



Actor Portrayal

Patient Monitoring Checklist

This checklist is intended for use by health care providers to identify and monitor some of the signs and symptoms associated with adverse reactions related to treatment with **KEYTRUDA + LENVIMA**. This checklist is intended to be used prior to each infusion of **KEYTRUDA** and during follow-up calls and visits while on treatment with **KEYTRUDA + LENVIMA**.

PATIENT NAME:

DATE:

NOTES:

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) or not microsatellite instability-high (MSI-H) as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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.

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 brochure and the accompanying **Prescribing Information**. The **Medication Guide** also is available.

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



PATIENT NAME: _____ DATE: _____

Side effects of KEYTRUDA

Instruct your patients to call or see you right away if they develop any new or worsening signs or symptoms, including:

Lung problems

- cough
- shortness of breath
- chest pain

Intestinal problems

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual

Hormone gland problems (*continued*)

- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in your mouth or in your nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

NOTES:

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

KEYTRUDA®
(pembrolizumab) Injection 100 mg

Side effects of KEYTRUDA (continued)

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with KEYTRUDA. Call or see your health care provider right away for any new or worsening signs or symptoms, which may include:

chest pain, irregular heartbeat, shortness of breath, swelling of ankles

confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs

double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight

persistent or severe muscle pain or weakness, muscle cramps

low red blood cells, bruising

Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include:

chills or shaking

itching or rash

flushing

shortness of breath or wheezing

dizziness

feeling like passing out

fever

back pain

Rejection of a transplanted organ or tissue. Your health care provider should tell you what signs and symptoms you should report and monitor you depending on the type of organ or tissue transplant that you have had.

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with KEYTRUDA. Your health care provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious. Your health care provider will check you for these problems during treatment with KEYTRUDA. Your health care provider may treat you with corticosteroid or hormone replacement medicines. Your health care provider may also need to delay or completely stop treatment with KEYTRUDA if you have severe side effects.

Common side effects of KEYTRUDA when given with LENVIMA® (lenvatinib) include: low levels of thyroid hormone, high blood pressure, feeling tired, diarrhea, joint and muscle pain, nausea, decreased appetite, vomiting, mouth sores, weight loss, stomach-area (abdominal) pain, urinary tract infection, protein in your urine, constipation, headache, bleeding, blisters or rash on the palms of your hands and soles of your feet, hoarseness, rash, liver problems, and kidney problems.

These are not all the possible side effects of KEYTRUDA. Talk to your health care provider for medical advice about side effects.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

NOTES:

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KEYTRUDA®
(pembrolizumab) Injection 100 mg

PATIENT NAME: _____

DATE: _____

Side effects of **LENVIMA**

Instruct your patients to call or see you right away if they start having any of these symptoms, if these symptoms get worse, or if they experience any side effects that are bothersome or do not go away. These are not all the possible side effects of LENVIMA.

High blood pressure (hypertension)

High blood pressure is a common side effect of LENVIMA and can be serious. Your blood pressure should be well controlled before you start taking LENVIMA.

Your blood pressure should be checked regularly during treatment with LENVIMA. If you develop blood pressure problems, you may be prescribed medicine to treat your high blood pressure.

Heart problems

LENVIMA can cause serious heart problems that may lead to death. Call your health care provider right away if you get symptoms of heart problems, such as:

- shortness of breath
- swelling of your ankles

Problem with blood clots in your blood vessels (arteries)

Get emergency medical help right away if you get any of the following symptoms:

- severe chest pain or pressure
- pain in your arms, back, neck, or jaw
- shortness of breath
- numbness or weakness on one side of your body
- trouble talking
- sudden severe headache
- sudden vision changes

Liver problems

LENVIMA may cause liver problems that may lead to liver failure and death. Your liver function should be checked before and during treatment with LENVIMA.

Tell your health care provider right away if you develop any of the following symptoms:

- your skin or the white part of your eyes turns yellow (jaundice)
- dark "tea-colored" urine
- light-colored bowel movements (stools)
- feeling drowsy, confused or loss of consciousness

Kidney problems

Kidney failure, which can lead to death, has happened with LENVIMA treatment. You should get regular blood tests to check your kidneys.

Increased protein in your urine (proteinuria)

Proteinuria is a common side effect of LENVIMA and can be serious. Your urine should be checked for protein before and during your treatment with LENVIMA.

Diarrhea

Diarrhea is a common side effect of LENVIMA and can be serious. If you get diarrhea, ask your health care provider about what medicines you can take to treat your diarrhea.

It is important to drink more water when you get diarrhea. Tell your health care provider or go to the emergency room if you are unable to drink enough liquids and your diarrhea is not able to be controlled.

An opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two or more body parts (fistula)

Get emergency medical help right away if you develop severe stomach (abdomen) pain.

Changes in the electrical activity of your heart called QT prolongation

QT prolongation can cause irregular heartbeats that can be life threatening.

You should receive blood tests before and during your treatment with LENVIMA to check the levels of potassium, magnesium, and calcium in your blood. The electrical activity of your heart may be checked with an electrocardiogram (ECG).

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



Side effects of **LENVIMA** (continued)

Low levels of blood calcium (hypocalcemia)

Your blood calcium levels should be checked during treatment with LENVIMA, and you may need to take a calcium supplement if your calcium levels are low.

A condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Call your health care provider right away if you have any of the signs or symptoms of RPLS during treatment with LENVIMA, including:

- severe headache
- seizures
- weakness
- confusion
- blindness or change in vision

Bleeding

LENVIMA may cause serious bleeding problems that may lead to death. Tell your health care provider if you develop any signs or symptoms of bleeding during treatment with LENVIMA, including:

- severe and persistent nose bleeds
- vomiting blood
- red or black (looks like tar) stools
- blood in your urine
- coughing up blood or blood clots
- heavy or new onset vaginal bleeding

Change in thyroid hormone levels

Your thyroid hormone levels should be checked before starting and every month during treatment with LENVIMA.

Wound healing problems

Wound healing problems have happened in some people who take LENVIMA. Tell your health care provider if you plan to have any surgery before or during treatment with LENVIMA.

You should stop taking LENVIMA at least 1 week before planned surgery. After surgery, you should be informed by your health care provider about when you may start taking LENVIMA again.

Severe jawbone problems (osteonecrosis)

Severe jawbone problems have happened in some people who take LENVIMA. Certain risk factors such as taking a bisphosphonate medicine or the medicine denosumab, having dental disease, or an invasive dental procedure may increase your risk of getting jawbone problems. Your mouth should be examined before you start and during treatment with LENVIMA. Tell your dentist that you are taking LENVIMA. It is important for you to practice good mouth care during treatment with LENVIMA.

Tell your health care provider right away if you have any signs or symptoms of jawbone problems during treatment with LENVIMA, including:

- jaw pain
- toothache
- sores on your gums

Tell your health care provider if you plan to have any dental procedures before or during treatment with LENVIMA. You should avoid having invasive dental procedures if possible, during treatment with LENVIMA. Stopping your bisphosphonate medicine before an invasive dental procedure may help decrease your risk of getting these jaw problems.

You should stop taking LENVIMA at least 1 week before planned dental surgery or invasive dental procedures. After dental procedures, you should be informed by your health care provider about when you may start taking LENVIMA again.

The most common side effects of LENVIMA when given in combination with KEYTRUDA® (pembrolizumab) include: decrease in thyroid hormone levels; tiredness; joint and muscle pain; nausea; decreased appetite; vomiting; mouth sores; weight loss; stomach-area (abdomen) pain; urinary tract infection; constipation; headache; bleeding; rash, redness, itching, or peeling of your skin on your hands and feet; hoarseness; and rash.

LENVIMA may cause fertility problems in males and females. Talk to your health care provider if this is a concern for you.

Your health care provider may need to reduce your dose of LENVIMA, or delay or completely stop treatment if you have certain side effects.

These are not all the possible side effects of LENVIMA. Talk to your health care provider for medical advice about side effects.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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



Selected Safety Information (*continued*)

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

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

- 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.

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.

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)

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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.

Arterial Thromboembolic Events

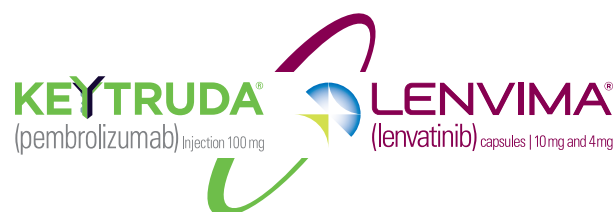
- Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.
- Among patients receiving LENVIMA with KEYTRUDA, 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.

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).



Selected Safety Information (*continued*)

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

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

Immune-Mediated Colitis (*continued*)

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.

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

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

Renal Failure or Impairment (*continued*)

- 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 $\geq 2+$ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

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.

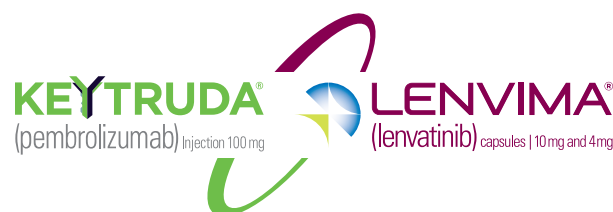
QT Interval Prolongation

- 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.

QTc = corrected QT interval.

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



Selected Safety Information (*continued*)

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

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

Immune-Mediated Endocrinopathies (*continued*)

Hypophysitis (*continued*)

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*)

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.

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.

MRI = magnetic resonance imaging; CNS = central nervous system.

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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

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

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.

Osteonecrosis of the Jaw (ONJ)

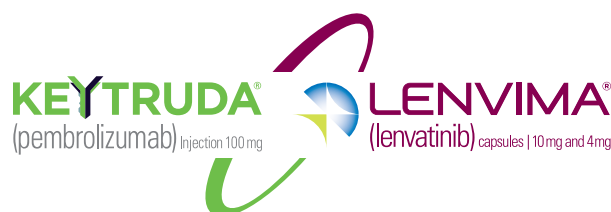
- ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ. Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA 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

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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*)

treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal*: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis; *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; *Endocrine*: Hypoparathyroidism; *Hematologic/Immune*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

Infusion-Related Reactions

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

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

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

Embryo-Fetal Toxicity (*continued*)

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 ($\geq 20\%$) 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.

Serious adverse reactions occurred in 51% of patients receiving LENVIMA and KEYTRUDA. Serious adverse reactions in $\geq 2\%$ 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 ($\geq 2\%$) 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 ($\geq 5\%$) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue

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Selected Safety Information (*continued*)

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

Increased Mortality in Patients With Multiple Myeloma

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

Embryofetal Toxicity

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

Adverse Reactions

- In KEYNOTE-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 ($\geq 2\%$) 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 ($\geq 2\%$) 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 ($\geq 20\%$) 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*)

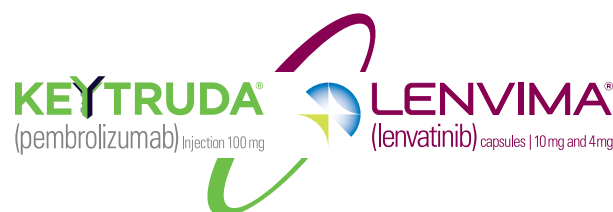
Adverse Reactions (*continued*)

- (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 ($\geq 20\%$) 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 $\geq 3\%$ 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 ($\geq 1\%$) 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%).
- Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common ($\geq 5\%$) 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 ($\geq 2\%$) 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%),

ALT = alanine aminotransferase.

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For your appropriate patients with advanced renal cell carcinoma or certain types of advanced endometrial carcinoma

Resources to inform patient dialogue and treatment management

FOR HEALTH CARE PROFESSIONALS

Available at: keytrudalenvimahcp.com/professional-resources

Dosage and Administration Guide:

Learn about the dosing, administration, and potential dosage modifications of KEYTRUDA + LENVIMA.

Adverse Reaction Management Guide:

Learn how to help manage adverse reactions in patients treated with KEYTRUDA + LENVIMA.

RESOURCES FOR PATIENTS AND CAREGIVERS

Available at: keytrudalenvima.com/treatment-tips

Symptom Tracker: Direct your patients to a tool that can help them keep track of symptoms.

Doctor Discussion Guide: Help guide your patients to have productive discussions with you.

Access and Co-pay Support: Learn more about financial information and help for KEYTRUDA + LENVIMA.

Treatment Support: Call **833-866-0789** to talk with a call center agent about KEYTRUDA + LENVIMA.

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 ($\geq 3\%$) 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 ($\geq 1\%$) was increased ALT (1.2%).
- The most common adverse reactions for KEYTRUDA in combination with LENVIMA (reported in $\geq 20\%$ 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.

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

Adverse Reactions (continued)

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.

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