Dosing and Adverse Reaction Management Guide

A guide to help monitor and manage adverse reactions in patients treated with **KEYTRUDA + LENVIMA**

Indications for KEYTRUDA + LENVIMA

Advanced Renal Cell Carcinoma

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

Advanced Endometrial Carcinoma

KEYTRUDA, in combination with LENVIMA, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Selected Safety Information for KEYTRUDA® (pembrolizumab)

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. 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.

Selected Safety Information for LENVIMA® (lenvatinib)

Hypertension

- In differentiated thyroid cancer (DTC), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In advanced renal cell carcinoma (RCC), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In unresectable hepatocellular carcinoma (HCC), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.
- Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Dosage and administration for KEYTRUDA + LENVIMA

When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold or discontinue KEYTRUDA as shown in this resource. Withhold, dose reduce, or discontinue LENVIMA as shown in this resource. No dose reductions are recommended for KEYTRUDA.

Dosage and administration for KEYTRUDA



Administered after dilution as an intravenous infusion over **30** minutes



Adults: 200 mg

or



Adults: 400 mg

- Continue treatment with KEYTRUDA until disease progression, unacceptable toxicity, or up to 24 months.
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

Dosage for LENVIMA for patients with advanced renal cell carcinoma or advanced endometrial carcinoma[a]



20 mg once daily at the same time each day

[a]When administered with KEYTRUDA.
LENVIMA is available in 4-mg and 10-mg capsules. Capsules are not shown at actual size.

- If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.
- Continue treatment with LENVIMA in combination with KEYTRUDA until disease progression or unacceptable toxicity.
- After completing 2 years of combination therapy, LENVIMA may be administered as a single agent until disease progression or until unacceptable toxicity for advanced renal cell carcinoma.
- The recommended dosage of LENVIMA for patients with **advanced renal cell carcinoma or advanced endometrial carcinoma and severe renal impairment** (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is **10 mg orally once daily**.
- The recommended dosage of LENVIMA for patients with **advanced renal cell carcinoma or advanced endometrial carcinoma and severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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

- 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.

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Dosage and administration for **KEYTRUDA + LENVIMA** (*continued*)

When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold or discontinue KEYTRUDA as shown in this resource. Withhold, dose reduce, or discontinue LENVIMA as shown in this resource. No dose reductions are recommended for KEYTRUDA.

Administration for LENVIMA for patients with advanced renal cell carcinoma or advanced endometrial carcinoma[a,b]



With or without food



Swallow LENVIMA capsules whole. Do not crush or chew

OR



Prepare oral suspension with water or apple juice

Note: See preparation below

OR



Prepare suspension for feeding tube administration with water

Note: See preparation below

[a]When administered with KEYTRUDA.
[b]At the same time each day.
LENVIMA is available in 4-mg and 10-mg capsules. Capsules are not shown at actual size.

Preparation of suspension

- Place the required number of capsules, up to a maximum of 5, in a small container (approximately 20 mL capacity) or syringe (20 mL). Do not break or crush capsules.
- Add 3 mL of liquid to the container or syringe. Wait 10 minutes for the capsule shell (outer surface) to disintegrate, then stir or shake the mixture for 3 minutes until capsules are fully disintegrated and administer the entire contents.
- Next, add an additional 2 mL of liquid to the container or syringe using a second syringe or dropper, swirl or shake and administer. Repeat this step at least once and until there is no visible residue to ensure all of the medication is taken.
- If 6 capsules are required for a dose, follow these instructions using 3 capsules at a time.

If LENVIMA suspension is not used at the time of preparation, LENVIMA suspension may be stored in a refrigerator at 36 ºF to 46 ºF (2 ºC to 8 ºC) for a maximum of 24 hours in a covered container. If not administered within 24 hours, the suspension should be discarded.

Note: Compatibility has been confirmed for polypropylene syringes and for feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube) and at least 6 French diameter (silicone tube).

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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

Immune-Mediated Pneumonitis

- KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Arterial Thromboembolic Events

- Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.
- Among patients receiving LENVIMA with KEYTRUDA, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information

Selected Safety Information for KEYTRUDA® (pembrolizumab)

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. 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.

<u>Immune-Mediated Pneumonitis</u>

- KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Selected Safety Information for LENVIMA® (lenvatinib)

Hypertension

- In differentiated thyroid cancer (DTC), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In advanced renal cell carcinoma (RCC), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In unresectable hepatocellular carcinoma (HCC), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.
- Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Arterial Thromboembolic Events

- Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.
- Among patients receiving LENVIMA with KEYTRUDA, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).
- Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

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KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information (*continued*)

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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

Immune-Mediated Colitis

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

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

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

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Hepatotoxicity

- Across clinical studies enrolling 1,327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients. 2% of patients discontinued LENVIMA due to hepatic encephalopathy and 1% discontinued due to hepatic failure.
- Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Renal Failure or Impairment

- Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).
- Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Proteinuria

- In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information (*continued*)

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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

Immune-Mediated Endocrinopathies (*continued*)

Hypophysitis

- KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Thyroid Disorders

- KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in <0.1% (1) of patients.
- Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

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

- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Diarrhea

- Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Fistula Formation and Gastrointestinal Perforation

- Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation

- In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.
- Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Hypocalcemia

- In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- Across clinical studies of 1,823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

QTc = corrected QT interval; MRI = magnetic resonance imaging.

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KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information (*continued*)

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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

Immune-Mediated Nephritis With Renal Dysfunction

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

Immune-Mediated Dermatologic Adverse Reactions

- KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with anti–PD-1/PD-L1 treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other anti–PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis; *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *Ocular*: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal*: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis;

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Hemorrhagic Events

- Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.
- Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

- LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.
- Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing

- Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

CNS = central nervous system.

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KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information (*continued*)

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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

Other Immune-Mediated Adverse Reactions (*continued*)

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; *Endocrine*: Hypoparathyroidism; *Hematologic/Immune*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Infusion-Related Reactions

- KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 reactions. For Grade 3 or Grade 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

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

Increased Mortality in Patients With Multiple Myeloma

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

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Osteonecrosis of the Jaw (ONJ)

- ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

  Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

  Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

  Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity

- Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of LENVIMA during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus; and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

Adverse Reactions

- In RCC, the most common adverse reactions (≥20%) observed in LENVIMA + KEYTRUDA–treated patients were fatigue (63%), diarrhea (62%), musculoskeletal pain (58%), hypothyroidism (57%), hypertension (56%), stomatitis (43%), decreased appetite (41%), rash (37%), nausea (36%), decreased weight (30%), dysphonia (30%), proteinuria (30%), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain (27%), hemorrhagic events (27%), vomiting (26%), constipation (25%), hepatotoxicity (25%), headache (23%), and acute kidney injury (21%).

  Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA in combination with KEYTRUDA, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm and subarachnoid hemorrhage.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information (*continued*)

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

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-581, when KEYTRUDA was administered in combination with LENVIMA to patients with advanced renal cell carcinoma (n=352), fatal adverse reactions occurred in 4.3% of patients. Serious adverse reactions occurred in 51% of patients; the most common (≥2%) were hemorrhagic events (5%), diarrhea (4%), hypertension, myocardial infarction, pneumonitis, and vomiting (3% each), acute kidney injury, adrenal insufficiency, dyspnea, and pneumonia (2% each).

  Permanent discontinuation of KEYTRUDA, LENVIMA, or both due to an adverse reaction occurred in 37% of patients; 29% KEYTRUDA only, 26% LENVIMA only, and 13% both. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA, LENVIMA, or the combination were pneumonitis, myocardial infarction, hepatotoxicity, acute kidney injury, rash (3% each), and diarrhea (2%).

  The most common adverse reactions (≥20%) observed with KEYTRUDA in combination with LENVIMA were fatigue (63%), diarrhea (62%), musculoskeletal disorders (58%), hypothyroidism (57%), hypertension (56%), stomatitis (43%), decreased appetite (41%), rash (37%), nausea (36%), weight loss, dysphonia and proteinuria (30% each), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain and hemorrhagic events (27% each), vomiting (26%), constipation and hepatotoxicity (25% each), headache (23%), and acute kidney injury (21%).

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

Serious adverse reactions occurred in 51% of patients receiving LENVIMA and KEYTRUDA. Serious adverse reactions in ≥2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 37% of patients; 26% LENVIMA only, 29% KEYTRUDA only, and 13% both drugs. The most common adverse reactions (≥2%) leading to permanent discontinuation of LENVIMA, KEYTRUDA, or both were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with KEYTRUDA. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-plantar erythrodysesthesia (11%), nausea (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), vomiting (6%), increased ALT (5%), and increased amylase (5%).

- In endometrial carcinoma, the most common adverse reactions (≥20%) observed in LENVIMA + KEYTRUDA–treated patients were hypothyroidism (67%), hypertension (67%), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), decreased weight (34%), abdominal pain (34%), urinary tract infection (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%).

  Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and KEYTRUDA, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

  Serious adverse reactions occurred in 50% of these patients receiving LENVIMA and KEYTRUDA. Serious adverse reactions with frequency ≥3% were hypertension (4.4%), and urinary tract infection (3.2%).

  Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of these patients. The most common (≥1%) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.8%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%).

ALT = alanine aminotransferase.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Selected Safety Information (*continued*)

Selected Safety Information for KEYTRUDA® (pembrolizumab) (*continued*)

Adverse Reactions (*continued*)

- In KEYNOTE-775, when KEYTRUDA was administered in combination with LENVIMA to patients with advanced endometrial carcinoma that was pMMR or not MSI-H (n=342), fatal adverse reactions occurred in 4.7% of patients. Serious adverse reactions occurred in 50% of these patients; the most common (≥3%) were hypertension (4.4%) and urinary tract infections (3.2%).

  Discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of KEYTRUDA (≥1%) was increased ALT (1.2%).

  The most common adverse reactions for KEYTRUDA in combination with LENVIMA (reported in ≥20% patients) were hypothyroidism and hypertension (67% each), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), abdominal pain and weight loss (34% each), urinary tract infections (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (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.

pMMR = mismatch repair proficient; MSI-H = microsatellite instability-high; ALT = alanine aminotransferase.

Selected Safety Information for LENVIMA® (lenvatinib) (*continued*)

Adverse Reactions (*continued*)

Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common (≥5%) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthenia (5%), and weight decreased (5%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common (≥2%) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (6%), decreased appetite (5%), vomiting (5%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2%).

Use in Specific Populations

- Because of the potential for serious adverse reactions in breastfed children, advise women to discontinue breastfeeding during treatment and for 1 week after last dose. LENVIMA may impair fertility in males and females of reproductive potential.
- No dose adjustment is recommended for patients with mild (creatinine clearance [CLcr] 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or endometrial carcinoma and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease.
- No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or endometrial carcinoma and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Fatal and serious adverse reactions in patients receiving **KEYTRUDA + LENVIMA** in the KEYNOTE-581/CLEAR trial

The safety of KEYTRUDA + LENVIMA in the first-line treatment of adult patients with advanced renal cell carcinoma was evaluated in the KEYNOTE-581/CLEAR trial at the protocol-specified interim analysis. Patients received KEYTRUDA 200 mg intravenously every 3 weeks in combination with LENVIMA 20 mg orally once daily (n=352), or LENVIMA 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of KEYTRUDA + LENVIMA was 17 months (range: 0.1–39).

Fatal adverse reactions occurred in 4.3% of patients treated with KEYTRUDA + LENVIMA, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of:

Arrhythmia	Increased blood creatinine	Nephritis
Autoimmune hepatitis	Multiple organ dysfunction syndrome	Pneumonitis
Dyspnea	Myasthenic syndrome	Ruptured aneurysm
Hypertensive crisis	Myocarditis	Subarachnoid hemorrhage

Serious adverse reactions occurred in 51% of patients receiving KEYTRUDA + LENVIMA.

Serious adverse reactions in ≥2% of patients receiving KEYTRUDA + LENVIMA were:

Hemorrhagic events (5%)	Pneumonitis (3%)	Dyspnea (2%)
Diarrhea (4%)	Vomiting (3%)	Pneumonia (2%)
Hypertension (3%)	Acute kidney injury (2%)	
Myocardial infarction (3%)	Adrenal insufficiency (2%)	

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Adverse reactions that led to **permanent discontinuation, dose interruption, and dose reduction** in the KEYNOTE-581/CLEAR trial

Permanent discontinuation, dose interruption, and dose reduction due to an adverse reaction in the KEYNOTE-581/CLEAR trial

	Permanent Discontinuation (%)	Dose Interruption (%)	Dose Reduction (%)
KEYTRUDA, **LENVIMA**, or both	37	78	–
KEYTRUDA + **LENVIMA**	13	39	–
KEYTRUDA	29	55	–
LENVIMA	26	73	69

- No dose reduction for **KEYTRUDA** is recommended.

The most common (≥2%) adverse reactions that resulted in permanent discontinuation of KEYTRUDA, LENVIMA, or both

- Pneumonitis (3%)
- Myocardial infarction (3%)
- Hepatotoxicity (3%)
- Acute kidney injury (3%)
- Rash (3%)
- Diarrhea (2%)

Most common (≥3%) adverse reactions in patients receiving KEYTRUDA + LENVIMA that resulted in interruption of KEYTRUDA

- Diarrhea (10%)
- Hepatotoxicity (8%)
- Fatigue (7%)
- Lipase increased (5%)
- Amylase increased (4%)
- Musculoskeletal pain (3%)
- Hypertension (3%)
- Rash (3%)
- Acute kidney injury (3%)
- Decreased appetite (3%)

ALT = alanine aminotransferase.

Most common (≥5%) adverse reactions in patients receiving KEYTRUDA + LENVIMA that resulted in dose reduction or interruption of LENVIMA

- Diarrhea (26%)
- Fatigue (18%)
- Hypertension (17%)
- Proteinuria (13%)
- Decreased appetite (12%)
- Palmar-plantar erythrodysesthesia (11%)
- Nausea (9%)
- Stomatitis (9%)
- Musculoskeletal pain (8%)
- Rash (8%)
- Increased lipase (7%)
- Abdominal pain (6%)
- Vomiting (6%)
- Increased ALT (5%)
- Increased amylase (5%)

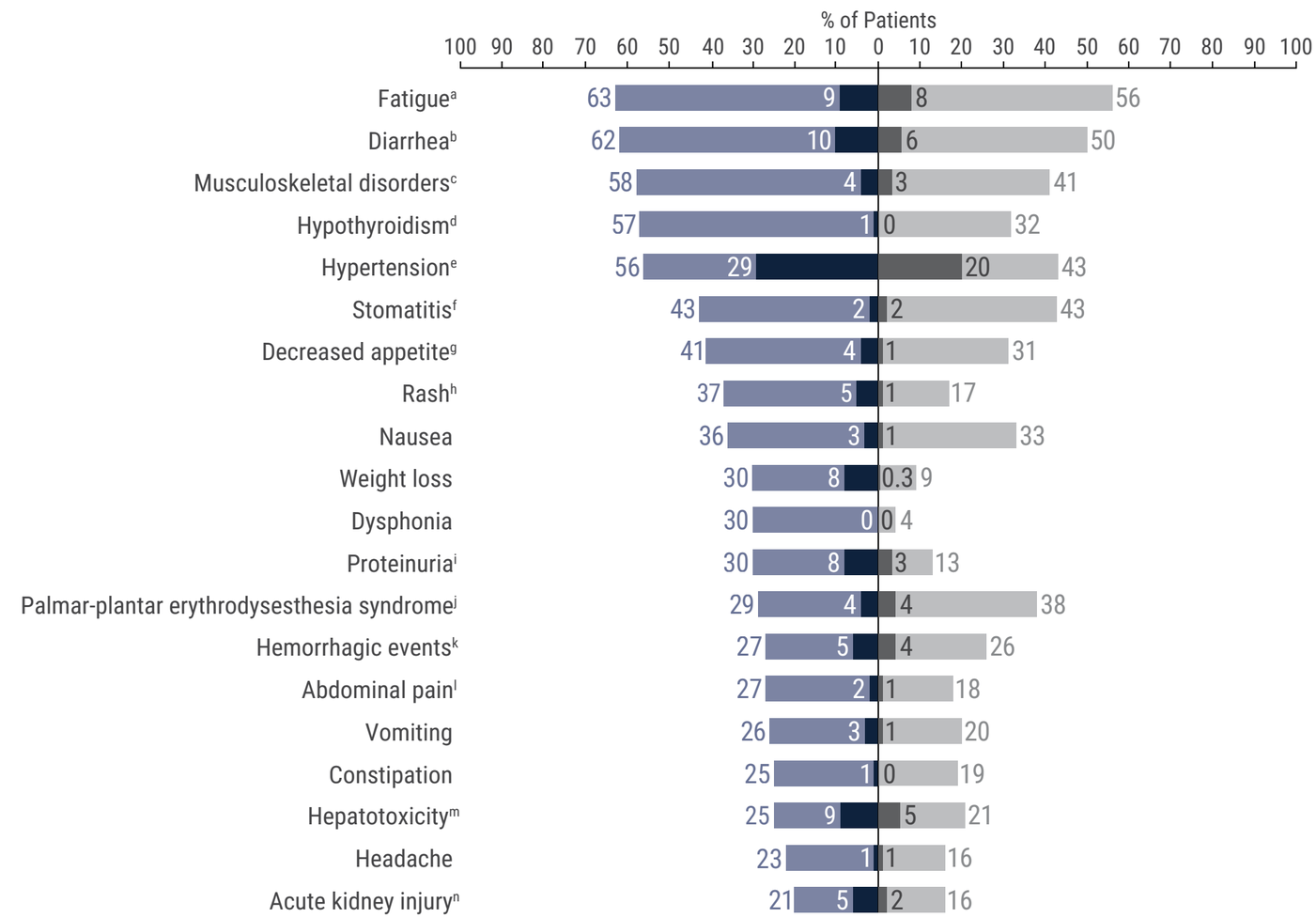
Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Adverse reactions in ≥20% of patients receiving **KEYTRUDA + LENVIMA** in the KEYNOTE-581/CLEAR trial



- Fifteen percent (15%) of patients treated with KEYTRUDA + LENVIMA received an oral prednisone equivalent to ≥40 mg daily for an immune-mediated adverse reaction.
- Clinically relevant adverse reactions (<20%) that occurred in patients receiving KEYTRUDA + LENVIMA were myocardial infarction (3%) and angina pectoris (1%).
- Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed on rechallenge in 3 patients receiving LENVIMA, in 10 patients receiving both KEYTRUDA and LENVIMA (n=38), and was not observed on rechallenge with KEYTRUDA alone (n=3).

[a] Includes asthenia, fatigue, lethargy, and malaise.
[b] Includes diarrhea and gastroenteritis.
[c] Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and pain in jaw.
[d] Includes hypothyroidism, increased blood thyroid stimulating hormone, and secondary hypothyroidism.
[e] Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure.
[f] Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.
[g] Includes decreased appetite and early satiety.
[h] Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.
[i] Includes hemoglobinuria, nephrotic syndrome, and proteinuria.
[j] Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, and plantar erythema.
[k] Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, and upper gastrointestinal hemorrhage.
[l] Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, and upper abdominal pain.
[m] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, and gamma-glutamyltransferase increased.
[n] Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic.

AST = aspartate aminotransferase.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Post hoc analysis: Median time to first onset of select adverse reactions with **KEYTRUDA + LENVIMA** in KEYNOTE-581/CLEAR (n=352)[1]

LIMITATION: This is a post hoc analysis based on data from KEYNOTE-581/CLEAR. No formal statistical testing was planned and, therefore, no conclusions can be drawn.

- As this information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgement and evaluation of a potential adverse reaction should it occur.
- Health care professionals should monitor and evaluate patients for the presence of potential adverse reactions throughout treatment with KEYTRUDA, in combination with LENVIMA, and following discontinuation.
- Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.
- Data does not represent a complete list of each adverse reaction that occurred during the CLEAR trial.
- The interquartile range (Q1:Q3) represents the time to onset (the earliest treatment-emergent adverse reaction [AR] start date) for the AR for the middle 50% of patients who experienced that AR from quartile 1 to quartile 3.
- ARs were chosen based on frequency of occurrence (in ≥30% of patients). ARs could have occurred while receiving LENVIMA and/or KEYTRUDA or within the protocol-defined follow-up period of 30 days after the patient's last dose. ARs were recorded until the end of the follow-up period or until resolution, whichever came first. Grading of ARs was performed according to Common Terminology Criteria for Adverse Events v4.03.

Median time to first onset
Interquartile range (Q1;Q3)
Minimum/maximum time to onset

Adverse Reaction Incidence, n (%)[b,c]	LENVIMA: Dose Interruption, n (%)[c]	LENVIMA: Dose Reduction, n (%)[c]	LENVIMA: Discontinuation, n (%)[c]	KEYTRUDA: Dose Interruption, n (%)[c]	KEYTRUDA: Discontinuation, n (%)[c]	Median time to first onset and range (weeks),[a] Q1–Q3 (MIN 0 3 6 9 12 15 18 21 24 27 30 33 36 MAX)
Hypertension[d] **198** (56.3)	32 (9.1)	42 (11.9)	3 (0.9)	11 (3.1)	1 (0.3)	0.1 – **3.0** – 126.9
Dysphonia **105** (29.8)	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.1 – **3.0** – 129.3
Fatigue[e] **222** (63.1)	39 (11.1)	34 (9.7)	2 (0.6)	26 (7.4)	1 (0.3)	0.1 – **4.4** – 128.3
Proteinuria[f] **105** (29.8)	27 (7.7)	36 (10.2)	6 (1.7)	8 (2.3)	2 (0.6)	0.1 – **5.1** – 125.1
Musculoskeletal pain[g] **204** (58.0)	21 (6.0)	9 (2.6)	1 (0.3)	12 (3.4)	2 (0.6)	0.1 – **6.4** – 148.6
Stomatitis[h] **152** (43.2)	18 (5.1)	16 (4.5)	1 (0.3)	4 (1.1)	0 (0.0)	0.1 – **6.6** – 125.9

Adapted with permission from Motzer R, George S, Merchan JR, et al. Characterization and management of adverse reactions from the CLEAR study in advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab. *Oncologist*. 2023;28(6):501–509. doi:10.1093/oncolo/oyac269

[a] Median time to first onset in patients who experienced the adverse reaction. Gray boxes represent Q1–Q3. Lines represent the range.
[b] Any grade.
[c] Percentages are based on the safety population of the KEYTRUDA + LENVIMA group (n=352). The safety population included all patients who received at least 1 dose of any study drug.
[d] Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure.
[e] Includes fatigue, asthenia, malaise, and lethargy.
[f] Includes hemoglobinuria, nephrotic syndrome, and proteinuria.
[g] Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain, pain in extremity, and pain in jaw.
[h] Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

Reference: 1. Motzer R, George S, Merchan JR, et al. Characterization and management of adverse reactions from the CLEAR study in advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab. *Oncologist*. 2023;28(6):501–509. doi:10.1093/oncolo/oyac269

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Post hoc analysis: Median time to first onset of select adverse reactions with **KEYTRUDA + LENVIMA** in KEYNOTE-581/CLEAR (n=352)[1] (*continued*)

LIMITATION: This is a post hoc analysis based on data from KEYNOTE-581/CLEAR. No formal statistical testing was planned and, therefore, no conclusions can be drawn.

- As this information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgement and evaluation of a potential adverse reaction should it occur.
- Health care professionals should monitor and evaluate patients for the presence of potential adverse reactions throughout treatment with KEYTRUDA, in combination with LENVIMA, and following discontinuation.
- Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.
- Data does not represent a complete list of each adverse reaction that occurred during the CLEAR trial.
- The interquartile range (Q1:Q3) represents the time to onset (the earliest treatment-emergent adverse reaction [AR] start date) for the AR for the middle 50% of patients who experienced that AR from quartile 1 to quartile 3.
- ARs were chosen based on frequency of occurrence (in ≥30% of patients). ARs could have occurred while receiving LENVIMA and/or KEYTRUDA or within the protocol-defined follow-up period of 30 days after the patient's last dose. ARs were recorded until the end of the follow-up period or until resolution, whichever came first. Grading of ARs was performed according to Common Terminology Criteria for Adverse Events v4.03.

Adverse Reaction Incidence, n (%)[b,c]	LENVIMA: Dose Interruption, n (%)[c]	LENVIMA: Dose Reduction, n (%)[c]	LENVIMA: Discontinuation, n (%)[c]	KEYTRUDA: Dose Interruption, n (%)[c]	KEYTRUDA: Discontinuation, n (%)[c]	Median time to first onset and range (weeks),[a] Q1–Q3 (MIN 0 3 6 9 12 15 18 21 24 27 30 33 36 MAX)
Rash[i] **131** (37.2)	20 (5.7)	14 (4.0)	5 (1.4)	10 (2.8)	8 (2.3)	0.1 — 11.4 — 127.4
Hypothyroidism[j] **200** (56.8)	6 (1.7)	4 (1.1)	1 (0.3)	5 (1.4)	2 (0.6)	0.1 — 14.3 — 93.1
Nausea **126** (35.8)	15 (4.3)	18 (5.1)	1 (0.3)	5 (1.4)	1 (0.3)	0.1 — 14.4 — 128.7
Decreased appetite[k] **143** (40.6)	16 (4.5)	27 (7.7)	1 (0.3)	9 (2.6)	1 (0.3)	0.1 — 14.6 — 150.1
Weight decreased **105** (29.8)	9 (2.6)	10 (2.8)	1 (0.3)	5 (1.4)	2 (0.6)	1.1 — 17.4 — 114.1
Diarrhea[l] **218** (61.9)	62 (17.6)	57 (16.2)	5 (1.4)	36 (10.2)	4 (1.1)	0.3 — 20.0 — 118.0

Median time to first onset | Interquartile range (Q1;Q3) | Minimum/maximum time to onset

Adapted with permission from Motzer R, George S, Merchan JR, et al. Characterization and management of adverse reactions from the CLEAR study in advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab. *Oncologist*. 2023;28(6):501–509. doi:10.1093/oncolo/oyac269

[a] Median time to first onset in patients who experienced the adverse reaction. Gray boxes represent Q1–Q3. Lines represent the range.
[b] Any grade.
[c] Percentages are based on the safety population of the KEYTRUDA + LENVIMA group (n=352). The safety population included all patients who received at least 1 dose of any study drug.
[i] Includes genital rash, infusion site rash, penile rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.
[j] Includes hypothyroidism, increased blood thyroid-stimulating hormone, and secondary hypothyroidism.
[k] Includes decreased appetite and early satiety.
[l] Includes diarrhea and gastroenteritis.

Reference: 1. Motzer R, George S, Merchan JR, et al. Characterization and management of adverse reactions from the CLEAR study in advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab. *Oncologist*. 2023;28(6):501–509. doi:10.1093/oncolo/oyac269

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Fatal and serious adverse reactions in patients receiving **KEYTRUDA + LENVIMA** in KEYNOTE-775/Study 309

The safety of KEYTRUDA + LENVIMA was investigated in KEYNOTE-775/Study 309, a multicenter, open-label, randomized (1:1) active-controlled trial of patients with advanced endometrial carcinoma that was pMMR or not MSI-H, who were previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial carcinoma that was pMMR or not MSI-H received KEYTRUDA 200 mg intravenously every 3 weeks with LENVIMA 20 mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

- The median duration of study treatment was 7.2 months (range: 1 day–26.8 months).
- The median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day–25.8 months); for LENVIMA it was 6.7 months (range: 1 day–26.8 months).

Fatal adverse reactions occurred in 4.7% of patients treated with KEYTRUDA + LENVIMA, including 2 cases of pneumonia, and 1 case of the following:

Acute kidney injury	Intestinal perforation	Myelodysplastic syndrome
Acute myocardial infarction	Lower gastrointestinal hemorrhage	Pulmonary embolism
Colitis	Malignant gastrointestinal obstruction	Right ventricular dysfunction
Decreased appetite	Multiple organ dysfunction syndrome	

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA + LENVIMA.

Serious adverse reactions (≥3%) were:

Hypertension (4.4%)	Urinary tract infection (3.2%)

pMMR = mismatch repair proficient; MSI-H = microsatellite instability-high.

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Adverse reactions that led to **discontinuation, dose interruption, and dose reduction** in KEYNOTE-775/Study 309

Discontinuation and interruption rates for KEYTRUDA and for LENVIMA, and dose reduction rate for LENVIMA due to adverse reactions in KEYNOTE-775/Study 309

	KEYTRUDA	LENVIMA
Discontinuation	15%	26%
Dose interruption	48%	58%
Dose reduction	N/A	67%

N/A = not applicable.

- No dose reduction for **KEYTRUDA** is recommended.

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of patients. Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of patients.

The most common (≥1%) adverse reaction leading to discontinuation of KEYTRUDA was:

Increased alanine aminotransferase (1.2%)

The most common (≥1%) adverse reactions leading to discontinuation of LENVIMA were:

Hypertension (2%)	Diarrhea (1.2%)	Proteinuria (1.2%)
Asthenia (1.8%)	Decreased appetite (1.2%)	Vomiting (1.2%)

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Most **common adverse reactions** that led to **dose interruption** and **dose reduction** in KEYNOTE-775/Study 309

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 48% of patients. Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of patients. Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients.

The most common (≥3%) adverse reactions leading to interruption of KEYTRUDA were:

- Diarrhea (8%)
- Increased alanine aminotransferase (4.4%)
- Increased aspartate aminotransferase (3.8%)
- Hypertension (3.5%)

The most common (≥2%) adverse reactions leading to interruption of LENVIMA were:

- Hypertension (11%)
- Diarrhea (11%)
- Proteinuria (6%)
- Decreased appetite (5%)
- Vomiting (5%)
- Increased alanine aminotransferase (3.5%)
- Fatigue (3.5%)
- Nausea (3.5%)
- Abdominal pain (2.9%)
- Weight decreased (2.6%)
- Urinary tract infection (2.6%)
- Increased aspartate aminotransferase (2.3%)
- Asthenia (2.3%)
- Palmar-plantar erythrodysesthesia (2%)

The most common (≥5%) adverse reactions resulting in dose reduction of LENVIMA were:

- Hypertension (18%)
- Diarrhea (11%)
- Palmar-plantar erythrodysesthesia syndrome (9%)
- Proteinuria (7%)
- Fatigue (7%)
- Decreased appetite (6%)
- Asthenia (5%)
- Weight decreased (5%)

• No dose reduction for **KEYTRUDA** is recommended.

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Adverse reactions occurring in ≥20% of patients receiving **KEYTRUDA + LENVIMA** in KEYNOTE-775/Study 309

	KEYTRUDA + LENVIMA (n=342)		Doxorubicin or Paclitaxel (n=325)	
Adverse Reaction	**All Grades[a] (%)**	**Grades 3–4 (%)**	**All Grades[a] (%)**	**Grades 3–4 (%)**
Hypothyroidism[b]	67	0.9	0.9	0
Hypertension[c]	67	39	6	2.5
Fatigue[d]	58	11	54	6
Diarrhea[e]	55	8	20	2.8
Musculoskeletal disorders[f]	53	5	27	0.6
Nausea	49	2.9	47	1.5
Decreased appetite[g]	44	7	21	0
Vomiting	37	2.3	21	2.2
Stomatitis[h]	35	2.6	26	1.2
Abdominal pain[i]	34	2.6	21	1.2
Weight loss	34	10	6	0.3
Urinary tract infection[j]	31	5	13	1.2
Proteinuria[k]	29	6	3.4	0.3
Constipation	27	0	25	0.6
Headache	26	0.6	9	0.3
Hemorrhagic events[l]	25	2.6	15	0.9
Palmar-plantar erythrodysesthesia[m]	23	2.9	0.9	0
Dysphonia	22	0	0.6	0
Rash[n]	20	2.3	4.9	0

[a]Graded per NCI-CTCAE v4.03.
[b]Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, primary hypothyroidism, secondary hypothyroidism.
[c]Includes hypertension, blood pressure increased, hypertensive crisis, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, blood pressure fluctuation.
[d]Includes fatigue, asthenia, malaise, lethargy.
[e]Includes diarrhea, gastroenteritis.
[f]Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw.
[g]Includes decreased appetite, early satiety.
[h]Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration.
[i]Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort.
[j]Includes urinary tract infection, cystitis, pyelonephritis.
[k]Includes proteinuria, protein urine present, hemoglobinuria.
[l]Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, injection site hemorrhage, melena, purpura, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, coital bleeding, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, vessel puncture site bruise.
[m]Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, skin reaction.
[n]Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, application site rash.

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

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Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Post hoc analysis: Median time to first onset of select adverse reactions in the pMMR or not MSI-H population from KEYNOTE-775/Study 309 (safety population), n=342[1–3]

LIMITATION: This is a post hoc analysis based on data from KEYNOTE-775/Study 309. No statistical testing was planned and, therefore, no conclusions can be drawn.

- As this information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgment and evaluation if a potential adverse reaction should occur.
- Health care professionals should monitor and evaluate patients for the presence of potential adverse reactions throughout treatment with KEYTRUDA, in combination with LENVIMA, and following discontinuation.
- Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.
- Data does not present a complete list of every AR that occurred during KEYNOTE-775/Study 309.
- The interquartile range (Q1:Q3) represents the time to onset (the earliest treatment-emergent AR start date) for the AR for the middle 50% of the patients who experienced that AR from Q1 to Q3.
- ARs could have occurred while receiving LENVIMA and/or KEYTRUDA or within the protocol-defined follow-up period of approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever came first.
- Grading of ARs was performed according to Common Terminology Criteria for Adverse Events v4.03.

Median time to first onset | Interquartile range (Q1;Q3) | Minimum/maximum time to onset

Adverse Reaction	Incidence[a] n	Incidence[a] %	Median Time to First Onset (weeks)[b]
Hypertension[c]	228	66.7%	MIN: 0.1 / Q1: 0.71 / Median: 2.1 / Q3: 3.50 / MAX: 39.0 weeks (0.1 – 2.1 – 39.0)
Fatigue[d]	198	57.9%	MIN: 0.1 / Q1: 1.00 / Median: 2.5 / Q3: 10.57 / MAX: 88.0 weeks (0.1 – 2.5 – 88.0)
Musculoskeletal disorders[e]	181	52.9%	MIN: 0.1 / Q1: 1.00 / Median: 3.1 / Q3: 9.00 / MAX: 93.7 weeks (0.1 – 3.1 – 93.7)
Proteinuria[f]	100	29.2%	MIN: 0.1 / Q1: 2.14 / Median: 3.8 / Q3: 9.36 / MAX: 76.0 weeks (0.1 – 3.8 – 76.0)
Stomatitis[g]	120	35.1%	MIN: 0.1 / Q1: 1.29 / Median: 3.9 / Q3: 8.64 / MAX: 77.9 weeks (0.1 – 3.9 – 77.9)
Decreased appetite[h]	152	44.4%	MIN: 0.1 / Q1: 1.21 / Median: 4.9 / Q3: 13.29 / MAX: 61.7 weeks (0.1 – 4.9 – 61.7)

Data cutoff date: October 26, 2020.

[a] All grades.
[b] Median time to first onset in patients who experienced the adverse reaction.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, and blood pressure fluctuation.
[d] Includes fatigue, asthenia, malaise, and lethargy.
[e] Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, and pain in jaw.
[f] Includes proteinuria, protein urine present, and hemoglobinuria.
[g] Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, and tongue ulceration.
[h] Includes decreased appetite and early satiety.

AR = adverse reaction.

References: 1. Colombo N, Lorusso D, Monk BJ, et al. Characterization and management of adverse reactions in patients with advanced endometrial cancer receiving lenvatinib plus pembrolizumab. *Oncologist*. 2024;29(1):25–35. doi:10.1093/oncolo/oyad201
2. Colombo N, Lorusso D, Monk BJ, et al. Supplement to: Characterization and management of adverse reactions in patients with advanced endometrial cancer receiving lenvatinib plus pembrolizumab. *Oncologist*. 2024;29(1):25–35. doi:10.1093/oncolo/oyad201
3. Interquartile range. Stat Trek. Accessed November 1, 2023. https://stattrek.com/statistics/dictionary?definition=IQR

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KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Post hoc analysis: Median time to first onset of select adverse reactions in the pMMR or not MSI-H population from KEYNOTE-775/Study 309 (safety population), n=342[1–3] (*continued*)

LIMITATION: This is a post hoc analysis based on data from KEYNOTE-775/Study 309. No statistical testing was planned and, therefore, no conclusions can be drawn.

- As this information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgment and evaluation if a potential adverse reaction should occur.
- Health care professionals should monitor and evaluate patients for the presence of potential adverse reactions throughout treatment with KEYTRUDA, in combination with LENVIMA, and following discontinuation.
- Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.
- Data does not present a complete list of every AR that occurred during KEYNOTE-775/Study 309.
- The interquartile range (Q1:Q3) represents the time to onset (the earliest treatment-emergent AR start date) for the AR for the middle 50% of the patients who experienced that AR from Q1 to Q3.
- ARs could have occurred while receiving LENVIMA and/or KEYTRUDA or within the protocol-defined follow-up period of approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever came first.
- Grading of ARs was performed according to Common Terminology Criteria for Adverse Events v4.03.

Median time to first onset | Interquartile range (Q1;Q3) | Minimum/maximum time to onset

Adverse Reaction	Incidence[a] n	Incidence[a] %	Median Time to First Onset (weeks)[b]
Nausea	169	49.4%	**MIN:** 0.1 / **Q1:** 1.43 / **Median:** 5.0 / **Q3:** 14.29 / **MAX:** 67.3 weeks **0.1** — **5.0** — **67.3**
Diarrhea[i]	188	55.0%	**MIN:** 0.1 / **Q1:** 2.43 / **Median:** 8.1 / **Q3:** 17.86 / **MAX:** 78.7 weeks **0.1** — **8.1** — **78.7**
Vomiting	125	36.5%	**MIN:** 0.1 / **Q1:** 2.71 / **Median:** 8.4 / **Q3:** 19.29 / **MAX:** 60.3 weeks **0.1** — **8.4** — **60.3**
Hypothyroidism[j]	229	67.0%	**MIN:** 2.0 / **Q1:** 3.14 / **Median:** 8.4 / **Q3:** 14.86 / **MAX:** 72.3 weeks **2.0** — **8.4** — **72.3**
Palmar-plantar erythrodysesthesia[k]	77	22.5%	**MIN:** 0.4 / **Q1:** 3.71 / **Median:** 10.0 / **Q3:** 15.86 / **MAX:** 77.7 weeks **0.4** — **10.0** — **77.7**
Weight decreased	117	34.2%	**MIN:** 0.1 / **Q1:** 6.14 / **Median:** 12.1 / **Q3:** 20.86 / **MAX:** 69.0 weeks **0.1** — **12.1** — **69.0**

Data cutoff date: October 26, 2020.

[a] All grades.
[b] Median time to first onset in patients who experienced the adverse reaction.
[i] Includes diarrhea and gastroenteritis.
[j] Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, primary hypothyroidism, and secondary hypothyroidism.
[k] Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, and skin reaction.

References: 1. Colombo N, Lorusso D, Monk BJ, et al. Characterization and management of adverse reactions in patients with advanced endometrial cancer receiving lenvatinib plus pembrolizumab. *Oncologist*. 2024;29(1):25–35. doi:10.1093/oncolo/oyad201
2. Colombo N, Lorusso D, Monk BJ, et al. Supplement to: Characterization and management of adverse reactions in patients with advanced endometrial cancer receiving lenvatinib plus pembrolizumab. *Oncologist*. 2024;29(1):25–35. doi:10.1093/oncolo/oyad201
3. Interquartile range. Stat Trek. Accessed November 1, 2023. https://stattrek.com/statistics/dictionary?definition=IQR

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KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

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Help manage your patients' adverse reactions to **KEYTRUDA**

- When administering KEYTRUDA in combination with LENVIMA, modify the dosage of one or both drugs as appropriate. Withhold or discontinue KEYTRUDA as shown in this resource.
- No dose reductions of KEYTRUDA are recommended.
- In general, withhold KEYTRUDA for severe (Grade 3) immune-mediated adverse reactions.
- Permanently discontinue KEYTRUDA for:
  - Life-threatening (Grade 4) immune-mediated adverse reactions.
  - Recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment.
  - An inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.
- Dosage modifications for KEYTRUDA for adverse reactions that require management that differs from these general guidelines are summarized on the following pages.

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.

Patient Counseling Information

Advise patients to read the FDA-approved patient labeling (Medication Guide).

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 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 immune-mediated adverse reactions are not controlled with corticosteroid therapy.
- Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (eg, endocrinopathies and dermatologic reactions) are discussed on the following pages.
- Additional monitoring and management considerations for selected immune-mediated adverse reactions are also discussed.

For information regarding Common Terminology Criteria for Adverse Events (CTCAE) grading, click here.

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

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FDA and CTCAE Definitions for an Adverse Event and Adverse Reaction

FDA Definitions for an Adverse Event and Adverse Reaction[1]

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

CTCAE Terms[2]

- **Grades**[a] refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
  - **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[b]
  - **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[c]
  - **Grade 4:** Life-threatening consequences; urgent intervention indicated.
  - **Grade 5:** Death related to AE.

Common Terminology Criteria for Adverse Events (CTCAE) grading definitions in this resource are listed according to version 4.0, which is the version that is used in the Prescribing Information for KEYTRUDA and for LENVIMA® (lenvatinib).

[a]A semicolon indicates "or" within the description of the grade.
[b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.[2]
[c]Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.[2]
ADL = activities of daily living.

References: 1. IND application reporting: safety reports. US Food and Drug Administration. Content current as of October 19, 2021. Accessed August 23, 2023. https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports **2.** National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Immune-Mediated Pneumonitis *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Please advise patients to contact their health care provider immediately for new or worsening cough, chest pain, or shortness of breath.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to immune-mediated pneumonitis.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL[1]	**Withhold**[a]
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated[1]	Permanently **discontinue**
Grade 4	Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)[1]	

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Immune-Mediated Colitis *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- Colitis may present with diarrhea.
- 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.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Please advise patients to contact their health care provider immediately for diarrhea or severe abdominal pain.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to immune-mediated colitis.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Abdominal pain; mucus or blood in stool[1]	**Withhold**[a]
Grade 3	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs[1]	**Withhold**[a]
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	Permanently **discontinue**

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

CMV = cytomegalovirus.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Immune-Mediated Hepatitis With No Tumor Involvement of the Liver

[see Warnings and Precautions]

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- Evaluate liver enzymes at baseline and periodically during treatment.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Please advise patients to contact their health care provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Severity Based on Prescribing Information for KEYTRUDA	Dosage Modification Based on Prescribing Information for KEYTRUDA
AST or ALT increases to more than 3 and up to 8 times ULN **or** total bilirubin increases to more than 1.5 and up to 3 times ULN	**Withhold**[a]
AST or ALT increases to more than 8 times ULN **or** total bilirubin increases to more than 3 times ULN	Permanently **discontinue**

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

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Immune-Mediated Hepatitis With Tumor Involvement of the Liver

[see Warnings and Precautions]

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- Evaluate liver enzymes at baseline and periodically during treatment.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Please advise patients to contact their health care provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Severity Based on Prescribing Information for KEYTRUDA	Dosage Modification Based on Prescribing Information for KEYTRUDA
Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN **or** baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	**Withhold**[a,b]
AST or ALT increases to more than 10 times ULN **or** total bilirubin increases to more than 3 times ULN	Permanently **discontinue**

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

[b]If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

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Adrenal Insufficiency *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- KEYTRUDA can cause primary or secondary adrenal insufficiency.
- For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity.
  - Systemic corticosteroids were required in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.
- Monitor patients for signs and symptoms of adrenal insufficiency.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients to contact their health care provider immediately for signs or symptoms of adrenal insufficiency.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to adrenal insufficiency.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Moderate symptoms; medical intervention indicated[1]	
Grade 3	Severe symptoms; hospitalization indicated[1]	**Withhold** until clinically stable or permanently **discontinue** depending on severity
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Hypophysitis *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- 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.
  - Systemic corticosteroids were required in 94% (16/17) of patients with hypophysitis; of these, the majority remained on systemic corticosteroids.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients to contact their health care provider immediately for signs or symptoms of hypophysitis.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to hypophysitis.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]
Grade 4	Life-threatening consequences; urgent intervention indicated[1]

Dosage Modification Based on Prescribing Information for KEYTRUDA

Withhold until clinically stable or permanently **discontinue** depending on severity

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Thyroid Disorders *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- Thyroid disorders can include thyroiditis, hyperthyroidism, and hypothyroidism.
- Thyroiditis can present with or without endocrinopathy.
- Hypothyroidism can follow hyperthyroidism.
- Evaluate thyroid function at baseline and periodically during treatment.
- Initiate treatment (hormone replacement for hypothyroidism or institute medical management for hyperthyroidism) as clinically indicated.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients to contact their health care provider immediately for signs or symptoms of hypothyroidism or hyperthyroidism.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to thyroid disorders.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]	**Withhold** until clinically stable or permanently **discontinue** depending on severity
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	

Dosage Modification Based on Prescribing Information for KEYTRUDA

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Type 1 Diabetes Mellitus, Which Can Present With Diabetic Ketoacidosis

[see Warnings and Precautions]

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- 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.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients to contact their health care provider immediately for signs or symptoms of type 1 diabetes.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to type 1 diabetes mellitus.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Fasting glucose value >ULN–160 mg/dL; Fasting glucose value >ULN–8.9 mmol/L[1]	
Grade 2	Fasting glucose value >160–250 mg/dL; Fasting glucose value >8.9–13.9 mmol/L[1]	
Grade 3	>250–500 mg/dL; >13.9–27.8 mmol/L; hospitalization indicated[1]	**Withhold** until clinically stable or permanently **discontinue** depending on severity
Grade 4	>500 mg/dL; >27.8 mmol/L; life-threatening consequences[1]	

ULN = upper limit of normal.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Immune-Mediated Nephritis With Renal Dysfunction *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- KEYTRUDA can cause immune-mediated nephritis.
- Evaluate creatinine at baseline and periodically during treatment.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients to contact their health care provider immediately for signs or symptoms of nephritis.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to renal and urinary disorders.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	**Creatinine increased:** >1–1.5 x baseline; >ULN–1.5 x ULN[1]	
Grade 2	**Creatinine increased:** >1.5–3.0 x baseline; >1.5–3.0 x ULN[1]	**Withhold**[a]
Grade 3	**Creatinine increased:** >3.0 baseline; >3.0–6.0 x ULN[1]	**Withhold**[a]
Grade 4	**Creatinine increased:** >6.0 x ULN[1]	Permanently **discontinue**

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

ULN = upper limit of normal.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Immune-Mediated Dermatologic Adverse Reactions *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- KEYTRUDA can cause immune-mediated rash or dermatitis.
- Exfoliative dermatitis, including SJS, DRESS, and TEN, has occurred with PD-1/PD-L1 blocking antibodies. Monitor patients for signs and symptoms of suspected severe skin reactions.
- Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients to contact their health care provider immediately for any signs or symptoms of severe skin reactions, SJS, or TEN.

Severity Based on Prescribing Information for KEYTRUDA	Dosage Modification Based on Prescribing Information for KEYTRUDA
Exfoliative Dermatologic Conditions: Suspected SJS, TEN, or DRESS	**Withhold**[a]
Exfoliative Dermatologic Conditions: Confirmed SJS, TEN, or DRESS	Permanently **discontinue**

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

SJS = Stevens-Johnson syndrome; DRESS = drug rash with eosinophilia and systemic symptoms; TEN = toxic epidermal necrolysis.

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Immune-Mediated Myocarditis *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their health care provider immediately for any new or worsening signs or symptoms.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to immune-mediated myocarditis.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Asymptomatic with laboratory (eg, BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities[1]	
Grade 2	Symptoms with mild to moderate activity or exertion[1]	Permanently **discontinue**
Grade 3	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated[1]	
Grade 4	Life-threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support)[1]	

IV = intravenous.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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Immune-Mediated Neurological Toxicities *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their health care provider immediately for any new or worsening signs or symptoms.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to immune-mediated neurological toxicities.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]	**Withhold**[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]	Permanently **discontinue**
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	

[a]Resume in patients with complete or partial resolution (Grade 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 less (or equivalent) within 12 weeks of initiating steroids.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

[see Warnings and Precautions]

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause).
- These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.
- Follow patients closely for evidence of transplant-related complications and intervene promptly.
- Consider the benefit vs risks of treatment with a PD-1/PD-L1 blockade antibody prior to or after an allogeneic HSCT.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications.

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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Increased Mortality in Patients With Multiple Myeloma When KEYTRUDA Is Added to a Thalidomide Analogue and Dexamethasone *[see Warnings and Precautions]*

Considerations

- In 2 randomized trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled trials.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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Other Immune-Mediated Adverse Reactions (IMARs) *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- The following clinically significant IMARs occurred in patients who received KEYTRUDA or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
  - *Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis.
  - *Nervous System:* Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.
  - *Ocular:* Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.
  - *Gastrointestinal:* Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis.
  - *Musculoskeletal and Connective Tissue:* Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis, 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.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA.
- Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their health care provider immediately for any new or worsening signs or symptoms.
- Advise patients of the risk of solid organ transplant rejection and to contact their health care provider immediately for signs or symptoms of organ transplant rejection.

PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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Infusion-Related Reactions *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management of KEYTRUDA here.
- KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis.
- Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Advise patients to contact their health care provider immediately for signs or symptoms of infusion-related reactions.

Severity Based on Prescribing Information for KEYTRUDA

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Mild[1]	**Interrupt** or **slow** the rate of infusion
Grade 2	Moderate[1]	
Grade 3	Severe[1]	**Stop** infusion and permanently **discontinue**
Grade 4	Life-threatening[1]	

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Embryo-Fetal Toxicity *[see Warnings and Precautions]*

Risk Summary

- Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman.
- Advise women of the potential risk to a fetus.
- Verify pregnancy status in females of reproductive potential prior to initiating KEYTRUDA.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Advise females of reproductive potential of the potential risk to a fetus and to inform their health care provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose.

Lactation

Risk Summary

- There are no data on the presence of KEYTRUDA in either animal or human milk or its effects on the breastfed child or on milk production.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Medication Guide).
- Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the last dose.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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Help manage your patients' adverse reactions to **LENVIMA**

Withhold, dose reduce, or discontinue LENVIMA based on the type and/or severity (grade) of the adverse reaction.

Recommended dosage reductions for LENVIMA for patients with advanced renal cell carcinoma or advanced endometrial carcinoma[a]

Recommended dosage	10 + 10	**20 mg** once daily
1st dosage reduction to	10 + 4	**14 mg** once daily
2nd dosage reduction to	10	**10 mg** once daily
3rd dosage reduction to	4 + 4	**8 mg** once daily

[a]When administered with KEYTRUDA.
LENVIMA is available in 4-mg and 10-mg capsules. Capsules are not shown at actual size.

- Recommendations for adverse reaction management, including dose modifications, are included in the Prescribing Information for LENVIMA and outlined to the left and in the following tables.
- When administering LENVIMA in combination with KEYTRUDA® (pembrolizumab), modify the dosage of one or both drugs as appropriate. Withhold, dose reduce, or discontinue LENVIMA as shown in this resource.
- The recommended dosage of LENVIMA for patients with **advanced renal cell carcinoma or advanced endometrial carcinoma and severe renal impairment** (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is **10 mg orally once daily**.
- The recommended dosage of LENVIMA for patients with **advanced renal cell carcinoma or advanced endometrial carcinoma and severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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FDA and CTCAE Definitions for an Adverse Event and Adverse Reaction

FDA Definitions for an Adverse Event and Adverse Reaction[1]

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

CTCAE Terms[2]

- **Grades**[a] refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
  - **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[b]
  - **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[c]
  - **Grade 4:** Life-threatening consequences; urgent intervention indicated.
  - **Grade 5:** Death related to AE.

Common Terminology Criteria for Adverse Events (CTCAE) grading definitions in this resource are listed according to version 4.0, which is the version that is used in the Prescribing Information for KEYTRUDA® (pembrolizumab) and for LENVIMA.

[a]A semicolon indicates "or" within the description of the grade.
[b]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.[2]
[c]Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.[2]
ADL = activities of daily living.

References: 1. IND application reporting: safety reports. US Food and Drug Administration. Content current as of October 19, 2021. Accessed August 23, 2023. https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports **2.** National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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Hypertension *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Control blood pressure (BP) prior to initiation of LENVIMA.
- Monitor BP after 1 week, then every 2 weeks for the first 2 months and at least monthly thereafter during treatment.
- Serious complications of poorly controlled hypertension have been reported.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients to undergo regular BP monitoring and to contact their health care provider if BP is elevated.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to hypertension.

Dosage Modification Based on Prescribing Information for LENVIMA

Grade 1	Systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg[1]	
Grade 2	Systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg; medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously WNL; monotherapy indicated[1]	
Grade 3	Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg; medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated[1]	**Withhold** for Grade 3 that persists despite optimal antihypertensive therapy **Resume** at reduced dose when hypertension is controlled at ≤Grade 2
Grade 4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated[1]	Permanently **discontinue**

WNL = within normal limits.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Cardiac Dysfunction *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Serious and fatal cardiac dysfunction can occur with LENVIMA.
- Monitor patients for clinical symptoms or signs of cardiac dysfunction.
- Cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypokinesia, or decrease in left or right ventricular ejection fraction of >20% from baseline have been reported with LENVIMA.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that LENVIMA can cause cardiac dysfunction and to immediately contact their health care provider if they experience any clinical symptoms of cardiac dysfunction.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to cardiac dysfunction.

Dosage Modification Based on Prescribing Information for LENVIMA

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]	**Withhold** until improves to Grade 0 to 1 or baseline **Resume** at a reduced dose or discontinue depending on the severity and persistence of adverse reaction
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	Permanently **discontinue**

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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Arterial Thromboembolic Events *[see Warnings and Precautions]*

Monitoring and Management

- The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.
  - Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials with LENVIMA.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke.

Severity Based on Prescribing Information for LENVIMA

Any grade of arterial thromboembolic event

Dosage Modification Based on Prescribing Information for LENVIMA

Permanently **discontinue**

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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Hepatotoxicity *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Monitor liver function prior to initiating LENVIMA.
- Monitor liver function every 2 weeks for the first 2 months and at least monthly thereafter during treatment.
- Serious hepatic adverse reactions and fatal events, including hepatic failure, acute hepatitis, and hepatorenal syndrome, have occurred in patients treated with LENVIMA.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that they will need to undergo laboratory tests to monitor liver function and to report any new symptoms indicating hepatic toxicity or failure.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to hepatobiliary disorders.

Dosage Modification Based on Prescribing Information for LENVIMA

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]	**Withhold** until improves to Grade 0 to 1 or baseline Either **resume** at a reduced dose or **discontinue** depending on severity and persistence of hepatotoxicity
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	Permanently **discontinue** for hepatic failure

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Renal Failure or Impairment *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Serious including fatal renal failure or impairment can occur with LENVIMA.
- Initiate prompt management of diarrhea or dehydration/hypovolemia.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that they will need to undergo regular laboratory tests to monitor kidney function.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to renal and urinary disorders.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]
Grade 4	Life-threatening consequences; urgent intervention indicated[1]

Dosage Modification Based on Prescribing Information for LENVIMA

Withhold until improves to Grade 0 to 1 or baseline
Resume at a reduced dose or **discontinue** depending on severity and persistence of renal impairment

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Proteinuria *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Monitor for proteinuria prior to initiating LENVIMA and periodically during treatment.
  - If proteinuria ≥2+ is detected on urine dipstick, obtain a 24-hour urine protein sample.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that they will need to undergo regular laboratory tests to monitor protein in urine.

Severity Based on Prescribing Information for LENVIMA

Dosage Modification Based on Prescribing Information for LENVIMA

≥2 g proteinuria in 24 hours	**Withhold** until ≤2 g of proteinuria per 24 hours **Resume** at a reduced dose Permanently **discontinue** for nephrotic syndrome

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Diarrhea *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Promptly initiate management of diarrhea.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients when to start standard anti-diarrheal therapy and to maintain adequate hydration.
- Advise patients to contact their health care provider if they are unable to maintain adequate hydration.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to diarrhea.

Dosage Modification Based on Prescribing Information for LENVIMA

Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline[1]	
Grade 2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline[1]	Persistent or intolerable Grade 2 or 3 adverse reaction: • **Withhold** until improves to Grade 0 to 1 or baseline • **Resume** at reduced dose
Grade 3	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL[1]	
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	Permanently **discontinue**

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Gastrointestinal Perforation *[see Warnings and Precautions]*

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that LENVIMA can increase the risk of gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain.

Severity Based on Prescribing Information for LENVIMA

Any grade of gastrointestinal perforation

Dosage Modification Based on Prescribing Information for LENVIMA

Permanently **discontinue**

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Fistula Formation *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that LENVIMA can increase the risk of fistula formation and to seek immediate medical attention for severe abdominal pain.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to fistula formation.[a]

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated[1]
Grade 2	Symptomatic; altered GI function[1]
Grade 3	Severely altered GI function; tube feeding, TPN or hospitalization indicated[1]
Grade 4	Life-threatening consequences; urgent intervention indicated[1]

Dosage Modification Based on Prescribing Information for LENVIMA

Permanently **discontinue**

[a]A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.
GI = gastrointestinal; TPN = total parenteral nutrition.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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QT Interval Prolongation *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- LENVIMA has been reported to prolong the QT/QTc interval.
- Monitor and correct electrolyte abnormalities at baseline and periodically during treatment.
- Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, or bradyarrhythmias, or those who are taking drugs known to prolong QT interval, including Class Ia and III antiarrhythmics.
- Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients who are at risk for QTc prolongation that they will need to undergo regular ECGs.
- Advise all patients that they will need to undergo laboratory tests to monitor electrolytes.

Severity Based on Prescribing Information for LENVIMA

For QT interval >500 ms or for >60 ms increase in baseline QT interval

Dosage Modification Based on Prescribing Information for LENVIMA

Withhold until improves to ≤480 ms or baseline
Resume at reduced dose

QTc = corrected QT interval; ECG = electrocardiogram; ms = millisecond.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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Hypocalcemia *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Monitor blood calcium levels at least monthly.
- Replace calcium as necessary during treatment.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients of the risks of hypocalcemia, that they will need to undergo laboratory tests to monitor calcium levels, and the potential requirement for calcium supplementation.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to hypocalcemia.

Dosage Modification Based on Prescribing Information for LENVIMA

Grade 1	Corrected serum calcium <LLN–8.0 mg/dL; <LLN–2.0 mmol/L; ionized calcium <LLN–1.0 mmol/L[1]	
Grade 2	Corrected serum calcium <8.0–7.0 mg/dL; <2.0–1.75 mmol/L; ionized calcium <1.0–0.9 mmol/L; symptomatic[1]	Persistent or intolerable Grade 2 or 3 adverse reaction: • **Withhold** until improves to Grade 0 to 1 or baseline • **Resume** at reduced dose
Grade 3	Corrected serum calcium <7.0–6.0 mg/dL; <1.75–1.5 mmol/L; ionized calcium <0.9–0.8 mmol/L; hospitalization indicated[1]	
Grade 4	Corrected serum calcium <6.0 mg/dL; <1.5 mmol/L; ionized calcium <0.8 mmol/L; life-threatening consequences[1]	Grade 4 laboratory abnormality: • **Withhold** until improves to Grade 0 to 1 or baseline • **Resume** at reduced dose Grade 4 adverse reaction: • Permanently **discontinue**

LLN = lower limit of normal.

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Reversible Posterior Leukoencephalopathy Syndrome (RPLS) *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Confirm the diagnosis of RPLS with MRI.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients of the signs and symptoms of RPLS and to contact their health care provider for new onset or worsening neurological function.

Severity Based on Prescribing Information for LENVIMA

Any grade of reversible posterior leukoencephalopathy syndrome

Dosage Modification Based on Prescribing Information for LENVIMA

Withhold and **resume** at a reduced dose upon recovery or permanently **discontinue** LENVIMA depending on severity and persistence of neurologic symptoms

MRI = magnetic resonance imaging.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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Hemorrhagic Events *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Serious including fatal hemorrhagic events can occur with LENVIMA.
- Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in patients treated with LENVIMA in clinical trials and in the post-marketing setting.
- In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.
- Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery).

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that LENVIMA can increase the risk for bleeding and to contact their health care provider for bleeding or symptoms of severe bleeding.

NCI-CTCAE Grading

Refer to PI and CTCAE for specific ARs related to hemorrhagic events.

Dosage Modification Based on Prescribing Information for LENVIMA

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated[1]	
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]	Persistent or intolerable Grade 2 or 3 adverse reaction: • **Withhold** until improves to Grade 0 to 1 or baseline • **Resume** at reduced dose
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[1]	
Grade 4	Life-threatening consequences; urgent intervention indicated[1]	Permanently **discontinue**

Reference: 1. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE). v4.0 Quick Reference 8.5x11. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

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Impairment of Thyroid-Stimulating Hormone Suppression/Thyroid Dysfunction

[see Warnings and Precautions]

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- LENVIMA impairs exogenous thyroid suppression.
- Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment.
- Treat hypothyroidism according to standard medical practice.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that LENVIMA can cause hypothyroidism and that their thyroid function should be monitored regularly during treatment.

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Impaired Wound Healing *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Impaired wound healing has been reported in patients who received LENVIMA.
- The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients that LENVIMA may impair wound healing.
- Advise patients to inform their health care provider of any planned surgical procedure.

Dosage Modification Based on Prescribing Information for LENVIMA

- **Withhold** for at least 1 week prior to elective surgery.
- Do not administer for at least 2 weeks following major surgery and until adequate wound healing.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

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Embryo-Fetal Toxicity and Lactation

Osteonecrosis of the Jaw (ONJ) *[see Warnings and Precautions]*

Monitoring and Management

- See general recommendations for adverse reaction management, including dose modifications, of LENVIMA here.
- Osteonecrosis of the jaw has been reported in patients receiving LENVIMA.
- Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment.
- Advise patients regarding good oral hygiene practices.
- Avoid invasive dental procedures, if possible, while on treatment with LENVIMA, particularly in patients at higher risk.
- For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.
- Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise patients regarding good oral hygiene practices and to have preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.
- Inform patients being treated with LENVIMA, particularly those who are at high risk for ONJ, to avoid invasive dental procedures, if possible, and to inform their health care provider of any planned dental procedures.
- Advise patients to immediately contact their health care provider for signs or symptoms associated with ONJ.

Dosage Modification Based on Prescribing Information for LENVIMA

- **Withhold** LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible.
- **Withhold** LENVIMA if ONJ develops and restart based on clinical judgment of adequate resolution.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

General Recommendations

Definitions and Terms
FDA and CTCAE Definitions for AE and AR

Cardiovascular
Hypertension
Cardiac Dysfunction
Arterial Thromboembolic Events

Hepatic
Hepatotoxicity

Renal
Renal Failure or Impairment
Proteinuria

Other Adverse Reactions
Diarrhea

Gastrointestinal
Gastrointestinal Perforation
Fistula Formation

Cardiovascular
QT Interval Prolongation

Other Adverse Reactions
Hypocalcemia

Neurological
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Other Adverse Reactions
Hemorrhagic Events

Endocrine
Impairment of Thyroid-Stimulating Hormone Suppression/ Thyroid Dysfunction

Systemic
Impaired Wound Healing

Bone
Osteonecrosis of the Jaw (ONJ)

Use in Specific Populations
Embryo-Fetal Toxicity and Lactation

Embryo-Fetal Toxicity *[see Warnings and Precautions]*

Risk Summary

- Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman.
- In animal reproduction studies, oral administration of LENVIMA during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.
- Advise pregnant women of the potential risk to a fetus.

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise females of reproductive potential of the potential risk to a fetus and to inform their health care provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

Lactation

Risk Summary

- It is not known whether LENVIMA is present in human milk; however, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma (see LENVIMA PI).

Patient Counseling Information

- Advise patients to read the FDA-approved patient labeling (Patient Information).
- Advise women to discontinue breastfeeding during treatment with LENVIMA and for 1 week after the last dose.

Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Before prescribing KEYTRUDA, please read the Selected Safety Information throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

Before prescribing LENVIMA, please read the Selected Safety Information throughout this document and the accompanying Prescribing Information and Patient Information.

For more information, please visit KeytrudaLenvimaHCP.com.

MERCK Eisai

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