

Monitoring and Management of Select Immune-Mediated Adverse Reactions (IMARs) and Other Adverse Reactions

The following guide provides an overview of select signs and symptoms that should be monitored in patients receiving **KEYTRUDA** or **KEYTRUDA QLEX**, as well as the management of select IMARs and other adverse reactions.

KEYTRUDA QLEX is approved for use in adult patients across solid tumor indications for KEYTRUDA—whether alone or in combination with other therapies.

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

SELECTED SAFETY INFORMATION

Contraindications

- KEYTRUDA QLEX is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients.

Severe and Fatal Immune-Mediated Adverse Reactions

- KEYTRUDA and KEYTRUDA QLEX are monoclonal antibodies that belong 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. 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.

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 2–8, 10–12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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FDA Definitions for Adverse Event and Adverse Reaction

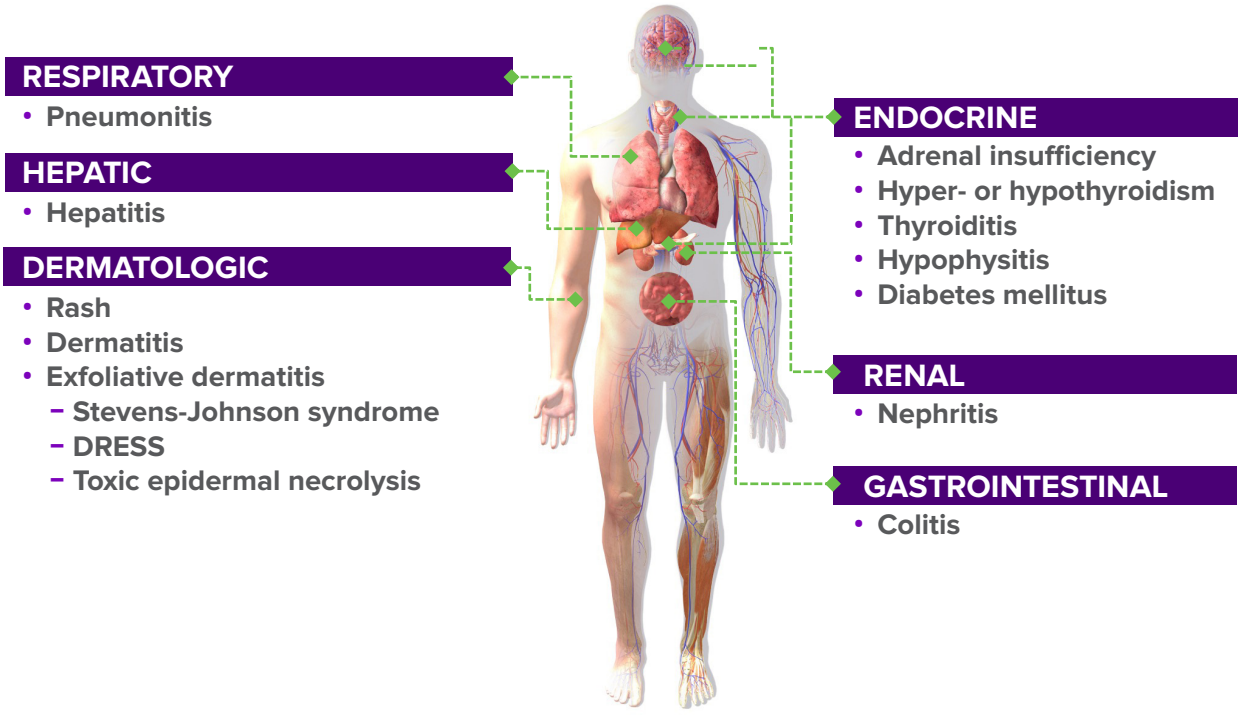
- **Adverse event (AE)** describes any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.[1]
- **Adverse reaction (AR)** describes any adverse event caused by a drug.[1]
  - Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.[1]

Immune-Mediated Adverse Reactions (IMARs)

- **IMARs** may result when the immune system is activated, leading to an attack on normal organ and tissue function.[2]

Severe and Fatal IMARs

- IMARs may be severe or fatal and can occur in any organ system or tissue. IMARs usually occur during treatment but may also occur after discontinuation.[2] Important IMARs listed here may not include all possible severe and fatal IMARs.



DRESS = drug rash with eosinophilia and systemic symptoms; FDA = Food and Drug Administration.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

- Withhold or permanently discontinue KEYTRUDA and KEYTRUDA QLEX depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA and KEYTRUDA QLEX require 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 and KEYTRUDA QLEX can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients. Immune-mediated pneumonitis occurred in 5% (13/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including fatal (0.4%), Grade 3 (2%), and Grade 2 (1.2%) adverse reactions.

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 1, 3–8, 10–12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

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Selected Immune-Mediated Adverse Reactions

The severity of adverse reactions for dose modifications included in the Prescribing Information for KEYTRUDA and KEYTRUDA QLEX is based on NCI-CTCAE version 4.0. The published NCI-CTCAE definitions evolve over time and more recent versions are available. Guidance on adverse reactions related to a specific treatment should be found in that product's prescribing information.



Immune-Mediated Pneumonitis

Monitoring and Management

- Monitor patients for signs and symptoms of pneumonitis
- Ask patients to immediately report new or worsening cough, chest pain, or shortness of breath

Severity[a]	Dosage Modification
Grade 2	Withhold[b]
Grade 3 or 4	Permanently discontinue



Immune-Mediated Colitis

Monitoring and Management

- Monitor patients for signs and symptoms of colitis, which may present with diarrhea
- Ask patients to immediately report diarrhea (loose stools) or more frequent bowel movements than usual; stools that are black, tarry, sticky, or have blood or mucus; or severe abdominal pain or tenderness
- CMV infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies

Severity[a]	Dosage Modification
Grade 2 or 3	Withhold[b]
Grade 4	Permanently discontinue

[a]Based on NCI-CTCAE v4.0. [b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg per day (or equivalent) within 12 weeks of initiating steroids.

CMV = cytomegalovirus; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Colitis

- KEYTRUDA and KEYTRUDA QLEX can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.
- Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 69% (33/48); additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients. Immune-mediated colitis occurred in 1.2% (3/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.8%) and Grade 2 (0.4%) adverse reactions.

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 1, 2, 4–8, 10–12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

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Selected Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Hepatitis

Monitoring and Management

- Evaluate liver enzymes at baseline and periodically during treatment
- Monitor patients for signs and symptoms of hepatitis
- Ask patients to immediately report jaundice, severe nausea or vomiting, pain on the right side of the abdomen, dark urine (tea colored), or easy bruising or bleeding

Severity[a]	Dosage Modification
No tumor involvement of the liver and either: • AST or ALT increases to >3 x and up to 8 x ULN or • Total bilirubin increases to >1.5 x and up to 3 x ULN	Withhold[b]
No tumor involvement of the liver and either: • AST or ALT increases to >8 x ULN or • Total bilirubin increases to >3 x ULN	Permanently discontinue
With tumor involvement of the liver[c] and either: • Baseline AST or ALT >1 x and up to 3 x ULN and increases to >5 x and up to 10 x ULN or • Baseline AST or ALT >3 x and up to 5 x ULN and increases to >8 x and up to 10 x ULN	Withhold[b]
With tumor involvement of the liver[c] and either: • AST or ALT increases to >10 x ULN or • Total bilirubin increases to >3 x ULN	Permanently discontinue

[a]Based on NCI-CTCAE v4.0. [b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg per day (or equivalent) within 12 weeks of initiating steroids. [c]If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA or KEYTRUDA QLEX based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Hepatotoxicity and Immune-Mediated Hepatitis

- KEYTRUDA and KEYTRUDA QLEX can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients. Immune-mediated hepatitis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%) adverse reactions.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

- KEYTRUDA and KEYTRUDA QLEX can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA and KEYTRUDA QLEX depending on severity. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Adrenal insufficiency occurred in 2% (5/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions.

Selected Immune-Mediated Adverse Reactions *(continued)*



Immune-Mediated Endocrinopathies

Monitoring and Management

Ask patients to immediately report signs and symptoms of immune-mediated endocrinopathies, which may include:

- Headaches that will not go away or unusual headaches
- Eye sensitivity to light
- Eye problems
- Rapid heartbeat
- Increased sweating
- Extreme tiredness
- Weight gain or weight loss
- Feeling more hungry or thirsty than usual
- Urinating more often than usual
- Hair loss
- Feeling cold
- Constipation
- Deepening voice
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive irritability, or forgetfulness

Adrenal Insufficiency

- KEYTRUDA and KEYTRUDA QLEX can cause primary or secondary adrenal insufficiency
- For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated

Severity[a]	Dosage Modification
Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity

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

Severity[a]	Dosage Modification
Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity

[a]Based on NCI-CTCAE v4.0.

NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Endocrinopathies *(continued)*

Hypophysitis

- KEYTRUDA and KEYTRUDA QLEX 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 and KEYTRUDA QLEX depending on severity.
- Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 1–4, 6–8, 10–12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

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Selected Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Endocrinopathies *(continued)*

Thyroid Disorders	
• Evaluate thyroid function at baseline and periodically during treatment • Hypothyroidism can follow hyperthyroidism	• Thyroiditis can present with or without endocrinopathy • Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated

Severity[a]	Dosage Modification
Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity

Type 1 Diabetes Mellitus		
• Type 1 diabetes mellitus can present with diabetic ketoacidosis	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes	• Initiate treatment with insulin as clinically indicated

Severity[a]	Dosage Modification
Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity



Immune-Mediated Nephritis With Renal Dysfunction

Monitoring and Management		
• Evaluate creatinine at baseline and periodically during treatment	• Monitor patients for signs and symptoms of nephritis	• Ask patients to immediately report decrease in the amount of urine, blood in the urine, swelling of the ankles, or loss of appetite

Severity[a]	Dosage Modification
Grade 2 or 3 increased blood creatinine	Withhold[b]
Grade 4 increased blood creatinine	Permanently discontinue

[a]Based on NCI-CTCAE v4.0. [b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg per day (or equivalent) within 12 weeks of initiating steroids.

NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Endocrinopathies *(continued)*

Thyroid Disorders

- KEYTRUDA and KEYTRUDA QLEX 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 and KEYTRUDA QLEX depending on severity.

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 1–5, 7, 8, 10–12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

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Selected Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Dermatologic Adverse Reactions

Monitoring and Management

- KEYTRUDA and KEYTRUDA QLEX can cause immune-mediated rash or dermatitis
- Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes
- Exfoliative dermatitis, including SJS, DRESS, and TEN, has occurred with anti–PD-1/PD-L1 treatments
- Ask patients to immediately report rash, itching, skin blistering or peeling, painful sores or ulcers in the mouth, nose, throat, or genital area, fever or flu-like symptoms, or swollen lymph nodes
- For exfoliative and nonexfoliative rashes, withhold or permanently discontinue KEYTRUDA and KEYTRUDA QLEX depending on severity

Severity[a]	Dosage Modification
Suspected SJS, TEN, or DRESS	Withhold[b]
Confirmed SJS, TEN, or DRESS	Permanently discontinue

Other Immune-Mediated Adverse Reactions (IMARs)

The following **clinically significant immune-mediated adverse reactions** occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA, KEYTRUDA QLEX, 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.

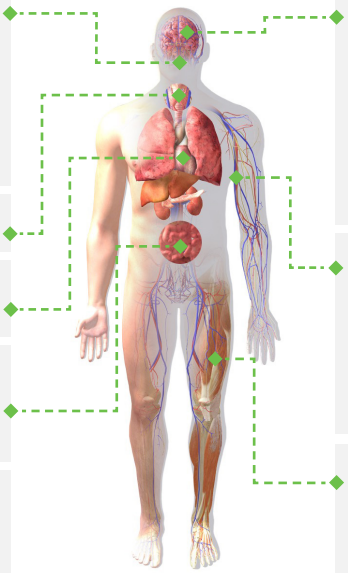
NERVOUS SYSTEM: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

ENDOCRINE: Hypoparathyroidism

CARDIAC/VASCULAR: Myocarditis, pericarditis, vasculitis

GASTROINTESTINAL: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis (2.8%), duodenitis

OTHER: Myocarditis-Myositis-Myasthenia Gravis (or Myasthenia-Like) Overlap syndrome, reported as the co-occurrence of either two or all three adverse reactions



OCULAR: Uveitis, iritis and other inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other IMARs, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss

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

MUSCULOSKELETAL/CONNECTIVE TISSUE: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica

[a]Based on NCI-CTCAE v4.0. [b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg per day (or equivalent) within 12 weeks of initiating steroids.

DRESS = drug rash with eosinophilia and systemic symptoms; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Endocrinopathies (*continued*)

Thyroid Disorders (*continued*)

- Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in <0.1% (1) of patients.

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 1–6, 8, 10–12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

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Hypersensitivity and Infusion- or Administration-Related Reactions

Monitoring and Management

- KEYTRUDA and KEYTRUDA QLEX can cause severe or life-threatening administration-related reactions, including hypersensitivity and anaphylaxis
- Monitor for signs and symptoms of infusion- and administration-related systemic reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever
- Infusion-related reactions have been reported in 0.2% of 2799 patients receiving KEYTRUDA
- Hypersensitivity and administration-related systemic reactions occurred in 3.2% (8/251) of patients receiving KEYTRUDA QLEX in combination with platinum-doublet chemotherapy, including Grade 2 (2.8%)

Severity[a]		Dosage Modification
KEYTRUDA: Infusion-related reaction **KEYTRUDA QLEX:** Hypersensitivity and administration-related systemic reactions	Grade 1 or 2	**KEYTRUDA:** Interrupt or slow the rate of infusion **KEYTRUDA QLEX:** Interrupt injection (if not already fully administered). If symptoms resolve, resume injection
	Grade 3 or 4	Stop the infusion or injection and permanently discontinue

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 GVHD, acute and chronic GVHD, hepatic VOD after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause)
- These complications may occur despite intervening therapy between anti–PD-1/PD-L1 treatments and allogeneic HSCT
- Follow patients closely for evidence of these complications and intervene promptly
- Consider the benefit vs risks of using anti–PD-1/PD-L1 treatments prior to or after an allogeneic HSCT

Increased Mortality in Patients With Multiple Myeloma

- In trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality
- Treatment of these patients with an anti–PD-1/PD-L1 treatment in this combination is not recommended outside of controlled trials

[a]Based on NCI-CTCAE v4.0.

GVHD = graft-versus-host disease; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; VOD = veno-occlusive disease.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Endocrinopathies *(continued)*

Thyroid Disorders (continued)

- Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

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Study MK-3475A-D77 Trial Information

Safety Results in Patients Who Received KEYTRUDA QLEX in Combination With Chemotherapy

KEYTRUDA QLEX

- The safety of KEYTRUDA QLEX compared to KEYTRUDA in patients with previously untreated metastatic NSCLC with no *EGFR*, *ALK* or *ROS1* genomic tumor aberrations was evaluated in study MK-3475A-D77. A total of 377 patients received either KEYTRUDA QLEX 790 mg/9,600 units every 6 weeks in combination with platinum-doublet chemotherapy (n=251) or KEYTRUDA 400 mg every 6 weeks in combination with platinum-doublet chemotherapy (n=126).
  - The pivotal study population and design were consistent with 2 of the approved indications for KEYTRUDA and KEYTRUDA QLEX, both in first-line treatment of NSCLC: For adult patients with metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations, in combination with pemetrexed and platinum chemotherapy; and for adult patients with metastatic squamous NSCLC, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound.

- Among patients who received KEYTRUDA QLEX, 58% were exposed for 6 months or longer and 3.2% were exposed for greater than 1 year.

- The median age of patients who received KEYTRUDA QLEX was 65 years (range: 39 to 87); 73% male, 63% White; 29% Asian, 4.8% multiple races, 2% Black or African American, 0.8% Alaska Native or American Indian; and 29% were of Hispanic or Latino ethnicity.

- **Serious adverse reactions** occurred in 39% of patients who received KEYTRUDA QLEX in combination with chemotherapy.
  - Serious adverse reactions in ≥1% of patients who received KEYTRUDA QLEX were pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%).

- **Fatal adverse reactions** occurred in 10% of patients who received KEYTRUDA QLEX in combination with chemotherapy including pneumonia (3.2%), neutropenic sepsis (2%), death not otherwise specified (1.6%), respiratory failure (1.2%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%).

- **Permanent discontinuation** of KEYTRUDA QLEX due to an adverse reaction occurred in 16% of patients.
  - Adverse reactions which resulted in permanent discontinuation of KEYTRUDA QLEX in ≥2% of patients included pneumonia and pneumonitis.

- **Dosage interruptions** of KEYTRUDA QLEX due to an adverse reaction occurred in 45% of patients.
  - Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia, anemia, thrombocytopenia, pneumonia, rash, and increased aspartate aminotransferase.

- **The most common adverse reactions (≥20%)** in patients who received KEYTRUDA QLEX in combination with chemotherapy were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).

ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; *EGFR* = epidermal growth factor receptor; NSCLC = non–small cell lung cancer; PD-L1 = programmed death ligand 1; *ROS1* = ROS proto-oncogene 1, receptor tyrosine kinase; TPS = tumor proportion score.

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Study MK-3475A-D77 Trial Information

Adverse Reactions Occurring in ≥10% of Patients With Metastatic NSCLC Receiving KEYTRUDA QLEX in Study MK-3475A-D77

Adverse Reaction	KEYTRUDA QLEX and Platinum-Doublet Chemotherapy (n=251)		KEYTRUDA and Platinum-Doublet Chemotherapy (n=126)	
	All Grades[a] (%)	Grades 3–4 (%)	All Grades[a] (%)	Grades 3–4 (%)
Gastrointestinal				
Nausea	25	1.2	25	0.8
Diarrhea[b]	16	2	14	0.8
Constipation	14	0	18	1.6
General				
Fatigue[c]	25	3.6	26	3.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[d]	21	2.4	30	2.4
Skin and Subcutaneous Tissue				
Rash[e]	18	2	19	0.8
Pruritus	12	0	13	0.8
Endocrine				
Hypothyroidism	14	0	12	0
Infections				
Pneumonia[f]	17	10	16	7
Nervous System				
Peripheral neuropathy[g]	11	0.4	14	0
Metabolism and Nutrition				
Decreased appetite	11	0.8	21	2.4
Hyperglycemia	11	0.8	11	0.8
Respiratory, Thoracic, and Mediastinal				
Cough[h]	10	0	11	0.8

Clinically relevant adverse reactions in <10% of patients who received **KEYTRUDA QLEX** included local injection-site reactions (2.4%).

[a]Graded per NCI-CTCAE v5.0. [b]Includes diarrhea, colitis, and enterocolitis. [c]Includes fatigue, asthenia. [d]Includes musculoskeletal pain, arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, noncardiac chest pain, and pain in extremity. [e]Includes rash, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, eczema, erythema multiforme, immune-mediated dermatitis, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin exfoliation. [f]Includes pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung abscess, pneumocystis jirovecii pneumonia, pneumonia bacterial, and pneumonia mycoplasmal. [g]Includes neuropathy peripheral, hypoaesthesia, neuralgia, paraesthesia, and peripheral sensory neuropathy. [h]Includes cough, productive cough, and upper-airway cough syndrome.

NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NSCLC = non–small cell lung cancer.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Endocrinopathies *(continued)*

Thyroid Disorders (continued)

- Thyroiditis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%). Hyperthyroidism occurred in 8% (20/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (3.2%). Hypothyroidism occurred in 14% (35/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (11%).

Before prescribing KEYTRUDA or KEYTRUDA QLEX, please read the additional Selected Safety Information (pages 1–8, 11, 12, 14, and 15) and the accompanying Prescribing Information for KEYTRUDA and KEYTRUDA QLEX. The Medication Guides for KEYTRUDA and KEYTRUDA QLEX also are available.

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Clinical Trials Experience: Adverse Reactions

- **The most common adverse reactions (≥20%) in patients who received KEYTRUDA QLEX in combination with chemotherapy** were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).
- **The most common adverse reactions (≥20%) in patients who received KEYTRUDA were:**
  - **As a single agent:** Fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism.
  - **In combination with chemotherapy or chemoradiotherapy:** Fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, hypothyroidism, radiation skin injury, dysphagia, dry mouth, and musculoskeletal pain.
- **The safety of KEYTRUDA QLEX for its approved indications has been established in adequate and well-controlled studies of KEYTRUDA QLEX in combination with platinum-doublet chemotherapy (study MK-3475A-D77) and KEYTRUDA, as a single agent or in combination therapy, across tumor types.**

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

Immune-Mediated Endocrinopathies *(continued)*

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 and KEYTRUDA QLEX depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Type 1 DM occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy.

Immune-Mediated Nephritis With Renal Dysfunction

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

Immune-Mediated Dermatologic Adverse Reactions

- KEYTRUDA and KEYTRUDA QLEX 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–programmed death receptor-1 (PD-1)/programmed death ligand 1 (PD-L1) treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA and KEYTRUDA QLEX depending on severity.
- Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38 patients. Immune-mediated dermatologic adverse reactions occurred in 1.6% (4/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 4 (0.8%) and Grade 3 (0.8%) adverse reactions.

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Summary

IMARs, which may be severe or fatal, can occur in any organ system or tissue. The following are some signs and symptoms of select IMARs and other adverse reactions that patients should report. This is not an exhaustive list.

Pneumonitis

- Cough
- Shortness of breath
- Chest pain

Colitis

- Diarrhea (loose stools) or more frequent bowel movements than usual
- Stools that are black, tarry, sticky, or have blood or mucus
- Severe abdominal pain or tenderness

Hepatitis

- Jaundice
- Severe nausea or vomiting
- Pain on the right side of the abdomen
- Dark urine (tea colored)
- Easy bruising or bleeding

Dermatologic Adverse Reactions

- Rash
- Itching
- Skin blistering or peeling
- Painful sores or ulcers in the mouth, nose, throat, or genital area
- Fever or flu-like symptoms
- Swollen lymph nodes

Endocrinopathies

- Headaches that will not go away or unusual headaches
- Eye sensitivity to light
- Eye problems
- Rapid heartbeat
- Increased sweating
- Extreme tiredness
- Weight gain or weight loss
- Feeling more hungry or thirsty than usual
- Urinating more often than usual
- Hair loss
- Feeling cold
- Constipation
- Deepening voice
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Nephritis

- Decrease in the amount of urine
- Blood in the urine
- Swelling of the ankles
- Loss of appetite

Hypersensitivity & Administration-Related Reactions

- Chills or shaking
- Itching or rash
- Flushing
- Shortness of breath or wheezing
- Dizziness
- Feeling like passing out
- Fever
- Back pain

Other IMARs

- Chest pain, irregular heartbeat, shortness of breath, swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps
- Low red blood cells, bruising

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying IMARs.

- 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 IMARs, initiate appropriate workup to exclude alternative etiologies, including infection.
- Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA and KEYTRUDA QLEX depending on severity of the IMAR.

- In general, if **KEYTRUDA** and **KEYTRUDA QLEX** require 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.

IMAR = immune-mediated adverse reaction; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

SELECTED SAFETY INFORMATION *(continued)*

Severe and Fatal Immune-Mediated Adverse Reactions *(continued)*

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, KEYTRUDA QLEX, or were reported with the use of other anti–PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis; *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *Ocular*: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal*: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis (2.8%), duodenitis; *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; *Endocrine*: Hypoparathyroidism; *Hematologic/Immune*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection; *Other*: Myocarditis-Myositis-Myasthenia Gravis (or Myasthenia-Like) Overlap syndrome, reported as the co-occurrence of either two or all three adverse reactions.

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Summary of Dose Modifications

Below are the dosage modifications for **KEYTRUDA** and **KEYTRUDA QLEX** *for select adverse reactions. In the top table, the modifications are aligned to severity based on grading in the NCI-CTCAE v4.0.[a] In the bottom table, the modifications are based on criteria from the Prescribing Information only, as they are not dependent on the grading for these adverse reactions.*

	Severity[a]			
Select Adverse Reactions	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Immune-mediated pneumonitis		**Withhold[b]**	**Permanently discontinue**	
Immune-mediated colitis		**Withhold[b]**		**Permanently discontinue**
Immune-mediated endocrinopathies			**Withhold until clinically stable or permanently discontinue depending on severity**	
Immune-mediated nephritis with renal dysfunction		**Withhold[b,c]**		**Permanently discontinue**
Infusion-related reactions (KEYTRUDA)	**Interrupt or slow the rate of infusion**		**Permanently discontinue**	
Hypersensitivity and administration-related systemic reactions (KEYTRUDA QLEX)	**Interrupt injection (if not already fully administered); Resume if symptoms resolve**		**Permanently discontinue**	

Select Adverse Reactions	**Dosage Modification**
Immune-mediated hepatitis with: • No tumor involvement of the liver and either: AST or ALT increases to >3 x and up to 8 x ULN or total bilirubin increases to >1.5 x and up to 3 x ULN • With tumor involvement of the liver[d] and either: Baseline AST or ALT >1 x and up to 3 x ULN and increases to >5 x and up to 10 x ULN or baseline AST or ALT >3 x and up to 5 x ULN and increases to >8 x and up to 10 x ULN	**Withhold[b]**
Immune-mediated hepatitis with: • No tumor involvement of the liver and either: AST or ALT increases to >8 x ULN or total bilirubin increases to >3 x ULN • With tumor involvement of the liver[d] and either: AST or ALT increases to >10 x ULN or total bilirubin increases to >3 x ULN	**Permanently discontinue**
Immune-mediated dermatologic adverse reactions: • Suspected SJS, TEN, or DRESS	**Withhold[b]**
Immune-mediated dermatologic adverse reactions: • Confirmed SJS, TEN, or DRESS	**Permanently discontinue**

[a]Based on NCI-CTCAE v4.0. [b]Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg per day (or equivalent) within 12 weeks of initiating steroids. [c]Grade refers to increased blood creatinine. [d]If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA and KEYTRUDA QLEX based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = drug rash with eosinophilia and systemic symptoms; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; ULN = upper limit of normal.

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SELECTED SAFETY INFORMATION *(continued)*

Hypersensitivity and Infusion- or Administration-Related Reactions

- KEYTRUDA and KEYTRUDA QLEX can cause severe or life-threatening administration-related reactions, including hypersensitivity and anaphylaxis. With KEYTRUDA and KEYTRUDA QLEX, monitor for signs and symptoms of infusion- and administration-related systemic reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Infusion-related reactions have been reported in 0.2% of 2799 patients receiving KEYTRUDA. 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. Hypersensitivity and administration-related systemic reactions occurred in 3.2% (8/251) of patients receiving KEYTRUDA QLEX in combination with platinum-doublet chemotherapy, including Grade 2 (2.8%). Interrupt injection (if not already fully administered) and resume if symptoms resolve for mild or moderate systemic reactions. For severe or life-threatening systemic reactions, stop injection and permanently discontinue KEYTRUDA QLEX.

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

Increased Mortality in Patients With Multiple Myeloma

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

Embryofetal Toxicity

- Based on their mechanism of action, KEYTRUDA and KEYTRUDA QLEX can each 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 or KEYTRUDA QLEX and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

- In study MK-3475A-D77, when KEYTRUDA QLEX was administered with chemotherapy in metastatic non–small cell lung cancer (NSCLC), serious adverse reactions occurred in 39% of patients. Serious adverse reactions in ≥1% of patients who received KEYTRUDA QLEX were pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%). Fatal adverse reactions occurred in 10% of patients including pneumonia (3.2%), neutropenic sepsis (2%), death not otherwise specified (1.6%), respiratory failure (1.2%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%). KEYTRUDA QLEX was permanently discontinued due to an adverse reaction in 16% of 251 patients. Adverse reactions which resulted in permanent discontinuation of KEYTRUDA QLEX in ≥2% of patients included pneumonia and pneumonitis. Dosage interruptions of KEYTRUDA QLEX due to an adverse reaction occurred in 45% of patients. Adverse reactions which required dosage interruption in ≥2% of patients included neutropenia, anemia, thrombocytopenia, pneumonia, rash, and increased aspartate aminotransferase. The most common adverse reactions (≥20%) were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).
- In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions (≥20%) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).
- In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and either paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 15% of 101 patients. The most frequent serious adverse reactions reported in at least 2% of patients were febrile neutropenia, pneumonia, and urinary tract infection. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs 36%) and peripheral neuropathy (31% vs 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

SELECTED SAFETY INFORMATION *(continued)*

Adverse Reactions *(continued)*

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

Lactation

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

References

1. US Food and Drug Administration. IND application reporting: safety reports. Content current as of October 19, 2021. Accessed June 22, 2026. https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports **2.** Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(4):252–264. doi:10.1038/nrc3239

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For additional copies of the Prescribing Information, please call 800-672-6372, visit keytrudahcp.com/qlex, or contact your Merck representative.

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