FDA-approved test, with disease progression after one or more prior lines of therapy.<br>• in combination with platinum and fluoropyrimidine chemotherapy, or<br>• tumors that express PD-L1 [CPS ≥1], or<br>• tumors that express PD-L1 [CPS ≥10] at the time of systemic therapy for patients with tumors of esophageal adenocarcinoma or GEJ adenocarcinoma (GEJ tumor with epicenter 1 to 5 cm into the esophagus). |
| **Advanced Cervical Cancer** | KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with newly diagnosed, locally advanced cervical cancer (LACC) that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), as determined by an FDA-approved test.<br>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. |
| **Advanced Biliary Tract Cancer (BTC)** | KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC). |
| **Advanced Merkel Cell Carcinoma (MCC)** | KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC). |
| **Adjuvant Treatment for RCC or Intermediate-Cell Carcinoma (RCC)** | KEYTRUDA is indicated for the adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate or high risk of recurrence, or with locally advanced disease, following nephrectomy or resection of metastatic lesions. |
| **Advanced Endometrial Carcinoma** | KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC).<br>KEYTRUDA, as a single agent, is indicated for the treatment of adult patients with advanced endometrial carcinoma (EC) that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), as determined by an FDA-approved test, who have disease progression during or following any prior systemic therapy and are not candidates for curative surgery or radiation. |
| **Advanced Cutaneous Squamous Cell Carcinoma (cSCC)** | 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. |
| **High-Risk Early-Stage or Advanced Triple-Negative Breast Cancer (TNBC)** | KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) as neoadjuvant treatment, and after surgery as adjuvant treatment.<br>KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) as determined by an FDA-approved test. |

Scroll below to review Selected Safety Information

View Cancer Types

### Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a PD-1 blocking antibody. Other drugs that target the PD-1 pathway in humans have resulted in severe 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 during or after treatment with KEYTRUDA. Immune-mediated adverse reactions usually first manifest during treatment, but they can also manifest after discontinuation of KEYTRUDA. Early identification and management are essential to ensure safe use of KEYTRUDA. Monitor patients for signs and symptoms that may be consistent with an immune-mediated adverse reaction. 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. Initiate medical management for control of immune-related toxicities as soon as possible. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

#### Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in patients receiving KEYTRUDA, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2, and permanently discontinue KEYTRUDA for Grade 3 or greater pneumonitis.

Pneumonitis occurred in patients receiving KEYTRUDA monotherapy or in combination therapy, including Grade 3, 4, and 5 pneumonitis. Pneumonitis occurred in 7% (81/1567) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (1.3%) and Grade 2 (4.7%) pneumonitis. Pneumonitis occurred in 3.4% (30/865) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for neoadjuvant treatment of NSCLC, including Grade 3 (0.8%) and Grade 2 (2.4%) pneumonitis. Pneumonitis occurred in 2.7% (25/913) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment, including Grade 3 (0.8%) and Grade 2 (1.8%) pneumonitis. Pneumonitis occurred in 3.5% (26/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including 2 Grade 5 events. Pneumonitis occurred in 2.9% (21/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including 1 Grade 5 event. Pneumonitis occurred in 4.7% (11/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (1.3%) and Grade 2 (3.4%) pneumonitis. Pneumonitis occurred in 4.1% (10/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (1.2%) and Grade 2 (2.9%) pneumonitis. Pneumonitis occurred in 26 (0.6%) of patients. Of the patients who were evaluated for pneumonitis, 54% were interrupted KEYTRUDA, 62% 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 immune-mediated colitis who were refractory to corticosteroid therapy. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3 colitis and permanently discontinue KEYTRUDA for Grade 4 colitis or recurrent colitis.

Colitis occurred in patients receiving KEYTRUDA, including perforation and fatal cases. Colitis occurred in 1.4% (22/1567) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) and Grade 2 (0.8%) colitis. Colitis occurred in 0.8% (7/865) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for neoadjuvant treatment of NSCLC, including Grade 3 (0.2%) and Grade 2 (0.2%) colitis. Colitis occurred in 0.8% (7/913) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.2%) and Grade 2 (0.2%) colitis. Colitis occurred in 1.1% (8/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) and Grade 2 (0.3%) colitis. Colitis occurred in 1.1% (8/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) and Grade 2 (0.3%) colitis. Colitis occurred in 1.3% (3/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) and Grade 2 (0.4%) colitis. Colitis occurred in 1.2% (3/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) and Grade 2 (0.4%) colitis. Colitis occurred in 26 (0.6%) of patients. Of the patients who were evaluated for colitis, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

#### Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.3% (5/1567) of patients receiving KEYTRUDA, including Grade 4 (0.1%) hepatitis. Monitor patients for abnormal liver tests prior to and during treatment with KEYTRUDA. Administer corticosteroids for Grade 2 or greater increased AST or ALT or total bilirubin. Withhold KEYTRUDA for Grade 2 increased AST or ALT or total bilirubin, and permanently discontinue KEYTRUDA for Grade 3 or greater increased AST or ALT or total bilirubin.

Hepatitis occurred in 1.4% (22/1567) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.3%) hepatitis. Hepatitis occurred in 1.4% (12/865) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.8%) and Grade 2 (0.3%) hepatitis. Hepatitis occurred in 1.1% (8/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) and Grade 2 (0.3%) hepatitis. Hepatitis occurred in 1.1% (8/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) and Grade 2 (0.3%) hepatitis. Hepatitis occurred in 0.9% (2/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) hepatitis. Hepatitis occurred in 0.8% (2/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) hepatitis. Hepatitis occurred in 26 (0.6%) of patients. Of the patients who were evaluated for hepatitis, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

#### 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% (12/1567) of patients receiving KEYTRUDA, including Grade 4 (0.1%) and Grade 3 (0.4%) adrenal insufficiency. Adrenal insufficiency occurred in 0.8% (7/865) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.2%) and Grade 2 (0.2%) adrenal insufficiency. Adrenal insufficiency occurred in 0.4% (3/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) adrenal insufficiency. Adrenal insufficiency occurred in 0.4% (3/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) adrenal insufficiency. Adrenal insufficiency occurred in 0.9% (2/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) adrenal insufficiency. Adrenal insufficiency occurred in 0.4% (1/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) adrenal insufficiency. Adrenal insufficiency occurred in 26 (0.6%) of patients. Of the patients who were evaluated for adrenal insufficiency, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

##### Hypophysitis and Immune-Mediated Hypophysitis

KEYTRUDA can cause immune-mediated hypophysitis. Immune-mediated hypophysitis occurred in 0.3% (5/1567) of patients receiving KEYTRUDA, including Grade 4 (0.1%) and Grade 3 (0.1%) hypophysitis. Monitor patients for changes in pituitary hormone levels and for signs and symptoms of hypophysitis, including headache, unusual pain, vision changes, and fatigue. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold KEYTRUDA for Grade 2 or 3 hypophysitis and permanently discontinue KEYTRUDA for Grade 4 hypophysitis. Hypophysitis occurred in 0.3% (2/865) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.2%) and Grade 2 (0.1%) hypophysitis. Hypophysitis occurred in 0.3% (2/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) hypophysitis. The incidence of new or worsening hypothyroidism was higher in 389 adult patients with cHL (11%) receiving KEYTRUDA as a single agent, including Grade 3 (0.3%) and Grade 2 (3.1%) hypophysitis. Hypophysitis occurred in 0.3% (2/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) hypophysitis. Hypophysitis occurred in 0.4% (1/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) hypophysitis. Hypophysitis occurred in 26 (0.6%) of patients. Of the patients who were evaluated for hypophysitis, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

##### 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. Hypothyroidism occurred in 7% (107/1567) of patients receiving KEYTRUDA, including Grade 3 (0.1%) hypothyroidism.

Hyperthyroidism occurred in 3.1% (48/1567) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (0.8%). A test for persistent discontinuation of KEYTRUDA for Grade 3 hyperthyroidism was not established. Thyroiditis occurred in 0.8% (13/1567) of patients receiving KEYTRUDA, including Grade 3 (0.1%) thyroiditis. Hypothyroidism occurred in 8% (69/865) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.1%) hypothyroidism. Hyperthyroidism occurred in 3.9% (34/865) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.2%) and Grade 2 (0.8%) hyperthyroidism. Thyroiditis occurred in 0.8% (7/865) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.1%) thyroiditis. Hypothyroidism occurred in 7% (52/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.1%) hypothyroidism. Hyperthyroidism occurred in 3.4% (25/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.3%) and Grade 2 (0.8%) hyperthyroidism. Thyroiditis occurred in 0.5% (4/735) of patients who received KEYTRUDA as a single agent and were retreated for recurrence, including Grade 3 (0.1%) thyroiditis. Hypothyroidism occurred in 9% (21/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) hypothyroidism. Hyperthyroidism occurred in 3.3% (8/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) and Grade 2 (2.1%) hyperthyroidism. Thyroiditis occurred in 0.4% (1/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) thyroiditis. Hypothyroidism occurred in 26 (0.6%) of patients. Of the patients who were evaluated for hypothyroidism, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

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

KEYTRUDA can cause type 1 DM, including cases 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 0.1% (2/1567) of patients receiving KEYTRUDA, including 1 case with diabetic ketoacidosis. Type 1 DM occurred in 0.3% (2/735) of patients who were retreated for recurrence, including 1 case with diabetic ketoacidosis. Type 1 DM occurred in 0.4% (1/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including 1 case with diabetic ketoacidosis. Type 1 DM occurred in 26 (0.6%) of patients. Of the patients who were evaluated for type 1 DM, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (5/1567) of patients receiving KEYTRUDA, including Grade 4 (0.1%) and Grade 3 (0.1%) nephritis. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2 or 3 nephritis and permanently discontinue KEYTRUDA for Grade 4 nephritis. Nephritis occurred in 0.3% (2/735) of patients who were retreated for recurrence, including 1 Grade 5 event. Nephritis occurred in 0.3% (2/735) of patients who were retreated for recurrence, including 1 Grade 5 event. Nephritis occurred in 0.4% (1/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) nephritis. Nephritis occurred in 0.4% (1/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) nephritis. Nephritis occurred in 26 (0.6%) of patients. Of the patients who were evaluated for nephritis, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

#### 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 necrosis, has occurred in patients receiving PD-1 blocking antibodies. Withhold KEYTRUDA depending on severity. Administer corticosteroids for severe or life-threatening rash. Rash occurred in 16% (252/1567) of patients receiving KEYTRUDA, including Grade 3 (1.1%) rash. Rash occurred in 14% (28/202) of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (2%) and Grade 2 (3.5%) rashes. Systemic corticosteroids were required in 54% (15/28) of patients. If the rash resolved, systemic corticosteroids were discontinued in 47% (7/15) of patients. Systemic corticosteroids were required in 54% (15/28) of patients who were retreated for recurrence. Systemic corticosteroids were required in 54% (15/28) of patients who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC. Systemic corticosteroids were required in 54% (15/28) of patients. If the rash resolved, systemic corticosteroids were discontinued in 47% (7/15) of 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 monotherapy or in combination therapy, including Grade 3, 4, and 5 events: myocarditis, myositis, uveitis, pancreatitis, including increases in amylase and lipase levels, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, sarcoidosis, necrotizing pancreatitis, encephalitis, hemolytic anemia, aplastic anemia, and hemolytic transfusion reactions. Myocarditis occurred in 0.4% (6/1567) of patients receiving KEYTRUDA, including Grade 3 (0.2%) and Grade 2 (0.2%) myocarditis. Myocarditis occurred in 0.4% (3/735) of patients who were retreated for recurrence, including Grade 3 (0.3%) myocarditis. Myocarditis occurred in 0.4% (3/735) of patients who were retreated for recurrence, including Grade 3 (0.3%) myocarditis. Myocarditis occurred in 0.4% (1/233) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.4%) myocarditis. Myocarditis occurred in 0.4% (1/242) of adult patients with resected NSCLC who received KEYTRUDA in combination with chemotherapy as neoadjuvant treatment of NSCLC, including Grade 3 (0.4%) myocarditis. Myocarditis occurred in 26 (0.6%) of patients. Of the patients who were evaluated for myocarditis, 58% were interrupted KEYTRUDA, 62% discontinued KEYTRUDA, and 71% had resolution.

#### Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% (4/1756) of patients in clinical studies. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or 2 infusion-related reactions. Discontinue KEYTRUDA for Grade 3 or 4 infusion-related reactions.

#### 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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced-intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for these complications and intervene promptly. Consider the benefit versus risks of treatment with KEYTRUDA 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 is not recommended outside of controlled trials.

### Adverse Reactions

##### Melanoma

Based on the recurrent-free survival (RFS) data in KEYNOTE-054, the most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue, rash, diarrhea, pruritus, and nausea. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (39%), diarrhea (30%), rash (29%), and nausea (21%).

In KEYNOTE-054, 496 patients with Stage IIIA (≥1 mm metastasis), IIIB, or IIIC melanoma were randomized to receive KEYTRUDA or ipilimumab. Of the patients randomized to receive KEYTRUDA, 99% received 200 mg every 3 weeks and 1% received 2 mg/kg every 3 weeks. The median duration of exposure was 11 months. The most common adverse reactions (≥20%) were fatigue (39%), diarrhea (30%), rash (29%), and nausea (21%). Serious adverse reactions occurred in 16% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (2%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 6% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 22% of patients. The most common adverse reaction (≥2%) resulting in dose delay was fatigue (3%). The most common adverse reaction (≥2%) leading to permanent discontinuation was fatigue (2%).

In KEYNOTE-006, 555 patients with melanoma were randomized to receive KEYTRUDA every 3 weeks, KEYTRUDA every 2 weeks, or ipilimumab. Of the patients randomized to receive KEYTRUDA, 98% received 200 mg every 3 weeks and 2% received 2 mg/kg every 3 weeks. The median duration of exposure was 7.4 months. The most common adverse reactions (≥20%) were fatigue (28%), diarrhea (25%), nausea (20%), and pruritus (20%). Serious adverse reactions occurred in 12% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (2%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 4% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 19% of patients. The most common adverse reaction (≥2%) resulting in dose delay was fatigue (3%). The most common adverse reaction (≥2%) leading to permanent discontinuation was fatigue (2%).

In KEYNOTE-001, 655 patients with melanoma were randomized to receive KEYTRUDA every 2 weeks, KEYTRUDA every 3 weeks, or chemotherapy. Of the patients randomized to receive KEYTRUDA, 1% received 10 mg/kg every 2 weeks and 99% received 200 mg every 3 weeks. The median duration of exposure was 8.4 months. The most common adverse reactions (≥20%) were fatigue (26%), pruritus (22%), and diarrhea (21%). Serious adverse reactions occurred in 14% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (2%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 9% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 41% of patients. The most common adverse reaction (≥2%) resulting in dose delay was fatigue (3%). The most common adverse reaction (≥2%) leading to permanent discontinuation was fatigue (2%).

##### Adjuvant Melanoma

In the adjuvant setting of KEYNOTE-054, the most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue, rash, diarrhea, pruritus, and nausea. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (39%), diarrhea (30%), rash (29%), and nausea (21%). Serious adverse reactions occurred in 16% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (2%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 6% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 22% of patients. The most common adverse reaction (≥2%) resulting in dose delay was fatigue (3%). The most common adverse reaction (≥2%) leading to permanent discontinuation was fatigue (2%).

##### NSCLC

Based on the recurrent-free survival (RFS) data in KEYNOTE-091, the most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue, musculoskeletal pain, cough, nausea, decreased appetite, rash, diarrhea, dyspnea, and pruritus. The most common adverse reactions (≥20%) were fatigue (39%), musculoskeletal pain (27%), cough (26%), nausea (25%), decreased appetite (24%), rash (23%), diarrhea (22%), dyspnea (21%), and pruritus (20%). Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (3%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 11% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 34% of patients. The most common adverse reaction (≥2%) resulting in dose delay was fatigue (3%). The most common adverse reaction (≥2%) leading to permanent discontinuation was fatigue (2%).

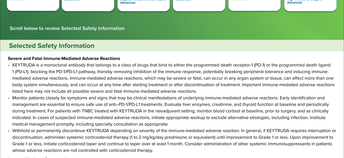
In KEYNOTE-189, 616 patients with metastatic nonsquamous NSCLC were randomized to receive KEYTRUDA or a placebo, each in combination with pemetrexed and platinum chemotherapy. Of the patients randomized to receive KEYTRUDA, 100% received 200 mg every 3 weeks. The median duration of exposure was 8.3 months. The most common adverse reactions (≥20%) were nausea (56%), fatigue (50%), constipation (31%), diarrhea (26%), decreased appetite (25%), rash (21%), and vomiting (20%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (3.7%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 18% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 39% of patients. The most common adverse reaction (≥2%) resulting in dose delay was neutropenia (3.4%). The most common adverse reaction (≥2%) leading to permanent discontinuation was pneumonitis (2.3%).

In KEYNOTE-407, 559 patients with squamous NSCLC were randomized to receive KEYTRUDA or a placebo, each in combination with carboplatin and either paclitaxel or paclitaxel protein-bound. Of the patients randomized to receive KEYTRUDA, 100% received 200 mg every 3 weeks. The median duration of exposure was 7.8 months. The most common adverse reactions (≥20%) were alopecia (41%), fatigue (40%), nausea (31%), peripheral neuropathy (27%), decreased appetite (25%), constipation (24%), rash (23%), diarrhea (22%), vomiting (21%), and cough (20%). Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonia (9%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 19% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 45% of patients. The most common adverse reactions (≥2%) resulting in dose delay were neutropenia (8%), anemia (4.3%), and decreased neutrophil count (3.2%). The most common adverse reactions (≥2%) leading to permanent discontinuation were peripheral neuropathy (4%), neutropenia (3.2%), and fatigue (2.1%).

In KEYNOTE-042, 637 patients with locally advanced or metastatic NSCLC were randomized to receive KEYTRUDA or chemotherapy. Of the patients randomized to receive KEYTRUDA, 98% received 200 mg every 3 weeks and 2% received 2 mg/kg every 3 weeks. The median duration of exposure was 5.8 months. The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (27%), decreased appetite (25%), nausea (24%), constipation (23%), cough (22%), diarrhea (21%), and anemia (20%). Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonia (7%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 19% of patients. Adverse reactions resulted in dose delay of KEYTRUDA in 42% of patients. The most common adverse reaction (≥2%) resulting in dose delay was anemia (4.2%). The most common adverse reaction (≥2%) leading to permanent discontinuation was pneumonitis (2.4%).

In KEYNOTE-189, 405 patients

# Select Cancer Types




Scroll below to review Selected Safety Information

## Selected Safety Information

### 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 and -2 (PD-L1 and PD-L2) 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 with KEYTRUDA. In cases with TNBC treated with KEYTRUDA in the neoadjuvant setting, monitor blood content at least once before, 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. In general, if KEYTRUDA requires withholding (see Dosage and Administration), resume only if adverse reaction returns to baseline. Administer high-dose corticosteroids (initial dose 1 to 2 mg/kg prophylactic or equivalent) until improvement to Grade 1 or less. Upon improvement to baseline, 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.3%), and Grade 2 (1.7%). 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. Pneumonitis resolved in 59% of patients with available follow-up.

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 3.9% (15) of patients. One patient died due to pneumonitis. Pneumonitis resolved in 84% (26/31) of patients who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (19/259) of patients with resected NSCLC who received KEYTRUDA as a single agent after 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 2.6% (6.5%) 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, complications may include bowel perforation and necessitate surgical evaluation. 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%). Systemic corticosteroids were required in 69% (33/48) of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.6% (16) and withholding in 0.6% (16) of patients. Colitis resolved in 83% of patients with available follow-up.

Immune-mediated colitis occurred in 2.1% (8/389) 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 1.5% (6) of patients. One patient died due to pneumonitis. Pneumonitis resolved in 84% (26/31) of patients who discontinued KEYTRUDA, and 77% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 79% (15/19) 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 resumed KEYTRUDA after symptom improvement. Hepatitis resolved in 74% of patients with available follow-up.

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 administer corticosteroids as clinically indicated. If liver enzymes recover to Grade 1 or baseline, restart KEYTRUDA and axitinib at reduced doses. Grade 3 and 4 increased 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. Increased ALT resolved to Grade 0 or 1 in 78% of patients. Increased AST resolved to Grade 0 or 1 in 82% of patients. 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 or AST Grade 3 or 4 was observed in 1 patient receiving KEYTRUDA, 18 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT or AST 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 (0.4%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Adrenal insufficiency resolved in 54% of patients with available follow-up.

*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 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.2%) 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% (1) and withholding in 0.3% (7) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

*Type 1 Diabetes Mellitus, 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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (4) of patients. All patients who were withheld resumed 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 in patients receiving KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (75/189) of patients treated with KEYTRUDA in the neoadjuvant setting, systemic steroids were required in 40% (30/75) of patients. Dermatologic adverse reactions led to permanent discontinuation in 0.5% (1) and withholding of KEYTRUDA in 0.5% (1) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Dermatologic adverse reactions resolved in 67% of 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, myocarditis, myositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis (1.5%), polymyalgia rheumatica, autoimmune hemolytic anemia, hemolytic anemia, aplastic anemia, hemorrhagic blood disorders, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, and systemic inflammatory response syndrome.

#### 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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Transplant complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment prior to or after an allogeneic HSCT.

#### Increased Mortality in Patients With Multiple Myeloma

In trials of 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 occurred in 6% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (21%), and nausea (21%). The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (21%), and nausea (21%). Adverse reactions were permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonitis, colitis, and diarrhea. KEYTRUDA was withheld as an adverse reaction in 25% of patients; the most common (≥1%) adverse reactions that led to treatment withholding were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions resolved in 58% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-048, adverse reactions were reported in 97% of patients who received KEYTRUDA as a single agent, including Grade 3 (31%), Grade 4 (3%), and Grade 5 (2%) adverse reactions. The most common adverse reactions (≥20%) were fatigue (33%), musculoskeletal pain (25%), rash (20%), and diarrhea (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (84%), increased glucose (74%), decreased lymphocytes (71%), increased AST (61%), increased ALT (57%), decreased magnesium (55%), decreased sodium (53%), decreased albumin (52%), decreased calcium (49%), decreased neutrophils (47%), and increased alkaline phosphatase (40%). KEYTRUDA was discontinued due to adverse reactions in 13% of patients; the most common (≥1%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%), pneumonia (2%), and acute kidney injury (1%). Adverse reactions resulted in withholding of KEYTRUDA in 26% of patients; the most common (≥1%) adverse reactions that led to treatment withholding were pneumonia (2%), fatigue (2%), and decreased neutrophil count (2%). Adverse reactions resolved in 58% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 151 patients with advanced NSCLC; the most common were pneumonitis (3%), pulmonary embolism (2.6%), and pneumonia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.6%), sepsis (0.3%), and immune-mediated hepatitis (0.3%). The most common adverse reactions (≥20%) were fatigue (35%), nausea (23%), and decreased appetite (20%). The most common laboratory abnormalities (≥20%) were anemia (74%), increased glucose (71%), increased AST (47%), increased ALT (46%), hypocalcemia (41%), hyponatremia (40%), hypophosphatemia (39%), increased alkaline phosphatase (38%), hypomagnesemia (37%), and lymphopenia (36%). KEYTRUDA was withheld due to adverse reactions in 17% of patients; the most frequent (≥2%) adverse reaction that led to treatment withholding was pneumonitis (2%). Adverse reactions resolved in 60% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and fatigue (2%). Fatal adverse reactions occurred in 5% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated hepatitis (0.3%). The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (30%), cough (25%), decreased appetite (23%), nausea (22%), dyspnea (21%), and rash (20%). The most common laboratory abnormalities (≥20%) were anemia (71%), hyponatremia (47%), increased glucose (46%), increased AST (45%), increased ALT (44%), hypocalcemia (43%), hypophosphatemia (41%), hypomagnesemia (40%), increased alkaline phosphatase (39%), and lymphopenia (38%). KEYTRUDA was withheld due to adverse reactions in 26% of patients; the most frequent (≥2%) adverse reaction that led to treatment withholding was pneumonitis (2%). Adverse reactions resolved in 60% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 18% of 194 patients with r/m, Serious adverse reactions occurred in 36% of patients. The most frequent serious adverse reactions were pneumonia, dyspnea, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions: 2 from cardiopulmonal failure and 1 from sepsis. The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (32%), diarrhea (22%), and pyrexia (22%). The most common laboratory abnormalities (≥20%) were anemia (84%), increased glucose (74%), increased AST (71%), increased ALT (70%), and hypocalcemia (68%). KEYTRUDA was withheld in 16% of patients; the most frequent adverse reaction leading to treatment withholding was pneumonia (2%). Adverse reactions resolved in 16% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 14% of 405 patients with stage III melanoma; adverse reactions leading to permanent discontinuation occurred in 10% of patients. The most common adverse reactions (≥20%) were fatigue (36%), diarrhea (29%), rash (21%), and nausea (20%). The most common laboratory abnormalities (≥20%) were increased glucose (70%), increased ALT (39%), increased AST (38%), and hypocalcemia (37%). KEYTRUDA was withheld due to adverse reactions in 24% of patients; the most common (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were diarrhea (2%), pneumonitis (2%), and colitis (2%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-189, KEYTRUDA was discontinued due to adverse reactions in 18% of 405 patients with NSCLC; serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, pneumonitis, dyspnea, pulmonary embolism, and pleural effusion. The most common adverse reactions (≥20%) were nausea (69%), fatigue (66%), constipation (37%), diarrhea (36%), vomiting (24%), decreased appetite (21%), abdominal pain (21%), peripheral edema (21%), and pyrexia (20%). The most common laboratory abnormalities (≥20%) were anemia (98%), decreased sodium (74%), decreased magnesium (71%), decreased neutrophils (69%), decreased lymphocytes (68%), decreased albumin (67%), increased glucose (66%), increased ALT (63%), increased AST (62%), and increased alkaline phosphatase (61%). KEYTRUDA was withheld due to adverse reactions in 30% of patients; the most frequent adverse reactions leading to withholding were pneumonitis (5%), pneumonia (4%), and pyrexia (4%). Adverse reactions resolved in 59% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-407, KEYTRUDA was discontinued due to adverse reactions in 19% of 278 patients with squamous NSCLC; serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions were pneumonia (12%), febrile neutropenia (3%), and sepsis (3%). The most common adverse reactions (≥20%) were fatigue (51%), nausea (31%), constipation (29%), diarrhea (28%), decreased appetite (25%), peripheral edema (24%), alopecia (23%), vomiting (20%), and rash (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (98%), decreased sodium (74%), decreased neutrophils (73%), decreased lymphocytes (71%), increased glucose (70%), decreased magnesium (69%), increased AST (65%), increased ALT (64%), decreased albumin (63%), decreased calcium (59%), and increased alkaline phosphatase (57%). KEYTRUDA was withheld due to adverse reactions in 36% of patients; the most frequent adverse reactions leading to withholding were pneumonia (8%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 59% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-590, KEYTRUDA was discontinued due to adverse reactions in 22% of 370 patients with esophageal cancer, adenocarcinoma of the gastroesophageal junction, or squamous cell carcinoma of the esophagus. Serious adverse reactions occurred in 69% of patients receiving KEYTRUDA in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, sepsis, febrile neutropenia, anemia, and pulmonary embolism. The most common adverse reactions (≥20%) were nausea (47%), diarrhea (41%), fatigue (40%), vomiting (24%), decreased appetite (24%), abdominal pain (24%), peripheral neuropathy (23%), and constipation (22%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (91%), decreased neutrophils (88%), decreased lymphocytes (84%), decreased sodium (79%), increased glucose (77%), increased AST (75%), increased ALT (74%), decreased albumin (73%), decreased magnesium (72%), increased alkaline phosphatase (71%), and decreased calcium (70%). KEYTRUDA was withheld due to adverse reactions in 41% of patients; the most frequent adverse reactions leading to withholding were pneumonia (6%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-826, KEYTRUDA was discontinued due to adverse reactions in 19% of 441 patients with cervical cancer; serious adverse reactions occurred in 48% of patients. The most frequent serious adverse reactions were hemorrhage, pneumonia, and fistula. The most common adverse reactions (≥20%) were anemia (52%), fatigue (51%), nausea (41%), diarrhea (36%), vomiting (24%), decreased appetite (23%), abdominal pain (22%), peripheral neuropathy (21%), and constipation (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (98%), decreased lymphocytes (88%), decreased neutrophils (88%), decreased sodium (77%), increased glucose (76%), increased AST (75%), increased ALT (74%), decreased albumin (73%), decreased magnesium (72%), increased alkaline phosphatase (71%), decreased calcium (70%), and hypocalcemia (69%). KEYTRUDA was withheld due to adverse reactions in 40% of patients; the most frequent adverse reactions leading to withholding were pneumonia (6%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, serious adverse reactions occurred in 58% of patients receiving KEYTRUDA in combination with chemotherapy and in 39% of patients receiving placebo in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients receiving KEYTRUDA in combination with chemotherapy were pneumonia, urinary tract infection, and vaginal hemorrhage. The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22%), nausea (21%), and alopecia (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (91%), decreased lymphocytes (84%), decreased neutrophils (84%), decreased sodium (77%), increased glucose (76%), increased AST (75%), increased ALT (74%), decreased albumin (73%), decreased magnesium (72%), increased alkaline phosphatase (71%), decreased calcium (70%), and hypocalcemia (69%). KEYTRUDA was withheld due to adverse reactions in 41% of patients; the most frequent adverse reactions leading to withholding were pneumonia (6%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. Serious adverse reactions occurred in 68% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia and pyrexia. The most common adverse reactions (≥20%) were fatigue (46%), nausea (42%), vomiting (28%), decreased appetite (26%), constipation (23%), abdominal pain (21%), peripheral edema (21%), and rash (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (96%), decreased sodium (85%), decreased neutrophils (84%), decreased lymphocytes (82%), increased AST (73%), increased ALT (72%), decreased albumin (71%), increased glucose (70%), decreased calcium (68%), and increased alkaline phosphatase (67%). KEYTRUDA was withheld due to adverse reactions in 40% of patients. The most frequent adverse reactions leading to withholding were pneumonia (5%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 14% of 493 patients with resected NSCLC; serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, pneumonitis, and pleural effusion. The most common adverse reactions (≥20%) were fatigue (47%), musculoskeletal pain (33%), diarrhea (22%), and pyrexia (21%). The most common laboratory abnormalities (≥20%) were anemia (74%), increased glucose (71%), increased AST (47%), increased ALT (46%), hypocalcemia (41%), hyponatremia (40%), hypophosphatemia (39%), increased alkaline phosphatase (38%), hypomagnesemia (37%), and lymphopenia (36%). KEYTRUDA was withheld due to adverse reactions in 25% of patients; the most frequent (≥2%) adverse reaction that led to permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). The most frequent (≥2%) adverse reactions that led to treatment withholding were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions resolved in 58% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-671, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued for adverse reactions in 18% of patients with NSCLC. Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA in combination with chemotherapy, and in 29% of patients receiving placebo in combination with chemotherapy. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia (3.2%), pulmonary embolism (2.5%), and sepsis (2.4%). The most common adverse reactions (≥20%) were nausea (59%), fatigue (49%), constipation (37%), diarrhea (32%), vomiting (28%), decreased appetite (25%), and rash (20%). The most common laboratory abnormalities (≥20%) were anemia (82%), increased glucose (77%), increased AST (75%), increased ALT (74%), decreased albumin (73%), decreased magnesium (72%), increased alkaline phosphatase (71%), decreased calcium (70%), decreased sodium (70%), hypocalcemia (69%), decreased neutrophils (68%), decreased lymphocytes (67%), and increased lipase (61%). KEYTRUDA was withheld due to adverse reactions in 41% of patients; the most frequent adverse reactions leading to withholding were pneumonia (5%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-522, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) 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, serious adverse reactions occurred in 30% of patients. The most frequent serious adverse reactions were pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 1.3% of patients receiving KEYTRUDA in combination with chemotherapy followed by surgery. The most common adverse reactions (≥20%) were nausea (82%), alopecia (61%), fatigue (58%), vomiting (42%), diarrhea (36%), constipation (24%), and rash (20%).

KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased ALT (3%), pneumonitis (2%), and increased AST (2%). The most common adverse reactions (≥20%) in patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab; those ≥3% were febrile neutropenia (8.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury (3.3% each).

KEYTRUDA was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation (≥1%) was pneumonitis (1.4%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=198), the most common adverse reactions (≥20%) were peripheral neuropathy (82%), nausea (58%), anemia (55%), fatigue (54%), decreased appetite (37%), diarrhea (36%), vomiting (34%), constipation (33%), hypothyroidism (32%), constipation and arthralgia (25% each), vomiting (20%), urinary tract infection (21%), rash (20%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (20%).

For patients treated with KEYTRUDA, chemotherapy, and placebo (n=200), the most common adverse reactions (≥20%) were peripheral neuropathy (82%), nausea (59%), fatigue (56%), alopecia (61%), diarrhea (36%), vomiting (28%), decreased appetite (26%), constipation (24%), arthralgia (21%), vomiting (20%), hypothyroidism and urinary tract infection (24% each), and rash (20%).

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. The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection (4%) and pneumonia (4%). The most common adverse reactions (≥20%) were fatigue (41%), nausea (40%), decreased appetite (27%), and diarrhea (23%). KEYTRUDA was withheld due to adverse reactions in 15% of patients; the most frequent adverse reaction leading to withholding was pneumonitis (2%). Adverse reactions resolved in 50% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. Serious adverse reactions occurred in 68% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia and pyrexia. The most common adverse reactions (≥20%) were fatigue (46%), nausea (42%), vomiting (28%), decreased appetite (26%), constipation (23%), abdominal pain (21%), peripheral edema (21%), and rash (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (96%), decreased sodium (85%), decreased neutrophils (84%), decreased lymphocytes (82%), increased AST (73%), increased ALT (72%), decreased albumin (71%), increased glucose (70%), decreased calcium (68%), and increased alkaline phosphatase (67%). KEYTRUDA was withheld due to adverse reactions in 40% of patients. The most frequent adverse reactions leading to withholding were pneumonia (5%), pneumonitis (4%), and pyrexia (4%). Adverse reactions resolved in 57% of patients who withheld KEYTRUDA for an adverse reaction.

In KEYNOTE-775, when KEYTRUDA was administered in combination with lenvatinib (KEYTRUDA + lenvatinib) to patients with advanced endometrial carcinoma, serious adverse reactions occurred in 63% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, pneumonia, and sepsis. The most common adverse reactions (≥20%) were hypertension (67%), diarrhea (66%), fatigue (59%), decreased appetite (49%), nausea (48%), vomiting (34%), abdominal pain (32%), arthralgia (31%), proteinuria (30%), palmar-plantar erythrodysesthesia syndrome (25%), stomatitis (24%), hemorrhages (22%), constipation (21%), and weight loss (20%). The most common laboratory abnormalities (≥20%) were increased AST (91%), increased ALT (90%), increased alkaline phosphatase (87%), increased glucose (86%), hypocalcemia (84%), hyponatremia (83%), hypophosphatemia (78%), anemia (74%), hypomagnesemia (71%), lymphopenia (70%), and increased lipase (69%). KEYTRUDA was withheld due to adverse reactions in 42% of patients; the most frequent adverse reactions leading to withholding were pneumonitis (3%), pneumonia (3%), and diarrhea (2%). Adverse reactions resolved in 59% of patients who withheld KEYTRUDA for an adverse reaction.

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 reactions (≥20%) in patients receiving KEYTRUDA were fatigue (37%), musculoskeletal pain (32%), nausea (28%), pruritus (22%), rash (21%), and decreased appetite (20%). The most common laboratory abnormalities (≥20%) were increased creatinine (74%), anemia (71%), hyponatremia (47%), increased glucose (46%), increased AST (45%), increased ALT (44%), hypercalcemia (41%), hypoalbuminemia (39%), hypermagnesemia (37%), hypocalcemia (36%), and hyperkalemia (21%). The most common adverse reactions (≥20%) in patients who received chemotherapy were nausea (49%), fatigue (47%), decreased appetite (32%), anemia (31%), alopecia (29%), constipation (25%), vomiting (24%), diarrhea (23%), and peripheral neuropathy (20%). The most common laboratory abnormalities (≥20%) were anemia (91%), increased glucose (71%), increased creatinine (67%), hyponatremia (65%), increased AST (61%), increased ALT (60%), hypoalbuminemia (59%), hypocalcemia (59%), hypermagnesemia (57%), hyperkalemia (31%), and hypercalcemia (20%). KEYTRUDA was withheld due to adverse reactions in 19% of patients; the most frequent adverse reaction leading to withholding was pneumonitis (2%). Adverse reactions resolved in 60% of patients who withheld KEYTRUDA for an adverse reaction.

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 was urinary tract infection (1.4%). The most common adverse reactions (≥20%) were fatigue (40%), musculoskeletal pain (28%), pruritus (27%), rash (21%), urinary tract infection (21%), diarrhea (20%), and decreased appetite (20%).

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-859, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, adverse reactions occurred in 72% of patients. The most common adverse reactions (≥20%) were alopecia (31%), fatigue (31%), nausea (31%), diarrhea (27%), vomiting (24%), abdominal pain (23%), constipation (22%), peripheral neuropathy (21%), and rash (20%). The most common laboratory abnormalities (≥20%) were decreased hemoglobin (98%),

# Select Appropriate Regimen

## Advanced Melanoma or Adjuvant Therapy for Melanoma

### INDICATIONS

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

**Adjuvant Therapy for Stage IIB, Stage IIC, or Stage III Melanoma**
KEYTRUDA is indicated for the adjuvant treatment of adult patients with cutaneous melanoma with involvement of lymph node(s) or metastatic disease, who have undergone complete resection, including total lymphadenectomy for node-positive disease.

Scroll below to review Selected Safety Information

- Advanced Melanoma KEYNOTE-006
- Adjuvant Therapy for Stage IIB, Stage IIC, or Stage III Melanoma KEYNOTE-054

## Selected Safety Information

### 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 (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. Initiate medical management promptly with KEYTRUDA in the investigational setting, monitor clinical course and function at frequent intervals, and consider 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 systemic corticosteroid therapy promptly for suspected immune-mediated adverse reactions.

Withhold or permanently discontinue KEYTRUDA depending on severity. In all cases, permanently discontinue KEYTRUDA if the adverse reaction requires systemic immunosuppressant administration, 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 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 Grade 3 (0.7%), Grade 4 (0.1%), and Grade 5 (0.1%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 13% (12/94) of patients who received KEYTRUDA and withholding in 0.9% (25) of patients, and did not resolve in 0.4% (11) of patients who received KEYTRUDA.

In KEYNOTE-054, pneumonitis 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 2.3% (9) of patients, and withholding of KEYTRUDA in 4.4% (17) patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

In KEYNOTE-045, pneumonitis in 7% (19/298) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2.6% (5) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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-refractive immune-mediated colitis. In cases of corticosteroid-refractive diarrhea, evaluate for infectious etiology. Immune-mediated colitis occurred in 1.9% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients. Colitis resolved in 40% (19/48) of patients who received KEYTRUDA and withholding in 0.5% (14) of patients, and resolved in 0.1% (3) of patients who received KEYTRUDA.

In KEYNOTE-054, colitis in 2% (7/389) 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 2.3% (9) of patients, and withholding of KEYTRUDA in 4.4% (17) patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

In KEYNOTE-045, colitis in 2% (5/298) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2.6% (5) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 79% (15/19) of patients. Hepatitis resolved in 47% (9/19) of patients who received KEYTRUDA and withholding in 0.1% (3) of patients, and resolved in 0.1% (2) of patients who received KEYTRUDA.

In KEYNOTE-054, hepatitis in 1.3% (5/389) 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 2.3% (9) of patients, and withholding of KEYTRUDA in 4.4% (17) patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

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 administer corticosteroids as clinically indicated. If liver enzymes increase to Grade 3 or 4 levels, withhold KEYTRUDA and axitinib. Grade 3 and 4 increases in ALT (20%) and increased aspartate aminotransferase (AST) (3%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids for a median duration of 1 month (range: 1 day to 5.6 months). Of these patients, 83% had resolution to Grade 1 or baseline. 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 or AST Grade 3-4 was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT or AST Grade 3-4 were rechallenged with both drugs.

#### Immune-Mediated Endocrinopathies

*Adrenal Insufficiency*

Adrenal insufficiency 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. Administer 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 91% (20/22) of patients. Adrenal insufficiency resolved in 41% (9/22) of patients who received KEYTRUDA and withholding in 0.1% (3) of patients. All patients who were withheld received KEYTRUDA after symptom improvement. Adrenal insufficiency did not resolve in patients who received KEYTRUDA.

*Hypophysitis*

Hypophysitis 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 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.2%) 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 resolved KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld resolved KEYTRUDA after symptom improvement.

Hypothyroidism occurred in 8% (21/259) of patients who received KEYTRUDA as a single agent. Hyperthyroidism occurred in 3.1% (8/259) of patients. Hypothyroidism resulted in 3.4% (9/259) of patients, of these, the majority remained on systemic corticosteroids. Hypothyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding of KEYTRUDA in 0.4% (1) of patients. All patients who were withheld resolved KEYTRUDA after symptom improvement.

#### Immune-Mediated Nephritis With Renal Dysfunction

Monitor patients for elevated serum creatinine. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) of patients. All patients who were withheld resolved KEYTRUDA after symptom improvement, of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

#### Immune-Mediated Dermatologic Adverse Reactions

Withhold or permanently discontinue KEYTRUDA depending on severity. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and systemic lupus erythematosus, has occurred in patients who received other drugs in this class. Immune-mediated dermatologic adverse reactions resulted in moderate vandetanib withdrawal, Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.7% (47/2799) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (0.3%) reactions. Rash led to permanent discontinuation in 40% (75/188) 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 resolved KEYTRUDA after symptom improvement, of these, none had recurrence.

#### 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. Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome, myasthenia gravis (exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, Ocular toxicities, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various neuropathies have been reported as adverse reactions. Acute kidney injury occurred 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. Immune-mediated pancreatitis, including 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, Hypoparathyroidism, Hypophysitis, posterior reversible encephalopathy syndrome, autoimmune anemia, aplastic anemia, hemolytic anemia, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection (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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Transplant complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatment and transplant. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment prior to or after an allogeneic HSCT.

#### Increased Mortality in Patients With Multiple Myeloma

In trials of 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 occurred in 6% of patients. The most common adverse reactions (≥20% with KEYTRUDA) were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). The most common adverse reactions (≥20% with KEYTRUDA and were between 2 and 5% greater than with ipilimumab) leading to permanent discontinuation due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (1.4%). In KEYNOTE-054, 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 patients with stage III melanoma (see Table 1).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients. Adverse reactions leading to permanent discontinuation of KEYTRUDA in 11% of patients were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (31%), diarrhea (31%), vomiting (28%), rash (25%), decreased appetite (24%), and cough (21%).

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 with advanced NSCLC. The most common adverse reactions (≥20%) were fatigue (50%), musculoskeletal pain (39%), nausea (31%), decreased appetite (26%), peripheral neuropathy (26%), constipation (24%), rash (24%), diarrhea (23%), and pneumonitis (20%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were fatigue (35%), musculoskeletal pain (29%), cough (28%), decreased appetite (25%), nausea (24%), dyspnea (23%), and rash (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 9% of 154 patients with advanced NSCLC; the most common were pneumonitis (2%), pneumonia (2%), and sepsis (2%). The most common adverse reactions (≥20%) were fatigue (35%), cough (25%), and nausea (20%).

In KEYNOTE-048, when KEYTRUDA was administered with chemotherapy or as a single agent in patients with recurrent or metastatic HNSCC, KEYTRUDA was discontinued due to adverse reactions in 15% of 276 patients with HNSCC. Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA with chemotherapy, the most frequent (≥2%) were pneumonia (6%), febrile neutropenia (3%), anemia (3%), and dyspnea (2%). Fatal adverse reactions occurred in 1.5% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated pneumonitis (0.3%). The most common adverse reactions (≥20%) were fatigue (50%), nausea (36%), decreased appetite (26%), rash (25%), and diarrhea (21%). In patients receiving KEYTRUDA as a single agent, the most frequent adverse reaction was fatigue (28%). The most common adverse reactions that led to permanent discontinuation of KEYTRUDA were fatigue (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

In KEYNOTE-522, when KEYTRUDA was administered with chemotherapy before surgery and as a single agent after surgery, patients who received KEYTRUDA had similar incidences of adverse reactions compared to patients who received placebo.

In KEYNOTE-045, KEYTRUDA was discontinued for adverse reactions in 14% of 411 patients. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) in patients receiving KEYTRUDA were fatigue (32%), musculoskeletal pain (25%), nausea (23%), pruritus (21%), rash (21%), decreased appetite (21%), and diarrhea (20%). The most common adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (2.2%), colitis (2.2%), and diarrhea (1.5%).

In KEYNOTE-054, when KEYTRUDA was administered as a single agent to patients with cHL, serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (36%), pruritus (29%), and rash (25%). The most frequent adverse reactions (≥2%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.2%), and pneumonitis (1.2%).

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 14% of 210 patients. Serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (36%), pruritus (29%), and rash (25%). The most frequent adverse reactions (≥2%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.2%), and pneumonitis (1.2%).

In KEYNOTE-204, KEYTRUDA was discontinued due to adverse reactions in 9% of 148 patients with cHL. Serious adverse reactions occurred in 36% of patients. The most frequent serious adverse reactions were pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions: 1 patient with myocarditis, 1 patient with pneumonitis, and 1 patient with sepsis. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 14% of patients. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2.7%) and myocarditis (2%). The most common adverse reactions (≥20%) were fatigue (35%), pruritus (23%), and nausea (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with MSI-H cancers, KEYTRUDA was discontinued due to adverse reactions in 9% of 233 patients. Serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions were immune-mediated adverse reactions, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were fatigue (36%), pruritus (22%), and diarrhea (21%). The most frequent adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2.6%), colitis (1.7%), pulmonary embolism (1.2%), sepsis (1.2%), and urinary tract infection (1.2%). The most common adverse reactions (≥20%) were fatigue (25%), pruritus (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-859, when KEYTRUDA was administered with chemotherapy before surgery and as a single agent after surgery, adverse reactions occurring in patients who received KEYTRUDA were similar to those occurring in patients who received KEYTRUDA as a monotherapy.

In KEYNOTE-868, when KEYTRUDA was administered with cisplatin plus fluorouracil before surgery and as a single agent after surgery, adverse reactions occurred in 100% of patients receiving KEYTRUDA in combination with chemotherapy before surgery. Serious adverse reactions occurred in 73% of patients receiving KEYTRUDA in combination with chemotherapy before surgery and in 46% of patients receiving KEYTRUDA as a single agent after surgery. The most common adverse reactions (≥20%) in patients receiving 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 MSI-H or dMMR EC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-775, when KEYTRUDA was administered with lenvatinib (EC cohort) or lenvatinib (HCC cohort), KEYTRUDA was discontinued due to adverse reactions in 26% of 413 patients. Serious adverse reactions occurred in 62% of patients. The most common adverse reactions (≥20%) were fatigue (59%), diarrhea (54%), hypertension (39%), decreased appetite (38%), abdominal pain (31%), nausea (30%), vomiting (24%), decreased weight (24%), hypothyroidism (23%), constipation (23%), and weight gain (20%).

In KEYNOTE-426, when KEYTRUDA was administered with axitinib or sunitinib, KEYTRUDA was discontinued due to adverse reactions in 10% of 429 patients. Serious adverse reactions occurred in 46% of patients. The most common adverse reactions (≥20%) were diarrhea (56%), hypertension (54%), fatigue (52%), stomatitis (40%), palmar-plantar erythrodysesthesia (39%), decreased appetite (38%), cough (32%), dysphonia (32%), nausea (31%), hypothyroidism (28%), rash (28%), constipation (24%), and vomiting (21%).

In KEYNOTE-091, when KEYTRUDA was administered in combination with pembrolizumab (pembrolizumab and capecitabine) or as a single agent (KEYTRUDA monotherapy) in patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2.6% (5) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 9% of 514 patients with advanced melanoma; adverse reactions leading to permanent discontinuation occurred in 6% of patients. The most common adverse reactions (≥20% with KEYTRUDA) were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). The most common adverse reactions (≥20% with KEYTRUDA and were between 2 and 5% greater than with ipilimumab) leading to permanent discontinuation due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (1.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (35%), pruritus (29%), and rash (25%). The most frequent adverse reactions (≥2%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.2%), and pneumonitis (1.2%).

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 14% of 210 patients. Serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (36%), pruritus (29%), and rash (25%). The most frequent adverse reactions (≥2%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.2%), and pneumonitis (1.2%).

In KEYNOTE-204, KEYTRUDA was discontinued in combination with brentuximab vedotin (KEYTRUDA in combination with brentuximab vedotin), 44% (n=247) were 65 years and older, and 26% (n=148) 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 vorhuvalimab exhibited 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.

**Before prescribing KEYTRUDA, please read the accompanying** Prescribing Information. The Medication Guide also is available.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = bacteriuria; BTC = biliary tract cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; CRT = chemoradiotherapy; HSCT = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; GVHD = graft-versus-host disease; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MCC = Merkel cell carcinoma; MSI-H = microsatellite instability-high; NMSC = non-muscle invasive bladder cancer; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal large B-cell lymphoma; TMB = tumor mutational burden.

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.
US-KEYONSET-211121

# Advanced NSCLC, Adjuvant, or Neoadjuvant and Adjuvant Therapy for Non–Small Cell Lung Cancer (NSCLC)

## INDICATIONS

**First-Line Combination Therapy in Nonsquamous mNSCLC**

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 epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

**First-Line Combination Therapy in Squamous mNSCLC**

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous non–small cell lung cancer (NSCLC).

**First-Line Monotherapy for Nonsquamous and Squamous Advanced NSCLC**

KEYTRUDA, as a monotherapy, is indicated for the first-line treatment of patients with non–small cell lung cancer (NSCLC) expressing programmed death ligand 1 [PD-L1] (tumor proportion score [TPS] ≥1%) as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, and is stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.

Continued on next page ›

Scroll below to review Selected Safety Information

## Selected Safety Information

### 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 with KEYTRUDA. 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. In general, if KEYTRUDA requires withholding 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 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.3%), and Grade 2 (1.7%). Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% (55/94) of patients with 11% (10/94) resolving during treatment and 48% (45/94) resolving after initiation of corticosteroids.

Pneumonitis occurred in 8% (213/89) 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 2.3% (5/213) of patients, and 2.3% (5/213) resolved. Of patients with pneumonitis who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (10/144) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (1.2%), 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 2% (3/144) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 55% 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. It is important to exclude infectious etiologies of diarrhea or colitis. Administer corticosteroids for Grade 2 or higher enterocolitis. 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%). Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Colitis resolved in 60% (29/48) of patients with 15% (7/48) resolving during treatment and 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. Colitis resolved in 85% (41/48) of patients.

Enterocolitis occurred in 8% (21/389) 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 2.3% (9/389) of patients, and 2.3% (9/389) resolved. Of patients with pneumonitis who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (10/144) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (1.2%), 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 2% (3/144) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 55% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 5 (0.1%), Grade 4 (0.3%), and Grade 3 (0.3%) reactions. Systemic corticosteroids were required in 79% (15/19) of patients. Hepatitis resolved in 47% (9/19) of patients with 16% (3/19) resolving during treatment and permanent discontinuation of KEYTRUDA in 0.4% (11) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hepatitis resolved in 74% (14/19) of 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 administer corticosteroids as clinically indicated. If liver enzymes recover to baseline, restart KEYTRUDA and axitinib at reduced dose. Elevations in ALT were more frequent (32%) and increased aspartate aminotransferase (AST) (3%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Increased ALT resolved in 71% (84/118) of patients. Increased AST resolved in 79% (92/116) of patients. 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 or AST flares was not observed. In patient receiving KEYTRUDA, 16 patients received steroids, and 24 patients receiving both. All patients with a recurrence of ALT or ALN subsequently recovered from the event.

#### Immune-Mediated Endocrinopathies

*Adrenal Insufficiency*

Adrenal insufficiency 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 (0.7%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Adrenal insufficiency resolved in 41% (9/22) of patients with 23% (5/22) resolving during treatment and permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*Hypophysitis*

Hypophysitis 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 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% (1) 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 initiation of 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 0.3% (8) of patients withheld dose.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.8%). It led to permanent discontinuation of KEYTRUDA in 0.3% (9) and withholding in 0.7% (19) of patients. Hyperthyroidism resolved in 72% (69/96) of patients with 19% (18/96) resolving during treatment.

Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.6%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.2% (6) of patients. Hypothyroidism resolved in 22% (53/237) of patients with 5% (12/237) resolving during treatment.

Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (1) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement, of these, none had recurrence. Hypophysitis resolved in 56% of the 9 patients.

#### Immune-Mediated Adverse Reactions

The following 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, myelitis, demyelination, myocarditis, pericarditis, vasculitis, nephritis, autoimmune cytopenias, myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, Ocular Uveitis, iritis and other ocular inflammatory toxicities can occur. Infusion reactions can be associated with administration of KEYTRUDA. Graft-versus-host disease (GVHD) can occur in patients 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. Immune-mediated dermatitis occurred in patients receiving PD-1/PD-L1–blocking antibodies. Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica. Endocrine: Hypoparathyroidism, Cushing's syndrome, adrenalitis, epididymo-orchitis, autoimmune hemolytic anemia, aplastic anemia, hemolytic anemia, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including bone marrow) 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Follow patients closely for these complications and intervene promptly, according to standard practices. Of 53 patients with cHL who received KEYTRUDA prior to their 1 of 2 treatments and allogeneic HSCT, 4 developed GVHD (1 fatal case). Of 7 patients with NSCLC who received KEYTRUDA prior to their 1 of 2 treatments and allogeneic HSCT, 1 developed GVHD (fatal case). Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment 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 occurred in 6% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). The most frequent adverse reaction leading to permanent discontinuation due to adverse reactions in 14% of 509 patients; the most common (≥3% were pneumonitis (3.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonitis (3.4%), colitis (2.2%), and diarrhea (1%). 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 KEYTRUDA-treated patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 11% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), rash (25%), diarrhea (24%), decreased appetite (21%), vomiting (21%), and pruritus (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 20% of 278 patients with advanced NSCLC; adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 13% of patients. The most common adverse reactions (≥20%) were KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), rash (25%), diarrhea (24%), decreased appetite (21%), vomiting (21%), and pruritus (20%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and pulmonary embolism (2%). The most common adverse reactions (≥20%) were fatigue (35%), musculoskeletal pain (31%), pruritus (25%), diarrhea (23%), cough (22%), nausea (21%), and rash (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 30% of 154 patients with advanced NSCLC; the most common were pneumonitis (3.9%), pulmonary embolism (2.6%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-001, KEYTRUDA monotherapy was discontinued due to adverse reactions in 9% of 682 patients with advanced NSCLC; the most common were pneumonitis (1.8%). The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

In KEYNOTE-048, when KEYTRUDA was administered with carboplatin and either paclitaxel or pemetrexed in first-line metastatic NSCLC, KEYTRUDA was discontinued due to adverse reactions in 11% of 282 patients with HNSCC; serious adverse reactions occurred in 49% of patients receiving KEYTRUDA in combination with chemotherapy. The most common adverse reactions (≥20%) were fatigue (36%), nausea (31%), constipation (27%), decreased appetite (26%), vomiting (21%), and rash (20%).

In KEYNOTE-012, KEYTRUDA was discontinued due to adverse reactions in 11% of 192 patients with HNSCC. Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in ≥2% of patients were dyspnea (4%), pneumonia (3%), and pleural effusion (2%). The most common adverse reactions (≥20%) were fatigue (40%), musculoskeletal pain (31%), upper respiratory tract infection (21%), and dyspnea (21%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (30%), pruritus (22%), and nausea (21%). The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (30%), pruritus (22%), and nausea (21%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring treatment discontinuation was urinary tract infection (3%). The most common adverse reactions (≥20%) were fatigue (47%), urinary tract infection (32%), pruritus (27%), asthenia (21%), diarrhea (21%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (51%), pruritus (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-810, when KEYTRUDA was administered with paclitaxel and trastuzumab with or without pertuzumab, the most common adverse reactions (≥20%) were alopecia (49%), fatigue (41%), nausea (40%), diarrhea (36%), vomiting (24%), decreased appetite (24%), peripheral neuropathy (23%), and abdominal pain (21%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, the most common adverse reactions (≥20%) were fatigue (49%), alopecia (43%), nausea (41%), vomiting (28%), diarrhea (27%), peripheral neuropathy (26%), constipation (24%), abdominal pain (22%), and decreased appetite (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab; those ≥3% were febrile neutropenia (1.8%), urinary tract infection (1.2%), anemia (1.1%), and acute kidney injury (0.3% each).

In KEYNOTE-590, when KEYTRUDA was administered in combination with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) adenocarcinoma, KEYTRUDA was discontinued for adverse reactions in 16% of patients receiving KEYTRUDA in combination with chemotherapy. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis, sepsis, acute kidney injury, and pneumonia (1% each). The most common adverse reactions (≥20%) were nausea (49%), fatigue (47%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-775, when KEYTRUDA was administered with lenvatinib and fluorouracil to patients with advanced endometrial carcinoma that progressed following platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 14% of 411 patients; those ≥2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were hypertension (61%), fatigue (49%), diarrhea (48%), decreased appetite (37%), nausea (36%), and vomiting (29%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 9% of 1,177 patients with high-risk, early-stage NSCLC; the most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (1.4%) and pneumonia (1.2%). The most common adverse reactions (≥20%) were fatigue (50%), pyrexia (24%), cough (24%), musculoskeletal pain (23%), and nausea (21%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 8% of 514 patients with NMSCs. Serious adverse reactions occurred in 26% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (24%), and diarrhea (21%).

In KEYNOTE-329, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer who had previously received platinum-containing chemotherapy and PD-1/PD-L1–blocking antibody, KEYTRUDA was discontinued for adverse reactions in 16% of patients. The most common adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin; the serious adverse reactions in ≥2% of patients were rash (6%), acute kidney injury (3%), and pneumonitis (2%). The most common adverse reactions (≥20%) were rash (67%), fatigue (50%), decreased appetite (34%), peripheral neuropathy (32%), diarrhea (31%), nausea (30%), pruritus (29%), alopecia (27%), weight loss (23%), and constipation (20%).

In KEYNOTE-426, when KEYTRUDA was administered with axitinib to patients with advanced RCC, KEYTRUDA was discontinued due to adverse reactions in 42% of patients; those ≥2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were diarrhea (57%), fatigue (56%), hypertension (52%), hepatotoxicity (49%), nausea (43%), and decreased appetite (32%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (1.5%), pneumonia (1.1%), and acute kidney injury (1.1%). The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (30%), pruritus (22%), and nausea (21%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring treatment discontinuation was urinary tract infection (3%). The most common adverse reactions (≥20%) were fatigue (47%), urinary tract infection (32%), pruritus (27%), asthenia (21%), diarrhea (21%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (51%), pruritus (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-858, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, the most common adverse reactions (≥20%) were fatigue (49%), alopecia (43%), nausea (41%), vomiting (28%), diarrhea (27%), peripheral neuropathy (26%), constipation (24%), abdominal pain (22%), and decreased appetite (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab; those ≥3% were febrile neutropenia (1.8%), urinary tract infection (1.2%), anemia (1.1%), and acute kidney injury (0.3% each).

In KEYNOTE-590, when KEYTRUDA was administered in combination with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) adenocarcinoma, KEYTRUDA was discontinued for adverse reactions in 16% of patients receiving KEYTRUDA in combination with chemotherapy. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis, sepsis, acute kidney injury, and pneumonia (1% each). The most common adverse reactions (≥20%) were nausea (49%), fatigue (47%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-775, when KEYTRUDA was administered with lenvatinib and fluorouracil to patients with advanced endometrial carcinoma that progressed following platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 14% of 411 patients; those ≥2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were hypertension (61%), fatigue (49%), diarrhea (48%), decreased appetite (37%), nausea (36%), and vomiting (29%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 9% of 1,177 patients with high-risk, early-stage NSCLC; the most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (1.4%) and pneumonia (1.2%). The most common adverse reactions (≥20%) were fatigue (50%), pyrexia (24%), cough (24%), musculoskeletal pain (23%), and nausea (21%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 8% of 514 patients with NMSCs. Serious adverse reactions occurred in 26% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (24%), and diarrhea (21%).

In KEYNOTE-329, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer who had previously received platinum-containing chemotherapy and PD-1/PD-L1–blocking antibody, KEYTRUDA was discontinued for adverse reactions in 16% of patients. The most common adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin; the serious adverse reactions in ≥2% of patients were rash (6%), acute kidney injury (3%), and pneumonitis (2%). The most common adverse reactions (≥20%) were rash (67%), fatigue (50%), decreased appetite (34%), peripheral neuropathy (32%), diarrhea (31%), nausea (30%), pruritus (29%), alopecia (27%), weight loss (23%), and constipation (20%).

In KEYNOTE-426, when KEYTRUDA was administered with axitinib to patients with advanced RCC, KEYTRUDA was discontinued due to adverse reactions in 42% of patients; those ≥2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions (≥20%) were diarrhea (57%), fatigue (56%), hypertension (52%), hepatotoxicity (49%), nausea (43%), and decreased appetite (32%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (1.5%), pneumonia (1.1%), and acute kidney injury (1.1%). The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (30%), pruritus (22%), and nausea (21%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring treatment discontinuation was urinary tract infection (3%). The most common adverse reactions (≥20%) were fatigue (47%), urinary tract infection (32%), pruritus (27%), asthenia (21%), diarrhea (21%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (51%), pruritus (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-858, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, the most common adverse reactions (≥20%) were fatigue (49%), alopecia (43%), nausea (41%), vomiting (28%), diarrhea (27%), peripheral neuropathy (26%), constipation (24%), abdominal pain (22%), and decreased appetite (20%).

#### Pediatric Use

In KEYNOTE-051, 113 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 years to 17 years) with advanced melanoma received KEYTRUDA 2 mg/kg every 3 weeks. The most common adverse reactions (≥20%) were pyrexia (31%) and headache (20%).

Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (33% vs 19%), leukopenia (16% vs 4%), neutropenia (16% vs 4%), headache (20% vs 8%), abdominal pain (20% vs 8%), thrombocytopenia (12% vs 3%), Grade 3 anemia (11% vs 3%), decreased lymphocyte count (5%), and decreased white blood cell count (11% vs 3%).

#### 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 to 75 years and 26% (n=148) 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.

**Before prescribing KEYTRUDA, please read the accompanying** Prescribing Information. The Medication Guide also is available.



Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.

US-KEYT-250172 (1/25)

# Advanced NSCLC, Adjuvant, or Neoadjuvant and Adjuvant Treatment of Non-Small Cell Lung Cancer (NSCLC) *(continued)*



## INDICATIONS

- **Second-Line or Greater Monotherapy for Nonsquamous and Squamous mNSCLC**

  KEYTRUDA, as a single agent, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express programmed death ligand 1 (PD-L1) [tumor proportion score (TPS) ≥1%] as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGF) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should receive targeted therapy before KEYTRUDA. FDA-approved companion diagnostic tests are available for PD-L1 and ALK.

- **Neoadjuvant Combination Therapy and Then Continued as Adjuvant Monotherapy After Surgery, for Resectable (Tumors ≥4 cm or Node Positive) NSCLC**

  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 following surgery.

- **Adjuvant Therapy for Stage IB (T2a [≥4 cm], Stage II, or Stage IIIA NSCLC**

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

Scroll below to review Selected Safety Information

## Selected Safety Information

### 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 blockers (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 with KEYTRUDA. 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 withholding or discontinuation, administer systemic corticosteroids (prednisone 0.5 to 2 mg/kg/day 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (2.1%). Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% of patients who received KEYTRUDA. Of patients with pneumonitis who received systemic corticosteroids, 71% (45/63) resolved. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients.

Pneumonitis occurred in 8% (21/389) 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 3.1% (12) of patients. One of these patients died. Pneumonitis resolved in 81% (17/21) of patients who discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 7% (20/267) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (1.2%), 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 2.6% (7) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 55% 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. It is important to exclude infectious etiologies of diarrhea or colitis. Immune-mediated colitis occurred in 1.9% (52/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in 69% (36/52) of patients. Colitis resolved in 63% of patients who received KEYTRUDA. KEYTRUDA was permanently discontinued for 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 recurrent colitis.

Colitis 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 3.1% (12) of patients. One of these patients died. Pneumonitis resolved in 81% (17/21) of patients who discontinued KEYTRUDA, and 71% had resolution.

Colitis occurred in 2% (5/267) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including Grade 3 (0.7%) adverse 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 0.5% (1) and withholding in 0.3% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

#### Immune-Mediated Hepatitis and Immune-Mediated Hepatitis with Normal Liver Enzymes

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (21/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 81% (17/21) of patients. Hepatitis resolved in 67% of patients who received KEYTRUDA. KEYTRUDA was permanently discontinued for hepatitis in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 25% had recurrent hepatitis.

Hepatitis occurred in 3.4% (13/389) of 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 3.1% (12) of patients. One of these patients died. Pneumonitis resolved in 81% (17/21) of patients who discontinued KEYTRUDA, and 71% had resolution.

Hepatitis occurred in 7% (18/267) of 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 (3%) 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 2.6% (7) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 55% discontinued KEYTRUDA, and 71% had resolution.

#### 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 91% (20/22) of patients. Adrenal insufficiency resolved in 41% of patients who received 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 0.5% (13/2799) of patients receiving KEYTRUDA, including 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% (1) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) 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 in patients receiving KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (1,126/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (3.2%) adverse reactions. Systemic corticosteroids were required in 34% (56/167) of patients, of these, the majority remained on systemic corticosteroids. Dermatologic reactions led to permanent discontinuation of KEYTRUDA 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, 13% had recurrent dermatologic reactions.

#### 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis sicca, myositis, polymyalgia rheumatica, vasculitis, and diabetes mellitus, myelitis and demyelination, Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss, 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 bone marrow) 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Follow patients closely for these complications and intervene promptly, including consideration of discontinuation of KEYTRUDA, per clinical guidelines. Transplant-related complications may occur despite intervening 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 occurred in 6% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). Severe adverse reactions occurred in 16% of patients. The most frequent (≥2%) severe adverse reactions were diarrhea (3.4%), colitis (2.2%), and diarrhea (2%). Serious adverse reactions occurred in 16% of patients receiving KEYTRUDA. Serious adverse reactions in ≥2% of patients included diarrhea (3.4%), colitis (2.2%), and dehydration (2%). KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with stage IB or IIA melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in KEYNOTE-054 with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 11% of 405 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. In KEYNOTE-799, when KEYTRUDA was administered in combination with cisplatin and fluorouracil (5-FU) chemotherapy, adverse reactions occurring in patients with esophageal cancer were similar to those occurring in KEYNOTE-590 with advanced esophageal cancer.

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 who received KEYTRUDA, carboplatin, and paclitaxel or paclitaxel protein-bound. The most common adverse reactions (≥20%) were fatigue, nausea, alopecia, diarrhea, decreased appetite, constipation, rash, peripheral neuropathy, pneumonia, and vomiting. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception of higher incidences of alopecia and new or worsening hypothyroidism.

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC. The most common were pneumonia (3%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse reactions in 13% of 281 patients with advanced NSCLC. The most common were pneumonia (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

# Advanced Head and Neck Squamous Cell Carcinoma (HNSCC) or Neoadjuvant Followed by Adjuvant Therapy for Resectable Locally Advanced HNSCC



## INDICATIONS

### Neoadjuvant Followed by Adjuvant Therapy for Resectable Locally Advanced HNSCC

KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) who are at high risk of recurrence (determined by PD-L1 CPS ≥1 as determined by an FDA-approved test), as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) or chemoradiotherapy (CRT), and as a single agent

### First-Line Combination Therapy in Metastatic or Unresectable, Recurrent HNSCC

KEYTRUDA, in combination with platinum and fluorouracil (5-FU), is indicated for the first-line treatment of patients with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

Continued on next page ›

Scroll below to review Selected Safety Information

Neoadjuvant Followed by Adjuvant Therapy for Resectable Locally Advanced HNSCC
KEYNOTE-689
First-Line Combination Therapy in Metastatic or Unresectable, Recurrent HNSCC
KEYNOTE-048

## Selected Safety Information

### 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 blockers (PD-L1 and PD-L2) blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, which could potentially result in 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 with KEYTRUDA. For suspected immune adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute withhold or permanent discontinuation of KEYTRUDA depending on severity [*see Dosage and Administration (2.2)*]. In general, if KEYTRUDA requires withholding 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 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 4.4% (94/2799) of patients receiving KEYTRUDA, including Grade 3 (0.9%), Grade 4 (0.1%), and Grade 5 (0.3%) in Study 1. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 71% (67/94) of patients with available information. Withhold KEYTRUDA in patients with suspected pneumonitis and evaluate with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Permanently discontinue KEYTRUDA for moderate or severe pneumonitis that does not improve or recurs during corticosteroid dose tapering. Permanently discontinue KEYTRUDA for life-threatening pneumonitis.

#### 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. It is important to exclude infectious etiologies of diarrhea or colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 3 colitis. 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%) in Study 1. Systemic corticosteroids were required in 88% (42/48) of patients. Colitis resolved in 60% (29/48) of patients with available information. Permanently discontinue KEYTRUDA for immune-mediated colitis of Grade 4 or recurrent Grade 3 colitis.

#### 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 79% (15/19) of patients. Hepatitis resolved in 58% (11/19) of patients with available information. Withhold KEYTRUDA in patients with severe or life-threatening hepatitis, and upon improvement to Grade 1 or less, initiate corticosteroid therapy. Permanently discontinue KEYTRUDA in patients with elevated AST/ALT or total bilirubin levels greater than 5 times the upper limit of normal.

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 administer corticosteroids as clinically indicated. If elevations are resolved to Grade 1 or baseline, restart KEYTRUDA and axitinib dose 2 and 4 levels lower, respectively. Grade 2 (20%) and increased aspartate aminotransferase (AST) (3%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids. Grade 3 (4%) and Grade 4 (1%) increased AST occurred in 5% of patients. Grade 2 (13%) and Grade 3 (3%) increased bilirubin occurred. 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 AST or ALT flares ≥3x baseline occurred in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of AST or ALT ≥3x baseline 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 91% (20/22) of patients. Adrenal insufficiency resolved in 41% (9/22) of patients. Permanently discontinue KEYTRUDA for severe or life-threatening adrenal insufficiency.

*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 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.2%) 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 of KEYTRUDA in 0.2% (6) of patients. All patients who were withheld from KEYTRUDA for hypophysitis resumed KEYTRUDA and completed the event.

*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 initiation of 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 0.2% (5) were withheld from KEYTRUDA.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding of KEYTRUDA in 0.5% (14) of patients. Hyperthyroidism resolved in 74% (71/96) of patients with available information.

Hypothyroidism occurred in 9.9% (277/2799) of patients receiving KEYTRUDA, including Grade 3 (0.7%) and Grade 2 (9.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding of KEYTRUDA in 0.2% (6) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Hypothyroidism resolved in 28% (77/277) of patients. Hypothyroidism can result in pituitary dysfunction.

Hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with NSCLC who received KEYTRUDA as a single agent or with platinum chemotherapy (16%) than in 1289 patients with NSCLC who received platinum chemotherapy (4.2%). The incidence of new or worsening hypothyroidism was 13% in 1010 patients with HNSCC who received KEYTRUDA as a single agent or with platinum chemotherapy and 3.4% in 1007 patients who received placebo with platinum chemotherapy. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC receiving 4 mg/kg every 2 weeks (10.8%) than in 587 patients who received 200 mg every 3 weeks (5.8%). The incidence of new or worsening hypothyroidism was 12% in 1019 patients with HNSCC who received KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) and Grade 2 (11%) reactions. Systemic corticosteroids were required in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) and Grade 2 (2.2%) reactions.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (2) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding of KEYTRUDA in 0.1% (2) of patients. All patients who were withheld resumed 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 PD-1/PD-L1 blocking antibodies. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 14% (398/2799) of patients receiving KEYTRUDA, including Grade 3 (1.1%) and Grade 2 (1.8%) reactions. Systemic corticosteroids were required in 40% (158/398) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (17) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Rash resolved in 63% (252/398) of 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, uveitis, facial and abducens nerve paresis, myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica, autoimmune hemolytic anemia, myocarditis, pericarditis, vasculitis, sarcoidosis, immune thrombocytopenia, and myasthenia gravis.

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Transplant complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatment and transplant. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment 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 occurred in 6% of patients. The most common adverse reactions (≥20% with KEYTRUDA and greater than ipilimumab) were fatigue (31%), rash (28%), and pruritus (26%). The most common adverse reactions (≥20% with KEYTRUDA and greater than chemotherapy) were nausea (29%) and fatigue (28%). Serious adverse reactions occurred in 16% of 509 patients; the most common (≥1% and greater than ipilimumab) were pneumonitis (2.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 13% of 354 patients who received KEYTRUDA and were exposed for 1 year; the most common (≥1%) were pneumonitis (2.5%), colitis (2.3%), and adrenal insufficiency (1.4%). 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 patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 11% of patients. The most common adverse reactions (≥20%) were nausea (56%), fatigue (51%), constipation (35%), rash (25%), decreased appetite (24%), vomiting (24%), diarrhea (23%), and pruritus (21%). Serious adverse reactions occurred in 42% of patients; the most common (≥2%) were pneumonia (8%), dyspnea (4%), pulmonary embolism (3%), pleural effusion (3%), and vomiting (2%). Fatal adverse reactions occurred in 2% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated pneumonitis (0.3%). Adverse reactions occurred in 13% of patients who received KEYTRUDA and were exposed for 1 year; the most common (≥1%) were pneumonia (3%), fatigue (2%), and nausea (1%). The most frequent (≥2%) adverse reaction that led to permanent discontinuation of KEYTRUDA was pneumonitis (2%). The most frequent (≥2%) adverse reactions that led to dose interruption of KEYTRUDA were pneumonia (3%), fatigue (2%), and pneumonitis (2%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and paclitaxel or nab-paclitaxel in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 559 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 11% of patients. The most common adverse reactions (≥20%) were alopecia (41%), fatigue (31%), nausea (31%), decreased appetite (23%), peripheral neuropathy (23%), constipation (22%), diarrhea (21%), and rash (20%). Serious adverse reactions occurred in 41% of patients; the most common (≥2%) were pneumonia (8%), febrile neutropenia (4%), anemia (3%), dyspnea (3%), pulmonary embolism (3%), and pneumonitis (2%). Fatal adverse reactions occurred in 5% of patients, including death due to unknown cause (0.4%), sepsis (0.2%), and immune-mediated pneumonitis (0.2%). Adverse reactions occurred in 13% of patients who received KEYTRUDA and were exposed for 1 year; the most common (≥1%) were pneumonia (3%), fatigue (2%), and anemia (1%). The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pneumonia (2%). The most frequent (≥2%) adverse reactions that led to dose interruption of KEYTRUDA were neutropenia (3%), pneumonia (3%), and fatigue (2%).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 18% of 404 patients who received at least one dose of single-agent KEYTRUDA; 11% experienced serious adverse reactions leading to permanent discontinuation of KEYTRUDA. The most common adverse reactions (≥20%) were nausea (40%), fatigue (36%), constipation (25%), diarrhea (24%), decreased appetite (23%), rash (22%), vomiting (21%), and pyrexia (20%). Serious adverse reactions occurred in 45% of patients; the most common (≥2%) were pneumonia (7%), pneumonitis (3%), pulmonary embolism (3%), dyspnea (3%), and pyrexia (2%). Fatal adverse reactions occurred in 4% of patients, including pneumonitis (1%), pneumonia (1%), and sepsis (1%). Adverse reactions occurred in 16% of patients who received KEYTRUDA and were exposed for 1 year; the most common (≥1%) were pneumonia (2%), fatigue (1%), and nausea (1%). The most frequent (≥2%) adverse reaction that led to permanent discontinuation of KEYTRUDA was pneumonitis (2%). The most frequent (≥2%) adverse reactions that led to dose interruption of KEYTRUDA were pneumonia (3%), fatigue (2%), and pneumonitis (2%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 16% of 637 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and fatigue (2%). Serious adverse reactions occurred in 41% of patients; the most common (≥2%) were pneumonia (3.3%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse reactions in 13% of 281 patients with HNSCC; the most common were pneumonitis (3%), pneumonia (3%), and fatigue (2%). The most common adverse reactions (≥20%) were fatigue (23%), 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 18% of 276 patients; the most common were pneumonia (3%), pneumonitis (2%), and febrile neutropenia (2%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (51%), constipation (31%), decreased appetite (31%), vomiting (29%), mucositis (28%), diarrhea (27%), stomatitis (27%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with carboplatin and paclitaxel or nab-paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 19% of 240 patients; the most common were pneumonia (3%), pneumonitis (2%), and febrile neutropenia (2%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (51%), alopecia (49%), peripheral neuropathy (37%), decreased appetite (31%), vomiting (29%), mucositis (28%), diarrhea (27%), and constipation (21%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 14% of 494 patients with HNSCC. Serious adverse reactions occurred in 26% of patients; the most common (≥2%) were pneumonia (4%), pneumonitis (2%), and pleural effusion (2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 14% of 564 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation was urinary tract infection (1.1%). The most common adverse reactions (≥20%) were fatigue (29%), urinary tract infection (23%), pruritus (21%), musculoskeletal pain (21%), rash (21%), and diarrhea (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction requiring permanent discontinuation was pneumonitis (1.1%). The most common adverse reactions (≥20%) were fatigue (30%), urinary tract infection (22%), pruritus (21%), musculoskeletal pain (21%), nausea (20%), and constipation (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 requiring permanent discontinuation was urinary tract infection (1.4%). The most common adverse reactions (≥20%) were fatigue (32%), musculoskeletal pain (26%), urinary tract infection (23%), pruritus (21%), and diarrhea (20%).

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-177, when KEYTRUDA was administered as a single agent to patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, adverse reactions occurring in 12% of patients included pneumonia (4.1%), diarrhea (3.1%), hemorrhage (2.3%), and vomiting (2.4%). KEYTRUDA was discontinued due to adverse reactions in 11% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were diarrhea (1.5%), colitis (1.5%), and pneumonitis (1.5%). The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonia (1.5%), diarrhea (1.5%), and pneumonitis (1.5%). The most common adverse reactions (≥20%) were fatigue (41%), musculoskeletal pain (30%), upper respiratory tract infection (29%), nausea (29%), pruritus (28%), rash (25%), diarrhea (24%), decreased appetite (21%), abdominal pain (20%), pyrexia (20%), cough (20%), fatigue (20%), and constipation (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with MSI-H or dMMR cancer, serious adverse reactions occurred in 36% of patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 9% of patients. The most frequent adverse reaction leading to permanent discontinuation was pneumonitis (1.2%). The most frequent adverse reactions (≥1%) that led to permanent discontinuation of KEYTRUDA were diarrhea (0.7%), interstitial lung disease (0.4%), increased aspartate aminotransferase (0.4%), and pneumonitis (0.4%).

Adverse reactions observed in KEYNOTE-590 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (20%), hyperthyroidism (7%), thyroiditis (2%), and hypophysitis (1%).

In KEYNOTE-689, the most common adverse reactions (≥20%) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), mucositis (33%), constipation (27%), hypothyroidism (27%), dysphagia (26%), nausea (25%), rash (24%), and decreased appetite (23%). 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 leading to permanent discontinuation of KEYTRUDA. The most common serious adverse reactions (≥2%) were dysphagia (3%), pneumonia (3%), radiation skin injury (2.8%), stomatitis (2.8%), and dehydration (2.5%). Fatal adverse reactions occurred in 0.6% (2) of patients, including respiratory failure, cardiac arrest, and sepsis. Adverse reactions occurred in 13% of patients who received KEYTRUDA and were exposed for 1 year; the most common (≥1%) were pneumonia (2.2%) and radiation skin injury (1.1%). The most frequent adverse reaction that led to permanent discontinuation of KEYTRUDA was pneumonia (1.1%). The most frequent adverse reactions that led to dose interruption of KEYTRUDA were pneumonia (3%), radiation skin injury (2.8%), and stomatitis (2.5%). In one patient who received KEYTRUDA, the most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 18% of 276 patients; the most common were pneumonia (3%), pneumonitis (2%), and febrile neutropenia (2%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (51%), constipation (31%), decreased appetite (31%), vomiting (29%), mucositis (28%), diarrhea (27%), stomatitis (27%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with carboplatin and paclitaxel or nab-paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 19% of 240 patients; the most common were pneumonia (3%), pneumonitis (2%), and febrile neutropenia (2%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (51%), alopecia (49%), peripheral neuropathy (37%), decreased appetite (31%), vomiting (29%), mucositis (28%), diarrhea (27%), constipation (21%), and abdominal pain (20%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 8% of 58 patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) adenocarcinoma who received KEYTRUDA as a single agent (n=29) or placebo (n=29). Serious adverse reactions occurred due to adverse reactions in 15% of 27 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis, colitis, acute kidney injury, and pneumonia (1% for each). The most common adverse reactions (≥20%) were fatigue (41%), nausea (37%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (24%), stomatitis (23%), and weight loss (23%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with MSI-H or dMMR gastrointestinal cancer, adverse reactions occurring in patients with esophagogastric cancer (n=107) were similar to those occurring in patients with other gastrointestinal cancers.

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with MSI-H or dMMR cancer receiving KEYTRUDA as a single agent, with a median duration of exposure of 11 months (range: 0.1 to 37.2 months), adverse reactions occurring in 40% of patients included pneumonitis (4.1%), diarrhea (3.1%), and hepatitis (2.1%). Fatal adverse reactions occurred in 1.4% of patients; these 2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and sepsis. The most common adverse reactions (≥20%) were fatigue (41%), musculoskeletal pain (30%), upper respiratory tract infection (29%), nausea (29%), pruritus (28%), rash (25%), diarrhea (24%), decreased appetite (21%), abdominal pain (20%), pyrexia (20%), cough (20%), fatigue (20%), and constipation (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction requiring permanent discontinuation was pneumonitis (1.1%). The most common adverse reactions (≥20%) were fatigue (30%), urinary tract infection (22%), pruritus (21%), musculoskeletal pain (21%), nausea (20%), and constipation (20%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 9% of 370 patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (32%), musculoskeletal pain (22%), urinary tract infection (21%), pruritus (20%), and rash (20%).

In KEYNOTE-361, KEYTRUDA was discontinued due to adverse reactions in 8% of 351 patients with mRCC. Serious adverse reactions occurred in 26% of patients who received KEYTRUDA, including pneumonia (2%), pneumonitis (2%), and pulmonary embolism (2%). Fatal adverse reactions occurred in 1% of patients within 30 days of start of treatment. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (24%), and diarrhea (21%).

In KEYNOTE-426, when KEYTRUDA was administered in combination with axitinib, KEYTRUDA was discontinued due to adverse reactions in 31% of 429 patients with advanced RCC; 16% experienced adverse reactions leading to permanent discontinuation of KEYTRUDA. The most common adverse reactions (≥20%) were diarrhea (56%), hypertension (39%), fatigue (37%), hepatotoxicity (36%), stomatitis/mucosal inflammation (29%), palmar-plantar erythrodysesthesia syndrome (26%), rash (25%), cough (22%), and constipation (21%).

In KEYNOTE-564, KEYTRUDA was discontinued due to adverse reactions in 30% of 461 patients with adjuvant RCC. The most common adverse reactions (≥10%) were diarrhea (34%), fatigue (31%), nausea (16%), asthenia (15%), pruritus (14%), and rash (13%).

In KEYNOTE-564, KEYTRUDA was administered in combination with axitinib or pembrolizumab (n=1 each) or sunitinib (n=3) for single interstitial pneumonitis, colitis, and hepatitis, respectively.

In KEYNOTE-564, KEYTRUDA was administered as a single agent (n=1) for hepatitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for pneumonitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for colitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hepatitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hypophysitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for adrenal insufficiency.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hypothyroidism.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hyperthyroidism.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for type 1 diabetes mellitus.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for nephritis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for myasthenic syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for encephalitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for myocarditis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for myositis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for rhabdomyolysis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for vasculitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for uveitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for pancreatitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for gastritis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for duodenitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for sialadenitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for facial and abducens nerve paresis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for sarcoidosis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for immune thrombocytopenia.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for autoimmune hemolytic anemia.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for myasthenia gravis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for polymyalgia rheumatica.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for Guillain-Barré syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemophagocytic lymphohistiocytosis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for systemic inflammatory response syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for cytokine release syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic cystitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic colitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic gastritis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic duodenitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic sialadenitis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic facial and abducens nerve paresis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic sarcoidosis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic immune thrombocytopenia.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic autoimmune hemolytic anemia.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic myasthenia gravis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic polymyalgia rheumatica.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic Guillain-Barré syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic hemophagocytic lymphohistiocytosis.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic systemic inflammatory response syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic cytokine release syndrome.

In KEYNOTE-564, KEYTRUDA was administered in combination with pembrolizumab (n=1) for hemorrhagic cystitis.

In KEYNOTE-564, KEYTRUDA was administered in combination

# Advanced Head and Neck Squamous Cell Carcinoma (HNSCC) or Neoadjuvant Followed by Adjuvant Therapy for Resectable Locally Advanced HNSCC



## INDICATIONS

### 1 First-Line Monotherapy in Metastatic or Unresectable, Recurrent HNSCC

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

### 2 Subsequent-Line Monotherapy in Recurrent or Metastatic HNSCC

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

**Scroll below to review Selected Safety Information**

- First-Line Monotherapy in Metastatic or Unresectable, Recurrent HNSCC KEYNOTE-048
- Subsequent-Line Monotherapy in Recurrent or Metastatic HNSCC

## Selected Safety Information

### 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 blockers (PD-L1 blockers). Per PD-1/PD-L1 blocking drug, 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 with KEYTRUDA. For HNSCC treated with KEYTRUDA in the neoadjuvant setting, monitor blood counts at least once every 3 weeks 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. KEYTRUDA requires management of severe immune reactions. For suspected immune reactions, administer systemic corticosteroids (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% (38/1129) of patients receiving KEYTRUDA, including Grade 3 (0.8%), Grade 4 (0.1%), and Grade 5 (0.3%) in Study 1. Additional corticosteroids were required in 67% (13/19) of patients with pneumonitis. Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 1.2% (14/1129) of patients. Of the pneumonitis events resolved, 54% (14/26) resolved to Grade 1 or 2 and 38% (10/26) resolved to Grade 3 or 4 after discontinuation of KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (7/100) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (2.2%), 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 2% (2/100) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 7% (7/100) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (2.2%), 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 2% (2/100) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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. It is important to exclude infectious etiologies of diarrhea and colitis. Administer corticosteroids for severe reactions. Withhold or permanently discontinue KEYTRUDA depending on severity.

Immune-mediated colitis occurred in 1.7% (19/1129) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Additional corticosteroids were required in 84% (16/19) of patients with colitis. Colitis led to permanent discontinuation of KEYTRUDA in 1.1% (13) and withholding in 0.9% (10) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Of the colitis events resolved, 24% (4/17) resolved to Grade 1 or 2 after discontinuation of KEYTRUDA.

#### Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a single agent

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (7/1129) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 71% (5/7) of patients with hepatitis. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.4% (5) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Of the hepatitis events resolved, 67% (2/3) resolved to Grade 1 or 2 after discontinuation of KEYTRUDA.

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 administer corticosteroids as clinically indicated. If liver enzymes increase to Grade 3 and return to baseline, restart KEYTRUDA and axitinib at reduced dose. If liver enzymes increase to Grade 4 (20x ULN) and recovered aspartate aminotransferase (AST)/alanine aminotransferase (ALT) values were at a higher frequency compared to patients receiving KEYTRUDA alone. Fifty-nine percent of the patients with recovered AST/ALT elevations received KEYTRUDA at a reduced dose, 24% had dose interruption, and 18% had permanent discontinuation of KEYTRUDA. 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 or ASTRA (n=34) elevations in patient receiving KEYTRUDA, 18 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT or 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 (0.7%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Of the adrenal insufficiency events resolved, 71% (5/7) resolved to Grade 1 or 2 after discontinuation of KEYTRUDA.

*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 0.9% (25/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.6%) 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 resumed KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

Hypothyroidism occurred in 8.4% (94/1129) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (3.8%). It led to permanent discontinuation of KEYTRUDA in 0.5% (6) and withholding in 2.3% (26) of patients. Hyperthyroidism occurred in 3.4% (39/1129) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.3%). It led to permanent discontinuation of KEYTRUDA in 0.2% (2) and withholding in 0.8% (9) of patients. Thyroiditis occurred in 0.6% (7/1129) of patients receiving KEYTRUDA, including Grade 2 (0.3%) reactions. It led to withholding of KEYTRUDA in 0.1% (1) of patients.

In patients with resected NSCLC who received KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), hypothyroidism occurred in 16% (16/100) of patients, including Grade 2 (2%) reactions. Hyperthyroidism occurred in 9% (9/100) of patients, including Grade 2 (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% (1) and withholding in 0.3% (3) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

*Thyroid Disorders at Baseline (DM), Which Can Present With Diabetic Ketoacidosis*

Hypothyroidism can be managed with hormone replacement. Hyperthyroidism can be managed with medical therapy. 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 0.2% (5) of patients withheld.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (3/1129) 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% (1) and withholding in 0.2% (2) of patients. All patients who were withheld resumed 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 in patients receiving anti–PD-1/PD-L1 treatments. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 14% (157/1129) of patients receiving KEYTRUDA, including Grade 3 (1.2%) and Grade 2 (0.4%) reactions. Rash led to permanent discontinuation in 40% (75/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (7) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Of the dermatologic events resolved, 50% (4/8) resolved to Grade 1 or 2 after discontinuation of KEYTRUDA.

#### 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, uveitis, facial and abducens nerve paresis, myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica, autoimmune hemolytic anemia, myocarditis, pericarditis, vasculitis, sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection, 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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for transplantation and care of patients before and after transplantation.

#### 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 occurred in 6% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). Serious adverse reactions occurred in 41% of patients. The most common (≥2%) serious adverse reactions included pneumonia, colitis, pyrexia, dyspnea, and pulmonary embolism. Fatal adverse reactions occurred in 1% of patients, including death due to unknown cause (0.4%), sepsis (0.2%), and immune-mediated adverse reactions (0.2%). Adverse reactions led to permanent discontinuation of KEYTRUDA in 9% of patients. The most common adverse reaction (≥2%) leading to permanent discontinuation of KEYTRUDA was pneumonitis (2%). Adverse reactions resulted in withholding of KEYTRUDA in 26% of patients. The most common adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), diarrhea (3%), and colitis (2%).

In KEYNOTE-048, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 14% of patients; adverse reactions occurred in 42% of patients. The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (20%), upper respiratory tract infection and pyrexia (18% each), and cough (17%). Serious adverse reactions occurred in 29% of patients. The most common (≥2%) serious adverse reactions included pneumonia (4%), aspiration pneumonia (3%), and dyspnea (2%). Fatal adverse reactions occurred in 3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated adverse reactions (0.3%). Adverse reactions led to permanent discontinuation of KEYTRUDA in 14% of patients. The most common adverse reaction (≥2%) leading to permanent discontinuation of KEYTRUDA was pneumonitis (2%). Adverse reactions resulted in withholding of KEYTRUDA in 26% of patients. The most common adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), diarrhea (3%), and colitis (2%).

In KEYNOTE-040, KEYTRUDA was discontinued due to adverse reactions in 9% of 300 patients with metastatic NSCLC; adverse reactions occurred in 67% of patients. The most frequent adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (25%), cough (24%), nausea (23%), and dyspnea (22%). Serious adverse reactions occurred in 49% of patients. The most frequent (≥2%) serious adverse reactions included pneumonia (8%), pulmonary embolism (3%), pleural effusion (2%), and dyspnea (2%). Fatal adverse reactions occurred in 5% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated adverse reactions (0.3%). Adverse reactions led to permanent discontinuation of KEYTRUDA in 9% of patients. The most frequent (≥2%) adverse reaction leading to permanent discontinuation of KEYTRUDA was pneumonitis (2%). Adverse reactions resulted in withholding of KEYTRUDA in 33% of patients. The most frequent adverse reactions leading to withholding of KEYTRUDA were pneumonitis (4%), fatigue (3%), diarrhea (3%), and pneumonia (2%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 638 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and pulmonary embolism (2%). The most common adverse reactions (≥20%) were fatigue (33%), musculoskeletal pain (25%), decreased appetite (21%), pneumonitis (13%), pulmonary embolism (12%), and pruritus (12%). Serious adverse reactions occurred in 58% of patients, including death due to unknown cause (4%), pneumonia (3%), and pulmonary embolism (2%). Fatal adverse reactions occurred in 5% of patients, including death due to unknown cause (4%) and pneumonia (0.6%). COVID-19 infection was reported in 3% of patients. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pneumonia (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), pneumonia (2%), fatigue (2%), and pulmonary embolism (2%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 9% of 154 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and pulmonary embolism (2%). The most common adverse reactions (≥20%) were fatigue (35%), musculoskeletal pain (25%), decreased appetite (23%), nausea (22%), and pruritus (20%). Serious adverse reactions occurred in 49% of patients. The most common (≥2%) serious adverse reactions included pneumonia (8%), pulmonary embolism (2%), and dyspnea (2%). Fatal adverse reactions occurred in 3% of patients, including pneumonia (1%), pulmonary embolism (1%), and sepsis (1%). The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pneumonia (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), pneumonia (2%), fatigue (2%), and pulmonary embolism (2%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of patients with urothelial cancer; adverse reactions occurred in 70% of patients. The most common adverse reactions (≥20%) were fatigue (32%), musculoskeletal pain (25%), nausea (24%), pruritus (22%), decreased appetite (21%), rash (20%), and diarrhea (20%). Serious adverse reactions occurred in 45% of patients. The most frequent (≥2%) serious adverse reactions included urinary tract infection (4%), pneumonia (3%), and pyrexia (2%). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest, cardiopulmonary failure, and sepsis (0.7% each). The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and fatigue (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), urinary tract infection (2%), fatigue (2%), and pyrexia (2%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with cisplatin-ineligible urothelial cancer; adverse reactions occurred in 67% of patients. The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (25%), decreased appetite (21%), nausea (20%), pruritus (20%), rash (20%), and constipation (20%). Serious adverse reactions occurred in 49% of patients. The most frequent (≥2%) serious adverse reactions included urinary tract infection (4%), pneumonia (3%), and pyrexia (2%). Fatal adverse reactions occurred in 3% of patients, including cardiac arrest (0.5%) and pneumonia (0.5%). The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pyrexia (2%). The most common adverse reactions (≥20%) that led to withholding of KEYTRUDA were pneumonitis (3%), urinary tract infection (2%), pyrexia (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (25%), constipation (24%), and nausea (20%).

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-177, KEYTRUDA was discontinued due to adverse reactions in 11% of 153 patients with microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC); adverse reactions occurred in 62% of patients. The most common adverse reactions (≥20%) were diarrhea (26%), nausea (24%), fatigue (24%), pyrexia (24%), rash (24%), and abdominal pain (21%). Serious adverse reactions occurred in 41% of patients. The most frequent (≥2%) serious adverse reactions included intestinal obstruction (4%), pyrexia (3%), acute kidney injury (3%), and pneumonia (2%). Fatal adverse reactions occurred in 2% of patients, including cardiac arrest (0.7%), pulmonary embolism (0.7%), sepsis (0.7%), and one patient each with cerebral hemorrhage, cerebrovascular accident, or pneumonitis. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (3%), pyrexia (2%), and intestinal obstruction (2%). Adverse reactions resulted in withholding of KEYTRUDA in 40% of patients. The most common adverse reactions (≥10%) were pneumonitis, pyrexia, musculoskeletal pain, diarrhea (22%), and nausea, fatigue, rash, and cough (20% each).

In KEYNOTE-177, KEYTRUDA was discontinued due to adverse reactions in 9% of 151 patients with MSI-H mCRC; adverse reactions occurred in 76% of patients. The most common adverse reactions (≥20%) were fatigue (32%), diarrhea (31%), nausea (29%), abdominal pain (25%), musculoskeletal pain (25%), decreased appetite (24%), rash (23%), vomiting (21%), and pyrexia (20%). Serious adverse reactions occurred in 45% of patients. The most frequent (≥2%) serious adverse reactions included intestinal obstruction (5%), pyrexia (4%), acute kidney injury (3%), pneumonia (3%), and dehydration (2%). Fatal adverse reactions occurred in 3% of patients, including cardiac arrest (1%), pulmonary embolism (1%), sepsis (1%), and urinary tract infection (1%). The most common adverse reactions (≥20%) were pyrexia (24%), rash (24%), and diarrhea (23%). The most frequent adverse reactions (≥2%) that led to permanent discontinuation of KEYTRUDA were pneumonitis (3%), pyrexia (2%), and intestinal obstruction (2%). Adverse reactions resulted in withholding of KEYTRUDA in 39% of patients. The most common adverse reactions (≥10%) were pneumonitis, pyrexia, acute kidney injury, hyponatremia, and anemia (10% each).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 58 patients with previously treated, advanced cervical cancer; adverse reactions occurred in 74% of patients. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (29%), diarrhea (26%), decreased appetite (24%), nausea (22%), abdominal pain (21%), and pruritus (21%). Serious adverse reactions occurred in 38% of patients. The most frequent (≥2%) serious adverse reactions included urinary tract infection (5%), pneumonia (3%), and pyrexia (3%). Fatal adverse reactions occurred in 2% of patients, including one patient each with cardiac arrest, cardiopulmonary failure, and sepsis. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (3%) and pyrexia (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), pyrexia (2%), and urinary tract infection (2%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 9% of 94 patients with previously treated, recurrent or metastatic cervical cancer; adverse reactions occurred in 79% of patients. The most common adverse reactions (≥20%) were fatigue (37%), musculoskeletal pain (29%), diarrhea (28%), decreased appetite (27%), nausea (26%), abdominal pain (23%), and pruritus (21%). Serious adverse reactions occurred in 39% of patients. The most frequent (≥2%) serious adverse reactions included urinary tract infection (5%), pneumonia (4%), and pyrexia (3%). Fatal adverse reactions occurred in 3% of patients, including one patient each with cardiac arrest, cardiopulmonary failure, and sepsis. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (3%) and pyrexia (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), pyrexia (2%), urinary tract infection (2%), and vaginal hemorrhage (2%).

In KEYNOTE-158, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, adverse reactions occurred in 96% of patients. The most common adverse reactions (≥20%) were alopecia (39%), fatigue (38%), nausea (37%), peripheral neuropathy (27%), vomiting (24%), decreased appetite (23%), abdominal pain (21%), diarrhea (21%), constipation (20%), and pyrexia (20%). Serious adverse reactions occurred in 52% of patients. The most frequent (≥2%) serious adverse reactions included urinary tract infection (5%), pneumonia (4%), pyrexia (3%), and vaginal hemorrhage (2%). Fatal adverse reactions occurred in 2% of patients, including one patient each with cardiac arrest, cardiopulmonary failure, and sepsis. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pyrexia (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), urinary tract infection (2%), pyrexia (2%), and vaginal hemorrhage (2%).

In KEYNOTE-158, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, adverse reactions occurred in 96% of patients. The most common adverse reactions (≥20%) were alopecia (39%), fatigue (38%), nausea (37%), peripheral neuropathy (27%), vomiting (24%), decreased appetite (23%), abdominal pain (21%), diarrhea (21%), constipation (20%), and pyrexia (20%). Serious adverse reactions occurred in 52% of patients. The most frequent (≥2%) serious adverse reactions included urinary tract infection (5%), pneumonia (4%), pyrexia (3%), and vaginal hemorrhage (2%). Fatal adverse reactions occurred in 2% of patients, including one patient each with cardiac arrest, cardiopulmonary failure, and sepsis. The most frequent (≥2%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pyrexia (2%). The most frequent (≥2%) adverse reactions that led to withholding of KEYTRUDA were pneumonitis (3%), pyrexia (2%), urinary tract infection

# Select a Cancer Type

## Relapsed or Refractory Classical Hodgkin Lymphoma (cHL)

### INDICATIONS

**Relapsed or Refractory cHL**

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 classical Hodgkin lymphoma (cHL), or cHL that has relapsed after 2 or more lines of therapy.

**Scroll below to review Selected Safety Information**

Relapsed or Refractory cHL
KEYNOTE-087

## Selected Safety Information

### 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 suspected immune-mediated adverse reactions with KEYTRUDA in the monotherapy setting, monitor clinical status and function 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 withholding 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.6%). Median time to onset was 4.4 months (range 1 day to 22.9 months). Pneumonitis resolved in 67% (63/94) of patients. Of patients with pneumonitis who received systemic corticosteroids, 59% (46/78) resolved, and of patients who were administered immunosuppressants in addition to systemic corticosteroids, 71% (10/14) resolved.

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 3.9% of patients. Of patients with pneumonitis who received systemic corticosteroids, 71% (22/31) discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (15/214) of 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 2% (4/214) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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 immune-mediated colitis. It is important to exclude infectious causes of diarrhea before initiating treatment with corticosteroids in patients with suspected immune-mediated colitis. 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%) adverse reactions. Median time to onset was 4.2 months (range 1 day to 19.4 months). Colitis resolved in 42% (20/48) of patients. Of patients with colitis who received systemic corticosteroids, 38% (15/39) resolved, and of patients who were administered immunosuppressants in addition to systemic corticosteroids, 67% (4/6) resolved. Colitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

Colitis occurred in 3% (11/389) 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 2.3% (9) of patients. Of patients with pneumonitis who received systemic corticosteroids, 71% (5/7) discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 8% (17/214) of 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 (3%) 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 2.8% (6/214) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 (0.5%), and Grade 2 (0.1%) reactions. Hepatitis resolved in 47% (9/19) of patients. Of patients with hepatitis who received systemic corticosteroids, 50% (5/10) were resolved in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Hepatitis occurred in 3% (11/389) of patients receiving KEYTRUDA as a single agent.

#### 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 administer corticosteroids as clinically indicated. In the clinical trial, 3 of 20 patients (15%) with Child-Pugh A cirrhosis and 3 of 6 patients (50%) with Child-Pugh B cirrhosis (n=20) and increased aspartate aminotransferase (AST) 20 were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids. Liver enzymes improved after dose modification or interruption in 5 of 6 patients (83%) with Child-Pugh B cirrhosis. 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 AST or ALT Grade 3 or greater was observed in 1 patient receiving KEYTRUDA as a single agent, 3 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of AST or ALT LLN subsequently received 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 (0.5%), and Grade 2 (0.1%) reactions. Symptoms resolved in 45% (10/22) of patients. Of patients who received systemic corticosteroids, 50% (11/22) had resolution. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld resumed 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 0.5% (13/2799) of patients receiving KEYTRUDA, including 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 resumed KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) of patients. All patients who were withheld resumed 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 in patients receiving KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (75/189) of patients. These reactions led to permanent discontinuation in 0.5% (2) and withholding of KEYTRUDA in 0.6% (1) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Rash resolved in 59% (44/75) of 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: Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), myositis/polymyositis, rhabdomyolysis and associated sequelae, myocarditis, uveitis, iritis and other ocular inflammatory toxicities, which can be associated with retinal detachment. Various neuropathies have been reported as immune-mediated reactions. Myocarditis was a rare event 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. Immune-mediated pancreatitis, including 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. Hypoparathyroidism, Ophthalmic Uveitis, iritis and other ocular inflammatory toxicities, aseptic meningitis, 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for the management of patients undergoing HSCT. 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 treatment 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 occurred in 4.1% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (21%), and nausea (21%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (21%), and nausea (21%). Serious adverse reactions occurred in 41% of patients. The most frequent (≥2%) serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 4% of patients. Adverse reactions that led to permanent discontinuation of KEYTRUDA were diarrhea (1%), colitis (1%), and pneumonitis (1%). Dose delays occurred in 9% of patients.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 18% of 405 patients; adverse reactions leading to permanent discontinuation occurred in 14% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (56%), nausea (56%), constipation (34%), rash (25%), and diarrhea (25%). Serious adverse reactions occurred in 44% of patients. The most frequent (≥2%) serious adverse reactions included pneumonia (6%), pulmonary embolism (3%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and either paclitaxel or nab-paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 19% of 278 patients; adverse reactions leading to permanent discontinuation occurred in 15% of patients. The most common adverse reactions (≥20%) were fatigue (55%), alopecia (31%), nausea (30%), diarrhea (27%), decreased appetite (26%), peripheral neuropathy (24%), constipation (21%), and vomiting (20%). Serious adverse reactions occurred in 49% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia (4%), febrile neutropenia (3%), anemia (2%), and pulmonary embolism (2%). The most common adverse reaction (≥20%) was alopecia (36%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and dyspnea (3%). Fatal adverse reactions occurred in 5% of patients, including pneumonitis, cardiac arrest, cardiopulmonary failure, and pneumonia (0.3% each), pulmonary embolism (0.2%), and pleural effusion (0.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 300 patients with advanced HNSCC; the most common were pneumonia (3%), dyspnea (3%), and pneumonitis (2%). The most common adverse reactions (≥20%) were fatigue (23%), constipation (21%), and nausea (20%).

In KEYNOTE-048, when KEYTRUDA was administered as monotherapy or with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 18% of 281 patients with advanced HNSCC; adverse reactions leading to permanent discontinuation occurred in 13% of patients. The most common adverse reactions (≥20%) were fatigue (23%), constipation (21%), and nausea (20%). The most common adverse reactions (≥20%) were fatigue (31%), decreased appetite (23%), nausea (22%), and constipation (20%). Serious adverse reactions occurred in 45% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia (6%), pulmonary embolism (3%), and sepsis (2%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 19% of 370 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and pleural effusion (2%). The most common adverse reactions (≥20%) were fatigue (25%), cough (21%), and nausea (20%).

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 9% of 210 patients with relapsed cHL; the most common were pneumonitis (3.8%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (23%).

In KEYNOTE-204, when KEYTRUDA was administered as monotherapy or with brentuximab vedotin, KEYTRUDA was discontinued due to adverse reactions in 16% of 148 patients with relapsed or refractory cHL; adverse reactions leading to permanent discontinuation occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (33%), pyrexia (23%), cough (21%), and nausea (20%). The most common adverse reactions (≥20%) were fatigue (35%), pyrexia (22%), and nausea (20%). Serious adverse reactions occurred in 41% of patients. The most frequent (≥2%) serious adverse reaction was pneumonia (3%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued for any adverse reactions in 18% of 561 patients with advanced HNSCC; adverse reactions leading to permanent discontinuation occurred in 13% of patients. The most common adverse reactions (≥20%) were fatigue (23%), constipation (21%), and nausea (20%). The most common adverse reactions (≥20%) were fatigue (31%), decreased appetite (23%), nausea (22%), and constipation (20%). Serious adverse reactions occurred in 45% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia (6%), pulmonary embolism (3%), and sepsis (2%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (20%), and pruritus (20%). The most common adverse reactions (≥20%) were fatigue (30%), nausea (21%), urinary tract infection, pneumonia, anemia, and pruritus (20% each). Serious adverse reactions occurred in 48% of patients. The most frequent (≥2%) serious adverse reactions were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and urosepsis. The most common adverse reaction (≥20%) was fatigue (30%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation was urinary tract infection (2.7%). The most common adverse reactions (≥20%) were fatigue (29%), musculoskeletal pain (25%), pruritus (24%), urinary tract infection (21%), and adrenal insufficiency (1%). The most common adverse reactions (≥20%) were fatigue (29%), pruritus (24%), and urinary tract infection (21%).

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 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-859, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) and trastuzumab, KEYTRUDA was discontinued due to adverse reactions in 12% of patients included pneumonia (1.6%), diarrhea (1.1%), hemorrhage (0.3%), and vomiting (0.4%). Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 19% of patients. The most common adverse reactions (≥20%) were fatigue (39%), nausea (38%), alopecia (29%), diarrhea (28%), vomiting (24%), decreased appetite (23%), and constipation (20%).

In KEYNOTE-590, when KEYTRUDA was discontinued due to adverse reactions in 8% of 354 patients with esophageal or gastroesophageal junction cancer, adverse reactions leading to permanent discontinuation occurred in 5% of patients. The most common adverse reactions (≥20%) were fatigue (35%), nausea (28%), vomiting (24%), decreased appetite (24%), abdominal pain (24%), diarrhea (23%), constipation (22%), and cough (21%).

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) adenocarcinoma 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 (≥1%) were pneumonia, acute kidney injury (2%), and pneumonitis (1%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (49%), vomiting (34%), fatigue (32%), decreased appetite (24%), constipation (24%), diarrhea (24%), stomatitis (23%), and weight loss (22%).

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

In KEYNOTE-868, when KEYTRUDA was administered with FOLFOX (platinum plus fluorouracil) and leucovorin therapy (5-FU) followed by brachytherapy (BT) in 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, sepsis, and pneumonitis. Permanent discontinuation due to any adverse reaction occurred in 19% of patients. The most common adverse reactions (≥20%) were fatigue (51%), nausea (49%), alopecia (46%), peripheral neuropathy (40%), diarrhea (39%), vomiting (24%), decreased appetite (24%), and constipation (20%). Serious adverse reactions occurred in 42% of patients. The most frequent (≥2%) serious adverse reactions were urinary tract infection (3%), vomiting (3%), fatigue (2%), pyrexia (2%), and pneumonia (2%). The most common adverse reaction (≥20%) was alopecia (52%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients including pneumonitis (1.8%), pneumonia (1.4%), and sepsis (1.1%). Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 29% of patients including pneumonitis (2.1%), pneumonia (1.8%), and sepsis (1.4%). The most common adverse reactions (≥20%) were alopecia (51%), fatigue (50%), nausea (46%), peripheral neuropathy (41%), diarrhea (36%), vomiting (24%), decreased appetite (23%), abdominal pain (22%), platelet disorder (21%), and constipation (20%). Serious adverse reactions occurred in 46% of patients.

In KEYNOTE-868, when KEYTRUDA was administered as monotherapy to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 15% of patients including pneumonitis (2.1%), pneumonia (1.8%), and sepsis (1.4%). Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 23% of patients including pneumonitis (2.1%), pneumonia (1.8%), and sepsis (1.4%). The most common adverse reactions (≥20%) were fatigue (24%), nausea (21%), and diarrhea (20%). Serious adverse reactions occurred in 30% of patients.

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients including pneumonitis (1.8%), pneumonia (1.4%), and sepsis (1.1%). Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 29% of patients including pneumonitis (2.1%), pneumonia (1.8%), and sepsis (1.4%). The most common adverse reactions (≥20%) were fatigue (50%), alopecia (46%), peripheral neuropathy (41%), diarrhea (36%), vomiting (24%), decreased appetite (23%), abdominal pain (22%), platelet disorder (21%), and constipation (20%). Serious adverse reactions occurred in 46% of patients.

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of 857 patients with biliary tract cancer; adverse reactions leading to permanent discontinuation occurred in 11% of patients. The most common adverse reactions (≥20%) were fatigue (41%), nausea (38%), vomiting (24%), decreased appetite (24%), constipation (21%), and rash (20%). Serious adverse reactions occurred in 50% of patients. The most common adverse reaction (≥20%) was fatigue (41%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 18% of 596 patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment; adverse reactions leading to permanent discontinuation occurred in 14% of patients. The most common adverse reactions (≥20%) were fatigue (34%), nausea (26%), diarrhea (24%), rash (23%), and pruritus (21%). The most common adverse reactions (≥20%) were fatigue (34%), nausea (26%), diarrhea (24%), rash (23%), and pruritus (21%). Serious adverse reactions occurred in 41% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia (4%), pulmonary embolism (3%), and pleural effusion (2%). The most common adverse reaction (≥20%) was fatigue (34%).

In KEYNOTE-671, when KEYTRUDA was administered with cisplatin and gemcitabine or cisplatin and gemcitabine-EDDP 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.

In the 221 and KEYNOTE-671 treated patients who received surgery following the neoadjuvant phase, 1.2% experienced delay of surgery (defined as on-study surgery >9 weeks after initiation of neoadjuvant KEYTRUDA) and 0.8% experienced delay of surgery due to adverse reactions occurring in the neoadjuvant phase. 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 (≥2%) serious adverse reactions reported in 2% of KEYTRUDA-treated patients were pneumonia (3%), pyrexia (2.4%), and urinary tract infection (2.4%). In KEYNOTE-671, the most common adverse reactions (≥20%) were nausea (58%), alopecia (56%), fatigue (49%), vomiting (34%), decreased appetite (31%), constipation (28%), diarrhea (27%), pruritus (23%), rash (22%), peripheral neuropathy (21%), and dysgeusia (20%). Serious adverse reactions occurred in 50% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia (6%), pyrexia (4%), urinary tract infection (3%), pulmonary embolism (3%), acute kidney injury (3%), pneumonitis (2%), and hepatitis (2%). The most common adverse reaction (≥20%) was fatigue (49%).

In KEYNOTE-775, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with MSI-H endometrial cancer, adverse reactions occurred in 26% of patients and included pneumonitis (2%), colitis (2%), and hepatitis (2%). The most common adverse reactions (≥20%) were fatigue (28%), nausea (26%), and diarrhea (26%). Serious adverse reactions occurred in 32% of patients. The most frequent (≥2%) serious adverse reaction was urinary tract infection (4

# Refractory or Relapsed Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

## INDICATIONS

### Select Cancer Types

**Refractory or Relapsed PMBCL**

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.

Scroll below to review Selected Safety Information

Refractory or Relapsed PMBCL
KEYTRUDA 170

## Selected Safety Information

### 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 suspected immune-mediated adverse reactions with KEYTRUDA in the monotherapy setting, monitor blood cortisol and thyroid tests 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. In general, if KEYTRUDA requires withholding 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.6%). Median time to onset was 3 months (range: 1 day to 23.9 months). Pneumonitis resolved in 67% (63/94) of patients. Of patients with pneumonitis who received systemic corticosteroids, 71% (45/63) resolved. Of patients with pneumonitis who did not receive systemic corticosteroids, 75% (24/32) resolved.

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 3.9% of patients, and 6 (1.9%) patients died due to pneumonitis. Pneumonitis resolved in 84% (26/31) of patients who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (7/103) of adult patients with resected NSCLC who received KEYTRUDA as a single agent after treatment of NSCLC, including fatal (2.1%), 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 2.9% (3/103) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 83% 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 immune-mediated colitis. It is important to exclude infectious causes of diarrhea before initiating treatment with corticosteroids. Perforation and hemorrhage may occur if not managed promptly.

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 83% (40/48) of patients with colitis. Of patients who received corticosteroids, the median dose was 60 mg prednisone equivalent per day (range: 10 to 200 mg). Immune-mediated 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. Colitis resolved in 89% (43/48) of 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 79% (15/19) of patients with immune-mediated hepatitis. Corticosteroids were 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. Hepatitis resolved in 74% (14/19) of 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 administer corticosteroids as clinically indicated. After recovery of liver enzymes to baseline, resume KEYTRUDA and axitinib at reduced dose. Grade 3 and 4 increased 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 for a median duration of 1 month (range: 2 days to 5.6 months). Increased ALT led to withholding of KEYTRUDA in 9%. 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 increase was not observed. Of patients who received systemic corticosteroids, 74% resolved to Grade 1 or baseline, and 24 patients receiving both. All patients with a recurrence of ALT ULN subsequently received them for events

#### 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 91% (20/22) of patients with adrenal insufficiency. Of patients who received 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 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% (1) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

##### Type 1 Diabetes Mellitus, 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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) 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 in patients receiving anti–PD-1/PD-L1 treatments. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (75/188) of patients treated with KEYTRUDA as a single agent in KEYNOTE-204, which was similar to the rate in patients treated with brentuximab vedotin in 40% (75/188) of patients. These reactions led to permanent discontinuation in 0.5% (2) and withholding of KEYTRUDA in 0.6% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Rash resolved in 57% (43/75) of 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: Cerebral hypophysitis, encephalitis, encephalitis, myelitis, and demyelination; myasthenic syndrome/myasthenia gravis (including exacerbation); myocarditis; myositis; uveitis (including iridocyclitis); Guillain-Barré syndrome; nerve paresis, autoimmune neuropathy; Ocular disorders, iritis and other ocular inflammatory toxicities can occur as associated with immune-mediated phenomena. Myocarditis was observed at a higher incidence in patients receiving KEYTRUDA 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; immune-mediated hemolytic anemia; Pancreatitis, including increases in serum amylase and lipase levels; Musculoskeletal and Connective Tissue Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%); Endocrine Hypophysitis; hypothyroidism; hyperthyroidism; thyroiditis; Solid organ transplant rejection; Hematologic Hemolytic anemia, aplastic anemia, hemolytic-uremic syndrome, 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 GVHD, and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Follow patients closely for these complications and intervene promptly according to standard practice. Consider the benefit vs risks of treatment with KEYTRUDA prior to or after an allogeneic HSCT.

#### Increased Mortality in Patients With Multiple Myeloma

In trials of 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 occurred in 4.1% of patients who received KEYTRUDA. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (26%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-048, KEYTRUDA was administered as a single agent and was discontinued due to adverse reactions in 14% of patients; permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥3%) were pneumonitis (3.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 61% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (42%), musculoskeletal pain (30%), and pruritus (24%). 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 KEYTRUDA-treated patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. In KEYNOTE-789, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 18% of 441 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. 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 16% of 278 patients who received KEYTRUDA, carboplatin, and either paclitaxel or paclitaxel protein-bound. In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 9% of 202 patients who received KEYTRUDA, carboplatin, and paclitaxel. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception of increased frequency of alopecia (36% vs 26%), peripheral neuropathy (31% vs 20%), and arthralgia (30% vs 19%) in patients receiving KEYTRUDA, carboplatin, and paclitaxel or paclitaxel protein-bound chemotherapy vs KEYTRUDA, pemetrexed, and platinum chemotherapy.

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and pneumonitis (2%). Serious adverse reactions occurred in 58% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (23%), pruritus (23%), and nausea (20%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 9% of 370 patients with advanced NSCLC; the most common were pneumonitis (3.8%), pneumonia (3.8%), and infusion reaction (2.2%). Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (23%), and nausea (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 10% of 154 patients with advanced NSCLC; the most common were pneumonitis (3.9%), pneumonia (2.6%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-045, KEYTRUDA monotherapy was discontinued due to adverse reactions in 9% of 266 patients with advanced NSCLC; the most common were pneumonitis (1.8%), the most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

In KEYNOTE-048, KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy. KEYTRUDA was discontinued due to adverse reactions in 18% of 281 patients who received KEYTRUDA, platinum, and FU chemotherapy. Serious adverse reactions occurred in 41% of patients. The most common (≥3%) were pneumonia (3.2%), pneumonitis (3.2%), and septic shock (3.4%). The most common adverse reactions (≥20%) were fatigue (51%), nausea (39%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 11% of 392 patients with advanced NSCLC. The most common were pneumonitis (2.3%), pneumonia (2.3%), and pleural effusion (2.3%). The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (23%), pruritus (23%), and nausea (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 9% of 154 patients with advanced NSCLC; the most common were pneumonitis (3.9%), pneumonia (2.6%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-045, KEYTRUDA monotherapy was discontinued due to adverse reactions in 9% of 266 patients with advanced NSCLC; the most common were pneumonitis (1.8%), the most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

In KEYNOTE-048, KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy. KEYTRUDA was discontinued due to adverse reactions in 18% of 281 patients who received KEYTRUDA, platinum, and FU chemotherapy. Serious adverse reactions occurred in 41% of patients. The most common (≥3%) were pneumonia (3.2%), pneumonitis (3.2%), and septic shock (3.4%). The most common adverse reactions (≥20%) were fatigue (51%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 11% of 392 patients with advanced NSCLC. The most common were pneumonitis (2.3%), pneumonia (2.3%), and pleural effusion (2.3%). The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (23%), pruritus (23%), and nausea (20%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 9% of 370 patients with advanced NSCLC; the most common were pneumonitis (3.8%), pneumonia (3.8%), and infusion reaction (2.2%). Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (25%), musculoskeletal pain (23%), and nausea (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 10% of 154 patients with advanced NSCLC; the most common were pneumonitis (3.9%), pneumonia (2.6%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%). The most common (≥2%) laboratory abnormalities were treated patients; those (2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (51%), nausea (39%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation of KEYTRUDA was urinary tract infection (2.7%). The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (26%), pruritus (24%), rash (21%), and urinary tract infection (21%). The most common adverse reactions (20% were fatigue (51%), nausea (39%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

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-859, when KEYTRUDA was administered in combination with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 22% of patients who received KEYTRUDA in combination with pemetrexed and platinum chemotherapy. Serious adverse reactions occurred in 41% of patients. The most common (≥2%) were pneumonia (3.4%), pneumonitis (2.3%), and pulmonary embolism (2.1%). The most common adverse reactions (≥20%) were nausea (29%), fatigue (28%), anemia (27%), decreased appetite (24%), constipation (22%), and vomiting (20%).

In KEYNOTE-671, KEYTRUDA was discontinued due to adverse reactions in 8% of 786 patients who received KEYTRUDA in combination with chemotherapy and immunotherapy. Serious adverse reactions occurred in 59% of patients receiving KEYTRUDA in combination with chemotherapy and immunotherapy. The most common (≥2%) were pneumonia (5%), pulmonary embolism (3.2%), and pneumonitis (2.3%). The most common adverse reactions (≥20%) were nausea (41%), alopecia (40%), fatigue (39%), vomiting (24%), decreased appetite (24%), constipation (23%), and weight loss (20%).

In KEYNOTE-590, when KEYTRUDA was administered in combination with fluorouracil and cisplatin, KEYTRUDA was discontinued due to adverse reactions in 16% of 236 patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 12% of patients receiving KEYTRUDA in combination with fluorouracil and cisplatin. The most frequent adverse reactions (≥1%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.3%), and pneumonitis (1.3%).

Adverse reactions observed in KEYNOTE-590 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (12%), and thyroiditis (3.4%) which occurred at a higher frequency.

In KEYNOTE-689, the most common adverse reactions (≥20%) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), mucositis (33%), nausea (32%), constipation (27%), hypothyroidism (25%), rash (24%), and dysphonia (21%). The most common laboratory abnormalities (≥20%) in the neoadjuvant phase of KEYNOTE-689, of the 351 patients who received at least one dose of single-agent KEYTRUDA, 11% experienced serious adverse reactions. The most common (≥2%) were pneumonia (2.3%) and pneumonitis (2.3%). Fatal adverse reactions occurred in 0.3% of patients. Adverse reactions that led to permanent discontinuation occurred in 6% (n=21) of patients, including respiratory failure, cystitis, infusion reaction, sepsis, and urinary tract infection (0.3% each). Adverse reactions that led to permanent discontinuation of KEYTRUDA occurred in 7% (n=24) of patients, including pneumonitis (2.3%), pneumonia (1.4%), and respiratory failure (0.6%). The most frequent adverse reaction that led to permanent discontinuation of KEYTRUDA was pneumonitis (2.3%). Adverse reactions that led to permanent discontinuation of KEYTRUDA occurred in 16% of patients; one patient was ethnicity-Edrick.

Of the 322 KEYTRUDA-treated patients who received surgery following the neoadjuvant phase, 1.2% experienced delay of surgery (defined as on-study surgery >9 weeks after initiation of neoadjuvant KEYTRUDA) and 0.3% did not undergo surgery due to adverse reactions. In the adjuvant phase of KEYNOTE-689, of the 295 patients who received at least one dose of KEYTRUDA, 38% experienced serious adverse reactions. The most frequent (≥2%) serious adverse reactions reported in 2% of KEYTRUDA-treated patients were pneumonia (2.4%), urinary tract infection (2.4%), and pneumonitis (2.0%), pneumonia (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhea (1.2%), gastrointestinal tube site complication (1.2%), and pulmonary embolism (1.2%). Fatal adverse reactions occurred in 1.4% of patients, including death not otherwise specified (0.4%), cardiac arrest (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/aspiration (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), and sudden death (0.4%). Adverse reactions that led to permanent discontinuation of KEYTRUDA occurred in 15% of patients. Adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2.4%), pneumonia (1.4%), and respiratory failure (0.7%).

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 18% of 281 patients who received KEYTRUDA, platinum, and FU chemotherapy. Serious adverse reactions occurred in 41% of patients. The most common (≥3%) were pneumonia (3.2%), pneumonitis (3.2%), and septic shock (3.4%). The most common adverse reactions (≥20%) were fatigue (51%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-355, when KEYTRUDA was administered in combination with paclitaxel protein-bound and carboplatin chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 19% of 595 patients who received KEYTRUDA, paclitaxel protein-bound, and carboplatin chemotherapy. Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA in combination with chemotherapy. The most common (≥2%) were pneumonia (4%), sepsis (3.4%), pneumonitis (2.5%), and pulmonary embolism (2.2%). The most common adverse reactions (≥20%) were alopecia (54%), fatigue (46%), nausea (41%), peripheral neuropathy (37%), decreased appetite (24%), vomiting (24%), diarrhea (23%), constipation (22%), abdominal pain (21%), and musculoskeletal pain (20%).

In KEYNOTE-355, when KEYTRUDA was administered in combination with paclitaxel and carboplatin chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 21% of patients. The most common adverse reactions (≥20%) were fatigue (49%), alopecia (48%), nausea (40%), peripheral neuropathy (37%), decreased appetite (25%), vomiting (24%), diarrhea (23%), constipation (22%), abdominal pain (21%), musculoskeletal pain (20%), and neutropenia (20%).

In KEYNOTE-355, 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) adenocarcinoma, the most common adverse reactions (≥20%) were nausea (49%), fatigue (47%), and vomiting (31%). Serious adverse reactions occurred in 16% of patients receiving KEYTRUDA in combination with chemotherapy. The most common serious adverse reactions (≥2%) were pneumonia (3.8%), acute kidney injury (3.8%), and dehydration (2.7%). Fatal adverse reactions occurred in 3.8% of patients receiving KEYTRUDA in combination with chemotherapy and included pneumonia (0.8%), acute kidney injury (0.8%), and sepsis (0.8%). KEYTRUDA was discontinued due to adverse reactions in 16% of patients; those (12% were adverse reactions, 3.8% were acute kidney injury, and 3.8% were pneumonia (0.8%). The most common adverse reactions (≥20%) were fatigue (50%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-355, when KEYTRUDA was administered with carboplatin and paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 21% of patients. The most common adverse reactions (≥20%) were fatigue (49%), alopecia (48%), nausea (40%), peripheral neuropathy (37%), decreased appetite (25%), vomiting (24%), diarrhea (23%), constipation (22%), abdominal pain (21%), and musculoskeletal pain (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) adenocarcinoma, the most common adverse reactions (≥20%) were nausea (49%), fatigue (47%), and vomiting (31%). Serious adverse reactions occurred in 16% of patients receiving KEYTRUDA in combination with chemotherapy. The most common serious adverse reactions (≥2%) were pneumonia (3.8%), acute kidney injury (3.8%), and dehydration (2.7%). Fatal adverse reactions occurred in 3.8% of patients receiving KEYTRUDA in combination with chemotherapy and included pneumonia (0.8%), acute kidney injury (0.8%), and sepsis (0.8%). KEYTRUDA was discontinued due to adverse reactions in 16% of patients; those (12% were adverse reactions, 3.8% were acute kidney injury, and 3.8% were pneumonia (0.8%). The most common adverse reactions (≥20%) were fatigue (50%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-158, KEYTRUDA was administered as a single agent to patients with MSI-H or dMMR cancer. KEYTRUDA was discontinued due to adverse reactions in 14% of patients; those (2% were urinary tract infection, pneumonia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (51%), nausea (39%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%). The most common (≥2%) laboratory abnormalities were treated patients; those (2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (51%), nausea (39%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation of KEYTRUDA was urinary tract infection (2.7%). The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (26%), pruritus (24%), rash (21%), and urinary tract infection (21%). The most common adverse reactions (20% were fatigue (51%), nausea (39%), constipation (31%), decreased weight (30%), stomatitis (29%), diarrhea (28%), decreased appetite (27%), and vomiting (21%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 19% of patients who received KEYTRUDA in combination with chemotherapy. Serious adverse reactions occurred in 58% of patients receiving placebo in combination with chemotherapy (n=177). Fatal adverse reactions occurred in 1.8% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 (0.6%) and sepsis (0.6%). The most common adverse reactions (≥20%) were alopecia (52%), fatigue (46%), nausea (41%), peripheral neuropathy (37%), decreased appetite (24%), vomiting (24%), diarrhea (23%), constipation (22%), and abdominal pain

# Locally Advanced or Metastatic Urothelial Cancer

## INDICATIONS

### First-Line Combination for Advanced Urothelial Cancer

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

### First-Line Monotherapy for Advanced Urothelial Carcinoma

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.

### Second-Line Monotherapy for Advanced Urothelial Carcinoma—Post–Platinum Failure

KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

- First-Line Combination for Advanced Urothelial Cancer
- First-Line Monotherapy for Advanced Urothelial Carcinoma
- KEYNOTE-052
- Second-Line Monotherapy for Advanced Urothelial Carcinoma—Post–Platinum Failure
- KEYNOTE-045

Scroll below to review Selected Safety Information

## Selected Safety Information

### 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 blockers (PD-L1 and PD-L2) 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 with KEYTRUDA. For 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 patients receiving KEYTRUDA monotherapy who require 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.3%), and Grade 2 (1.7%). Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% of patients with events reported.

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 3.9% (15/389) of patients. Of the pneumonitis events, 82% (32/39) resolved, 15% (6/39) discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (19/268) of 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 2.6% (7/268) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 33% discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 7% (20/275) of patients with resected SCLC 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 2.6% (7/275) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 33% 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 additional alternative infectious 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%). Systemic corticosteroids were required in 69% (33/48) of patients. Colitis resolved in 60% of patients with events reported.

Immune-mediated colitis occurred in 2% (7/389) 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 0.8% (3/389) of patients. Of the pneumonitis events, 71% (5/7) resolved, 29% (2/7) discontinued KEYTRUDA, and 71% had resolution.

Hypothyroidism 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 5 (0.1%), Grade 4 (0.1%), and Grade 3 (0.3%) reactions. Systemic corticosteroids were required in 79% (15/19) of patients. Hepatitis resolved in 47% of patients with events reported.

Hypothyroidism occurred in 7% (27/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grades 3-4 in 2% of patients. All patients who were hypothyroid required long-term thyroid hormone replacement.

#### 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 administer corticosteroids as soon as needed. After the event resolves to Grade 0 or 1, resume KEYTRUDA and axitinib at reduced dose. Grade 3 ALT elevation (20%) and increased aspartate aminotransferase (AST) (3%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Liver enzymes returned to Grade 0 or 1 in 71% of patients. The events led to permanent discontinuation of KEYTRUDA in 3% and dose interruption in 9% of patients. Among the 52 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or as both (n=15), recurrence of ALT elevation Grade 3 was observed in 2 patients receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT elevation Grade 3 were rechallenged with axitinib.

#### Immune-Mediated Endocrinopathies

*Adrenal Insufficiency*

Adrenal insufficiency 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 91% (20/22) of patients. Adrenal insufficiency resolved in 45% of patients with 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 diagnosed with adrenal insufficiency received other 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 0.5% (13/2799) of patients receiving KEYTRUDA, including 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% (1) and withholding in 0.3% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) 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 in patients receiving KEYTRUDA. Monitor patients for suspected severe dermatologic reactions. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.1% (30/2799) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 40% (12/30) 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 the 16 patients, 13 (81%) had recurrence of the reaction.

#### 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, uveitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune hepatitis, hepatitis with histopathologic findings of granulomatous inflammation, sarcoidosis, immune thrombocytopenia, myositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis (1.5%), and pneumonitis in the context of organizing pneumonia. Cases of solid organ transplant rejection have been reported in patients receiving KEYTRUDA.

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for transplantation and care after transplantation. Of the 11 treatments and allogeneic HSCT, 4 allow patients closely for these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment 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 occurred in 4.1% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). Severe adverse reactions occurred in the adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (3.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (3.4%). In KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with stage IB or IIA melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients. The most common adverse reactions (≥20%) were nausea (56%), fatigue (40%), constipation (29%), rash (25%), decreased appetite (24%), and vomiting (21%). Severe adverse reactions occurred in 57% of patients receiving KEYTRUDA. The most frequent severe adverse reactions were anemia (13%), pneumonia (9%), and pulmonary embolism (4%). Serious adverse reactions occurred in 58% of patients. The most frequent serious adverse reactions were pneumonia (9%), anemia (5%), and pulmonary embolism (4%).

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 18% of 278 patients. The most common adverse reactions (≥20%) were fatigue (49%), alopecia (41%), nausea (39%), decreased appetite (31%), peripheral neuropathy (31%), constipation (28%), diarrhea (27%), rash (25%), vomiting (24%), pyrexia (22%), and cough (21%). Severe adverse reactions occurred in 59% of patients receiving KEYTRUDA. The most frequent severe adverse reactions were anemia (16%), pneumonia (9%), febrile neutropenia (8%), and pulmonary embolism (5%). Serious adverse reactions occurred in 62% of patients. The most frequent serious adverse reactions were pneumonia (9%), anemia (8%), febrile neutropenia (7%), and pulmonary embolism (5%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC. The most common were pneumonitis (3%), pneumonia (3%), and dyspnea (3%). Severe adverse reactions occurred in 47% of patients receiving KEYTRUDA. The most frequent were pneumonia (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse reactions in 13% of 281 patients with advanced HNSCC. The most common were pneumonitis (3.8%). The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (23%), nausea (20%), and rash (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (37%), decreased appetite (26%), nausea (25%), pruritus (22%), rash (21%), diarrhea (20%), and urinary tract infection (20%). The most frequent adverse reactions (≥2%) were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (37%), decreased appetite (26%), nausea (25%), pruritus (22%), rash (21%), and diarrhea (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 requiring treatment discontinuation was urinary tract infection (3%). The most common adverse reactions (≥20%) were fatigue (49%), musculoskeletal pain (30%), pruritus (24%), rash (23%), urinary tract infection (21%), and diarrhea (20%). Severe adverse reactions occurred in 16% of patients. The most common severe reactions (≥2%) were urinary tract infection (3%) and hematuria (2%).

In KEYNOTE-158, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer who had received prior platinum-containing chemotherapy and PD-1/PD-L1 blockade, KEYTRUDA was discontinued due to adverse reactions in 16% of 200 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 any adverse reaction occurred in 12% of patients. The most common adverse reactions (≥20%) were fatigue (51%), rash (47%), and diarrhea (31%). The most frequent adverse reactions (≥3%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.4%), and pneumonitis (1.4%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with locally advanced or metastatic urothelial cancer who had received prior platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 9% of 351 patients. No fatal adverse reactions occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 11% of patients. The most frequent adverse reactions that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.1%), and pneumonitis (1.1

# High-Risk Non-Muscle Invasive Bladder Cancer

## INDICATIONS

### High-Risk Non-Muscle Invasive Bladder Cancer

KEYTRUDA, as a single agent, is indicated for the treatment of patients with Bacillus Calmette-Guérin (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.

High-Risk Non-Muscle Invasive Bladder Cancer KEYNOTE-057

Scroll below to review Selected Safety Information

## Selected Safety Information

### 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 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially leading to enhanced immune response 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 suspected immune-mediated adverse reactions with KEYTRUDA in the monotherapy setting, monitor clinical status and function promptly, 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. In general, withhold KEYTRUDA for any grade 3 immune-mediated adverse reaction, until improvement to grade 1 or less. Permanently discontinue KEYTRUDA for any grade 4 immune-mediated adverse reaction, except endocrinopathies managed with replacement therapy. Administer high-dose 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 Grade 4 (0.1%), Grade 3 (0.9%), and Grade 2 (2.4%). Fatal cases (0.1%) were reported. Pneumonitis occurred in 6.7% (53/796) of patients receiving KEYTRUDA in the adjuvant setting, monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 3 pneumonitis and permanently discontinue KEYTRUDA for Grade 4 pneumonitis or recurrent Grade 3 pneumonitis.

#### Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with immune-mediated colitis. It is important to exclude infectious causes of diarrhea before initiating corticosteroids for immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 3 colitis and permanently discontinue KEYTRUDA for Grade 4 colitis or recurrent Grade 3 colitis.

Immune-mediated colitis occurred in 1.7% (46/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 67% (31/46) of patients, of these, the majority remained on systemic corticosteroids. Hepatitis 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.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 79% (15/19) of patients, of these, the majority remained on systemic corticosteroids. 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. Monitor patients for abnormal liver test results prior to and periodically during treatment.

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 administer corticosteroids as clinically indicated. Dose reduce axitinib for Grade 3 AST or ALT elevations. Withhold KEYTRUDA for Grade 4 AST or ALT elevations. Withhold axitinib for Grade 4 AST or ALT elevations. Permanently discontinue KEYTRUDA and axitinib for elevated bilirubin concentrations (ALT/AST [20%] and increased aspartate aminotransferase [AST] [3%] were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients in renal cell carcinoma (RCC) clinical trials received corticosteroids for any reason. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.5% (3) and withholding in 0.5% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

#### Hypophysitis and Immune-Mediated Hypophysitis

KEYTRUDA can cause immune-mediated hypophysitis. Immune-mediated hypophysitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (0.3%) reactions. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Monitor patients for signs and symptoms of hypophysitis.

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 administer corticosteroids as clinically indicated. Dose reduce axitinib for Grade 3 AST or ALT elevations. Withhold KEYTRUDA for Grade 4 AST or ALT elevations. Withhold axitinib for Grade 4 AST or ALT elevations. Permanently discontinue KEYTRUDA and axitinib for elevated bilirubin concentrations (ALT/AST [20%] and increased aspartate aminotransferase [AST] [3%] were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients in renal cell carcinoma (RCC) clinical trials received corticosteroids for any reason. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.5% (3) and withholding in 0.5% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.1% (2) 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 PD-1/PD-L1 blocking antibodies. Withhold or permanently discontinue KEYTRUDA depending on severity. Administer corticosteroids for severe or life-threatening rash. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.8% (51/2799) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (1.1%) reactions. Bullous dermatitis occurred 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. Monitor patients for signs and symptoms of dermatitis.

#### 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: Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), myositis/polymyositis, rhabdomyolysis (and associated sequelae), myocarditis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, including diabetic ketoacidosis, hypoparathyroidism, adrenal insufficiency, hypophysitis, hypopituitarism, and systemic inflammatory response syndrome. Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant complications, and hemophagocytic lymphohistiocytosis.

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Transplant complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatment and transplant. Follow patients for these complications. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment prior to or after an allogeneic HSCT.

#### Increased Mortality in Patients With Multiple Myeloma

In trials of 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 occurred in 6% of patients. The most common adverse reactions (≥20% with KEYTRUDA and less than ipilimumab) were fatigue (26%), diarrhea (21%), and rash (21%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 14% of 509 patients with stage III melanoma; adverse reactions leading to permanent discontinuation occurred in 9% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (56%), diarrhea (28%), rash (24%), and nausea (21%).

In KEYNOTE-001, KEYTRUDA was administered with pembrolizumab and platinum chemotherapy in metastatic nonsquamous NSCLC. KEYTRUDA was discontinued due to adverse reactions in 16% of 616 patients; adverse reactions leading to permanent discontinuation occurred in 11% of patients. The most common adverse reactions (≥20%) were fatigue (53%), nausea (39%), constipation (28%), decreased appetite (26%), rash (25%), diarrhea (24%), vomiting (23%), and dyspnea (20%).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients; adverse reactions leading to permanent discontinuation occurred in 14% of patients. The most common adverse reactions (≥20%) were nausea (69%), fatigue (56%), constipation (37%), rash/dermatitis (36%), diarrhea (31%), vomiting (28%), decreased appetite (25%), abdominal pain (24%), and weight loss (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 278 patients; adverse reactions leading to permanent discontinuation occurred in 11% of patients. The most common adverse reactions (≥20%) were fatigue (50%), nausea (31%), alopecia (30%), decreased appetite (25%), diarrhea (24%), constipation (22%), rash (21%), peripheral neuropathy (21%), and pneumonia (20%).

In KEYNOTE-042, when KEYTRUDA was administered as monotherapy in patients with advanced NSCLC, the most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (25%), decreased appetite (23%), and nausea (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 15% of 154 patients with advanced NSCLC; the most common were pneumonitis (3%), pulmonary embolism (2.6%), and pleural effusion (2.6%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-045, KEYTRUDA monotherapy was discontinued due to adverse reactions in 9% of 266 patients with advanced UC; the most common were pneumonitis (3.8%), pneumonia (2.6%), and sepsis (2.6%). The most common adverse reactions (≥20%) were fatigue (25%), constipation (23%), and nausea (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 18% of 441 patients with advanced HNSCC; adverse reactions leading to permanent discontinuation occurred in 13% of patients. The most common adverse reactions (≥20%) were fatigue (23%), constipation (21%), and septic shock (21%). The most common adverse reactions (≥20%) were fatigue (51%), nausea (39%), constipation (31%), decreased appetite (30%), vomiting (27%), diarrhea (26%), rash (24%), and pyrexia (20%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with UC; the most common were pneumonitis (2.2%), pneumonia (2.2%), and sepsis (2.2%). The most common adverse reactions (≥20%) were fatigue (26%), urinary tract infection (21%), and musculoskeletal pain (20%).

In KEYNOTE-061, KEYTRUDA was discontinued due to adverse reactions in 13% of 592 patients with HER2- gastric or gastroesophageal junction adenocarcinoma; adverse reactions leading to permanent discontinuation occurred in 11% of patients. The most common adverse reactions (≥20%) were fatigue (32%), nausea (27%), anemia (21%), and vomiting (21%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 14% of 1,533 patients with advanced MSI-H cancer; adverse reactions leading to permanent discontinuation occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (31%), pruritus (22%), and diarrhea (21%).

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 14% of 94 patients with cHL. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA; those ≥1% were pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions other than disease progression 2 from complications of allogeneic HSCT after KEYTRUDA and 1 from pneumonitis. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (32%), diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

In KEYNOTE-204, KEYTRUDA was discontinued due to adverse reactions in 9% of 148 patients with cHL. Serious adverse reactions occurred in 16% of patients; those reported in ≥1% were pneumonia, pyrexia, and pulmonary embolism. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (26%), diarrhea (22%), nausea (21%), and cough (20%).

In KEYNOTE-177, KEYTRUDA was discontinued due to adverse reactions in 8% of 153 patients with MMRD-, Serious adverse reactions occurred in 26% of patients; those ≥2% were pneumonia, diarrhea, and small intestinal obstruction. The most common adverse reactions (≥20%) were fatigue (36%), diarrhea (34%), rash (24%), and abdominal pain (22%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 58 patients with MMRD-. Serious adverse reactions occurred in 26% of patients; those ≥2% were pneumonia, diarrhea, and small intestinal obstruction. The most common adverse reactions (≥20%) were fatigue (36%), diarrhea (34%), rash (24%), and abdominal pain (22%).

In KEYNOTE-426, when KEYTRUDA was administered with axitinib and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ tumors with a positive 1 to 5 centimeters distal to the GEJ tumors 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 (≥1%) were pneumonia, pyrexia, and pneumonitis (3% each). The most common adverse reactions (≥20%) were fatigue (49%), diarrhea (46%), hypertension (39%), nausea (36%), fatigue (32%), decreased appetite (24%), constipation (24%), dysphonia (24%), vomiting (24%), stomatitis (23%), and weight loss (22%).

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

In KEYNOTE-868, when KEYTRUDA was administered with FOLFOX (platinum plus fluorouracil) and leucovorin therapy (5-FU) 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, pneumonitis, and sepsis. Serious adverse reactions occurred in 48% of patients. KEYTRUDA was discontinued due to adverse reactions in 19% of patients. Fatigue and sepsis (3% each) led to permanent discontinuation of KEYTRUDA. The most common adverse reactions (≥20%) were alopecia (54%), nausea (51%), fatigue (49%), diarrhea (36%), vomiting (34%), decreased appetite (29%), peripheral neuropathy (28%), abdominal pain (26%), dysgeusia (24%), constipation (23%), and anemia (20%).

In KEYNOTE-775, when KEYTRUDA was administered with lenvatinib to patients with advanced endometrial carcinoma that progressed after platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 411 patients; adverse reactions leading to permanent discontinuation occurred in 15% of patients. The most common adverse reactions (≥20%) were hypertension (67%), diarrhea (61%), palmar-plantar erythrodysesthesia syndrome (31%), stomatitis (29%), abdominal pain (26%), fatigue (26%), nausea (25%), decreased appetite (24%), constipation (22%), and weight loss (20%).

In KEYNOTE-695, when KEYTRUDA was administered with trastuzumab and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ tumors with greater than 5 centimeters distal to the GEJ tumors who were not candidates for surgical resection or definitive chemoradiation, KEYTRUDA was discontinued due to adverse reactions in 15% of 257 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonia, pyrexia, and pneumonitis (2% each). The most common adverse reactions (≥20%) were fatigue (47%), diarrhea (46%), nausea (41%), vomiting (32%), decreased appetite (24%), constipation (22%), and weight loss (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or metastatic urothelial carcinoms. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (1.5%), pneumonia (1.1%), and sepsis (1.1%). The most common treated patients; those ≥2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (30%), musculoskeletal pain (25%), decreased appetite (23%), and nausea (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%). The most common adverse reactions (≥20%) were fatigue (29%), urinary tract infection (27%), pruritus (25%), rash (23%), pulmonary embolism (21%), pyrexia (20%), and urinary tract infection (21%). The most common adverse reactions (≥20%) were fatigue (29%), musculoskeletal pain (20%), and diarrhea (20%).

Adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as 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-855, when KEYTRUDA was administered with vinblastine and fluorouracil to patients with metastatic or locally advanced cutaneous SCC, KEYTRUDA was discontinued due to adverse reactions in 12% of patients included pneumonia (4.1%), diarrhea (1.5%), hemorrhagic (2.3%), and vomiting (2.4%). Serious adverse reactions occurred in 61% of patients; those ≥2% were pneumonia, febrile neutropenia, and sepsis. The most common adverse reactions (≥20%) were fatigue (51%), discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonia (2.2%), diarrhea (2.2%), and vomiting (1.5%). The most common adverse reactions (≥20%) were fatigue (51%), nausea (49%), constipation (39%), vomiting (38%), decreased appetite (36%), diarrhea (36%), stomatitis (27%), and weight loss (22%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 14% of 509 patients with stage III melanoma; adverse reactions leading to permanent discontinuation occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (56%), diarrhea (28%), rash (24%), and nausea (21%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 14% of 493 patients with stage IB-IIIA NSCLC; adverse reactions leading to permanent discontinuation occurred in 10% of patients. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (22%), and cough (20%).

In KEYNOTE-091, KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy. KEYTRUDA was discontinued due to adverse reactions in 18% of 441 patients with advanced HNSCC; adverse reactions leading to permanent discontinuation occurred in 13% of patients. The most common adverse reactions (≥20%) were fatigue (23%), constipation (21%), and septic shock (21%). The most common adverse reactions (≥20%) were fatigue (51%), nausea (39%), constipation (31%), decreased appetite (30%), vomiting (27%), diarrhea (26%), rash (24%), and pyrexia (20%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 11% of 782 patients with NSCLC. Serious adverse reactions occurred in 26% of patients; those ≥2% were pneumonia, pyrexia, pneumonitis, and pulmonary embolism. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (32%), diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 8% of 58 patients with MMRD-. Serious adverse reactions occurred in 26% of patients; those ≥2% were pneumonia, diarrhea, and small intestinal obstruction. The most common adverse reactions (≥20%) were fatigue (36%), diarrhea (34%), rash (24%), and abdominal pain (22%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with MMRD-. Serious adverse reactions occurred in 26% of patients; those ≥2% were pneumonia, diarrhea, and small intestinal obstruction. The most common adverse reactions (≥20%) were fatigue (36%), diarrhea (34%), rash (24%), and abdominal pain (22%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 8% of 58

# Advanced MSI-H/dMMR Cancers

## INDICATIONS

### Advanced MSI-H/dMMR Cancers

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.

Scroll below to review Selected Safety Information


- Advanced MSI-H/dMMR Cancers
- KEYNOTE-158, KEYNOTE-164, KEYNOTE-966


## Selected Safety Information

### 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 blockers (PD-1, blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially leading to enhanced antitumor immune response. 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. 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 patients receiving KEYTRUDA, consider withholding dose for clinically significant, moderate systemic corticosteroid therapy (> 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 Grade 4 (0.1%), Grade 3 (0.9%), and Grade 2 (2.4%). Fatal cases (0.1%) were reported. Pneumonitis occurred in 6.7% (53/796) of patients who received KEYTRUDA in a single-arm, including Grade 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 1.4% (11/796) of patients. Of the pneumonitis events in KEYTRUDA-treated patients, 1.4% (11/796) led to discontinuation of KEYTRUDA, and 71% had resolution.

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 2.6% (10/389) of patients. Of the pneumonitis events in KEYTRUDA-treated patients, 2.3% (9/389) led to discontinuation of KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 6% (21/389) of 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 2% (8/389) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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 immune-mediated colitis. It is important to exclude infectious causes of diarrhea before initiating corticosteroids for immune-mediated colitis. Monitor patients for signs and symptoms of enterocolitis.

Withhold or permanently discontinue KEYTRUDA depending on severity. Administer corticosteroids and, if there is no improvement within 5 days, add other immunosuppressants. 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 colitis occurred in 2.1% (58/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (1.2%) reactions. Systemic corticosteroids were required in 84% (49/58) of patients, of these, the majority remained on systemic corticosteroids. Infliximab was required in 1.7% (1/58) of patients. Immune-mediated 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.

#### 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 79% (15/19) of patients, of these, the majority remained on systemic corticosteroids. Infliximab was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of the patients receiving KEYTRUDA, hepatitis resolved in 74% of 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 administer corticosteroids as clinically indicated. If liver enzymes recover to Grade 1 or baseline, restart KEYTRUDA and axitinib at reduced doses. Grade 3 and 4 increased 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 for a median duration of 1 month (range: 1 day to 5.6 months). Increased ALT led to withholding of KEYTRUDA in 7%. 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 or ASTincreased ALT elevation Grade 3 or greater occurred in 1 patient who received KEYTRUDA and axitinib.

#### 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. Administer insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.4%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Hormone replacement was required in 64% (14/22) of patients. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.1% (3) 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 0.5% (13/2799) of patients receiving KEYTRUDA, including 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% (1) 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 initiation of 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 0.3% (8) withheld for thyroiditis.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.8% (22) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of the patients receiving KEYTRUDA in 237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.6%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in 0.4% (11) and withholding in 2.1% (58) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of the patients receiving KEYTRUDA, hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 195 patients with MSI-H/dMMR cancers who received KEYTRUDA as a single agent (12%) compared to 1,533 patients who received KEYTRUDA across multiple tumor types (7%). The incidence of new or worsening hypothyroidism was also higher in patients who received KEYTRUDA in combination with chemotherapy (16%) compared to patients who received KEYTRUDA as a single agent (7%).

Type 1 Diabetes Mellitus, Which Can Present With Diabetic Ketoacidosis

Withhold patients for hyperglycemia or other signs and symptoms of diabetes mellitus. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (4) 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 in patients receiving KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.7% (47/2799) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (1.1%) reactions. Systemic corticosteroids were required in 40% (19/48) 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 the patients receiving KEYTRUDA, dermatologic reactions resolved in 67% of 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: Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), myositis/polymyositis, rhabdomyolysis (and associated sequelae), myocarditis, uveitis, iritis and other ocular inflammatory reactions, pancreatitis including increased serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, uveitis, iritis, and other ocular inflammatory reactions, hemolytic anemia, aplastic anemia, hemolytic uremic syndrome, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, histiocytic necrosis of lymph nodes (Kikuchi lymphadenitis), sarcoidosis

# Advanced MSI-H/dMMR Colorectal Cancer (CRC)

## INDICATIONS

### Advanced MSI-H/dMMR Colorectal Cancer

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H/dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

Scroll below to review Selected Safety Information

Advanced MSI-H/dMMR Colorectal Cancer, and KEYNOTE-177

## Selected Safety Information

### 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 (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 suspected immune-mediated adverse reactions with KEYTRUDA in the monotherapy setting, monitor clinical status and function 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. In general, withhold KEYTRUDA for any grade 3 immune-mediated adverse reaction, discontinue, administer systemic corticosteroids 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 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 Grade 4 (0.1%), Grade 3 (0.9%), and Grade 2 (2.4%). Fatal cases (0.1%) were reported. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% (55/94) of patients with KEYTRUDA.

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 3.9% of patients. Of the patients who developed pneumonitis, 82% (23/28) resolved, including 68% (13/19) who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (19/289) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2% (6/289) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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 immune-mediated colitis. It is important to exclude infectious causes of diarrhea before initiating treatment with corticosteroids. Consider additional antimicrobial agents to treat infectious causes. 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 88% (42/48) of patients. Colitis resolved in 60% (29/48) of patients with KEYTRUDA.

Immune-mediated colitis occurred in 2% (8/389) 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 1.5% of patients. Of the patients who developed pneumonitis, 83% (5/6) resolved, including 67% (2/3) who discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 8% (23/289) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2.4% (7/289) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 79% (15/19) of patients. Hepatitis resolved in 47% (9/19) of patients with KEYTRUDA.

Monitor patients for changes in liver function. Administer systemic corticosteroids for Grade 2 or higher, initiate supportive treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity. Administer KEYTRUDA for Grade 3 or 4 immune-mediated adverse reactions.

#### 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. Administer insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Adrenal insufficiency resolved in 41% (9/22) of patients with KEYTRUDA.

##### 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 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 initiate 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 0.2% (5) of patients.

Hyperthyroidism occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.5% (13) 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 (0.6%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.2% (6) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with MSI-H/dMMR cancers who received KEYTRUDA as a single agent (22%) than in 5,932 patients with non-MSI-H/dMMR cancers who received KEYTRUDA as a single agent (12%).

Hypothyroidism occurred in 13% (50/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grade 3 (1.5%) and Grade 2 (10.8%) reactions. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC receiving in 11% of patients receiving KEYTRUDA as a single agent for adjuvant treatment, including Grade 3 (0.3%) and Grade 2 (10.4%) reactions. Hypothyroidism led to withholding of KEYTRUDA in 1.4% (4) of 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%) and Grade 2 (21%) reactions.

##### 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% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) 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 in patients receiving KEYTRUDA. Monitor patients for suspected severe dermatologic reactions. Administer systemic corticosteroids for Grade 3 or higher reactions. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.5%), and Grade 2 (1.1%) reactions. Systemic corticosteroids were required in 40% (19/48) 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 the 48 patients, 40 (83%) had resolution.

#### 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: Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), myositis/polymyositis, rhabdomyolysis (and associated sequelae), myocarditis, uveitis, iritis and other ocular inflammatory reactions, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, uveitis, iritis, and other ocular inflammatory reactions, hemolytic anemia, aplastic anemia, hemolytic uremic syndrome, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, and complications of allogeneic HSCT.

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for the management of patients undergoing HSCT. 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 before or after an allogeneic HSCT.

#### Increased Mortality in Patients With Multiple Myeloma

In trials of 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 occurred in 4.3% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%). Severe adverse reactions occurred in 16% of patients. The most common (≥2%) severe adverse reactions were diarrhea (3.1%), pneumonitis (2.9%), and colitis (2.2%). Fatal adverse reactions occurred in 1.1% of patients, including death due to unknown cause (0.4%), sepsis (0.2%), and immune-mediated adverse reactions (0.2%). Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 13% of patients. Adverse reactions resulted in withholding of KEYTRUDA in 25% of patients. The most common adverse reactions (≥20%) leading to withholding of KEYTRUDA were diarrhea (3.1%), fatigue (2.9%), pneumonitis (2.7%), rash (2.5%), and nausea (2.3%).

In KEYNOTE-045, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 9% of 411 patients; adverse reactions leading to permanent discontinuation occurred in 4.4% of patients. The most common adverse reactions (≥20%) were fatigue (33%), pruritus (25%), rash (22%), diarrhea (21%), nausea (21%), and decreased appetite (20%). Severe adverse reactions occurred in 19% of patients. The most frequent (≥2%) severe adverse reactions were pneumonitis, diarrhea, and pyrexia. Fatal adverse reactions occurred in 1.5% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated adverse reactions (0.3%). Adverse reactions resulted in withholding of KEYTRUDA in 25% of patients. The most common adverse reactions (≥20%) leading to withholding of KEYTRUDA were pneumonitis (3.2%), diarrhea (2.9%), fatigue (2.7%), and rash (2.4%).

In KEYNOTE-054, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 14% of 507 patients. The most frequent adverse reactions (≥10%) were diarrhea, rash, and fatigue. The most common severe adverse reactions (≥2%) were diarrhea (2.4%) and colitis (2.2%).

In KEYNOTE-048, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 10% of 281 patients. The most frequent adverse reactions (≥10%) were fatigue, musculoskeletal pain, rash, diarrhea, nausea, decreased appetite, peripheral neuropathy, pyrexia, and cough. The most common severe adverse reactions (≥2%) were pneumonia, sepsis, and pyrexia.

In KEYNOTE-045, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 9% of 296 patients. The most frequent adverse reactions (≥10%) were fatigue, musculoskeletal pain, pruritus, rash, diarrhea, nausea, decreased appetite, and hypothyroidism. The most common severe adverse reactions (≥2%) were pneumonia, sepsis, and pyrexia.

In KEYNOTE-054, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 14% of 507 patients. The most frequent adverse reactions (≥10%) were diarrhea, rash, and fatigue. The most common severe adverse reactions (≥2%) were diarrhea (2.4%) and colitis (2.2%).

In KEYNOTE-061, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 11% of 592 patients. The most frequent adverse reactions (≥10%) were fatigue, musculoskeletal pain, diarrhea, nausea, pruritus, rash, decreased appetite, and vomiting. The most common severe adverse reactions (≥2%) were anemia (2%) and pyrexia (2%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 14% of 1,233 patients. The most common adverse reactions (≥20%) were fatigue (33%), musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), rash (26%), diarrhea (25%), and nausea (21%).

In KEYNOTE-177, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 22% of patients. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), rash (26%), diarrhea (25%), and nausea (21%).

In KEYNOTE-426, when KEYTRUDA was administered in combination with carfilzomib and dexamethasone, KEYTRUDA was discontinued due to adverse reactions in 21% of patients. The most common adverse reactions (≥20%) were fatigue (45%), upper respiratory tract infection (39%), diarrhea (37%), cough (32%), musculoskeletal pain (30%), hypertension (28%), pneumonia (25%), and dyspnea (24%).

In KEYNOTE-091, when KEYTRUDA was administered as a single agent, KEYTRUDA was discontinued due to adverse reactions in 16% of patients. The most frequent adverse reactions (≥10%) were musculoskeletal pain, fatigue, rash, and cough. The most common severe adverse reactions (≥2%) were pneumonia and pyrexia.

In KEYNOTE-189, when KEYTRUDA was administered in combination with pemetrexed and platinum chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 18% of 405 patients. The most common adverse reactions (≥20%) were nausea (40%), fatigue (39%), constipation (31%), rash (25%), diarrhea (24%), vomiting (24%), decreased appetite (23%), abdominal pain (21%), peripheral neuropathy (21%), and pruritus (20%).

In KEYNOTE-407, when KEYTRUDA was administered in combination with carboplatin and paclitaxel or nab-paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 19% of 278 patients. The most common adverse reactions (≥20%) were fatigue (47%), alopecia (36%), nausea (31%), peripheral neuropathy (27%), diarrhea (23%), decreased appetite (21%), and constipation (20%).

In KEYNOTE-355, when KEYTRUDA was administered in combination with chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 595 patients. The most common adverse reactions (≥20%) were alopecia (34%), nausea (33%), fatigue (32%), peripheral neuropathy (25%), diarrhea (24%), vomiting (24%), decreased appetite (23%), abdominal pain (21%), and constipation (20%).

In KEYNOTE-590, when KEYTRUDA was administered in combination with cisplatin and fluorouracil, KEYTRUDA was discontinued due to adverse reactions in 15% of 370 patients. The most common adverse reactions (≥20%) were nausea (40%), fatigue (32%), decreased appetite (24%), constipation (24%), vomiting (24%), diarrhea (22%), stomatitis (21%), and weight loss (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most frequently reported adverse reactions (≥20%) were nausea, fatigue, vomiting, constipation, decreased appetite, and peripheral neuropathy.

In KEYNOTE-826, when KEYTRUDA was administered in combination with paclitaxel and platinum chemotherapy (bevacizumab initiation was optional), KEYTRUDA was discontinued due to adverse reactions in 15% of patients. The most common adverse reactions (≥20%) were alopecia (59%), fatigue (51%), nausea (40%), diarrhea (36%), vomiting (24%), decreased appetite (24%), abdominal pain (22%), peripheral neuropathy (21%), and constipation (20%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients. The most common adverse reactions (≥20%) were alopecia (59%), fatigue (51%), nausea (40%), diarrhea (36%), vomiting (24%), decreased appetite (24%), abdominal pain (22%), peripheral neuropathy (21%), and constipation (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most frequently reported adverse reactions (≥20%) were nausea, fatigue, vomiting, constipation, decreased appetite, and peripheral neuropathy. Serious adverse reactions occurring in ≥2% of patients included pneumonia, pneumonitis, embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 67% of patients receiving KEYTRUDA in combination with gemcitabine and cisplatin. Fatal adverse reactions occurred in 2.7% of patients receiving KEYTRUDA in combination with gemcitabine and cisplatin.

KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥5%) resulting in permanent discontinuation were increased ALT (1.5%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) were fatigue (45%), nausea (40%), alopecia (61%), rash (22%), constipation (20%), diarrhea (19%), vomiting (19%), peripheral neuropathy (19%), decreased appetite (19%), and headache (10%), although 29% of patients received KEYTRUDA for more than 6 months.

In KEYNOTE-355, when KEYTRUDA was administered in combination with chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of patients. The most common adverse reactions (≥20%) were alopecia (34%), nausea (33%), fatigue (32%), peripheral neuropathy (25%), diarrhea (24%), vomiting (24%), decreased appetite (23%), abdominal pain (21%), and constipation (20%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients. The most common adverse reactions (≥20%) were alopecia (59%), fatigue (51%), nausea (40%), diarrhea (36%), vomiting (24%), decreased appetite (24%), abdominal pain (22%), peripheral neuropathy (21%), and constipation (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most frequently reported adverse reactions (≥20%) were nausea, fatigue, vomiting, constipation, decreased appetite, and peripheral neuropathy. Serious adverse reactions occurring in ≥2% of patients included pneumonia, pneumonitis, embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 67% of patients receiving KEYTRUDA in combination with gemcitabine and cisplatin. Fatal adverse reactions occurred in 2.7% of patients receiving KEYTRUDA in combination with gemcitabine and cisplatin.

KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥5%) resulting in permanent discontinuation were increased ALT (1.5%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) were fatigue (45%), nausea (40%), alopecia (61%), rash (22%), constipation (20%), diarrhea (19%), vomiting (19%), peripheral neuropathy (19%), decreased appetite (19%), and headache (10%), although 29% of patients received KEYTRUDA for more than 6 months.

In KEYNOTE-355, when KEYTRUDA was administered in combination with chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of patients. The most common adverse reactions (≥20%) were alopecia (34%), nausea (33%), fatigue (32%), peripheral neuropathy (25%), diarrhea (24%), vomiting (24%), decreased appetite (23%), abdominal pain (21%), and constipation (20%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients. The most common adverse reactions (≥20%) were alopecia (59%), fatigue (51%), nausea (40%), diarrhea (36%), vomiting (24%), decreased appetite (24%), abdominal pain (22%), peripheral neuropathy (21%), and constipation (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most frequently reported adverse reactions (≥20%) were nausea, fatigue, vomiting, constipation, decreased appetite, and peripheral neuropathy. Serious adverse reactions occurring in ≥2% of patients included pneumonia, pneumonitis, embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 67% of patients receiving KEYTRUDA in combination with gemcitabine and cisplatin. Fatal adverse reactions occurred in 2.7% of patients receiving KEYTRUDA in combination with gemcitabine and cisplatin.

KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥5%) resulting in permanent discontinuation were increased ALT (1.5%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) were fatigue (45%), nausea (40%), alopecia (61%), rash (22%), constipation (20%), diarrhea (19%), vomiting (19%), peripheral neuropathy (19%), decreased appetite (19%), and headache (10%), although 29% of patients received KEYTRUDA for more than 6 months.

#### Pediatric Use

In KEYNOTE-051, 113 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 years to 17 years) with advanced PD-L1–positive melanoma received KEYTRUDA 2 mg/kg every 3 weeks. The most common adverse reactions (≥20%) were pyrexia (24%), rash (22%), and headache (20%). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (24% vs 13%), leukopenia (16% vs 3%), hypothyroidism (15% vs 6%), abdominal pain (13%), thrombocytopenia (12%), Grade 3 anemia (11%), decreased lymphocyte count (5%), and decreased white blood cell count (11%).

#### 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 years and older, and 26% (n=148) 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.

**Before prescribing KEYTRUDA, please read the accompanying** Prescribing Information. The Medication Guide also is available.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = bacteriuria; BTC = biliary tract cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; CRT = chemoradiotherapy; cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; ESRD = end-stage renal disease; FIGO = International Federation of Gynecology and Obstetrics; GVHD = graft-versus-host disease; HCC = hepatocellular carcinoma; HSCT = hematopoietic stem cell transplantation; IU/mL = international units per milliliter; kg = kilogram; mg = milligram; mL = milliliter; MSI-H = microsatellite instability-high; NMSC = non-muscle invasive bladder cancer; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal large B-cell lymphoma; TMB = tumor mutational burden

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.
US-KEYONSET-211121

# Advanced HER2-Negative Gastric or GEJ Adenocarcinoma

## INDICATIONS

### First-Line Combination Therapy for Advanced HER2-Negative Gastric or GEJ Adenocarcinoma

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.

Select cancer type/area to see indications

**Scroll below to review Selected Safety Information**

First-Line Combination Therapy for Advanced HER2-Negative Gastric or GEJ Adenocarcinoma
KEYNOTE-859

## Select Cancer Types

## Selected Safety Information

### Severe and Fatal Immune-Mediated 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 suspected severe or life-threatening immune reactions, administer high-dose corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) and withhold further doses, promptly initiate additional systemic immunosuppressants in patients who receive KEYTRUDA in the monotherapy setting, monitor blood cortisol at least 3 months. Consider administration of 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.2%), and Grade 2 (1.8%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resulted in permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld from KEYTRUDA due to pneumonitis resumed KEYTRUDA after symptom improvement. Of patients who received systemic corticosteroids for pneumonitis, 84% (79/94) had improvement or resolution.

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 3.1% (12) of patients. Of the patients who developed pneumonitis, 42% (13/31) resolved. Of the 18 patients discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (15/208) 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 2% (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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. It is important to exclude infectious etiologies of diarrhea or colitis. Administer corticosteroids for severe reactions. Withhold doses for intolerable reactions. 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) of patients. Immune-mediated colitis resulted in permanent discontinuation of KEYTRUDA in 0.4% (12) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of patients who received systemic corticosteroids for colitis, 74% (34/46) had improvement or resolution.

Immune-mediated colitis occurred in 3% (11/389) 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 1.3% (5) of patients. Of the patients who developed pneumonitis, 42% (13/31) resolved. Of the 18 patients discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (15/208) 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 2% (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

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 79% (15/19) of patients. Immune-mediated hepatitis resulted in permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of patients who received systemic corticosteroids for hepatitis, 79% (15/19) had improvement or resolution.

Immune-mediated hepatitis occurred in 3% (11/389) 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 1.3% (5) of patients. Of the patients who developed pneumonitis, 42% (13/31) resolved. Of the 18 patients discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (15/208) 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 2% (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

#### Hypophysitis and Uveitis

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 3 (0.2%) and Grade 2 (0.3%) 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.

Uveitis occurred in 0.2% (5/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.1%) reactions. Uveitis led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of patients who received systemic corticosteroids for uveitis, 75% (3/4) had improvement or resolution.

#### 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 3 (0.2%) and Grade 2 (0.3%) 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.

#### Uveitis

KEYTRUDA can cause immune-mediated uveitis, iridocyclitis, and choroiditis. Evaluate patients, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and vogt-koyanagi-harada like syndrome, as soon as possible for ophthalmologic symptoms. Administer corticosteroids for severe reactions. Withhold or permanently discontinue KEYTRUDA depending on severity. Uveitis occurred in 0.2% (5/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.1%) reactions. Uveitis led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of patients who received systemic corticosteroids for uveitis, 75% (3/4) had improvement or resolution.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.1% (2) 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 acute generalized exanthematous pustulosis, has occurred in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of skin exfoliation and treat promptly. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.1% (31/2799) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 40% (12/31) of patients. These reactions led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding of KEYTRUDA in 0.6% (17) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of patients who received systemic corticosteroids for dermatitis, 75% (9/12) had improvement or resolution.

#### 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, myelitis, demyelination, and sensory neuropathy; hypophysitis; uveitis; pancreatitis; enterocolitis; pneumonitis; hypothyroidism; hyperthyroidism; type 1 diabetes mellitus, including cases of diabetic ketoacidosis; hypoparathyroidism; adrenal insufficiency; hypophysitis; hypopituitarism; and systemic inflammatory response syndrome. Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, and hemolytic anemia.

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for the management of these complications. Of the 11 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 treatment 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 of KEYTRUDA were pneumonitis (1.4%) and colitis (1.1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-048, KEYTRUDA was administered as a single agent and was discontinued due to adverse reactions in 14% of 300 patients; permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥3%) were pneumonitis (3.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonia (2.4%). When KEYTRUDA was administered with chemotherapy, it 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 KEYTRUDA-treated patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 11% of 405 patients; the most common (≥1%) were pneumonitis (1.5%) and renal failure (1%). When KEYTRUDA was administered as a single agent to patients with PD-L1 expression (TPS ≥1%), adverse reactions occurring in patients with TPS ≥1% were similar to those occurring in patients with TPS ≥50%.

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 559 patients with pneumonitis (2.9%) and acute kidney injury (2%) the most common adverse reactions (≥20%) were alopecia (36%), fatigue (31%), nausea (31%), peripheral neuropathy (24%), and decreased appetite (21%).

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 559 patients with pneumonitis (2.9%) and acute kidney injury (2%) the most common adverse reactions (≥20%) were alopecia (36%), fatigue (31%), nausea (31%), peripheral neuropathy (24%), and decreased appetite (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were fatigue (35%), decreased appetite (25%), nausea (23%), pneumonia (23%), and pruritus (20%). Fatal adverse reactions occurred in 7% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated adverse reactions (0.3%). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia (8%), pulmonary embolism (2%), dyspnea (2%), and pneumonitis (2%).

In KEYNOTE-024, when KEYTRUDA was administered with carboplatin and pemetrexed in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 154 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were nausea (32%), fatigue (31%), constipation (27%), decreased appetite (25%), vomiting (24%), rash (22%), and diarrhea (20%). Fatal adverse reactions occurred in 5% of patients, including pneumonitis (3.9%), pulmonary embolism (0.6%), and sepsis (0.6%). Serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia (6%), pulmonary embolism (3%), and pneumonitis (2%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of 151 patients with metastatic urothelial carcinoma; the most common were pneumonitis (2%), pneumonia (2%), and sepsis (2%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (26%), decreased appetite (24%), pruritus (22%), rash (21%), and diarrhea (20%). Fatal adverse reactions occurred in 5% of patients, including sepsis (2%), cardiac arrest (0.7%), and pneumonitis (0.7%). Serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, pneumonia, and pneumonitis.

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 reactions (≥20%) were fatigue (37%), musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), pruritus (24%), rash (23%), and diarrhea (21%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 8% of 153 patients with RMSCL. Serious adverse reactions occurred in 26% of patients and included pneumonia (3%), urinary tract infection (2%), and pyrexia (2%). Fatal adverse reactions occurred in 2% of patients and included sepsis (1%) and death of unknown cause (1%). The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), rash (23%), fatigue (22%), and diarrhea (21%).

In KEYNOTE-329, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer who had received prior platinum-containing chemotherapy and PD-(L)1 inhibitor therapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 290 patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 13% of patients. The most frequent adverse reaction (≥2%) leading to permanent discontinuation was pneumonitis (2%). The most frequent adverse reactions that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.4%), and pneumonia (1.4%).

Adverse reactions observed in KEYNOTE-001 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (17%), hyperthyroidism (8%), and thyroiditis (3%).

In KEYNOTE-598, the most common adverse reactions (≥20%) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (35%), musculoskeletal pain (29%), constipation (27%), hypothyroidism (25%), nausea (24%), rash (23%), and decreased appetite (21%).

In the neoadjuvant phase of KEYNOTE-689, of the 397 patients who received at least one dose of single-agent KEYTRUDA, 11% experienced serious adverse reactions. The most frequent serious adverse reaction was pneumonia (1.5%). Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 10% of patients. The most frequent adverse reaction leading to permanent discontinuation was pneumonitis (0.8%), including 1 fatal adverse reaction. Adverse reactions leading to permanent discontinuation were seen in 6% of patients receiving KEYTRUDA in combination with chemoradiation. The most frequent adverse reaction leading to permanent discontinuation was sepsis (0.7%) and pneumonia (0.7%).

In the neoadjuvant phase of KEYNOTE-689, of the 397 patients who received at least one dose of single-agent KEYTRUDA, 11% experienced serious adverse reactions. The most frequent serious adverse reaction was pneumonia (1.5%). Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 10% of patients. The most frequent adverse reaction leading to permanent discontinuation was pneumonitis (0.8%), including 1 fatal adverse reaction. Adverse reactions leading to permanent discontinuation were seen in 6% of patients receiving KEYTRUDA in combination with chemoradiation. The most frequent adverse reaction leading to permanent discontinuation was sepsis (0.7%) and pneumonia (0.7%).

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 18% of 441 patients with HNSCC; serious adverse reactions occurred in 49% of patients. The most common adverse reactions (≥20%) were nausea (31%), fatigue/asthenia (31%), stomatitis (30%), vomiting (24%), constipation (21%), decreased appetite (21%), pneumonia (21%), and septic shock (21%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 18% of 441 patients with HNSCC; serious adverse reactions occurred in 49% of patients. The most common adverse reactions (≥20%) were nausea (31%), fatigue/asthenia (31%), stomatitis (30%), vomiting (24%), constipation (21%), decreased appetite (21%), pneumonia (21%), and septic shock (21%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).

Of the 321 KEYTRUDA-treated patients who received surgery following the neoadjuvant phase, 1.2% experienced delay of surgery (defined as re-shot surgery ≥7 days after initiation of subsequent KEYTRUDA dose) due to adverse reactions. Of the 321 patients who received surgery following the neoadjuvant phase, 1.2% experienced delay of surgery (defined as re-shot surgery ≥7 days after initiation of subsequent KEYTRUDA dose) 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 ≥1% of patients were pneumonia (2.4%), urinary tract infection (1.6%), and pyrexia (1.2%). Fatal adverse reactions occurred in 0.4% of patients, including 1 patient each with pneumonitis, sepsis, and death of unknown cause. Adverse reactions leading to permanent discontinuation of KEYTRUDA were reported in 17% of patients. The most frequent adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2.4%), COVID-19 (2.4%), death not otherwise specified (1.2%), diarrhea (1.2%), pyelonephritis (1.2%), pulmonary tube rib complication (1.2%), and urinary tract infection (1.2%). Adverse reactions leading to interruption of KEYTRUDA occurred in 31% of patients. The most frequent adverse reactions leading to interruption were hyperkalemia (0.4%), pyelonephritis (0.4%), hyperglycemia (0.4%), hypercalcemia (0.4%), hyponatremia (0.4%), sepsis (0.4%), and pneumonia (0.4%). COVID-19 (4.8%) resulting in hospitalization was reported in 12% of patients. Adverse reactions leading to dose reduction of KEYTRUDA occurred in 4.7% of 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 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 of KEYTRUDA were pneumonitis (1.4%) and colitis (1.1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-048, when KEYTRUDA was administered as a single agent, adverse reactions occurring in patients with stage IIB or IIC melanoma were similar to those occurring in KEYTRUDA-treated patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 11% of 405 patients; the most common (≥1%) were pneumonitis (1.5%) and renal failure (1%). When KEYTRUDA was administered as a single agent to patients with PD-L1 expression (TPS ≥1%), adverse reactions occurring in patients with TPS ≥1% were similar to those occurring in patients with TPS ≥50%.

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 559 patients with pneumonitis (2.9%), pulmonary embolism (2.9%), and sepsis (2.9%). The most common adverse reactions (≥20%) were alopecia (36%), fatigue (31%), nausea (31%), peripheral neuropathy (24%), and decreased appetite (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were fatigue (35%), decreased appetite (25%), nausea (23%), pneumonia (23%), and pruritus (20%). Fatal adverse reactions occurred in 7% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated adverse reactions (0.3%). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia (8%), pulmonary embolism (2%), dyspnea (2%), and pneumonitis (2%).

In KEYNOTE-024, when KEYTRUDA was administered with carboplatin and pemetrexed in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 154 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were nausea (32%), fatigue (31%), constipation (27%), decreased appetite (25%), vomiting (24%), rash (22%), and diarrhea (20%). Fatal adverse reactions occurred in 5% of patients, including pneumonitis (3.9%), pulmonary embolism (0.6%), and sepsis (0.6%). Serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, pneumonia, and pneumonitis.

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 reactions (≥20%) were fatigue (37%), musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), pruritus (24%), rash (23%), and diarrhea (21%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 8% of 153 patients with RMSCL. Serious adverse reactions occurred in 26% of patients and included pneumonia (3%), urinary tract infection (2%), and pyrexia (2%). Fatal adverse reactions occurred in 2% of patients and included sepsis (1%) and death of unknown cause (1%). The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), rash (23%), fatigue (22%), and diarrhea (21%).

In KEYNOTE-329, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer who had received prior platinum-containing chemotherapy and PD-(L)1 inhibitor therapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 290 patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 13% of patients. The most frequent adverse reaction (≥2%) leading to permanent discontinuation was pneumonitis (2%). The most frequent adverse reactions that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.4%), and pneumonia (1.4%).

Adverse reactions observed in KEYNOTE-001 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (17%), hyperthyroidism (8%), and thyroiditis (3%).

In KEYNOTE-598, the most common adverse reactions (≥20%) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (35%), musculoskeletal pain (29%), constipation (27%), hypothyroidism (25%), nausea (24%), rash (23%), and decreased appetite (21%).

In the neoadjuvant phase of KEYNOTE-689, of the 397 patients who received at least one dose of single-agent KEYTRUDA, 11% experienced serious adverse reactions. The most frequent serious adverse reaction was pneumonia (1.5%). Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 10% of patients. The most frequent adverse reaction leading to permanent discontinuation was pneumonitis (0.8%), including 1 fatal adverse reaction. Adverse reactions leading to permanent discontinuation were seen in 6% of patients receiving KEYTRUDA in combination with chemoradiation. The most frequent adverse reaction leading to permanent discontinuation was sepsis (0.7%) and pneumonia (0.7%).

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 ≥1% of patients were pneumonia (2.4%), urinary tract infection (1.6%), and pyrexia (1.2%). Fatal adverse reactions occurred in 0.4% of patients, including 1 patient each with pneumonitis, sepsis, and death of unknown cause. Adverse reactions leading to permanent discontinuation of KEYTRUDA were reported in 17% of patients. The most frequent adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (2.4%), COVID-19 (2.4%), death not otherwise specified (1.2%), diarrhea (1.2%), pyelonephritis (1.2%), pulmonary tube rib complication (1.2%), and urinary tract infection (1.2%). Adverse reactions leading to interruption of KEYTRUDA occurred in 31% of patients. The most frequent adverse reactions leading to interruption were hyperkalemia (0.4%), pyelonephritis (0.4%), hyperglycemia (0.4%), hypercalcemia (0.4%), hyponatremia (0.4%), sepsis (0.4%), and pneumonia (0.4%). COVID-19 (4.8%) resulting in hospitalization was reported in 12% of patients. Adverse reactions leading to dose reduction of KEYTRUDA occurred in 4.7% of 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 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 of KEYTRUDA were pneumonitis (1.4%) and colitis (1.1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-048, when KEYTRUDA was administered as a single agent, adverse reactions occurring in patients with stage IIB or IIC melanoma were similar to those occurring in KEYTRUDA-treated patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 11% of 405 patients; the most common (≥1%) were pneumonitis (1.5%) and renal failure (1%). When KEYTRUDA was administered as a single agent to patients with PD-L1 expression (TPS ≥1%), adverse reactions occurring in patients with TPS ≥1% were similar to those occurring in patients with TPS ≥50%.

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 559 patients with pneumonitis (2.9%), pulmonary embolism (2.9%), and sepsis (2.9%). The most common adverse reactions (≥20%) were alopecia (36%), fatigue (31%), nausea (31%), peripheral neuropathy (24%), and decreased appetite (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were fatigue (35%), decreased appetite (25%), nausea (23%), pneumonia (23%), and pruritus (20%). Fatal adverse reactions occurred in 7% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated adverse reactions (0.3%). Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia (8%), pulmonary embolism (2%), dyspnea (2%), and pneumonitis (2%).

In KEYNOTE-024, when KEYTRUDA was administered with carboplatin and pemetrexed in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 154 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were nausea (32%), fatigue (31%), constipation (27%), decreased appetite (25%), vomiting (24%), rash (22%), and diarrhea (20%). Fatal adverse reactions occurred in 5% of patients, including pneumonitis (3.9%), pulmonary embolism (0.6%), and sepsis (0.6%). Serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were urinary tract infection, pneumonia, and pneumonitis.

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 reactions (≥20%) were fatigue (37%), musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), pruritus (24%), rash (23

Select a Topic

# Advanced Esophageal or GEJ Carcinoma

## INDICATIONS

### Advanced Esophageal or GEJ Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) adenocarcinoma with epicenter 1 to 5 centimeters above the GEJ carcinoma that is not amenable to surgical resection or definitive combined modality therapy, and

- in combination with platinum- and fluoropyrimidine-based chemotherapy for patients with tumors that express PD-L1 [CPS ≥1].
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of microsatellite instability-high or mismatch repair deficient tumors as determined by an FDA-approved test.

Scroll below to review Selected Safety Information

Advanced Esophageal or GEJ Carcinoma
KEYNOTE-590, KEYNOTE-859, KEYNOTE-181

## Selected Safety Information

### 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.

Early identification and management are essential to minimize the risk of severe or fatal sequelae. Monitor patients for signs and symptoms that may be consistent with any immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti–PD-1/PD-L1 treatments. Evaluate liver enzymes, and thyroid function at baseline and periodically during treatment. For mild or moderate (Grade 2 or 3) infusion-related reactions, consider dose interruption or slowing the rate of infusion. Withhold or permanently discontinue treatment depending on severity. Administer systemic corticosteroids and, if appropriate, perform additional workup for suspected immune-mediated adverse reactions, initiate appropriate medical management to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity. Administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.6%) adverse reactions. Pneumonitis occurred in 6.7% (53/796) of patients who received KEYTRUDA in combination with chemotherapy, including Grade 3 (2.5%) and Grade 2 (3.4%) adverse reactions. Pneumonitis occurred in 13.1% (39/298) 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 2.1% (59/2799) of patients, and 0.4% (11/2799) had recurrent pneumonitis. Pneumonitis resolved in 62% (37/59) of discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7.7% (23/298) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2.6 (8.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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 testing to confirm the presence of cytomegalovirus infection/reactivation by an alternative method before treatment with antiviral therapy.

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%) adverse reactions. Colitis led to discontinuation of KEYTRUDA in 0.6% (16/2799) of patients. Complete resolution occurred in 42% (20/48) of patients.

Pneumonitis occurred in 8% (21/389) 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 2.6% (10/389) of patients, and 1.5% (6/389) had recurrent pneumonitis. Pneumonitis resolved in 67% (4/6) of discontinued KEYTRUDA, and 77% had resolution.

Withhold or permanently discontinue KEYTRUDA depending on severity. Administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue 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 Hepatitis and Hepatotoxicity

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. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

Hepatitis occurred in 2.4% (7/298) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 1% (3/298) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% discontinued KEYTRUDA, and 71% had resolution.

KEYTRUDA With ADIs

KEYTRUDA in combination with adcetris 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 adcetris, and administer corticosteroids as clinically indicated. If liver enzymes do not return to baseline, delay adcetris and resume KEYTRUDA within 3 and 5 weeks, respectively. Grade 3 (5%) and Grade 4 (2%) increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids. Of these patients, 83% had resolution to Grade 1 or baseline. Of the 41% patients who did not receive steroids, 50% had resolution. Among the 52 patients who were rechallenged with either KEYTRUDA (n=3) or adcetris (n=34) administered as a single agent or as part with both (n=15), recurrence of ALT or AST to Grade 3 or 4 occurred in 1 patient receiving KEYTRUDA, 16 patients receiving adcetris, and 24 patients receiving both. All patients with a recurrence of ALT or AST to Grade 3 or 4 UAN subsequently recovered from the event.

#### Immune-Mediated Endocrinopathies

Adrenal Insufficiency

Adrenal insufficiency 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. Administer insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (0.1%) reactions. Hypophysitis occurred in 0.4% (12/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.1%) reactions. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

Hypophysitis occurred in 6.4% (25/389) of patients with cHL receiving KEYTRUDA as a single agent, including Grades 3 4 in 1.8% of patients. Hypophysitis led to discontinuation of KEYTRUDA in 1.8% (7/389) of patients, and 1.3% (5/389) had recurrent hypophysitis. Hypophysitis resolved in 56% (14/25) of patients.

KEYTRUDA With ADIs

KEYTRUDA in combination with adcetris 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 adcetris, and administer corticosteroids as clinically indicated. If liver enzymes do not return to baseline, delay adcetris and resume KEYTRUDA within 3 and 5 weeks, respectively. Grade 3 (5%) and Grade 4 (2%) increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids. Of these patients, 83% had resolution to Grade 1 or baseline. Of the 41% patients who did not receive steroids, 50% had resolution. Among the 52 patients who were rechallenged with either KEYTRUDA (n=3) or adcetris (n=34) administered as a single agent or as part with both (n=15), recurrence of ALT or AST to Grade 3 or 4 occurred in 1 patient receiving KEYTRUDA, 16 patients receiving adcetris, and 24 patients receiving both. All patients with a recurrence of ALT or AST to Grade 3 or 4 UAN subsequently recovered from the event.

#### Immune-Mediated Endocrinopathies

Adrenal Insufficiency

Adrenal insufficiency 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. Administer insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (0.1%) reactions. Hypophysitis occurred in 0.4% (12/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.1%) reactions. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

Hypophysitis

Hypophysitis 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 0.9% (25/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.6%) reactions. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.3% (8) of patients. All patients who were withheld resumed 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 initiation of 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 0.2% of patients.

Hyperthyroidism occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.8% (22) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.6%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.2% (6) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Hypophysitis occurred in 0.4% (12/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.1%) reactions. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.3% (8) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

Hypophysitis occurred in 6.4% (25/389) of patients with cHL receiving KEYTRUDA as a single agent, including Grades 3 4 in 1.8% of patients. Hypophysitis led to discontinuation of KEYTRUDA in 1.8% (7/389) of patients, and 1.3% (5/389) had recurrent hypophysitis. Hypophysitis resolved in 56% (14/25) of patients.

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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (4) of patients. All patients who were withheld resumed 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 in patients receiving anti–PD-1/PD-L1 treatments. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (75/189) of patients receiving KEYTRUDA as a single agent for adjuvant treatment of MCC, including Grade 3 (3.2%) and Grade 2 (11%) adverse reactions. These reactions led to permanent discontinuation in 0.5% (1) and withholding of KEYTRUDA in 0.5% (1) of patients. All patients who were withheld resumed KEYTRUDA after symptom improvement. Of these, none had recurrence. Rash resolved in 50% (4/8) of 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: Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome, Guillain-Barré syndrome, hemolytic anemia, aplastic anemia, thrombocytopenia, myocarditis, pericarditis, vasculitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including elevations in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, uveitis, iritis, and other ocular inflammatory toxicities can occur in association 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. Immune-mediated myocarditis occurred in 0.3% (1/298) of patients who received KEYTRUDA. Myositis, Musculoskeletal and Connective Tissue Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica, Hypophysitis, Uveitis, Pancreatitis, Gastritis, Duodenitis, Sialadenitis, Colitis, Myocarditis, Pericarditis, Vasculitis, Nephritis, Systemic inflammatory response syndrome, Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, hemolytic anemia.

#### 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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Follow patients closely for these complications when administering treatments administered before or after KEYTRUDA. Of 11 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 treatment 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 occurred in 4.1% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-001, KEYTRUDA was administered as a single agent to 655 patients with advanced melanoma. KEYTRUDA was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 36% of patients receiving KEYTRUDA. The most frequent serious adverse reactions were pneumonitis (2.4%) and pyrexia (1.8%). In KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with stage IB or IIC melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in patients with stage III melanoma.

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. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. In KEYNOTE-756, when KEYTRUDA was administered with paclitaxel and carboplatin, or paclitaxel and nab-paclitaxel, in patients with metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 397 patients. Serious adverse reactions occurred in 49% of patients.

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 16% of 559 patients. Serious adverse reactions occurred in 59% of patients receiving KEYTRUDA. In KEYNOTE-775, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy, and continued as single-agent treatment, serious adverse reactions occurred in 44% of patients. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception of the following: KEYTRUDA was discontinued due to adverse reactions in 9% of 278 patients with advanced NSCLC, the most common adverse reactions (≥20%) were fatigue (33%), musculoskeletal pain (25%), nausea (24%), decreased appetite (21%), and rash (20%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and dyspnea (2%). Serious adverse reactions occurred in 58% of patients receiving KEYTRUDA. The most frequent serious adverse reactions were pneumonia (13%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with advanced NSCLC; the most common were pneumonitis (1.9%), pneumonia (1.5%), and sepsis (0.4%). The most common adverse reactions (≥20%) were fatigue (28%), nausea (21%), and decreased appetite (20%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 11% of 154 patients with advanced NSCLC; the most common were pneumonitis (2%), pneumonia (2%), and dyspnea (2%). Serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions were pneumonia (8%), pulmonary embolism (3%), dyspnea (3%), and pleural effusion (3%). The most common adverse reaction (≥20%) was fatigue (26%).

In KEYNOTE-048, when KEYTRUDA was administered with carboplatin and either paclitaxel or paclitaxel protein-bound, and continued as single-agent treatment, KEYTRUDA was discontinued due to adverse reactions in 17% of 281 patients with advanced NSCLC; the most common were pneumonitis (2%), pneumonia (2%), and dyspnea (2%). Serious adverse reactions occurred in 41% of patients. The most frequent serious adverse reactions were pneumonia (7%), dyspnea (3%), and pulmonary embolism (3%). The most common adverse reaction (≥20%) was fatigue (23%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 19% of 370 patients with advanced NSCLC. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions were pneumonia (7%), pneumonitis (3%), pulmonary embolism (2.2%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-061, KEYTRUDA was discontinued due to adverse reactions in 13% of 592 patients with gastric cancer; adverse reactions leading to permanent discontinuation occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (33%), diarrhea (24%), and nausea (21%).

In KEYNOTE-062, KEYTRUDA was discontinued due to adverse reactions in 18% of 154 patients with gastric cancer; adverse reactions leading to permanent discontinuation occurred in 15% of patients. The most common adverse reactions (≥20%) were fatigue (25%), nausea (23%), and decreased appetite (21%).

In KEYNOTE-590, KEYTRUDA was discontinued due to adverse reactions in 18% of 497 patients with esophageal cancer; adverse reactions leading to permanent discontinuation occurred in 14% of patients. The most common adverse reactions (≥20%) were fatigue (33%), diarrhea (25%), nausea (23%), and decreased appetite (21%).

In KEYNOTE-859, when KEYTRUDA was administered with chemotherapy before surgery and continued as single-agent treatment after surgery, KEYTRUDA was discontinued due to adverse reactions in 19% of 790 patients. The most common adverse reactions (≥20%) were fatigue (35%), nausea (29%), constipation (23%), and anemia (21%).

In KEYNOTE-868, when KEYTRUDA was administered with chemotherapy before surgery and continued as single-agent treatment after surgery, KEYTRUDA was discontinued due to adverse reactions in 21% of 397 patients. The most common adverse reactions (≥20%) were fatigue (40%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22%), nausea (21%), and decreased appetite (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of 790 patients. The most frequent adverse reactions were pneumonitis (2%) and pneumonia (2%). Serious adverse reactions occurred in 54% of patients. The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (26%), nausea (25%), decreased appetite (24%), constipation (24%), abdominal pain (22%), peripheral neuropathy (21%), and vomiting (20%).

In KEYNOTE-177, when KEYTRUDA was administered as a single agent to patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, KEYTRUDA was discontinued due to adverse reactions in 11% of 153 patients. The most common adverse reactions (≥20%) were fatigue (30%), diarrhea (27%), abdominal pain (23%), nausea (22%), and decreased appetite (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with microsatellite instability-high or mismatch repair deficient metastatic cancer, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with previously treated rare cancers. The most common adverse reactions (≥20%) were fatigue (31%), diarrhea (22%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with previously treated metastatic cervical cancer, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with previously treated cervical cancer. The most common adverse reactions (≥20%) were fatigue (31%), diarrhea (22%), and pruritus (20%).

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. The most common adverse reactions (≥20%) were fatigue (31%), diarrhea (22%), and pruritus (20%). Serious adverse reactions (≥2%) were fatigue (2%), abdominal pain (2%), pneumonia (2%), and vomiting (2%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of 790 patients. The most frequent adverse reactions were pneumonitis (2%) and pneumonia (2%). Serious adverse reactions occurred in 54% of patients. The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (27%), diarrhea (26%), nausea (25%), decreased appetite (24%), constipation (24%), abdominal pain (22%), peripheral neuropathy (21%), and vomiting (20%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients, including 3 cases of hemorrhage, 2 cases each of sepsis and ulcerative colitis, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with postoperative pulmonary embolism, hemorrhagic cystitis, hepatitis, hypophysitis, myocarditis, pneumonitis, and respiratory failure. Adverse reactions leading to permanent discontinuation of KEYTRUDA in combination with chemotherapy with or without bevacizumab; those ≥3% were febrile neutropenia (8.8%), urinary tract infection (5.2%), anemia (4.4%), sepsis, and acute kidney injury (3.1% each).

KEYTRUDA was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation (≥1%) was pneumonitis (2%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common adverse reactions (≥20%) were peripheral neuropathy (82%), nausea (58%), fatigue (57%), alopecia (55%), diarrhea (53%), decreased appetite (43%), vomiting (40%), abdominal pain (37%), arthralgia (27%), constipation and arthralgia (26% each), vomiting (26%), urinary tract infection (21%), rash (20%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (20%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=199), the most common adverse reactions (≥20%) were peripheral neuropathy (82%), alopecia (56%), fatigue (51%), nausea (46%), diarrhea (36%), constipation (28%), arthralgia (27%), vomiting (26%), hypertension and urinary tract infection (24% each), and rash (21%).

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. The most common adverse reactions (≥20%) were fatigue (31%), diarrhea (22%), and pruritus (20%). Serious adverse reactions (≥2%) were fatigue, abdominal pain, pneumonia, pneumonitis, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. In KEYNOTE-158, KEYTRUDA was discontinued for adverse reactions in 2% of patients. In KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased ALT (1.5%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) in patients receiving KEYTRUDA in combination with chemotherapy were nausea (52%), fatigue (51%), vomiting (33%), decreased appetite (29%), constipation (28%), diarrhea (27%), peripheral neuropathy (24%), alopecia (24%), abdominal pain (24%), hemorrhage (22%), and rash (21%).

In KEYNOTE-355, when KEYTRUDA and chemotherapy (paclitaxel, protein-bound, or gemcitabine and carboplatin) were administered to patients with metastatic triple-negative breast cancer, KEYTRUDA was discontinued due to adverse reactions in 15% of 596 patients. Serious adverse reactions occurred in 21% of patients, including cardio-respiratory arrest (0.7%) and septic shock (0.5%). Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemotherapy. The most common adverse reactions (≥20%) were alopecia (49%), nausea (46%), fatigue (36%), diarrhea (32%), constipation (25%), vomiting (24%), peripheral neuropathy (23%), decreased appetite (22%), and anemia (20%). The most frequent (≥1%) serious adverse reactions were anemia, febrile neutropenia, and pneumonia.

In KEYNOTE-355, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with metastatic or recurrent endometrial carcinoma, KEYTRUDA was discontinued due to adverse reactions in 18% of patients. Serious adverse reactions occurred in 48% of patients. The most common adverse reactions (≥20%) were alopecia (51%), fatigue (51%), nausea (46%), diarrhea (36%), vomiting (24%), decreased appetite (23%), peripheral neuropathy (22%), abdominal pain (21%), and constipation (20%).

In KEYNOTE-811, when KEYTRUDA was administered in combination with trastuzumab and chemotherapy to patients with HER2+ metastatic gastric or gastroesophageal junction adenocarcinoma, KEYTRUDA was discontinued due to adverse reactions in 15% of patients including nausea (2.1%), vomiting (2.1%), and pneumonitis (1.4%). The most common adverse reactions (≥20%) were nausea (67%), fatigue (57%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with resected stage IB (T2b N0 M0) or stage IIA (T3 N0 M0) or stage IIB (T2b N0 M0) or stage IIC (T3 N0 M0) melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in patients with stage III melanoma.

In KEYNOTE-091, when KEYTRUDA was administered as a single agent for adjuvant treatment of NSCLC, KEYTRUDA was discontinued due to adverse reactions in 14% of 1,067 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 36% of patients receiving KEYTRUDA. The most frequent serious adverse reactions were pneumonitis (2.4%) and pyrexia (1.8%). The most common adverse reaction (≥20%) with KEYTRUDA was fatigue (26%), constipation (20%), nausea (20%), and cough (20%).

In KEYNOTE-054, when KEYTRUDA was administered as a single agent for adjuvant treatment of stage III melanoma, adverse reactions occurred in 42% of patients; these (2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (30%), diarrhea (21%), rash (21%), and pruritus (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 was urinary tract infection (2.7%). Adverse reactions occurred in 57% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (31%), urinary tract infection (23%), pruritus (21%), and rash (21%).

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, KEYTRUDA was administered to 233 patients 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, pneumonitis, and sepsis. Serious adverse reactions occurred in 49% of patients. The most common adverse reactions (≥20%) were fatigue (47%), nausea (37%), diarrhea (36%), vomiting (25%), and pruritus (20%). The most frequent serious adverse reactions (≥2%) were fistula (3.4%), hemorrhage (2.7%), and pneumonia (2.4%). KEYTRUDA was discontinued in 18% of patients due to adverse reactions.

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 was pneumonitis (1.1%). Adverse reactions occurred in 61% of patients receiving KEYTRUDA. The most common (≥20%) were fatigue (28%), urinary tract infection (22%), pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA in combination with chemotherapy were nausea (52%), fatigue (51%), vomiting (33%), decreased appetite (29%), constipation (28%), diarrhea (27%), peripheral neuropathy (24%), alopecia (24%), abdominal pain (24%), hemorrhage (22%), and rash (21%).

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 was urinary tract infection (2.7%). Adverse reactions occurred in 57% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (31%), urinary tract infection (23%), pruritus (21%), and rash (21%).

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, KEYTRUDA was administered to 233 patients 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, pneumonitis, and sepsis. Serious adverse reactions occurred in 49% of patients. The most common adverse reactions (≥20%) were fatigue (47%), nausea (37%), diarrhea (36%), vomiting (25%), and pruritus (20%). The most frequent serious adverse reactions (≥2%) were fistula (3.4%), hemorrhage (2.7%), and pneumonia (2.4%). KEYTRUDA was discontinued in 18% of patients due to adverse reactions.

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction resul

# Advanced Cervical Cancer

## INDICATIONS

- **In Combination With Chemoradiotherapy for FIGO 2014 Stage III-IVA 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 that is associated with hydronephrosis causing kidney, or ureteral to vaginal, organs (FIGO 2014 Stage III-IVA).
  FIGO = International Federation of Gynecology and Obstetrics
- **First-Line Combination Therapy for Persistent, Recurrent, or Metastatic Cervical Cancer**
  KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express programmed death ligand 1 (PD-L1) [combined positive score (CPS) ≥1], as determined by an FDA-approved test.
- **Second-Line Monotherapy for Recurrent or Metastatic Cervical Cancer**
  KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic cervical cancer whose tumors express programmed death ligand 1 (PD-L1) [combined positive score (CPS) ≥1], as determined by an FDA-approved test.
- **In Combination With Chemoradiotherapy for FIGO 2014 Stage III-IVA Cervical Cancer**
- **First-Line Combination Therapy for Persistent, Recurrent, or Metastatic Cervical Cancer**
  KEYNOTE-826
- **Second-Line Monotherapy for Recurrent or Metastatic Cervical Cancer**
  KEYNOTE-158

**Scroll below to review Selected Safety Information**

## Selected Safety Information

### 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 blocking

# Advanced Biliary Tract Cancer (BTC)

INDICATIONS

**Combination Therapy for Advanced 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).

**Combination Therapy for Advanced Biliary Tract Cancer**
KEYNOTE-966

Scroll to below to review Selected Safety Information

## Select Cancer Types

Bladder Cancer | Cervical Cancer | Classical Hodgkin Lymphoma | Colorectal Cancer | Endometrial Carcinoma | Esophageal Cancer | Gastric Cancer | Head and Neck Squamous Cell Cancer | Hepatocellular Carcinoma | Melanoma | Merkel Cell Carcinoma | Non-Small Cell Lung Cancer | Primary Mediastinal Large B-Cell Lymphoma | Renal Cell Carcinoma | Small Cell Lung Cancer | Solid Tumors | Urothelial Carcinoma

## Selected Safety Information

### 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 blocking antibody (anti-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 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. 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.2%), and Grade 2 (1.8%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% of patients receiving KEYTRUDA in 1.1% (28) and withholding in 0.9% (26) of patients, and was permanently discontinued in 0.8% (22) of 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 3.1% (12) of patients, and to withholding of KEYTRUDA in 4.1% (16) of patients. All patients with pneumonitis discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 4% (11/289) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2% (6/289) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 83% 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. It is important to exclude infectious etiologies. Immune-mediated colitis occurred in 2.2% (62/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (1.0%) adverse reactions. Systemic corticosteroids were required in 68% (42/62) of patients. Colitis resolved in 56% of patients receiving KEYTRUDA in 0.7% (19) and withholding in 0.6% (16) of patients, and was permanently discontinued for 0.7% (19) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Colitis occurred in 6% (21/389) 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 2.3% (9) of patients, and to withholding of KEYTRUDA in 2.6% (10) of patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

Colitis occurred in 5% (14/289) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2% (6/289) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 83% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated hepatitis occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 5 (0.1%), Grade 4 (0.4%), Grade 3 (0.6%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 63% (24/38) of patients. Hepatitis resolved in 58% of patients receiving KEYTRUDA in 0.6% (17) and withholding in 0.3% (8) of patients, and was permanently discontinued for 0.4% (11) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hepatitis occurred in 3% (13/389) 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 2.3% (9) of patients, and to withholding of KEYTRUDA in 2.6% (10) of patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

#### Hypophysitis 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 (0.2%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 74% (14/19) of patients. Hepatitis resolved in 63% of patients who were required in 1% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. All patients who discontinued KEYTRUDA for hepatitis resolved to Grade 1 or less.

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 administer corticosteroids as clinically indicated. After recovery of liver enzymes to Grade 1 or baseline, resume KEYTRUDA and axitinib at reduced dose. Hepatitis (22%) and increased aspartate aminotransferase (AST) (31%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids. Increased AST resolved to Grade 1 or baseline in 79% of patients. Of the patients with AST elevations, 3.2% discontinued KEYTRUDA. 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 AST elevations Grade 3 or greater occurred in 1 patient receiving KEYTRUDA, 4 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of AST elevations Grade 3 or greater discontinued KEYTRUDA.

#### 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 91% (20/22) of patients. Adrenal insufficiency resolved in 45% of patients receiving KEYTRUDA in 0.2% (5) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. All patients who discontinued KEYTRUDA for adrenal insufficiency resolved to Grade 1 or less.

*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 0.5% (13/2799) of patients receiving KEYTRUDA, including 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% (1) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypothyroidism occurred in 21% (82/389) of 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 2.3% (9) of patients, and to withholding of KEYTRUDA in 2.6% (10) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. All patients who discontinued KEYTRUDA for pneumonitis resolved to Grade 1 or less.

#### Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) 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 in patients receiving KEYTRUDA. Monitor patients for signs and symptoms of skin exfoliation and bullous reactions. Initiate treatment of severe reactions. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 14% (398/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (2.4%) reactions. Systemic corticosteroids were required in 40% (158/398) 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. All patients who discontinued KEYTRUDA for dermatologic reactions resolved to Grade 1 or less.

#### 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: Cerebral hypophysitis, aseptic meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), myositis/polymyositis, rhabdomyolysis (and associated sequelae), myocarditis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis sicca, hypophysitis, uveitis, conjunctivitis, eosinophilia, solid organ transplant rejection, infusion related reactions, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including tissue graft) rejection, hemolytic anemia.

#### 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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. These complications may occur even if intervening therapy between anti–PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit-vs-risks of using anti–PD-1/PD-L1 treatment 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 occurred in 6% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

The most common adverse reactions (≥20%) with KEYTRUDA were arthralgia (22%) and fatigue (20%). KEYTRUDA was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 43% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonitis (3.1%), colitis (2.4%), and diarrhea (1.4%). KEYTRUDA was withheld as an adverse reaction in 34% of patients; the most common (≥1%) adverse reactions that led to treatment withholding were pneumonitis (2.4%), colitis (2.4%), diarrhea (2.2%), and rash (1.8%).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients who received at least one dose of any component of KEYTRUDA. The most common adverse reactions (≥20%) of KEYTRUDA were nausea (40%), fatigue (36%), constipation (29%), rash (25%), and decreased appetite (21%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and either paclitaxel or nab-paclitaxel, serious adverse reactions occurred in 49% of 292 patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 19% of patients. The most common adverse reactions (≥20%) were fatigue (51%), alopecia (48%), nausea (41%), peripheral neuropathy (37%), decreased appetite (25%), diarrhea (24%), vomiting (24%), and constipation (20%).

In KEYNOTE-048, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 18% of 441 patients who received at least one dose of any component of KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (51%), nausea (40%), alopecia (36%), constipation (29%), rash (25%), decreased appetite (21%), diarrhea (20%), and vomiting (20%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 682 patients with advanced NSCLC. The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (25%), decreased appetite (21%), and nausea (20%).

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 44% of 397 patients who received at least one dose of any component of KEYTRUDA. The most frequent serious adverse reactions were pneumonia (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 hepatitis (0.3%). Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 26% of patients. The most common adverse reactions (≥20%) were nausea (46%), alopecia (38%), fatigue (36%), vomiting (29%), constipation (28%), diarrhea (27%), decreased appetite (23%), and rash (20%).

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. The most frequent serious adverse reaction was pneumonia (1.4%). Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 16% of patients. The most common adverse reactions (≥20%) were nausea (28%), fatigue (27%), diarrhea (25%), vomiting (22%), and decreased appetite (20%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (30%), rash (21%), and pruritus (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 reactions (≥20%) were fatigue (38%), musculoskeletal pain (30%), decreased appetite (25%), nausea (24%), rash (21%), pruritus (20%), diarrhea (20%), cystitis (20%), pulmonary embolism (20%), pyrexia (20%), and urinary tract infection (20%). The most common adverse reactions (≥20%) were fatigue (59%), nausea (24%), and rash (21%).

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-859, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) with or without bevacizumab (n=301), KEYTRUDA was discontinued due to adverse reactions in 12% of patients included pneumonia (1.1%), diarrhea (1.1%), hemorrhage (0.3%), and vomiting (0.4%). Adverse reactions occurred in 61% of patients who received KEYTRUDA in combination with chemotherapy with or without bevacizumab. KEYTRUDA was permanently discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (1.3%), colitis (1.3%), pulmonary embolism (1.3%), sepsis (1%), and adrenal insufficiency (1%). The most common adverse reactions (≥20%) were fatigue (29%), nausea (28%), and alopecia (21%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) with or without bevacizumab (n=307), 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%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (29%), alopecia (28%), diarrhea (27%), cystitis (21%), pulmonary embolism (21%), pyrexia (21%), and urinary tract infection (21%). The most common adverse reactions (≥20%) were fatigue (59%), nausea (24%), and rash (21%).

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-859, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) with or without bevacizumab (n=301), KEYTRUDA was discontinued due to adverse reactions in 12% of patients included pneumonitis (1.1%), diarrhea (1.1%), hemorrhage (0.3%), and vomiting (0.4%). Adverse reactions occurred in 61% of patients who received KEYTRUDA in combination with chemotherapy with or without bevacizumab. KEYTRUDA was permanently discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (1.3%), colitis (1.3%), pulmonary embolism (1.3%), sepsis (1%), and adrenal insufficiency (1%). The most common adverse reactions (≥20%) were fatigue (29%), nausea (28%), and alopecia (21%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with locally advanced unresectable or metastatic urothelial carcinoma (n=307), 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%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (29%), alopecia (28%), diarrhea (27%), cystitis (21%), pulmonary embolism (21%), pyrexia (21%), and urinary tract infection (21%). The most common adverse reactions (≥20%) were fatigue (59%), nausea (24%), and rash (21%).

In KEYNOTE-158, when KEYTRUDA was administered with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ tumors with a positive 1 to 5 combined positive score (CPS), KEYTRUDA was not controlled 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 (≥1%) were pneumonitis (1.6%), acute kidney injury (1%), and pneumonia (1%). The most common adverse reactions (≥20%) were nausea (59%), decreased appetite (44%), fatigue (37%), vomiting (29%), constipation (28%), diarrhea (26%), stomatitis (23%), and weight loss (23%).

Adverse reactions occurring in patients with MSI-H cancer were similar to those occurring in patients with other solid tumors.

In KEYNOTE-811, when KEYTRUDA was administered in combination with trastuzumab, fluoropyrimidine, and platinum chemotherapy, serious adverse reactions occurred in 48% of patients. The most frequent (≥2%) serious adverse reactions were pneumonia (3.4%), diarrhea (2.4%), acute kidney injury (2.3%), dehydration (2%), and pneumonitis (2%). Fatal adverse reactions occurred in 2.4% of patients, including cardiac arrest (0.7%), pneumonitis (0.7%), and sepsis (0.3%). Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 19% of patients. The most common adverse reactions (≥20%) were nausea (62%), fatigue (51%), vomiting (32%), diarrhea (30%), decreased appetite (27%), constipation (26%), anemia (25%), abdominal pain (24%), peripheral neuropathy (23%), neutropenia (22%), alopecia (21%), and stomatitis (20%).

In KEYNOTE-775, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with PMBCL. Serious adverse reactions occurred in 26% of patients with PMBCL. The most common serious adverse reaction was pneumonitis (2.3%). Fatal adverse reactions occurred in 1.9% of patients with PMBCL, including 1 patient with pneumonitis 2 days of start of treatment. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue, and diarrhea (21%).

In KEYNOTE-335, when KEYTRUDA was administered in combination with enfortumab vedotin to patients with locally advanced or metastatic urothelial cancer who were not candidates for cisplatin-containing chemotherapy (n=442), KEYTRUDA was discontinued due to adverse reactions in 16% of patients. The most common adverse reactions in ≥20% of patients receiving KEYTRUDA in combination with enfortumab vedotin were alopecia (52%), peripheral neuropathy (51%), fatigue (50%), pruritus (46%), diarrhea (38%), nausea (35%), weight loss (33%), decreased appetite (32%), rash (31%), dysgeusia (30%), dry eye (25%), and constipation (24%).

In KEYNOTE-426, when KEYTRUDA was administered as a single agent for adjuvant treatment of RCC, KEYTRUDA was discontinued due to adverse reactions in 14% of patients; these <2% were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (26%), musculoskeletal pain (23%), pruritus (22%), and diarrhea (21%).

In KEYNOTE-564, KEYTRUDA was discontinued due to adverse reactions in 11% of 488 patients with high-risk RCC. Serious adverse reactions occurred in 26% of patients. The most common serious adverse reactions were pneumonitis (1.4%), adrenal insufficiency (1.2%), and pneumonia (1%). The most common adverse reactions (≥20%) were fatigue (26%), musculoskeletal pain (23%), pruritus (22%), and diarrhea (21%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 9% of 597 patients with adjuvant melanoma; adverse reactions leading to permanent discontinuation occurred in 9% of patients. The most common adverse reactions (≥20%) were fatigue (49%), rash (25%), and nausea (21%).

The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-177, KEYTRUDA was discontinued due to adverse reactions in 9% of 151 patients with advanced MSI-H or dMMR CRC; adverse reactions leading to permanent discontinuation occurred in 7% of patients. The most common adverse reactions (≥20%) were fatigue (32%), diarrhea (28%), nausea (25%), abdominal pain (23%), and pruritus (20%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 9% of 58 patients with advanced MSI-H or dMMR CRC; adverse reactions leading to permanent discontinuation occurred in 7% of patients. The most common adverse reactions (≥20%) were fatigue (34%), diarrhea (28%), nausea (24%), and pruritus (21%).

In KEYNOTE-164, KEYTRUDA was discontinued due to adverse reactions in 9% of 107 patients with advanced MSI-H or dMMR CRC; adverse reactions leading to permanent discontinuation occurred in 7% of patients. The most common adverse reactions (≥20%) were fatigue (32%), diarrhea (28%), nausea (25%), abdominal pain (23%), and pruritus (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were adverse reactions of pneumonitis (1.3%) and hepatotoxicity (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 were neutropenia (8%), thrombocytopenia (6%), anemia (6%), and hepatotoxicity (2%). KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased AST (1.5%), increased alanine aminotransferase (ALT) (1.3%), and hepatotoxicity (1.3%). The most common adverse reactions (≥20%) were fatigue (61%), nausea (58%), constipation (32%), vomiting (30%), pyrexia (26%), decreased appetite (24%), rash (24%), diarrhea (23%), and abdominal pain (20%).

In KEYNOTE-355, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, adverse reactions occurred in 98% of patients who received KEYTRUDA in combination with chemotherapy. KEYTRUDA was discontinued in 18% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 infection (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA were neutropenia (12%), anemia (6%), decreased white blood cell count (4%), pyrexia (3.8%), fatigue (3.6%), chromaturia (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.2%).

In KEYNOTE-091 and KEYNOTE-942, adverse reactions occurring in patients with MCC (n=115) were generally similar to those occurring in patients with melanoma or NSCLC.

In KEYNOTE-522, KEYTRUDA was administered in combination with paclitaxel and carboplatin, followed by KEYTRUDA as a single agent, and with doxorubicin 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 triple-negative breast cancer. The most common adverse reactions (≥20%) were alopecia (49%), nausea (46%), fatigue (42%), anemia (32%), pyrexia (30%), neutropenia, pneumonia, peripheral neuropathy, embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 2.1% of patients receiving KEYTRUDA, including cardiac arrest (2%).

KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased ALT (1.5%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) in patients receiving KEYTRUDA in combination with chemotherapy were alopecia (61%), nausea (58%), constipation (32%), vomiting (30%), pyrexia (26%), decreased appetite (24%), rash (24%), diarrhea (23%), and abdominal pain (20%), decreased appetite (24%), rash (24%), diarrhea (23%), and abdominal pain (20%).

In KEYNOTE-355, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma, adverse reactions occurred in 98% of patients who received KEYTRUDA in combination with chemotherapy. KEYTRUDA was discontinued in 18% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 infection (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA were neutropenia (12%), anemia (6%), decreased white blood cell count (4%), pyrexia (3.8%), fatigue (3.6%), chromaturia (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.2%).

In KEYNOTE-177 and KEYNOTE-164, 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 single agent.

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-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were adverse reactions of pneumonitis (1.3%) and hepatotoxicity (1.3%). Adverse reactions leading to interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA were neutropenia (8%), thrombocytopenia (6%), anemia (6%), and hepatotoxicity (2%). KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue (61%), nausea (58%), alopecia (38%), diarrhea (27%), vomiting and rash (26% each), cough (22%), decreased appetite (21%), and headache (20%).

### Lactation

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

### Pediatric Use

In KEYNOTE-051, 113 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 years to 17 years) received KEYTRUDA 2 mg/kg every 3 weeks. The most common adverse reactions (≥20%) were pyrexia (39%), fatigue (31%), and vomiting (22%). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (39% vs 18%), leukopenia (16% vs 3%), thrombocytopenia (15% vs 2%), abdominal pain (23% vs 11%), thrombocytopenia (22% Grade 3 anemia (11% vs 3%), decreased lymphocyte count (5%), and decreased white blood cell count (11% vs 3%).

### Geriatric Use

Of the 594 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in combination with enfortumab vedotin, 44% (n=261) were 65 to 75 years and 26% (n=154) 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.

**Before prescribing KEYTRUDA, please read the accompanying** Prescribing Information. The Medication Guide **also is available.**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = bacteriuria; BTC = biliary tract cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; CRT = chemoradiotherapy; GEJ = cadenosine squamous cell carcinoma; dMMR = mismatch repair deficient; EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; GVHD = graft-versus-host disease; HCC = hepatocellular carcinoma; HSCT = hematopoietic stem cell transplantation; MCC = Merkel cell carcinoma; MSI-H = microsatellite instability-high; NMIBC = non-muscle invasive bladder cancer; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal large B-cell lymphoma; RCC = renal cell carcinoma

# Advanced Merkel Cell Carcinoma (MCC)

INDICATIONS

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

Scroll below to review Selected Safety Information

Advanced Merkel Cell Carcinoma
KEYNOTE-017
KEYNOTE-991

## Select Safety Information

### 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 (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 with KEYTRUDA. Initiate treatment with KEYTRUDA in the monotherapy setting, monitor blood counts at baseline and periodically, 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. 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 Grade 5 (0.1%), Grade 4 (0.2%), Grade 3 (0.9%), and Grade 2 (2.2%). Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% (55/94) of patients who had available information.

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 3.1% of patients. Of the patients who developed pneumonitis, 74% resolved, 42% resolved after KEYTRUDA discontinued KEYTRUDA, and 71% had resolution.

Pneumonitis occurred in 7% (21/289) of adult patients with resected NSCLC who received KEYTRUDA as a single agent before and/or after treatment of NSCLC, including fatal (0.3%), 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 2% (6/289) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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 immune-mediated colitis. It is important to exclude infectious causes of diarrhea before initiating treatment with corticosteroids. Consider additional monitoring and antiviral therapy to treat infectious gastrointestinal infections.

Immune-mediated colitis occurred in 1.9% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.6%). Systemic corticosteroids were required in 83% (40/48) of patients with colitis who had available information. Colitis resolved in 42% (20/48) of patients. Fifty percent of patients who had permanent discontinuation of KEYTRUDA or 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 54% had colitis recurrence.

Colitis occurred in 3% (11/389) 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 2.3% (9/389) of patients. Of the patients who developed pneumonitis, 82% resolved, 42% resolved after KEYTRUDA discontinued KEYTRUDA, and 77% had resolution.

#### Immune-Mediated Hepatitis

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 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 79% (15/19) of patients with hepatitis who had available information. Hepatitis resolved in 37% (7/19) 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, 44% had recurrence of hepatitis.

#### 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 administer corticosteroids as clinically indicated. Refer to the axitinib Prescribing Information for dose modification guidelines. Grade 3 and 4 increases in ALT (20%) and increased aspartate aminotransferase (AST) (13%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients in renal cell carcinoma (RCC) clinical trials received systemic steroids. Liver enzyme elevations led to discontinuation of KEYTRUDA in 3.4% (5/145) of patients. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or as part with both (n=55), recurrence of ALT or AST Grade 3-4 was observed in 2 patient receiving KEYTRUDA, 8 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT or AST Grade 3-4 were rechallenged with KEYTRUDA in combination with axitinib.

#### 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. Administer insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.7%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients with adrenal insufficiency who had available information. 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 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 initiate 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 0.3% (8) of patients withheld.

Hypothyroidism occurred in 8% (216/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (5.8%). It led to permanent discontinuation of KEYTRUDA in 0.3% (9) and withholding in 1.4% (39) of patients. Hyperthyroidism occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 21 (27/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 21% had recurrence of hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with NSCLC (KEYNOTE-189) receiving KEYTRUDA in combination with chemotherapy (34%) compared to 1157 patients receiving chemotherapy alone (7%). The incidence of new or worsening hypothyroidism was higher in 1019 patients with NSCLC (KEYNOTE-407) receiving KEYTRUDA in combination with chemotherapy (31%) compared to 1008 patients receiving chemotherapy alone (5.8%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC occurring in 11% of patients receiving KEYTRUDA as a single agent and adjuvant treatment, including 0.2% Grade 4, 1.4% Grade 3, and 5% Grade 2 reactions. The incidence of new or worsening hypothyroidism was higher in 616 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%) and Grade 2 (5.8%).

##### 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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (2) 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 in patients receiving KEYTRUDA. Monitor patients for suspected severe dermatologic reactions. Administer at least trials in moderate noninfectious rashes. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 14% (398/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.9%), and Grade 2 (2.4%) reactions. Systemic corticosteroids were required in 40% (75/188) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (18) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 11% had recurrence of rash.

#### 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hypophysitis, myocarditis, hemolytic anemia (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, Ocular Uveitis, iritis and other ocular inflammatory toxicities can occur in association 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. Myocarditis, including fatal cases, has occurred in patients who received other PD-1/PD-L1 blockers. Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica. Endocrine: Hypoparathyroidism. Other (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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for transplantation and care after transplantation. Of 11 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 treatment before 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 occurred in 6% of patients. The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-054, KEYTRUDA was administered as an adjuvant treatment to 509 patients with melanoma. KEYTRUDA was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. The most common serious adverse reactions were diarrhea (2%) and pneumonitis (2%). In KEYNOTE-716, 490 patients with stage IB or IIA melanoma were administered as a single agent to patients with stage IB or IIC melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in KEYNOTE-054 with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. Adverse reactions leading to discontinuation of KEYTRUDA occurred in 11% of patients, including death due to unknown cause (0.4%), sepsis (0.3%), and immune-mediated adverse reactions (3.2%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (35%), rash (25%), diarrhea (24%), and decreased appetite (21%). Serious adverse reactions occurred in 42% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (7%), pulmonary embolism (4%), and pleural effusion (2.2%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 638 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and pulmonary embolism (2%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (3%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-407, KEYTRUDA in combination with chemotherapy was discontinued due to adverse reactions in 19% of 278 patients with squamous NSCLC; the most common adverse reactions (≥20%) were peripheral neuropathy (25%), fatigue (24%), and nausea (21%). Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions were pneumonia (7%), febrile neutropenia (6%), and pulmonary embolism (4%). Overall 49% of patients received KEYTRUDA as a single agent.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy as metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. Adverse reactions leading to discontinuation of KEYTRUDA occurred in 11% of patients, including death due to unknown cause (0.4%), sepsis (0.3%), and immune-mediated adverse reactions (3.2%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (35%), rash (25%), diarrhea (24%), and decreased appetite (21%). Serious adverse reactions occurred in 42% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (7%), pulmonary embolism (4%), and pleural effusion (2.2%).

In KEYNOTE-048, when KEYTRUDA was administered with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 18% of 281 patients with recurrent or metastatic HNSCC; the most common adverse reactions (≥20%) were fatigue (33%), nausea (23%), pneumonia (23%), pneumonitis (21%), and septic shock (21%). The most common adverse reactions (≥20%) were fatigue (59%), constipation (37%), nausea (36%), decreased appetite (33%), diarrhea (32%), rash (25%), and vomiting (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 11% of 152 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and pulmonary embolism (2%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (3%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with advanced urothelial carcinoma; adverse reactions leading to permanent discontinuation occurred in 4% of patients. The most common adverse reactions (≥20%) were fatigue (30%), nausea (25%), decreased appetite (23%), rash (21%), and pruritus (20%). Serious adverse reactions occurred in 47% of patients. The most common serious adverse reactions were urinary tract infection, pneumonia, and urosepsis. The most common adverse reaction (≥20%) was fatigue (30%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation was urinary tract infection (2.7%). Serious adverse reactions occurred in 19% of patients. The most common serious adverse reactions were urinary tract infection (2.7%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (29%), pruritus (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-177, when KEYTRUDA was administered as a single agent to patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC, KEYTRUDA was discontinued due to adverse reactions in 12% of patients included pneumonia (1.1%), diarrhea (1.1%), hemorrhage (2.3%), and vomiting (2.4%). Serious adverse reactions occurred in 41% of patients. The most common serious adverse reactions were intestinal obstruction (3.4%) and pneumonia (3.4%).

In KEYNOTE-177, when KEYTRUDA was administered as a single agent to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) adenocarcinoma who are 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 (≥1%) were pneumonitis (3%), acute kidney injury (2%), and pneumonia (1%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (30%), decreased appetite (24%), vomiting (21%), diarrhea (20%), abdominal pain (20%), and stomatitis (20%), and weight loss (20%).

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-868, when KEYTRUDA was administered with FOLFOX platinum plus external beam radiation therapy (EBRT) followed by brachytherapy (BT) to patients with PGCA 2004 Siege III-IVA cervical cancer, fatal adverse reactions occurred in 1.4% of 294 patients, including 1 case each (0.3%) of large intestinal perforation, sepsis, and pneumonitis. Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 23% of patients. The most common adverse reactions (≥20%) were fatigue (51%), nausea (47%), diarrhea (40%), alopecia (36%), vomiting (34%), decreased appetite (31%), peripheral neuropathy (30%), and constipation (29%). Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions were anemia (5%), urinary tract infection (3%), pyrexia (3%), pulmonary embolism (2%), sepsis (2%), and vomiting (2%).

In KEYNOTE-826, KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) with or without bevacizumab (n=307). In 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 radio-sensitizing agent. Fatal adverse reactions occurred in 4.6% of patients, including 2 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 disseminated intravascular coagulation, hemoperitoneum, pneumonitis, and pulmonary embolism. Adverse reactions resulted in permanent discontinuation of KEYTRUDA in combination with chemotherapy with or without bevacizumab; these 23% were febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury (3.3% each).

KEYTRUDA was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation (≥1%) was pneumonitis (1.3%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common adverse reactions (≥20%) were peripheral neuropathy (82%), alopecia (58%), fatigue (57%), nausea (46%), diarrhea (35%), decreased appetite (33%), vomiting (31%), constipation (29%), abdominal pain (27%), hypertension (24%), arthralgia (21%), cough (21%), hypertension and urinary tract infection (20% each), and rash (19%).

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. The most common serious adverse reactions were pneumonia (4.1%), urinary tract infection (3.1%), and pelvic infections (4.1% each). The most common adverse reactions (≥20%) were fatigue (43%), decreased appetite (23%), nausea (22%), and vomiting (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with chemotherapy (gemcitabine and cisplatin), KEYTRUDA was discontinued for adverse reactions in 15% of patients receiving placebo in combination with chemotherapy (n=777). Fatal adverse reactions occurred in 1.8% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 infection (0.4%) and pneumonitis (0.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions (≥20%) were nausea (61%), fatigue (59%), vomiting (39%), decreased appetite (36%), constipation (28%), diarrhea (27%), rash (25%), and abdominal pain (21%).

In KEYNOTE-091, when KEYTRUDA was administered as adjuvant monotherapy to patients with resected NSCLC, KEYTRUDA was discontinued for adverse reactions in 14% of 595 patients. The most common adverse reactions (≥1%) were pneumonitis (1.3%), diarrhea (1.2%), and colitis (1%). Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (2%), pneumonitis (2%), and pulmonary embolism (1.5%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (26%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued for adverse reactions in 18% of 281 patients with recurrent or metastatic HNSCC; the most common adverse reactions (≥20%) were fatigue (33%), nausea (23%), pneumonia (23%), pneumonitis (21%), and septic shock (21%). The most common adverse reactions (≥20%) were fatigue (59%), constipation (37%), nausea (36%), decreased appetite (33%), diarrhea (32%), rash (25%), and vomiting (21%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 11% of 152 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (2%), and pulmonary embolism (2%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (3%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with advanced urothelial carcinoma; adverse reactions leading to permanent discontinuation occurred in 4% of patients. The most common adverse reactions (≥20%) were fatigue (30%), nausea (25%), decreased appetite (23%), rash (21%), and pruritus (20%). Serious adverse reactions occurred in 47% of patients. The most common serious adverse reactions were urinary tract infection, pneumonia, and urosepsis. The most common adverse reaction (≥20%) was fatigue (30%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation was urinary tract infection (2.7%). Serious adverse reactions occurred in 19% of patients. The most common serious adverse reactions were urinary tract infection (2.7%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions (≥20%) were fatigue (29%), pruritus (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-177, when KEYTRUDA was administered as a single agent to patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) CRC, KEYTRUDA was discontinued due to adverse reactions in 12% of patients included pneumonia (1.1%), diarrhea (1.1%), hemorrhage (2.3%), and vomiting (2.4%). Serious adverse reactions occurred in 41% of patients. The most common serious adverse reactions were intestinal obstruction (3.4%) and pneumonia (3.4%).

In KEYNOTE-177, when KEYTRUDA was administered as a single agent to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) adenocarcinoma who are 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 (≥1%) were pneumonitis (3%), acute kidney injury (2%), and pneumonia (1%). The most common adverse reactions (≥20%) were fatigue (36%), nausea (30%), decreased appetite (24%), vomiting (21%), diarrhea (20%), abdominal pain (20%), and stomatitis (20%), and weight loss (20%).

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-868, when KEYTRUDA was administered with FOLFOX platinum plus external beam radiation therapy (EBRT) followed by brachytherapy (BT) to patients with PGCA 2004 Siege III-IVA cervical cancer, fatal adverse reactions occurred in 1.4% of 294 patients, including 1 case each (0.3%) of large intestinal perforation, sepsis, and pneumonitis. Adverse reactions resulted in permanent discontinuation of KEYTRUDA in 23% of patients. The most common adverse reactions (≥20%) were fatigue (51%), nausea (47%), diarrhea (40%), alopecia (36%), vomiting (34%), decreased appetite (31%), peripheral neuropathy (30%), and constipation (29%). Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions were anemia (5%), urinary tract infection (3%), pyrexia (3%), pulmonary embolism (2%), sepsis (2%), and vomiting (2%).

In KEYNOTE-826, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) with or without bevacizumab (n=307). In 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 radio-sensitizing agent. Fatal adverse reactions occurred in 4.6% of patients, including 2 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 disseminated intravascular coagulation, hemoperitoneum, pneumonitis, and pulmonary embolism. Adverse reactions resulted in permanent discontinuation of KEYTRUDA in combination with chemotherapy with or without bevacizumab; these 23% were febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury (3.3% each).

KEYTRUDA was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation (≥1%) was pneumonitis (1.3%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common adverse reactions (≥20%) were peripheral neuropathy (82%), alopecia (58%), fatigue (57%), nausea (46%), diarrhea (35%), decreased appetite (33%), vomiting (31%), constipation (29%), abdominal pain (27%), hypertension (24%), arthralgia (21%), cough (21%), hypertension and urinary tract infection (20% each), and rash (19%).

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. The most common serious adverse reactions were pneumonia (4.1%), urinary tract infection (3.1%), and pelvic infections (4.1% each). The most common adverse reactions (≥20%) were fatigue (43%), decreased appetite (23%), nausea (22%), and vomiting (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients receiving placebo in combination with chemotherapy (n=777). Fatal adverse reactions occurred in 1.8% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 infection (0.4%) and pneumonitis (0.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions (≥20%) were nausea (61%), fatigue (59%), vomiting (39%), decreased appetite (36%), constipation (28%), diarrhea (27%), rash (25%), and abdominal pain (21%).

In KEYNOTE-091, when KEYTRUDA was administered as adjuvant monotherapy to patients with resected NSCLC, KEYTRUDA was discontinued for adverse reactions in 14% of 595 patients. The most common adverse reactions (≥1%) were pneumonitis (1.3%), diarrhea (1.2%), and colitis (1%). Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. The most common serious adverse reactions were pneumonia (2%), pneumonitis (2%), and pulmonary embolism (1.5%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (26%), and rash (20%).

#### Pediatric Use

In KEYNOTE-051, 113 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 years to 17 years) received KEYTRUDA 2 mg/kg every 3 weeks. The most common adverse reactions (≥20%) were pyrexia (37%), fatigue (29%), and vomiting (20%).

Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (33% vs 19%), leukopenia (16% vs 3%), hypothyroidism (15% vs 2%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (11%), decreased lymphocyte count (5%), and decreased white blood cell count (11%).

#### 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 years and older, and 26% (n=148) 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.

**Before prescribing KEYTRUDA, please read the accompanying** Prescribing Information. The Medication Guide also is available.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = brachytherapy; BTC = biliary tract cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; CRT = chemoradiotherapy; EBRT = cadenza squamous cell carcinoma; dMMR = mismatch repair deficient; EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; GEJ = gastroesophageal junction; HNSCC = head and neck squamous cell carcinoma; HSCT = hematopoietic stem cell transplantation; IU/L = international units per liter; MSI-H = microsatellite instability-high; NMIBC = non-muscle invasive bladder cancer; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal large B-cell lymphoma; TMB = tumor mutational burden.

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.
US-KEYT-250727-172

MERCK

# Adjuvant Treatment of RCC or Advanced Renal Cell Carcinoma (RCC)

INDICATIONS

**Adjuvant Treatment for Renal Cell Carcinoma**

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

**Advanced Renal Cell Carcinoma**

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

Scroll below to review Selected Safety Information

## Select Chapter Types

Adjuvant Treatment for Renal Cell Carcinoma (RCC)
Advanced Renal Cell Carcinoma (RCC)
KEYNOTE-426

## Selected Safety Information

### 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 blockers (PD-1, PD-L1 and PD-L2) that block the PD-1/PD-L1 signaling 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 with KEYTRUDA. 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% (38/1128) of patients receiving KEYTRUDA, including Grade 3 (0.5%), Grade 2 (2.1%), and Grade 4 (0.1%) adverse reactions. Pneumonitis resulted in corticosteroids were required in 67% (19/38) of patients who had pneumonitis. Of patients who received corticosteroids for pneumonitis, 74% (14/19) had resolution. Pneumonitis occurred in 1.3% (38) and withholding in 0.9% (28) of patients, and resulted in 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. Pneumonitis occurred in 8% (3/38) of patients who received KEYTRUDA in combination with chemotherapy.

Pneumonitis occurred in 8% (21/389) 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 2.6% (10) of patients, and withholding of KEYTRUDA in 2.1% (8) of patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (10/144) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (1.2%), 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 2% (3/144) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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. It is important to exclude infectious etiologies. Immune-mediated colitis occurred in 1.6% (18/1128) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Colitis resulted in corticosteroids were required in 89% (16/18) of patients who had colitis. Of patients who received corticosteroids for colitis, 63% (10/16) had resolution. Colitis occurred in 1.3% (18) and withholding in 0.8% (11) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Colitis occurred in 3% (4/144) of patients who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC.

#### Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (9/1299) of patients receiving KEYTRUDA, including Grade 4 (0.2%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Hepatitis resulted in corticosteroids were required in 100% (9/9) of patients who had hepatitis. Of patients who received corticosteroids for hepatitis, 67% (6/9) had resolution. Hepatitis occurred in 0.8% (10) and withholding in 0.5% (6) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hepatitis occurred in 0.7% (1/144) of patients who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC.

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 administer corticosteroids as clinically indicated. If liver enzymes increase to Grade 3 (AST or ALT greater than 5 to 20 times ULN or total bilirubin greater than 3 to 10 times ULN) or Grade 4 (AST or ALT greater than 20 times ULN or total bilirubin greater than 10 times ULN), permanently discontinue KEYTRUDA and axitinib. Hepatic toxicity (20%) and increased aspartate aminotransferase (AST) (3%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids for a median duration of 1 month (range: 1 day to 5.6 months). Of these patients, 83% had resolution to Grade 1 or baseline. Among the 52 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=15), recurrence of ALT or ALT/AST rises was observed in 2 patients receiving KEYTRUDA, 9 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT or ALT/AST rises ≥ ULN subsequently recovered from the event.

#### Immune-Mediated Endocrinopathies

*Adrenal Insufficiency*

Adrenal insufficiency 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 (0.5%), and Grade 2 (0.2%) reactions. Adrenal insufficiency occurred in 0.8% (10) of patients who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC.

*Hypophysitis*

Hypophysitis can cause inflammation and hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.5% (14/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%) reactions. Hypophysitis occurred in 1.4% (36/2555) of patients who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC, RCC, or urothelial carcinoma (UC). Hypophysitis led to withholding of KEYTRUDA in 0.2% (5) and discontinuation in 0.2% (4) 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 initiation of 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 0.2% (4) of patients withheld KEYTRUDA.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.9% (25) of patients. Hyperthyroidism led to withholding of KEYTRUDA in 0.4% (1) of patients who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC.

Hypothyroidism occurred in 8% (217/2799) of patients receiving KEYTRUDA, including Grade 3 (0.6%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 3.1% (79) of patients who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC. Hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with MSKCC prognostic risk group poor (16%) compared to 1114 patients with MSKCC prognostic risk group intermediate (8%) or 300 patients with MSKCC prognostic risk group favorable (5%).

Type 1 Diabetes Mellitus (DM), New-Onset DM, 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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (2) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement, of those, 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 in patients receiving PD-1/PD-L1 blocking antibodies. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.8% (51/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (1.2%) reactions. Dermatologic reactions led to withholding in 40% (75/188) 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 those, none had recurrence. Rash resolved in 50% of the 4 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: Cerebral hypophysitis, myocarditis, pericarditis, vasculitis, pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, uveítis, iritis and other inflammatory ocular disorders, retinal vascular occlusion, Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, Ocular Myasthenia, myositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis, polymyalgia rheumatica, and systemic inflammatory response syndrome. Hemophagocytic lymphohistiocytosis (HLH), secondary to immune dysregulation, has occurred in patients treated with KEYTRUDA. Histiocytic necrosis of lymphoid tissues (Kikuchi lymphadenitis) can occur. Sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, and hemolytic anemia have occurred.

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Monitor patients closely for these complications. Follow established guidelines for the management of these complications. Of 11 patients 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 treatment 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 occurred in 6% of patients. The most common adverse reactions (≥20% with KEYTRUDA and less than ipilimumab) were fatigue (26%), cough (20%), and pruritus (20%). The most common adverse reactions (≥20% with KEYTRUDA and were higher than ipilimumab) were fatigue (26%), cough (20%), nausea (20%), and pruritus (20%). Serious adverse reactions occurred in 41% of patients; the most common (≥2%) were pneumonitis (3.4%), colitis (2.2%), and diarrhea (2%). Serious adverse reactions occurred in 41% of patients receiving KEYTRUDA; the most common (≥2%) were pneumonitis (3.4%), colitis (2.2%), and diarrhea (2%). Serious adverse reactions occurred in 36% of patients receiving ipilimumab; the most common (≥2%) were diarrhea (3%), colitis (2.9%), and pneumonitis (2.2%). Fatal adverse reactions occurred in 1.5% of patients, including death due to unknown cause (0.4%), sepsis (0.2%), and immune-mediated pneumonitis, myocarditis, and myocardial infarction (0.2% each). Fatal adverse reactions occurred in 2.5% of patients receiving KEYTRUDA; the most common was sepsis (0.2%). Fatal adverse reactions occurred in 2.3% of patients receiving ipilimumab; the most common was sepsis (0.7%). The most frequent (≥5%) adverse reactions that led to permanent discontinuation of KEYTRUDA were diarrhea (5%), colitis (5%), and pneumonitis (5%). The most frequent (≥5%) adverse reactions that led to withholding of KEYTRUDA were diarrhea (8%), colitis (6%), pneumonitis (5%), and pyrexia (5%).

In KEYNOTE-048, KEYTRUDA was discontinued due to adverse reactions in 9% of patients with cHL. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA; these cHL were pneumonia, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions that began during treatment: 2 from complications of allogeneic HSCT and 1 from sepsis. The most common adverse reactions (≥20%) were fatigue (33%), musculoskeletal pain (32%), upper respiratory tract infection (29%), diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of 296 patients with advanced NSCLC. Serious adverse reactions occurred in 16% of patients receiving KEYTRUDA; these cHL were pneumonia, pneumonia, dyspnea, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions that began during treatment: 2 from complications of allogeneic HSCT and 1 from sepsis. The most common adverse reactions (≥20%) were fatigue (33%), musculoskeletal pain (32%), upper respiratory tract infection (29%), diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 16% of 509 patients with stage III melanoma who received KEYTRUDA as a single agent. Serious adverse reactions occurred in 16% of patients; these included pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Fatal adverse reactions occurred in 0.4% of patients including death due to unknown cause (0.4%), sepsis (0.2%), and immune-mediated pneumonitis (0.2%). The most common adverse reactions (≥20%) were fatigue (40%), diarrhea (28%), rash (25%), pruritus (22%), and nausea (21%). The most frequent (≥5%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (5%), colitis (5%), and hepatitis (5%). The most frequent (≥5%) adverse reactions that led to withholding of KEYTRUDA were diarrhea (8%), colitis (6%), pneumonitis (5%), and pyrexia (5%).

In KEYNOTE-189, KEYTRUDA was discontinued due to adverse reactions in 14% of 405 patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism, which was discontinued in 0.2%. Serious adverse reactions occurred in 37% of patients receiving KEYTRUDA; these included pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.2%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-407, KEYTRUDA was discontinued due to adverse reactions in 15% of 278 patients with squamous NSCLC. Serious adverse reactions occurred in 48% of patients; these included pneumonia (11%), febrile neutropenia (4.7%), and sepsis (3.6%). The most common adverse reactions (≥20%) were fatigue (51%), alopecia (31%), diarrhea (31%), nausea (29%), decreased appetite (25%), rash (24%), constipation (21%), and cough (20%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC. The most common were pneumonitis (3.1%), pulmonary embolism (2.4%), and pneumonia (2.2%). The most common adverse reaction (≥20%) was fatigue (21%).

In KEYNOTE-024, KEYTRUDA was discontinued due to adverse reactions in 9% of 154 patients with advanced NSCLC. The most common were pneumonitis (3.9%), pulmonary embolism (2.6%), and pleural effusion (2.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-010, KEYTRUDA was discontinued due to adverse reactions in 9% of 518 patients with advanced NSCLC. The most common were pneumonitis (2.7%), pneumonia (2.3%), and sepsis (2.1%). The most common adverse reaction (≥20%) was fatigue (26%).

In KEYNOTE-061, KEYTRUDA was discontinued due to adverse reactions in 19% of 592 patients with HNSCC. Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia, dyspnea, and cellulitis. The most common adverse reactions (≥20%) were fatigue (45%), musculoskeletal pain (30%), nausea (29%), decreased appetite (28%), rash (25%), diarrhea (23%), and constipation (20%).

In KEYNOTE-048, KEYTRUDA was discontinued due to adverse reactions in 17% of 882 patients with HNSCC. Serious adverse reactions occurred in 49% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were pneumonia (6%), dyspnea (3.2%), pneumonitis (2.9%), and sepsis (2.6%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and nausea (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (32%), musculoskeletal pain (30%), nausea (26%), pruritus (22%), rash (21%), decreased appetite (21%), and diarrhea (20%). The most frequent (≥5%) adverse reactions that led to permanent discontinuation of KEYTRUDA were pneumonitis (5%), urinary tract infection, pneumonia, and pneumonitis. The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (36%), musculoskeletal pain (32%), nausea (28%), pruritus (25%), rash (23%), and decreased appetite (21%).

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 urinary tract infection (2.7%). The most common adverse reactions (≥20%) were fatigue (36%), urinary tract infection (27%), pruritus (24%), musculoskeletal pain (21%), rash (21%), and urinary tract infection (21%). The most common adverse reactions (≥20%) were fatigue (35%), pruritus (24%), rash and urinary tract infection (21% each).

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-859, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) and bevacizumab (n=301), 16% of patients discontinued KEYTRUDA due to adverse reactions. Adverse reactions in ≥2% of patients included pneumonia (4.1%), diarrhea (3.1%), hemorrhage (2.3%), and vomiting (2.4%). Adverse reactions occurred in 61% of patients who received KEYTRUDA, paclitaxel, carboplatin, and bevacizumab. KEYTRUDA was discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (2.3%), pneumonia (1.7%), and acute kidney injury (1.3%). The most common adverse reactions (≥20%) were alopecia (51%), fatigue (50%), peripheral neuropathy (41%), nausea (40%), fatigue (50%), pruritus (40%), diarrhea (38%), alopecia (35%), weight loss (33%), decreased appetite (32%), constipation (29%), rash (28%), vomiting (24%), and stomatitis (23%).

In KEYNOTE-868, when KEYTRUDA was administered with FOLFOX (platinum plus equivalent folate derivative) followed by bevacizumab (n=338), 14% of patients discontinued KEYTRUDA due to adverse reactions. Adverse reactions occurred in 74% of patients; these ≥2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and sepsis. The most common adverse reactions (≥20%) were fatigue (50%), musculoskeletal pain (40%), nausea (39%), peripheral neuropathy (38%), diarrhea (37%), decreased appetite (31%), and vomiting (25%).

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 reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (2.3%), urinary tract infection (1.5%), and pneumonia (1.1%). The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (36%), musculoskeletal pain (32%), nausea (28%), pruritus (25%), rash (23%), and decreased appetite (21%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with cisplatin-ineligible urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (26%), musculoskeletal pain (22%), pruritus (21%), and urinary tract infection (21%). The most common adverse reactions (≥20%) were fatigue (25%), pruritus (24%), rash (21%), and urinary tract infection (21%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 233 patients with MSI-H or dMMR cancer. The most common adverse reactions (≥20%) were fatigue (32%), diarrhea (27%), pruritus (24%), nausea (23%), abdominal pain (22%), pyrexia (21%), vomiting (21%), and decreased appetite (20%).

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. The most common adverse reactions (≥20%) were fatigue (34%), diarrhea (29%), musculoskeletal pain (28%), and infections (24%). The most common adverse reactions (≥20%) were fatigue (40%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and nausea (21%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. Grade 3-5 adverse reactions occurred in 68% of patients; the most frequent were neutropenia, anemia, and vomiting. Serious adverse reactions occurred in 54% of patients; the most common were pneumonia (3%), urinary tract infection (2.2%), and anemia (1.9%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions (≥20%) were nausea, fatigue, decreased appetite, vomiting, constipation, rash, diarrhea, peripheral neuropathy, and weight loss. The most common adverse reactions (≥20%) were nausea (61%), fatigue (56%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-775 and KEYNOTE-981, adverse reactions occurring in patients with MSI-H endometrial cancer were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-775, when KEYTRUDA was administered with lenvatinib (n=411), KEYTRUDA was discontinued for adverse reactions in 40% of patients, the most frequent (≥5%) were hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (3.2%), dehydration (3%), and pneumonitis (2.9%). Serious adverse reactions occurred in 67% of patients; the most frequent (≥2%) were hepatotoxicity (9%), diarrhea (4.4%), and acute kidney injury (3.2%). The most common were hepatotoxicity (25%), diarrhea/colitis (19%), acute kidney injury (9.6%), and cerebrovascular accident (2.2%). The most common adverse reactions (≥30%) were fatigue (51%), urinary tract infection (37%), vomiting (36%), diarrhea (35%), stomatitis (34%), musculoskeletal pain (34%), decreased appetite (34%), hypothyroidism (28%), palmar-plantar erythrodysesthesia (28%), proteinuria (25%), rash (25%), cough (23%), and constipation (21%).

In KEYNOTE-868, when KEYTRUDA was administered with FOLFOX (platinum plus equivalent folate derivative) followed by bevacizumab (n=301), 20% of patients discontinued KEYTRUDA due to adverse reactions. Adverse reactions occurred in 82% of patients; these ≥2% were urinary tract infection, pneumonia, acute kidney injury, pneumonia, and sepsis. The most common adverse reactions (≥20%) were fatigue (54%), musculoskeletal pain (47%), nausea (46%), peripheral neuropathy (45%), diarrhea (43%), decreased appetite (36%), vomiting (35%), decreased weight (29%), abdominal pain (26%), palmar-plantar erythrodysesthesia syndrome (23%), 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 proximal to GEJ) adenocarcinoma (n=274), KEYTRUDA was discontinued for adverse reactions in 18% of patients. Serious adverse reactions occurred in 70% of patients; the most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonia, sepsis, acute kidney injury, and pneumonitis (1% each). The most common adverse reactions (≥20%) were nausea (59%), fatigue (57%), vomiting (37%), stomatitis (34%), constipation (30%), diarrhea (26%), decreased appetite (25%), abdominal pain (24%), palmar-plantar erythrodysesthesia syndrome (21%), and weight loss (20%).

In KEYNOTE-590, when KEYTRUDA was administered with cisplatin and fluorouracil to patients with esophageal or GEJ adenocarcinoma (n=373), KEYTRUDA was discontinued for adverse reactions in 16% of patients. Serious adverse reactions occurred in 58% of patients; the most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonia, sepsis, and pneumonitis (1% each). The most common adverse reactions (≥20%) were nausea (58%), fatigue (56%), vomiting (36%), stomatitis (33%), constipation (29%), diarrhea (26%), decreased appetite (25%), abdominal pain (24%), palmar-plantar erythrodysesthesia syndrome (21%), and weight loss (20%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of patients. Grade 3-5 adverse reactions occurred in 68% of patients; the most frequent were neutropenia, anemia, and vomiting. Serious adverse reactions occurred in 54% of patients; the most common were pneumonia (3%), urinary tract infection (2.2%), and anemia (1.9%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions (≥20%) were nausea, fatigue, decreased appetite, vomiting, constipation, rash, diarrhea, peripheral neuropathy, and weight loss. The most common adverse reactions (≥20%) were nausea (61%), fatigue (56%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

In KEYNOTE-091, KEYTRUDA was discontinued for adverse reactions in 14% of 340 patients with resected NSCLC who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC. Serious adverse reactions occurred in 20% of patients; these included pneumonia (2.9%), pneumonitis (2.6%), and sepsis (2.4%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and nausea (20%).

In KEYNOTE-091, KEYTRUDA was discontinued due to adverse reactions in 13% of 1177 patients with resected NSCLC who received KEYTRUDA as a single agent as adjuvant treatment of NSCLC. Serious adverse reactions occurred in 19% of patients; these included pneumonia (2.5%), pneumonitis (2.1%), and sepsis (1.9

# Advanced Endometrial Carcinoma

## INDICATIONS

**Primary Advancement or Recurrent 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.

**Advanced MSI-H/dMMR Endometrial Carcinoma**

KEYTRUDA, as a single agent, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is microsatellite instability-high (MSI-H) or mismatch repair deficient (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.

**Scroll below to review Selected Safety Information**

## Selected Safety Information

### 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 blockers (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.

Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Monitor patients for signs and symptoms that may be consistent with any immune-mediated adverse reactions, and evaluate clinical chemistries including liver enzyme tests, creatinine, and thyroid function at baseline and periodically during treatment. Initiate medical management promptly to control symptoms and minimize complications. Depending on the severity of the immune-mediated adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. If hormone-replacement therapy is sufficient to control the immune-mediated adverse reaction, KEYTRUDA may be resumed. Based on the severity of the immune-mediated adverse reaction, withhold KEYTRUDA and administer high-dose corticosteroids for a minimum duration of 10 days (range 1 day to 3 months). Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue 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% (38/1128) of patients receiving KEYTRUDA, including Grade 5 (0.1%), Grade 4 (0.2%), Grade 3 (1.2%), and Grade 2 (2%). Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 1.3% (35) and improved to Grade 1 or 2 in 1.9% (21) of patients with 0.5% (6) having recurrence.

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 3.1% (12) of patients. Of the pneumonitis events, 2.4% (nine) resolved, 4.2% (sixteen) improved to Grade 1 or 2, and 0.5% (two) discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 4.1% (16/389) 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 2.6% (10) 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 immune-mediated colitis. It is important to exclude infectious etiologies of diarrhea/colitis. Immune-mediated colitis occurred in 1.6% (18/1128) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 89% (16/18) of patients. Colitis resolved in 50% (9) of patients who received corticosteroids. Of patients receiving KEYTRUDA, 0.4% (5) discontinued KEYTRUDA for colitis.

Colitis occurred in 3% (11/389) 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 1.5% (6) of patients. Of the pneumonitis events, 2.4% (nine) resolved, 4.2% (sixteen) improved to Grade 1 or 2, and 0.5% (two) discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 4.1% (16/389) 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 2.6% (10) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (7/1128) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 71% (5/7) of patients. Hepatitis resolved in 71% (5) of patients who received corticosteroids. Of patients receiving KEYTRUDA, 0.4% (5) discontinued KEYTRUDA for hepatitis.

Hepatitis occurred in 4% (14/389) of patients with cHL receiving KEYTRUDA as a single agent, including Grades 3-4 in 2.6% of patients. All patients who were hepatitis B surface antigen positive and/or hepatitis C virus antibody positive were enrolled in clinical trials.

#### KEYTRUDA With mFOLFOX6

KEYTRUDA in combination with mFOLFOX6 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 mFOLFOX6 administration, and consider corticosteroids as needed. After the recovery of liver enzymes to baseline, resume KEYTRUDA and mFOLFOX6 at the discretion of the physician. Grade 3 (2%) and increased aspartate aminotransferase (AST) (3%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids. Liver enzymes returned to baseline or Grade 1 in 75% of patients. Of patients who received KEYTRUDA, 1.4% discontinued for hepatitis. Among the 52 patients who were rechallenged with either KEYTRUDA (n=3) or avelumab (n=34) administered as a single agent or with both (n=15), recurrence of AST or ALT Grade 3-4 was observed in 1 patient receiving KEYTRUDA, 16 patients receiving avelumab, and 24 patients receiving both. All patients with a recurrence of AST or ALT LLN-sufficient recovered to the event level.

#### 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 (0.4%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Of patients receiving KEYTRUDA, 0.1% (3) discontinued KEYTRUDA for adrenal insufficiency. All patients who were adrenal insufficiency resolved.

*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 0.5% (14/2799) of patients receiving KEYTRUDA, including Grade 3 (0.2%) 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% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*Hypothyroidism*

KEYTRUDA can cause immune-mediated hypothyroidism. Hypothyroidism can present after a variable period of time. Manage hypothyroidism with thyroid hormone replacement. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypothyroidism occurred in 8% (221/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (3.3%) reactions. Hypothyroidism led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*Hyperthyroidism*

KEYTRUDA can cause immune-mediated hyperthyroidism. Hyperthyroidism can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hyperthyroidism can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hyperthyroidism occurred in 3.6% (101/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (2.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients, of these, the majority remained on systemic corticosteroids. Hyperthyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (9) 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 0.5% (14/2799) of patients receiving KEYTRUDA, including Grade 3 (0.2%) 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% (1) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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% (8/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 88% (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 in patients receiving KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (75/189) of patients. These reactions led to permanent discontinuation in 0.5% (2) and withholding of KEYTRUDA in 0.6% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, none had recurrence. Rash resolved in 50% of the 75 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis sicca, myositis, polymyalgia rheumatica, vasculitis including giant cell arteritis, autoimmune hemolytic anemia, thrombocytopenia, aplastic anemia, hemolytic uremic syndrome, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection (including corneal graft).

#### 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 GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Patients who received anti-PD-1/PD-L1 treatments before and after allogeneic HSCT were observed with GVHD-related events in 7 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 of KEYTRUDA were pneumonitis (1.4%) and colitis (1.1%). Fatal adverse reactions occurred in 1.1% of patients, including death due to pneumonitis (0.4%) and myocarditis (0.2%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-048, KEYTRUDA was administered as a single agent and was discontinued due to adverse reactions in 14% of 882 patients who permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 67% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 3.1% of patients, including death due to pneumonitis (0.8%) and sepsis (0.4%). In KEYNOTE-048, KEYTRUDA was administered as a single agent to patients with stage III or IIIC melanoma; adverse reactions occurring in patients with stage III or IIIC melanoma were similar to those occurring in KEYNOTE-006 with stage IV melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. In KEYNOTE-799, when KEYTRUDA was administered in combination with platinum chemotherapy and paclitaxel following surgery, KEYTRUDA was discontinued due to adverse reactions in 26% of 784 patients who received KEYTRUDA, platinum chemotherapy, and paclitaxel. 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 20% of 278 patients who received KEYTRUDA, carboplatin, and paclitaxel or paclitaxel protein-bound. In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy, the most frequent adverse reactions (≥20%) were fatigue (56%), nausea (40%), anemia (39%), rash (25%), diarrhea (25%), vomiting (24%), decreased appetite (23%), and constipation (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 19% of 101 patients with advanced NSCLC; the most common were pneumonitis (3%), pulmonary embolism (2.4%), and pneumonia (2.4%). The most common adverse reactions (≥20%) were fatigue (51%), alopecia (36%), nausea (31%), peripheral neuropathy (31%), pneumonitis (29%), diarrhea (28%), decreased appetite (25%), rash (24%), and constipation (20%).

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3.8%), pneumonia (3.3%), and pulmonary embolism (2.4%). The most common adverse reactions (≥20%) were fatigue (35%), constipation (23%), and nausea (20%).

In KEYNOTE-048, when KEYTRUDA was administered with chemotherapy as first-line treatment for patients with metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 15% of 192 patients with HNSCC. Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonia (4%). The most common adverse reactions (≥20%) were fatigue, decreased appetite, and respiratory failure. The most common adverse reaction (≥20%) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were similar to those occurring in patients with NSCLC receiving KEYTRUDA with chemotherapy. In KEYNOTE-189, the most frequent adverse reactions of facial edema and new or worsening hypothyroidism.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy as first-line treatment for patients with metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 14% of 405 patients who received KEYTRUDA, pemetrexed, and platinum chemotherapy. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to any adverse reaction occurred in 31% of patients. The most frequent (≥3%) adverse reaction leading to permanent discontinuation was pneumonitis (3.2%). The most frequent adverse reactions (≥20%) were nausea (56%), fatigue (55%), constipation (31%), rash (29%), decreased appetite (26%), vomiting (24%), and stomatitis (23%).

In KEYNOTE-671, when KEYTRUDA was administered with platinum-containing chemotherapy as neoadjuvant treatment and continued as single-agent adjuvant treatment after surgery, KEYTRUDA was discontinued due to adverse reactions in 13% of 397 patients who received KEYTRUDA. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most common serious adverse reactions (≥2%) were pneumonia (3%), urinary tract infection (2.5%), and pyrexia (2%). The most common adverse reactions (≥20%) were fatigue (59%), nausea (57%), anemia (34%), alopecia (31%), vomiting (28%), constipation (25%), diarrhea (24%), and peripheral neuropathy (23%).

In KEYNOTE-522, when KEYTRUDA was administered with platinum and fluorouracil-based chemotherapy as neoadjuvant treatment and continued as single-agent adjuvant treatment after surgery, KEYTRUDA was discontinued due to adverse reactions in 26% of 390 patients who received KEYTRUDA. Serious adverse reactions occurred in 41% of patients. The most common serious adverse reactions (≥2%) were pneumonia (3%), urinary tract infection (2.6%), and pyrexia (2%). The most common adverse reactions (≥20%) were nausea (76%), fatigue (59%), alopecia (49%), anemia (41%), vomiting (36%), diarrhea (34%), constipation (29%), decreased appetite (28%), peripheral neuropathy (27%), rash (25%), and palmar-plantar erythrodysesthesia syndrome (21%).

In KEYNOTE-775, when KEYTRUDA was administered with lenvatinib and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) adenocarcinoma 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 (≥1%) were pneumonitis, colitis, and pneumonia (1%). The most common adverse reactions (≥20%) were fatigue (56%), diarrhea (52%), decreased appetite (44%), hypertension (40%), stomatitis (27%), and vomiting (24%).

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

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to 148 patients plus pelvic external beam radiotherapy (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, sepsis, and pneumonitis. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 18% of patients. The most common adverse reactions (≥20%) were fatigue (49%), musculoskeletal pain (30%), diarrhea (28%), nausea (27%), and pruritus (21%).

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 reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (1.1%), pneumonia (1.1%), and urinary tract infection (1.1%). The most common adverse reactions (≥20%) in patients who received KEYTRUDA were fatigue (41%), musculoskeletal pain (32%), nausea (28%), pruritus (22%), rash (21%), decreased appetite (21%), and constipation (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 urinary tract infection (1.4%). The most common adverse reactions (≥20%) were fatigue (47%), musculoskeletal pain (32%), pruritus (24%), urinary tract infection (21%), and decreased appetite (20%).

In KEYNOTE-158, 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) adenocarcinoma who were not candidates for surgical resection or definitive chemoradiation, KEYTRUDA was discontinued due to adverse reactions in 16% of 370 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis, colitis, and pneumonia (1%). The most common adverse reactions (≥20%) were fatigue (56%), nausea (52%), decreased appetite (44%), constipation (40%), vomiting (36%), anemia (34%), diarrhea (33%), and weight loss (33%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with metastatic or locally advanced cervical cancer, KEYTRUDA was discontinued due to adverse reactions in 14% of 98 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (2%), diarrhea (1%), and acute kidney injury (1%). The most common adverse reactions (≥20%) were fatigue (39%), musculoskeletal pain (29%), diarrhea (22%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with metastatic or locally advanced cervical cancer, KEYTRUDA was discontinued due to adverse reactions in 14% of 94 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (2%), diarrhea (1%), acute kidney injury (1%), and cerebrovascular accident (1%). The most common adverse reactions (≥20%) were fatigue (39%), musculoskeletal pain (29%), diarrhea (22%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic MSI-H cancer, KEYTRUDA was discontinued due to adverse reactions in 11% of 233 patients. The most common adverse reactions resulting in permanent discontinuation (≥1%) were pneumonitis (1.3%), acute kidney injury (1.3%), and pneumonia (1.3%). The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (32%), diarrhea (22%), pruritus (22%), nausea (21%), and cough (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic MSI-H noncolorectal cancer, KEYTRUDA was discontinued due to adverse reactions in 16% of 61 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were pneumonitis (3.3%), pneumonia (3.3%), and acute kidney injury (3.3%). The most common adverse reactions (≥20%) were fatigue (43%), musculoskeletal pain (33%), diarrhea (23%), and pruritus (23%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with PMBCL. Serious adverse reactions occurred in 26% of patients with PMBCL receiving KEYTRUDA. The most common serious adverse reactions (≥2%) were pneumonia (4%), pyrexia (2%), and pneumonitis (2%). Fatal adverse reactions occurred in 2% of patients, including death due to unknown cause (0.8%), sepsis (0.8%), and immune-mediated myocarditis (0.8%). The most common adverse reactions (≥20%) were fatigue (51%), musculoskeletal pain (32%), pyrexia (28%), diarrhea (26%), and rash (23%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic gastric cancer, KEYTRUDA was discontinued due to adverse reactions in 11% of 107 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were fatigue (2.8%), pneumonitis (2.8%), and acute kidney injury (1.9%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (21%), and nausea (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic biliary tract cancer, including cancer of the gallbladder and hepatobiliary junction, KEYTRUDA was discontinued due to adverse reactions in 11% of 104 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (2.9%), hepatic failure (1.9%), and pneumonia (1.9%). The most common adverse reactions (≥20%) were fatigue (35%), musculoskeletal pain (21%), abdominal pain (20%), decreased appetite (20%), and nausea (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic anal cancer, KEYTRUDA was discontinued due to adverse reactions in 11% of 94 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (2.1%), pneumonia (2.1%), and hepatic failure (2.1%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (29%), musculoskeletal pain (29%), decreased appetite (28%), nausea (26%), diarrhea (24%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic cervical cancer, KEYTRUDA was discontinued due to adverse reactions in 14% of 98 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (2%), diarrhea (1%), acute kidney injury (1%), and cerebrovascular accident (1%). The most common adverse reactions (≥20%) were fatigue (39%), musculoskeletal pain (29%), diarrhea (22%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic vaginal or vulvar cancer, KEYTRUDA was discontinued due to adverse reactions in 14% of 51 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (2%), pneumonia (2%), and sepsis (2%). Serious adverse reactions occurred in 35% of patients receiving KEYTRUDA. The most common serious adverse reactions (≥2%) were pneumonia (4%), urinary tract infection (2%), and sepsis (2%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (27%), musculoskeletal pain (24%), decreased appetite (24%), nausea (22%), diarrhea (20%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced or metastatic cervical, vaginal, or vulvar cancer, KEYTRUDA was discontinued due to adverse reactions in 14% of 149 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (2%), pneumonia (2%), and sepsis (2%). The most common adverse reactions (≥20%) were fatigue (34%), musculoskeletal pain (28%), diarrhea (22%), decreased appetite (22%), nausea (21%), constipation (20%), and pruritus (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with recurrent locally advanced cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a single agent.

In KEYNOTE-204, when KEYTRUDA was administered with brentuximab vedotin and 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 cHL, the most frequent adverse reactions (≥20%) were alopecia (49%), nausea (46%), fatigue (45%), vomiting (34%), pneumonia (33%), pneumonitis, pyrexia, embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 29% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 2% of patients receiving KEYTRUDA, including 1 case each (0.1%) KEYTRUDA discontinued in 21% of patients due to adverse reactions. The most common reactions (≥1%) resulting in permanent discontinuation were increased ALT (1.5%), and pneumonitis (1.2%). The most common adverse reactions (≥20%) in patients receiving KEYTRUDA in combination with chemotherapy were alopecia (81%), rash (52%), decreased appetite (47%), vomiting and rash (36% each), cough (22%), 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, 113 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 years to 17 years) with PD-L1 expressing advanced PMBCL, TCRBCL, or PNMBCL received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months.

Adverse reactions that occurred at a ≥10% higher rate in pediatric patients were comparable to those reported in adults receiving KEYTRUDA 2 mg/kg every 3 weeks. These included pyrexia (28%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (11%), decreased lymphocyte count (5%), and decreased white blood cell count (11%).

### 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 years and older, and 26% (n=148) 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.

**Before prescribing KEYTRUDA, please read the accompanying** Prescribing Information. The Medication Guide also is available.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = brachytherapy; BTC = biliary tract cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; CRT = chemoradiotherapy; cSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EBRT = external beam radiation therapy; FIGO = International Federation of Gynecology and Obstetrics; GEJ = gastroesophageal junction; HNSCC = head and neck squamous cell carcinoma; HSCT = hematopoietic stem cell transplantation; LLN = lower limit of normal; MSI-H = microsatellite instability-high; NMIBC = non-muscle invasive bladder cancer; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal large B-cell lymphoma; TMB = tumor mutational burden.

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.

US-KEYONDT-211121

# Advanced Cutaneous Squamous Cell Carcinoma (cSCC)

## INDICATIONS

**Advanced cSCC**

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.

Advanced cSCC = recurrent or metastatic cSCC or locally advanced cSCC not curable by surgery or radiation.

Scroll below to review Selected Safety Information

Advanced cSCC
KEYNOTE-629

## Selected Safety Information

### 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 blockers (PD-1, PD-L1 and PD-L2) blocking the binding interactions between these receptors and their ligands. PD-1 is an immune checkpoint protein that regulates T cell activation, tolerance, and 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 with KEYTRUDA. Initiate treatment with KEYTRUDA in the monitored setting. Monitor patients for at least 1 hour after administration of KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity.

In patients with cSCC, KEYNOTE-629 and KEYNOTE-689, withhold KEYTRUDA in the monitored setting for new-onset moderate or severe immune-mediated adverse reactions. Permanently discontinue KEYTRUDA for any persistent grade 3 immune-mediated adverse reaction that recurs at any grade, any grade 4 immune-mediated adverse reaction, and any life-threatening immune-mediated adverse reaction. Administer high-dose corticosteroids (initial dose of 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 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 4.4% (21/480) of patients receiving KEYTRUDA, including Grade 3 (0.8%), Grade 2 (2.5%), and Grade 1 (1.0%) reactions. Steroids or corticosteroids were required in 67% (13/19) of patients who had sufficient information to evaluate. Pneumonitis resulted in 1.3% (3/236) and withholding in 0.8% (2/236) of patients who received KEYTRUDA monotherapy. Pneumonitis resulted in discontinuation of KEYTRUDA in 0.4% (1/236) of patients. Pneumonitis resolved in 84% (16/19) of 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 brentuximab vedotin. Pneumonitis led to discontinuation of KEYTRUDA in 2.1% (8/389) of patients, including Grade 4 (0.3%), Grade 3 (0.8%), and Grade 2 (1%) reactions. Pneumonitis resolved in 77% (24/31) of patients.

Pneumonitis occurred in 8% (21/289) of adult patients with r/r, 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 brentuximab vedotin. Pneumonitis led to discontinuation of KEYTRUDA in 2.4% (7/289) of patients, including Grade 3 (1.4%) and Grade 2 (1%) reactions. Pneumonitis resolved in 67% (14/21) of patients.

Pneumonitis occurred in 8% (37/389) of 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 2.6% (10/389) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 33% 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 immune-mediated colitis, consider testing for cytomegalovirus infection/reactivation by an appropriate method. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated colitis occurred in 1.7% (8/479) of patients receiving KEYTRUDA, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 88% (7/8) of patients, of these, the majority remained on systemic corticosteroids. Hyperglycemia led to permanent discontinuation of KEYTRUDA in 0.5% (4) and withholding in 0.3% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Colitis occurred in 3% (13/389) 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 brentuximab vedotin. Pneumonitis led to discontinuation of KEYTRUDA in 1.3% (5) and withholding in 0.8% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Colitis resolved in 84% (16/19) of patients.

Colitis occurred in 3% (9/289) of adult patients with r/r, 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 brentuximab vedotin. Colitis led to permanent discontinuation of KEYTRUDA in 1.4% (4/289) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Colitis resolved in 67% (6/9) of patients.

Colitis occurred in 3% (12/389) of 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 2.6% (10/389) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 33% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Hepatitis and Hepatotoxicity

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (3/479) patients receiving KEYTRUDA, including Grade 4 (0.2%) and Grade 3 (0.2%) reactions. Systemic corticosteroids were required in 67% (2/3) of patients, of these, the majority remained on systemic corticosteroids. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (1) and withholding in 0.2% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hepatitis resolved in 67% (2/3) of 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 administer corticosteroids as clinically indicated. See the axitinib Prescribing Information for dose modification guidelines. Grade 3 and 4 increased ALT occurred in 4% (20/482) and increased aspartate aminotransferase (AST) 2.5% were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Increased ALT led to permanent discontinuation of KEYTRUDA in 0.8% (4) and withholding in 2.5% (12) of patients. 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 or AST Grade 3 or greater did not occur. Increased ALT resolved in 75% (15/20) of patients, including 24 patients receiving both. All patients with a recurrence of ALT or AST LLN 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% (2/239) of patients receiving KEYTRUDA, including Grade 4 (0.4%) Grade 3 (0.4%), and Grade 2 (0.4%) reactions. Symptoms were controlled with hormone replacement in 1.3% (3/239) of patients. Adrenal insufficiency led to 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 0.8% (2/239) of patients receiving KEYTRUDA, including Grade 3 (0.4%) and Grade 2 (0.4%) 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 0.4% (1) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (0.2/239) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.3% 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% (0.2/239) 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% (0.2) and withholding in 0.1% (0.2) 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 in patients receiving anti–PD-1/PD-L1 treatments. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 40% (75/188) of patients receiving KEYTRUDA, including Grade 3 (3.2%) and Grade 2 (6%) reactions. Systemic corticosteroids were required in 40% (75/188) of patients. These reactions led to permanent discontinuation in 0.5% (2) and withholding of KEYTRUDA in 0.6% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Rash resolved in 67% (2/3) of 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: Cerebral vascular vasculitis, pancreatitis, including elevations in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, uveitis, iritis, pneumothorax, myasthenic syndrome (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, Ocular Lesions, iritis and other ocular inflammatory events can occur as isolated events or in association with systemic immune-related adverse reactions. Ocular inflammatory events, including uveitis, occurred 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. Hemolytic anemia, including fatal cases, has been reported in patients receiving anti–PD-1/PD-L1 treatments. Myocarditis, Musculoskeletal and Connective Tissue Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), Polymyalgia rheumatica, Hypophysitis, Systemic inflammatory response syndrome, Histiocytic necrotic lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant rejection, and Hemophagocytic lymphohistiocytosis.

#### 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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. Follow patients closely for these complications and intervene promptly according to standard guidelines. Of 53 patients with cHL who received KEYTRUDA before and after an allogeneic HSCT, 3 developed GVHD.

#### 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 occurred in 4.1% of patients. The most common adverse reactions (≥20% with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-002, KEYTRUDA was administered as a single agent and was discontinued due to adverse reactions in 11% of 357 patients; permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥5%) were pneumonitis 2.4%, colitis 2.2%, and diarrhea 1%). Serious adverse reactions occurred in 36% of patients receiving KEYTRUDA. The most frequent serious adverse reaction was pneumonitis (2.4%). In KEYNOTE-189, 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 KEYTRUDA-treated patients with stage III melanoma.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 25% of patients. The most common adverse reactions (≥20%) were nausea (56%), fatigue (51%), constipation (31%), diarrhea (31%), decreased appetite (29%), rash (25%), and vomiting (22%).

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 16% of 278 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 19% of patients. The most common adverse reactions (≥20%) were fatigue (50%), alopecia (41%), nausea (31%), decreased appetite (26%), diarrhea (25%), peripheral neuropathy (24%), constipation (22%), and rash (20%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 558 patients with advanced NSCLC; the most common were pneumonitis (3%), pneumonia (3%), and febrile neutropenia (2%). Fatal adverse reactions occurred in 1.4% of patients, including pneumonitis (0.4%), cardiac arrest (0.2%), pneumonia (0.2%), pulmonary embolism (0.2%), and pleural effusion (0.2%). The most common adverse reaction (≥20%) was fatigue (25%).

In KEYNOTE-042, when KEYTRUDA monotherapy was discontinued due to adverse reactions in 11% of 636 patients with advanced NSCLC; the most common were pneumonitis (1.8%). The most common adverse reactions (≥20%) were decreased appetite (25%), fatigue (23%), and nausea (20%).

In KEYNOTE-048, when KEYTRUDA was administered with carboplatin and paclitaxel or paclitaxel protein-bound, KEYTRUDA was discontinued due to adverse reactions in 18% of 596 patients with metastatic NSCLC; the most common adverse reactions (≥20%) were fatigue (35%), alopecia (27%), nausea (26%), peripheral neuropathy (23%), and constipation (20%).

In KEYNOTE-048, when KEYTRUDA was administered with carboplatin and paclitaxel or paclitaxel protein-bound, KEYTRUDA was discontinued due to adverse reactions in 19% of 596 patients with metastatic NSCLC; the most common adverse reactions (≥20%) were fatigue (35%), alopecia (27%), nausea (26%), peripheral neuropathy (23%), and constipation (20%).

In KEYNOTE-048, when KEYTRUDA was administered with carboplatin and paclitaxel or paclitaxel protein-bound, KEYTRUDA was discontinued due to adverse reactions in 19% of 596 patients with metastatic NSCLC; the most common adverse reactions (≥20%) were fatigue (35%), alopecia (27%), nausea (26%), peripheral neuropathy (23%), and constipation (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (25%), nausea (24%), pruritus (22%), rash (21%), decreased appetite (21%), and constipation (21%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with cisplatin-ineligible locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (25%), nausea (23%), pruritus (22%), rash (21%), decreased appetite (21%), and constipation (21%).

In KEYNOTE-061, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation of KEYTRUDA was autoimmune hepatitis (1.4%). The most common adverse reactions (≥20%) were fatigue (29%), musculoskeletal pain (26%), pruritus (24%), rash (21%), diarrhea (21%), and nausea (20%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 351 patients with MSI-H cancer. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (22%), pruritus (21%), and rash (21%).

In KEYNOTE-177, KEYTRUDA was discontinued due to adverse reactions in 9% of 153 patients with MSI-H cancer. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), gastrointestinal pain (27%), diarrhea (25%), and nausea (24

# High-Risk Early-Stage or Advanced Triple-Negative Breast Cancer (TNBC)

## INDICATIONS

**High-Risk Early-Stage 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.

**Advanced Triple-Negative Breast Cancer (TNBC)**

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express programmed death ligand 1 (PD-L1) [combined positive score (CPS) ≥10], as determined by an FDA-approved test.

Scroll below to review Selected Safety Information

## Select Important Safety Information

## Selected Safety Information

### 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.

Inform 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 with KEYTRUDA. For 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 Grade 3 (0.9%), Grade 4 (0.1%), and Grade 5 (0.1%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 71% (67/94) of patients who had available resolution information.

Pneumonitis occurred in 6% (21/389) 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 3.1% (12/389) of patients. One of these patients died. Pneumonitis resolved in 76% (16/21) of patients who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (19/280) of adult patients with PMBCL who received KEYTRUDA as a single agent for adjunct 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 2.9% (8/280) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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. It is important to exclude infectious etiologies of diarrhea or colitis. Immune-mediated colitis occurred in 1.9% (52/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in 69% (36/52) of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.7% (19/2799) of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (1/) and withholding in 0.5% (1/) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Colitis resolved in 85% (44/52) of 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 3.1% (12/389) of patients. One of these patients died. Pneumonitis resolved in 77% (24/31) of patients who discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (19/280) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjunct 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 2.9% (8/280) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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. It is important to exclude infectious etiologies of diarrhea or colitis. Immune-mediated colitis occurred in 1.9% (52/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in 69% (36/52) of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.7% (19/2799) of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (1/) and withholding in 0.5% (1/) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Colitis resolved in 85% (44/52) of patients.

Hypersensitivity and Immune-Mediated Hepatitis

#### Hepatitis 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 74% (14/19) 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. Hepatitis resolved in 74% (14/19) of 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 administer corticosteroids as clinically indicated. If liver enzymes do not return to baseline, reduce the dose of axitinib. Grade 3 and 4 increased ALT (20%) and increased aspartate aminotransferase (AST) (15%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids for a median duration of 1 month (range: 1 day to 5.6 months). Increased ALT resolved to Grade 0 or 1 in 79%. 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 or AST Grade 3 or 4 was observed in 7 patients (8%) upon rechallenge.

#### Hypersensitivity 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 74% (14/19) 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. Hepatitis resolved in 74% (14/19) of 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 administer corticosteroids as clinically indicated. If liver enzymes do not return to baseline, reduce the dose of axitinib. Grade 3 and 4 increased ALT (20%) and increased aspartate aminotransferase (AST) (15%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids for a median duration of 1 month (range: 1 day to 5.6 months). Increased ALT resolved to Grade 0 or 1 in 79%. 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 or AST Grade 3 or 4 was observed in 7 patients (8%) upon rechallenge.

#### 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 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 54% (6/13) 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.

#### 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 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 54% (6/13) 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 initiation of 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 0.1% (2/) of patients withheld.

Hypothyroidism occurred in 8% (216/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (3.8%). It led to permanent discontinuation of KEYTRUDA in 0.3% (7) and withholding in 0.7% (18/) of patients. Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.2% (5/) of patients. Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.6%). It led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.2% (5/) of patients. Hypothyroidism occurred in 8% (216/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (3.8%). It led to permanent discontinuation of KEYTRUDA in 0.3% (7) and withholding in 0.7% (18/) of patients. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (0.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.2% (5/) of patients. Hypophysitis occurred in 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7/) of patients. Hypophysitis occurred in 0.5% (13/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7/) of patients. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (0.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.2% (5

## Selected Safety Information

**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 (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 immune-mediated 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 control at baseline, prior to surgery, and as clinically indicated. In cases of possible 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.

**Pneumonitis, Medical Treatment**

- KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.7%), Grade 2 (1.9%), and Grade 1 (3.2%). Fatal cases occurred in 0.2% (6/3434) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. Pneumonitis resolved in 59% of patients with KEYTRUDA after the last dose.
- Pneumonitis occurred in 8% (31/389) of adult patients with cHL, receiving KEYTRUDA as a single agent, including Grades 3 4 or 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 2.1% (8) of patients. Of patients who developed pneumonitis, 62% (24) resolved, 26% (10) resolved, 5% (2) discontinued KEYTRUDA, and 7% had resolution.
- Pneumonitis occurred in 3% (10/383) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including trial (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 days to 22 months). Pneumonitis led to discontinuation of KEYTRUDA in 2% (6.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 5% discontinued KEYTRUDA, and 71% had resolution.

**Hepatitis, Medical Treatment**

- 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 diarrhea, consider additional causes including infectious etiology. Immune-mediated colitis occurred in 1.7% (68/3799) 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% (47/68) of patients with immune-mediated colitis. Immune-mediated 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.
- Immune-mediated colitis occurred in 1% (3/389) of patients with cHL, receiving KEYTRUDA as a single agent, including Grades 3 4 or 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 2.1% (8) of patients. Of the patients who developed pneumonitis, 62% (24) resolved, 26% (10) resolved, 5% (2) discontinued KEYTRUDA, and 7% had resolution.
- Pneumonitis occurred in 3% (10/383) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including trial (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 days to 22 months). Pneumonitis led to discontinuation of KEYTRUDA in 2% (6.5%) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Pneumonitis resolved in 79% of the 19 patients.

**Hepatitis, Medical Treatment**

- KEYTRUDA can cause immune-mediated hepatitis. Hepatocellular hepatitis with acute symptoms associated with mass effect such as headache, cholestasis, or visual field defects may be consistent with a case of hepatocellular hepatitis with cholestasis. Withhold or permanently discontinue KEYTRUDA depending on severity. Hepatocytitis 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 59% (10/17) of patients with immune-mediated hepatitis. Immune-mediated hepatitis 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; of these, none had recurrence.

*Hepatocytitis, Medical Treatment in Patients with Hepatocellular Carcinoma Who Received Prior Anti-PD-1/PD-L1 Treatment*

- KEYTRUDA can cause immune-mediated hepatitis. Hepatocellular hepatitis with acute symptoms associated with mass effect such as headache, cholestasis, or visual field defects may be consistent with a case of hepatocellular hepatitis with cholestasis. Withhold or permanently discontinue KEYTRUDA depending on severity. Hepatocytitis 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 59% (10/17) of patients with immune-mediated hepatitis. Immune-mediated hepatitis 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; of these, none had recurrence.

*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. 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 88% (15/17) of patients with immune-mediated hypophysitis. 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; of these, none had recurrence.

*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 0.5% (16/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.2%). Immune-mediated thyroiditis 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.

*Hyperthyroidism*

- KEYTRUDA can cause immune-mediated hyperthyroidism. Hyperthyroidism can present with acute symptoms associated with mass effect such as tachycardia, arrhythmias, palpitations, or mental status changes. Initiate medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hyperthyroidism occurred in 3.4% (95/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (0.8%) reactions. Systemic corticosteroids were required in 8% (8/95) of patients with immune-mediated hyperthyroidism. Hyperthyroidism 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; of these, none had recurrence. Hyperthyroidism resolved in 79% of the 19 patients.

*Hypothyroidism*

- KEYTRUDA can cause immune-mediated hypothyroidism. Hypothyroidism can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypothyroidism can cause hypopituitarism. Initiate hormone replacement for hypothyroidism or institute medical management of hypothyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypothyroidism occurred in 9.8% (276/2799) of patients receiving KEYTRUDA, including Grade 3 (0.3%) and Grade 2 (9.2%). Immune-mediated hypothyroidism led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hypothyroidism resolved in 19% of the 52 patients.

*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% (7/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%) and Grade 3 (0.1%) reactions. Immune-mediated type 1 DM 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. Type 1 DM 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 non-exfoliative 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 39% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of KEYTRUDA in 0.1% (2) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. Immune-mediated dermatologic adverse reactions resolved in 79% of the 28 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 types of uveitis, including anterior uveitis, posterior uveitis, and panuveitis, can occur. Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis, sialadenitis, colitis, hepatitis, including autoimmune hepatitis, hepatic failure, bile duct obstruction, and sclerosing cholangitis. Endocrine: Hypophysitis can present with inflammatory and headache symptoms. Hypophysitis can progress to hypopituitarism. Adrenal insufficiency, including primary and secondary adrenal insufficiency and adrenal crisis. Hypophysitis, diabetes insipidus, and pituitary hormone disorders can occur. Musculoskeletal: Sarcoidosis, polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica. Hematologic/Immunologic: Hemolytic anemia, aplastic anemia, hemorrhagic diathesis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, graft-versus-host disease (including cases in patients who received prior stem cell transplant).

**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 GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced-intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti-PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

**Increased Mortality in Patients With Multiple Myeloma**

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

**Embryofetal Toxicity**

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

**Adverse Reactions**

- In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent discontinuation of KEYTRUDA were colitis (1.4%), autoimmune hepatitis (1.1%), and pneumonitis (0.4%); symptomatic CHF (0.4%); and myocarditis (0.2%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).
- In KEYNOTE-001, KEYTRUDA was discontinued due to adverse reactions in 10% of 357 patients with melanoma. The most common adverse reactions (≥20%) were KEYTRUDA as a single agent, including fatigue (29%), diarrhea (26%), rash (24%), and nausea (21%).
- In KEYNOTE-048, KEYTRUDA was discontinued due to adverse reactions in 14% of 508 patients who received KEYTRUDA as a single agent, including adverse reactions in 14% of 509 patients, the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 41% of KEYTRUDA-treated patients. The most common adverse reactions (≥20%) were fatigue (46%), diarrhea (28%), and rash (25%). 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 KEYTRUDA-treated patients with stage III melanoma.
- In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 405 patients. The most common adverse reactions (≥20%) were nausea (56%), fatigue (56%), constipation (35%), anemia (33%), and acute kidney injury (22%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), anemia (33%), and decreased appetite (21%). Serious adverse reactions occurred in 45% of patients.
- 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 common adverse reactions (≥20%) were peripheral neuropathy (31%), alopecia (31%), fatigue (31%), nausea (29%), decreased appetite (23%), constipation (21%), and rash (20%). Serious adverse reactions occurred in 60%.
- In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 16% of 559 patients. The most common adverse reactions (≥20%) were alopecia (41%), fatigue (40%), nausea (31%), peripheral neuropathy (31%), constipation (26%), decreased appetite (26%), diarrhea (26%), vomiting (22%), and rash (20%). Serious adverse reactions occurred in 59%.
- In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients who received NSCLC; the most common adverse reactions (≥5%) were pneumonitis (3.3%), fatigue (2.4%), and pneumonia (2.4%). The most common adverse reactions (≥20%) were fatigue (36%), decreased appetite (26%), nausea (20%), and cough (20%). Serious adverse reactions occurred in 58%.
- In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with cisplatin-eligible advanced urothelial carcinoma. Serious adverse reactions occurred in 49% of patients receiving KEYTRUDA. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%).
- In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 14% of 296 patients with advanced urothelial carcinoma who received NSCLC. The most common adverse reaction requiring permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Serious adverse reactions occurred in 49% of KEYTRUDA-treated patients. The most common adverse reactions (≥20%) were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased appetite (21%), nausea (21%), and rash (20%).
- In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 148 patients with MSI-H cancer. The most common adverse reaction requiring permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Serious adverse reactions occurred in 28% of patients. The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (22%), pruritus (22%), and rash (21%).
- In KEYNOTE-164, KEYTRUDA was discontinued in combination with chemotherapy in 12% of 107 patients with MSI-H cancer. The most common adverse reactions leading to permanent discontinuation were sepsis (7.5%) and pneumonia (3.7%). The most common adverse reactions (≥20%) were fatigue (33%), constipation (20%), and rash (20%).
- In KEYNOTE-061, KEYTRUDA was discontinued in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 9% of 225 patients with HNSCC. The most common adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). The most common adverse reactions (≥20%) were nausea (51%), fatigue (49%), constipation (37%), vomiting (32%), mucosal inflammation (31%), diarrhea (29%), decreased appetite (29%), stomatitis (25%), and cough (22%).
- In KEYNOTE-671, KEYTRUDA was discontinued due to adverse reactions in 19% of 396 patients with cHL, adverse reactions occurred in 26% of patients receiving KEYTRUDA with platinum-containing chemotherapy, gemcitabine, and gastrointestinal hemorrhage (0.4%). Permanent discontinuation of adjuvant KEYTRUDA due to adverse reactions occurred in 17% of patients. The most common adverse reactions (≥20%) were fatigue (32%), nausea (30%), alopecia (30%), neutropenia (28%), anemia (25%), neutropenia (15%), and pyrexia (13%).
- In KEYNOTE-564, KEYTRUDA was discontinued due to adverse reactions in 13% of 494 patients with RCC. The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (25%), diarrhea (23%), pruritus (23%), and hypothyroidism (21%).
- In KEYNOTE-091, KEYTRUDA was discontinued in combination with chemotherapy due to adverse reactions in 10% of 597 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%) pneumonitis.

**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, 113 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 years to 17 years) received KEYTRUDA at 200 mg every 3 weeks. The median duration of exposure to KEYTRUDA was 4.2 months (range: 1 days to 25 months).
- Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults were pyrexia (13%), neutropenia (10%), vomiting (10%), nasopharyngitis (10%), headache (21%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (17%), decreased lymphocyte count (13%), and decreased white blood cell count (11%).

**Geriatric Use**

- Of the 564 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in clinical trials with euthanasia weeds, 44% (247) were 65 years and older, 15 (446) 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.

**Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BT = brachytherapy; BTC = biliary tract cancer; cHL = classical Hodgkin lymphoma; CRC = colorectal cancer; CRT = chemoradiotherapy; CSCC = cutaneous squamous cell carcinoma; dMMR = mismatch repair deficient; EBRT = external beam radiotherapy; EC = esophageal adenocarcinoma; ESCC = esophageal squamous cell carcinoma; GEJ = gastroesophageal junction; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MCC = Merkel cell carcinoma; MSI-H = microsatellite instability-high; NMSC = non-muscle invasive bladder cancer; NSCLC = non-small cell lung cancer; PMBCL = primary mediastinal large B-cell lymphoma; TNBC = triple-negative breast cancer.

Copyright © 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.
US-KEYB-250821-0135

# Definitions

| | |
|---|---|
| ALK = anaplastic lymphoma kinase | EGFR = epidermal growth factor receptor |
| ALT = alanine aminotransferase | EV = ertumaxomab-wxwz |
| AST = aspartate aminotransferase | FDA = US Food and Drug Administration |
| CAP-using EPR antimicrobial | FIGO = International Federation of Gynecology and Obstetrics |
| BCG = Bacillus Calmette-Guérin | G1 = grandmesenchymal epithelial |
| BT = bis-trichenoyl | G2 = grandmesenchymal mixed |
| BTC = biliary tract cancer | GEJ = gastroesophageal junction |
| CBC = complete blood count | GGT = gamma-glutamyl transferase |
| CR = carcinoma in situ | HER2 = human epidermal growth factor receptor 2 |
| CRC = colorectal cancer | HNSCC = head and neck squamous cell carcinoma |
| CPP-confirmed positive score | HSCT = hematopoietic stem cell transplantation |
| CSC = colorectal cancer | IL2 = interleukin 2 |
| CT = computed tomography | IRR = infusion-related reaction |
| CSCC = cutaneous squamous cell carcinoma | IV = intravenous |
| dMMR = mismatch repair deficient | LDH = lactate dehydrogenase |
| dMMR = mismatch repair proficient | MMR = mismatch repair |
| EBRT = external beam radiation therapy | mNSCLC = metastatic non-small cell lung cancer |

| | |
|---|---|
| MSI-H = microsatellite instability-high | |
| mUC = metastatic urothelial cancer | |
| NCCN = National Comprehensive Cancer Network | |
| NSCLC = non-small cell lung cancer | |
| PD-1 = programmed death receptor-1 | |
| PD-L1 = programmed death ligand-1 | |
| PMDS = primary mediastinal b-cell lymphoma | |
| PPE = palmoplantar erythrodysesthesia | |
| SJS = Stevens-Johnson syndrome | |
| TEN = toxic epidermal necrolysis | |
| TMZ = triple-negative breast cancer | |
| TPS = tumor proportion score | |
| UC = ulcerative colitis | |
| ULN = upper limit of normal | |
| WHO = Women's Health Initiative | |

Scroll below to review Selected Safety Information

## Selected Safety Information

### 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 with KEYTRUDA. For patients with TMZ treated with KEYTRUDA in the neoadjuvant setting, monitor blood counts at baseline and 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. Administer corticosteroids and, if appropriate, hormone replacement therapy. In most cases of KEYTRUDA-induced adverse reactions, administration of systemic corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue 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 Grade 5 (0.1%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.6%). Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis resolved in 59% of patients who received corticosteroids after a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld permanently from KEYTRUDA for pneumonitis (n=36) or withheld for pneumonitis (n=26) received systemic corticosteroids.

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 3.9% (15) of patients, and to withholding of KEYTRUDA in 3.1% (12) of patients. All patients with pneumonitis discontinued KEYTRUDA, and 77% had resolution.

Pneumonitis occurred in 7% (20/304) of patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.3%), 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 2% (6.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 53% 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. It is important to exclude infectious etiologies of diarrhea or colitis. Administer corticosteroids for Grade 2 or higher infectious 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%). Systemic corticosteroids were required in 69% (33/48) of patients. Colitis resolved in 58% of patients who received corticosteroids after a median duration of 7 days (range: 1 day to 1.3 months). 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 recurrent colitis.

Immune-mediated colitis occurred in 2% (7/389) 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 3.9% (15) of patients, and to withholding of KEYTRUDA in 3.1% (12) of patients. All patients who were withheld permanently from KEYTRUDA for pneumonitis (n=36) or withheld for pneumonitis (n=26) received systemic corticosteroids. All patients who discontinued KEYTRUDA for pneumonitis, and 77% had resolution.

#### 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 79% (15/19) of patients. Hepatitis resolved in 63% of patients who received corticosteroids after a median duration of 14 days (range: 1 day to 1.3 months). 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, 22% had recurrent hepatitis.

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 administer corticosteroids as soon as needed. After the event resolves to Grade 1 or baseline, restart KEYTRUDA and axitinib dosing at reduced dose. Grade 3 (5%) and Grade 4 (2%) increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased AST received systemic corticosteroids for a median duration of 7 days (range: 1 day to 1.3 months). Of these patients, 71% had resolution to baseline AST levels. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or as part with both (n=55), recurrence of ALT or AST Grade 3-4 was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axi, and 24 patients receiving both. All patients with a recurrence of ALT or AST 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 (0.4%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 91% (20/22) of patients. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 25% had recurrent adrenal insufficiency.

*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 0.5% (13/2799) of patients receiving KEYTRUDA, including 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% (1) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*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% (5/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in 0.1% (3) 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 initiation of 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 0.1% (2) of patients withheld KEYTRUDA.

Hyperthyroidism occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including Grade 3 (0.5%) and Grade 2 (2.8%). It led to permanent discontinuation of KEYTRUDA in 0.2% (5) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 7% had recurrent hyperthyroidism.

Hypothyroidism occurred in 9% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.6%) and Grade 2 (8.2%). It led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.2% (6) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 2% had recurrent hypothyroidism.

Hypothyroidism occurred in 17% (65/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grade 3 (1.5%) and Grade 2 (15%). Hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 198 patients with HNSCC who received KEYTRUDA as a single agent (26%; 51/198), including Grade 3 (2.5%) and Grade 2 (23%). Hypothyroidism led to permanent discontinuation of KEYTRUDA in 1.5% (6) of patients with cHL and in 0.5% (1) of patients with HNSCC, and to withholding of KEYTRUDA in 2.1% (8) of patients with cHL and in 1.5% (3) of patients with HNSCC. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 4% had recurrent hypothyroidism.

#### 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% (4) 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 in patients receiving KEYTRUDA. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 14% (398/2799) of patients receiving KEYTRUDA, including Grade 3 (1.1%) and Grade 2 (0.6%) reactions. Bullous dermatitis occurred in 40% (75/188) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (17) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Of these, 11% had recurrent dermatitis.

#### 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: Guillain-Barré syndrome, myasthenic syndrome, encephalitis, uveitis, iritis and other ocular inflammatory toxicities, pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, myositis, rhabdomyolysis (and associated sequelae), hypophysitis, vasculitis, and solid organ transplant rejection.

Infusion-Related Reactions

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

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

Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti–PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, acute chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile pneumonitis. These complications may occur even if intervening therapy between anti–PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti–PD-1/PD-L1 treatment 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 included colitis (1.4%) and pneumonitis (1.1%). Fatal adverse reactions occurred in 1.1% of patients, including death due to unknown cause (0.4%), and myocardial infarction (0.2%). The most common adverse reactions (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-054, KEYTRUDA was administered as adjuvant treatment for melanoma. Adverse reactions led to KEYTRUDA being permanently discontinued due to adverse reactions in 14% of 509 patients; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 19% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 0.4% of patients receiving KEYTRUDA, including cardiac arrest (0.2%). In KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with stage IB or IC melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in patients with stage III melanoma.

In KEYNOTE-695, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 19% of 406 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), anemia (31%), decreased appetite (28%), rash (26%), vomiting (25%), and diarrhea (22%).

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; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (2%), pneumonia (2%), and acute kidney injury (2%). The most common adverse reactions (≥20%) were fatigue (51%), alopecia (49%), nausea (47%), decreased appetite (31%), rash (29%), diarrhea (28%), constipation (25%), and peripheral neuropathy (20%).

In KEYNOTE-042, when KEYTRUDA was administered with carboplatin and paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 11% of 599 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (1.3%) and acute kidney injury (1.3%). The most common adverse reactions (≥20%) were alopecia (48%), fatigue (47%), nausea (39%), constipation (25%), and peripheral neuropathy (23%).

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 18% of 405 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and acute kidney injury (2%). The most common adverse reactions (≥20%) were nausea (59%), fatigue (56%), anemia (39%), decreased appetite (29%), vomiting (28%), constipation (26%), diarrhea (25%), rash (22%), and pyrexia (21%).

In KEYNOTE-021, when KEYTRUDA was administered with carboplatin and pemetrexed, KEYTRUDA was discontinued due to adverse reactions in 10% of 123 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pneumonia (2%). The most common adverse reactions (≥20%) were nausea (39%), fatigue (37%), alopecia (29%), anemia (28%), vomiting (24%), stomatitis (23%), and weight loss (23%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and paclitaxel/nab-paclitaxel, KEYTRUDA was discontinued due to adverse reactions in 13% of 278 patients; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (2%) and pneumonia (2%). The most common adverse reactions (≥20%) were alopecia (49%), fatigue (47%), nausea (36%), peripheral neuropathy (23%), decreased appetite (23%), diarrhea (22%), and constipation (20%).

In KEYNOTE-355, when KEYTRUDA was administered with chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 290 patients. The most frequent adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 13% of patients receiving KEYTRUDA in combination with chemotherapy. The most frequent adverse reactions (≥10%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1.4%), and pneumonitis (1.4%).

Adverse reactions observed in KEYNOTE-001 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (17%), hyperthyroidism (7%), and pruritus (39%), which occurred more frequently.

In KEYNOTE-689, the most common adverse reactions (≥20%) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), mucositis (33%), nausea (32%), constipation (27%), hypothyroidism (25%), rash (24%), and diarrhea (21%). Serious adverse reactions occurred in 39% of patients. 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, including 1 fatal adverse reaction of pneumonitis. KEYTRUDA was discontinued due to adverse reactions in 9% of patients. The most common adverse reactions leading to discontinuation were pneumonitis (0.6%), colitis (0.6%), and dyspnea (0.6%). Fatal adverse reactions occurred in 0.3% of patients, including respiratory failure, colitis, cause of infection, sepsis, and sudden death. In the adjuvant phase of KEYTRUDA, of the 284 patients who received at least one dose of KEYTRUDA, 38% experienced serious adverse reactions. The most frequent serious adverse reactions reported in 1% of KEYTRUDA patients were pneumonitis, urinary tract infection, and acute kidney injury. In the neoadjuvant phase of KEYTRUDA, of the 361 patients who received at least one dose of KEYTRUDA, 98% experienced adverse reactions. The most frequent adverse reactions reported in ≥10% of KEYTRUDA patients were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), mucositis (33%), nausea (32%), constipation (27%), hypothyroidism (25%), rash (24%), diarrhea (21%), vomiting (19%), decreased appetite (19%), dysgeusia (18%), dysphonia (14%), hemorrhage (13%), alopecia (13%), pruritus (12%), dyspepsia (12%), pneumonitis (11%), dysphagia (11%), pancytopenia (10%), and hypothyroidism (10%). The most common laboratory abnormalities (≥20%) were increased creatinine (74%), anemia (71%), increased alkaline phosphatase (54%), increased aspartate aminotransferase (47%), increased alanine aminotransferase (46%), hyponatremia (45%), lymphopenia (44%), hyperglycemia (41%), hypokalemia (40%), leukopenia (39%), hypercalcemia (38%), hypophosphatemia (36%), hyperkalemia (34%), hypomagnesemia (34%), hyperbilirubinemia (33%), and neutropenia (32%). The most common adverse reactions (≥20%) leading to permanent discontinuation were pneumonitis (4%), radiation skin injury (4%), and weight loss (3%).

In KEYNOTE-091, KEYTRUDA was administered as adjuvant treatment for NSCLC. Adverse reactions led to KEYTRUDA being permanently discontinued due to adverse reactions in 14% of 1,177 patients; the most common (≥1%) were pneumonitis (2.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 42% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 1.2% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated myocarditis (0.2%). The most common adverse reactions (≥20%) were fatigue (28%), musculoskeletal pain (20%), upper respiratory tract infection (20%), pyrexia (24%), cough (24%), nausea (22%), and rash (20%).

In KEYNOTE-522, when KEYTRUDA was administered with paclitaxel and carboplatin and as adjuvant treatment, serious adverse reactions occurred in 14% of 290 patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 12% of patients receiving KEYTRUDA in combination with chemotherapy. The most frequent adverse reactions (≥1%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1%), and pneumonitis (1%).

Adverse reactions observed in KEYNOTE-001 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (17%), hyperthyroidism (7%), and pruritus (39%), which occurred more frequently.

In KEYNOTE-048, the most common adverse reactions (≥20%) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), mucositis (33%), nausea (32%), constipation (27%), hypothyroidism (25%), rash (24%), and diarrhea (21%). Serious adverse reactions occurred in 39% of patients. 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, including 1 fatal adverse reaction of pneumonitis. KEYTRUDA was discontinued due to adverse reactions in 9% of patients. The most common adverse reactions leading to discontinuation were pneumonitis (0.6%), colitis (0.6%), and dyspnea (0.6%). Fatal adverse reactions occurred in 0.3% of patients, including respiratory failure, colitis, cause of infection, sepsis, and sudden death. In the adjuvant phase of KEYTRUDA, of the 284 patients who received at least one dose of KEYTRUDA, 38% experienced serious adverse reactions. The most frequent serious adverse reactions reported in 1% of KEYTRUDA patients were pneumonitis, urinary tract infection, and acute kidney injury. In the neoadjuvant phase of KEYTRUDA, of the 361 patients who received at least one dose of KEYTRUDA, 98% experienced adverse reactions. The most frequent adverse reactions reported in ≥10% of KEYTRUDA patients were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), mucositis (33%), nausea (32%), constipation (27%), hypothyroidism (25%), rash (24%), diarrhea (21%), vomiting (19%), decreased appetite (19%), dysgeusia (18%), dysphonia (14%), hemorrhage (13%), alopecia (13%), pruritus (12%), dyspepsia (12%), pneumonitis (11%), dysphagia (11%), pancytopenia (10%), and hypothyroidism (10%). The most common laboratory abnormalities (≥20%) were increased creatinine (74%), anemia (71%), increased alkaline phosphatase (54%), increased aspartate aminotransferase (47%), increased alanine aminotransferase (46%), hyponatremia (45%), lymphopenia (44%), hyperglycemia (41%), hypokalemia (40%), leukopenia (39%), hypercalcemia (38%), hypophosphatemia (36%), hyperkalemia (34%), hypomagnesemia (34%), hyperbilirubinemia (33%), and neutropenia (32%). The most common adverse reactions (≥20%) leading to permanent discontinuation were pneumonitis (4%), radiation skin injury (4%), and weight loss (3%).

In KEYNOTE-054, KEYTRUDA was discontinued due to adverse reactions in 14% of 509 patients with adjuvant melanoma; adverse reactions leading to permanent discontinuation of KEYTRUDA were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 19% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 0.4% of patients receiving KEYTRUDA, including cardiac arrest (0.2%). The most common adverse reactions (≥20%) were fatigue (35%), musculoskeletal pain (25%), diarrhea (22%), pruritus (22%), rash (21%), nausea (20%), and cough (20%).

In KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with stage IB or IIC melanoma, adverse reactions occurring in patients with stage IB or IIC melanoma were similar to those occurring in patients with stage III melanoma.

In KEYNOTE-091, when KEYTRUDA was administered as adjuvant treatment for NSCLC, adverse reactions led to KEYTRUDA being permanently discontinued due to adverse reactions in 14% of 1,177 patients; the most common (≥1%) were pneumonitis (2.4%), colitis (2.2%), and diarrhea (1%). Serious adverse reactions occurred in 42% of patients receiving KEYTRUDA. Fatal adverse reactions occurred in 1.2% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated myocarditis (0.2%). The most common adverse reactions (≥20%) were fatigue (28%), musculoskeletal pain (20%), upper respiratory tract infection (20%), pyrexia (24%), cough (24%), nausea (22%), and rash (20%).

In KEYNOTE-522, when KEYTRUDA was administered with paclitaxel and carboplatin and as adjuvant treatment, serious adverse reactions occurred in 14% of 290 patients. The most frequent serious adverse reaction was pneumonia (2.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 12% of patients receiving KEYTRUDA in combination with chemotherapy. The most frequent adverse reactions (≥1%) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1%), and pneumonitis (1%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 14% of patients with cHL. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA. Serious adverse reactions occurring in ≥2% of patients included pneumonia (4%), pyrexia (3%), acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions: 1 from cardiopulmonary arrest, 1 from sepsis, and 1 from pneumonitis. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (33%), diarrhea (23%), and pyrexia (21%).

In KEYNOTE-204, KEYTRUDA was administered in combination with brentuximab vedotin and was discontinued due to adverse reactions occurred in 16% of patients. The most frequent adverse reactions were peripheral neuropathy (4%), diarrhea (4%), and pneumonitis (3%). Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions were pneumonia (6%), pyrexia (4%), acute kidney injury, febrile neutropenia, and sepsis. Three patients died from adverse reactions: 1 from cardiopulmonary arrest, 1 from sepsis, and 1 from pneumonitis. The most common adverse reactions (≥20%) were fatigue (36%), musculoskeletal pain (33%), diarrhea (23%), and pyrexia (21%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 9% of 266 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reactions (≥20%) were musculoskeletal pain (30%), upper respiratory tract infection (29%), pyrexia (24%), cough (24%), nausea (22%), and rash (20%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 19% of 370 patients with cisplatin-ineligible urothelial carcinoma. The most common adverse reactions (≥20%) were fatigue (49%), musculoskeletal pain (30%), nausea (28%), decreased appetite (25%), pruritus (24%), diarrhea (23%), peripheral edema (22%), and urinary tract infection (21%).

In KEYNOTE-361, KEYTRUDA was discontinued due to adverse reactions in 8% of 153 patients with mUC. The most common adverse reactions (≥20%) were fatigue (34%), nausea (27%), decreased appetite (25%), diarrhea (22%), and pruritus (20%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction requiring permanent discontinuation of KEYTRUDA was pneumonitis (2%). The most common adverse reactions (≥20%) were fatigue (31%), musculoskeletal pain (30%), pruritus (27%), colitis (21%), pulmonary embolism (21%), pyrexia (20%), and urinary tract infection (21%). The most common adverse reactions (≥20%) were fatigue (29%), nausea (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-177, KEYTRUDA was administered as a single agent to patients with previously untreated MSI-H or dMMR metastatic CRC. 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, KEYTRUDA was administered as a single agent to patients with MSI-H cancer. Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in patients with other MSI-H cancers who received KEYTRUDA as a single agent.

In KEYNOTE-177, KEYTRUDA was administered as a single agent to patients with previously untreated MSI-H or dMMR metastatic CRC. Adverse reactions occurred in 40% of patients; the most frequent (≥5%) were hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (3.2%), dehydration (3%), and pneumonitis (2.8%). Fatal adverse reactions occurred in 1.4% of patients, including cardiac arrest (0.4%), and pneumonitis (0.4%). Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 12% of patients. The most common adverse reactions (≥20%) were hepatotoxicity (28%), diarrhea/colitis (19%), acute kidney injury (19%), and cerebrovascular accident (12%). The most common adverse reactions (≥10%) worsening from baseline were hyponatremia (52%), lymphopenia (51%), hyperglycemia (50%), anemia (49%), hypocalcemia (47%), hypophosphatemia (28%), hyperkalemia (28%), thromboembolic/vascular infarction (27%), hypocalcemia (25%), rash (23%), cough (23%), and constipation (21%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with previously treated MSI-H cancer, adverse reactions occurred in 41% of patients. The most frequent (≥5%) were hepatotoxicity (9%), diarrhea (6%), acute kidney injury (5%), dehydration (5%), and pneumonitis (5%). Fatal adverse reactions occurred in 2% of patients, including pneumonitis (0.7%), cardiac arrest (0.7%), and cerebrovascular accident (0.2%). Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 14% of patients. The most common adverse reactions (≥20%) were fatigue (26%), musculoskeletal pain (20%), upper respiratory tract infection (20%), pyrexia (24%), cough (24%), nausea (22%), and rash (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with previously treated MSI-H cancer, adverse reactions occurred in 41% of patients. The most frequent (≥5%) were hepatotoxicity (9%), diarrhea (6%), acute kidney injury (5%), dehydration (5%), and pneumonitis (5%). Fatal adverse reactions occurred in 2% of patients, including pneumonitis (0.7%), cardiac arrest (0.7%), and cerebrovascular accident (0.2%). Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 14% of patients. The most common adverse reactions (≥20%) were fatigue (26%), musculoskeletal pain (20%), upper respiratory tract infection (20%), pyrexia (24%), cough (24%), nausea (22%), and rash (20%).

In KEYNOTE-158, when KEYTRUDA was administered as a single agent to patients with previously treated MSI-H cancer, adverse reactions occurred in 41% of patients. The most frequent (≥5%) were hepatotoxicity (9%), diarrhea (6%), acute kidney injury (5%), dehydration (5%), and pneumonitis (5%). Fatal adverse reactions occurred in 2% of patients, including pneumonitis (0.7%), cardiac arrest (0.7%), and cerebrovascular accident (0.2%). Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 14% of patients. The most common adverse reactions (≥20%) were fatigue (26%), musculoskeletal pain (20%), upper resp