For the first-line treatment of adult patients with advanced renal cell carcinoma (RCC)

KEYTRUDA + LENVIMA: Dosing and Adverse Reaction Management Guide

How to monitor and help manage select adverse reactions

Indication for KEYTRUDA + LENVIMA

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

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 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.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

KEYTRUDA + LENVIMA:
Recommended dosage and administration

When administering KEYTRUDA in combination with LENVIMA for the first-line treatment of adult patients with advanced renal cell carcinoma, modify the dosage of one or both drugs as appropriate. Withhold or discontinue KEYTRUDA. 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.

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.

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*)

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.

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.

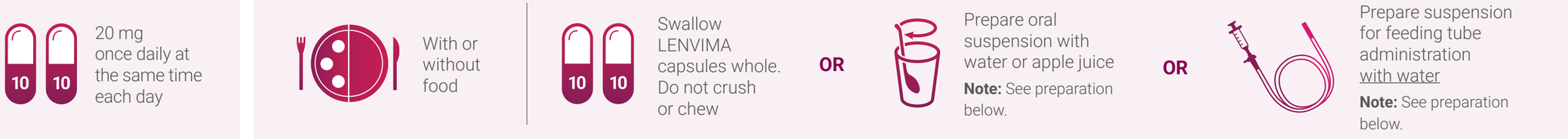
KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

For the first-line treatment of adult patients with advanced renal cell carcinoma

KEYTRUDA + LENVIMA:
Recommended dosage and administration (*continued*)

When administering KEYTRUDA in combination with LENVIMA for the first-line treatment of adult patients with advanced renal cell carcinoma, modify the dosage of one or both drugs as appropriate. Withhold or discontinue KEYTRUDA. Withhold, dose reduce, or discontinue LENVIMA as shown in this resource. No dose reductions are recommended for KEYTRUDA.

Dosage and administration for LENVIMA[a]



[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 or up to 2 years.
- After completing 2 years of combination therapy, LENVIMA may be administered as a single agent until disease progression or until unacceptable toxicity.
- The recommended dosage of LENVIMA for patients with **advanced renal cell 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** and **severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

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 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

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.

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.

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

Adverse reactions 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 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%)	Vomiting (3%)
Diarrhea (4%)	Acute kidney injury (2%)
Hypertension (3%)	Adrenal insufficiency (2%)
Myocardial infarction (3%)	Dyspnea (2%)
Pneumonitis (3%)	Pneumonia (2%)

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

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

Immune-Mediated Colitis (*continued*)

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.

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

Hepatotoxicity (*continued*)

- 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.

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.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Adverse reactions in the KEYNOTE-581/CLEAR trial (*continued*)

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 only	29	55	–
LENVIMA only	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%)	Acute kidney injury (3%)
Myocardial infarction (3%)	Rash (3%)
Hepatotoxicity (3%)	Diarrhea (2%)

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

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

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*)

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.

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.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

Most **common adverse reactions** that resulted in **dose reduction or interruption** in the KEYNOTE-581/CLEAR trial

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

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

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

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

ALT = alanine aminotransferase.

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

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%.

QTc = corrected QT interval.

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

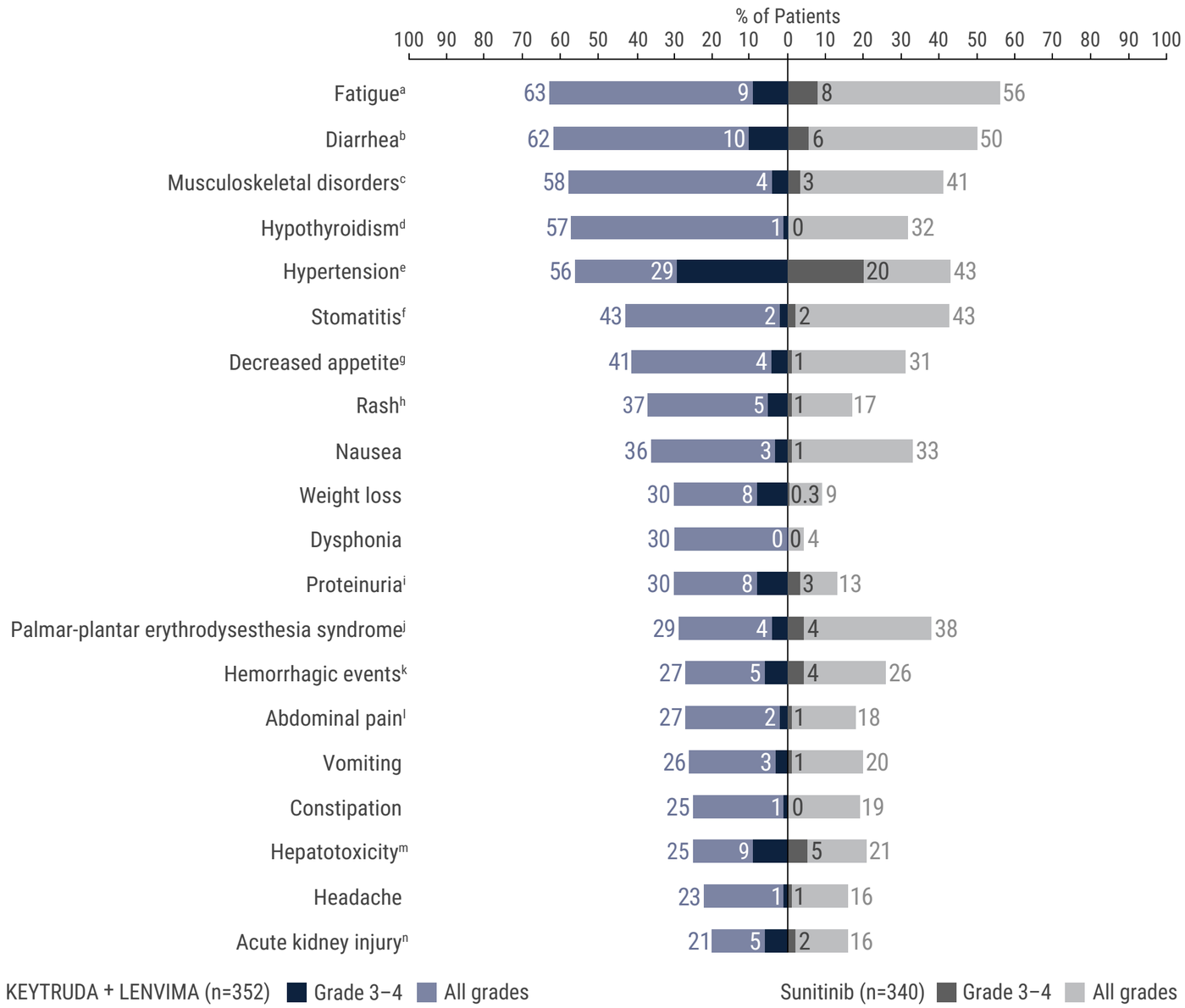
Before prescribing LENVIMA, please read the additional Selected Safety Information throughout this brochure and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

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, malaise.
[b] Includes diarrhea, 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, pain in jaw.
[d] Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism.
[e] Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, 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, stomatitis.
[g] Includes decreased appetite, 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, rash pustular.
[i] Includes hemoglobinuria, nephrotic syndrome, proteinuria.
[j] Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, 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, upper gastrointestinal hemorrhage.
[l] Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, 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, 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, nephropathy toxic.

AST = aspartate aminotransferase.

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.

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.

Chart 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.
[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.

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

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.

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

Managing adverse reactions to **LENVIMA**

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.
- Recommendations for adverse reaction management, including dose modifications, are included in the Prescribing Information for LENVIMA and outlined below and on the following pages.

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

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

- When administering LENVIMA in combination with KEYTRUDA for the treatment of adult patients with advanced renal cell carcinoma, modify the dosage of one or both drugs, as appropriate, or withhold, dose reduce, or discontinue LENVIMA as shown in this resource.
- The recommended dosage of LENVIMA for patients with **advanced renal cell 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** 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*)

Immune-Mediated Endocrinopathies (*continued*)

Thyroid Disorders (*continued*)

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.

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

QT Interval Prolongation (*continued*)

- 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.

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.

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

How **LENVIMA** is supplied

Images are not shown at actual size.

- LENVIMA capsules are supplied in cartons of 6 cards.
- Each card is a 5-day blister card.

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

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

Immune-Mediated Endocrinopathies (*continued*)

Thyroid Disorders (*continued*)

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.

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

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

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

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.

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

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 below.

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.

Recommended Adverse Reaction Monitoring and Management for KEYTRUDA

Adverse Reaction	Monitoring and Management[a]	Severity[b]	Dosage Modification
Immune-mediated pneumonitis *[see Warnings and Precautions]*	• See general recommendations listed above this chart.	• Grade 2	• **Withhold.**[c]
		• Grade 3 or 4	• Permanently **discontinue.**
Immune-mediated colitis *[see Warnings and Precautions]*	• 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.	• Grade 2 or 3	• **Withhold.**[c]
		• Grade 4	• Permanently **discontinue.**
Immune-mediated hepatitis with no tumor involvement of the liver *[see Warnings and Precautions]*	• See general recommendations listed above this chart.	• 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.**[c]
		• AST or ALT increases to more than 8 times ULN or total bilirubin increases to more than 3 times ULN	• Permanently **discontinue.**
Immune-mediated hepatitis with tumor involvement of the liver[d] *[see Warnings and Precautions]*	• See general recommendations listed above this chart.	• 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.**[c]
		• ALT or AST increases to more than 10 times ULN or total bilirubin increases to more than 3 times ULN	• Permanently **discontinue.**

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 below.
- Additional monitoring and management considerations for selected immune-mediated adverse reactions are also discussed.

[a]Advise patients to review the FDA-approved patient labeling (Medication Guide).
[b]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
[c]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.
[d]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.

CMV = cytomegalovirus; ULN = upper limit of normal.

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.

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

Help manage your patients' adverse reactions to **KEYTRUDA** (*continued*)

Recommended Adverse Reaction Monitoring and Management for KEYTRUDA

Adverse Reaction	Monitoring and Management[a]	Severity[b]	Dosage Modification
Immune-mediated endocrinopathies		• Grade 3 or 4	• **Withhold** until clinically stable or permanently **discontinue** depending on severity.
Adrenal insufficiency [see Warnings and Precautions]	• 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.		
Hypophysitis [see Warnings and Precautions]	• 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.		
Thyroid disorders [see Warnings and Precautions]	• 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.		
Type 1 diabetes mellitus [see Warnings and Precautions]	• 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. **Withhold** KEYTRUDA depending on severity.		
Immune-mediated nephritis with renal dysfunction *[see Warnings and Precautions]*	• See general recommendations listed on the previous page.	• Grade 2 or 3 increased blood creatinine	• **Withhold**.[c]
		• Grade 4 increased blood creatinine	• Permanently **discontinue**.
Immune-mediated dermatologic adverse reactions *[see Warnings and Precautions]*	• Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. **Withhold** or permanently **discontinue** depending on severity.		
Immune-mediated exfoliative dermatologic conditions *[see Warnings and Precautions]*	• See general recommendations listed on the previous page.	• Suspected SJS, TEN, or DRESS	• **Withhold**.[c]
		• Confirmed SJS, TEN, or DRESS	• Permanently **discontinue**.
Immune-mediated myocarditis *[see Warnings and Precautions]*	• See general recommendations listed on the previous page.	• Grade 2, 3, or 4	• Permanently **discontinue**.
Immune-mediated neurological toxicities *[see Warnings and Precautions]*	• See general recommendations listed on the previous page.	• Grade 2	• **Withhold**.[c]
		• Grade 3 or 4	• Permanently **discontinue**.

[a]Advise patients to review the FDA-approved patient labeling (Medication Guide).
[b]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
[c]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; TEN = toxic epidermal necrolysis; DRESS = drug rash with eosinophilia and systemic symptoms.

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.

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

Help manage your patients' adverse reactions to **KEYTRUDA** (*continued*)

Recommended Adverse Reaction Monitoring and Management for KEYTRUDA

Adverse Reaction	Monitoring and Management[a]	Severity[b]	Dosage Modification
Complications of allogeneic HSCT *[see Warnings and Precautions]*	• Follow patients closely for evidence of transplant-related complications such as hyperacute GVHD, acute and chronic GVHD, hepatic VOD, and steroid-requiring febrile syndrome. • Intervene promptly. • Consider the benefit vs risks of using anti–PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.	• See general recommendations listed on page 11.	
Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone *[see Warnings and Precautions]*	• 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.		
Other immune-mediated adverse reactions, including ocular *[see Warnings and Precautions]*	• 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.	• See general recommendations listed on page 11.	
Infusion-related reactions *[see Warnings and Precautions]*	• Monitor for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.	• Grade 1 or 2	• Interrupt or slow the rate of infusion.
		• Grade 3 or 4	• Stop infusion and permanently **discontinue**.

[a]Advise patients to review the FDA-approved patient labeling (Medication Guide).
[b]Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

GVHD = graft-versus-host disease; VOD = veno-occlusive disease; HSCT = hematopoietic stem cell transplantation.

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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.

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

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

Recommended Adverse Reaction Monitoring and Management for LENVIMA

Adverse Reaction	Monitoring and Management	Severity[a]	Dosage Modification
Hypertension *[see Warnings and Precautions]*	• Control BP prior to initiation. • Monitor BP after 1 week, then every 2 weeks for the first 2 months and at least monthly thereafter during treatment.	• Grade 3	• **Withhold** for Grade 3 that persists despite optimal antihypertensive therapy. • **Resume** at a reduced dose when hypertension is controlled at ≤ Grade 2.
		• Grade 4	• Permanently **discontinue**.
Cardiac dysfunction *[see Warnings and Precautions]*	• Monitor patients for clinical symptoms or signs of cardiac dysfunction.	• Grade 3	• **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	• Permanently **discontinue**.
Arterial thromboembolic events *[see Warnings and Precautions]*	• 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.	• Any grade	• Permanently **discontinue**.
Hepatotoxicity *[see Warnings and Precautions]*	• Monitor liver function prior to initiation. • Monitor liver function 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.	• Grade 3 or 4	• **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. • Permanently **discontinue** for hepatic failure.
Renal failure or impairment *[see Warnings and Precautions]*	• Initiate prompt management of diarrhea or dehydration/hypovolemia.	• Grade 3 or 4	• **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.
Proteinuria *[see Warnings and Precautions]*	• Monitor for proteinuria prior to initiation and periodically during treatment. – If proteinuria ≥2+ on urine dipstick, obtain a 24-hour urine protein sample.	• 2 g or greater in 24 hours	• **Withhold** until less than or equal to 2 g of proteinuria per 24 hours. • **Resume** at a reduced dose. • Permanently **discontinue** for nephrotic syndrome.
Diarrhea *[see Warnings and Precautions]*	• Promptly initiate management of diarrhea.	• Persistent or intolerable Grade 2 or 3 adverse reaction	• **Withhold** until improves to Grade 0 to 1 or baseline. • **Resume** at a reduced dose.
		• Grade 4 adverse reaction	• Permanently **discontinue**.
Gastrointestinal perforation *[see Warnings and Precautions]*		• Any grade	• Permanently **discontinue**.
Fistula formation *[see Warnings and Precautions]*		• Grade 3 or 4	• Permanently **discontinue**.
QT prolongation *[see Warnings and Precautions]*	• Monitor/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 QT interval, including Class Ia and III antiarrhythmics.	• >500 ms or >60 ms increase from baseline	• **Withhold** until improves to ≤480 ms or baseline. • **Resume** at a reduced dose.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.
BP = blood pressure; HCC = hepatocellular carcinoma; ms = millisecond.

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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.

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

Help manage your patients' adverse reactions to **LENVIMA** (*continued*)

Recommended Adverse Reaction Monitoring and Management for LENVIMA

Adverse Reaction	Monitoring and Management	Severity[a]	Dosage Modification
Hypocalcemia *[see Warnings and Precautions]*	• Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment.	• Persistent or intolerable Grade 2 or 3 adverse reaction • Grade 4 laboratory abnormality	• **Withhold** until improves to Grade 0 to 1 or baseline. • **Resume** at a reduced dose.
		• Grade 4 adverse reaction	• Permanently **discontinue**.
Reversible posterior leukoencephalopathy syndrome (RPLS) *[see Warnings and Precautions]*	• Confirm the diagnosis of RPLS with magnetic resonance imaging.	• Any grade	• **Withhold** until fully resolved. • **Resume** at a reduced dose or **discontinue** depending on severity and persistence of neurologic symptoms.
Hemorrhagic events *[see Warnings and Precautions]*	• Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery).	• Persistent or intolerable Grade 2 or 3 adverse reaction	• **Withhold** until improves to Grade 0 to 1 or baseline. • **Resume** at a reduced dose.
		• Grade 4 adverse reaction	• Permanently **discontinue**.
Impairment of thyroid-stimulating hormone suppression/ thyroid dysfunction *[see Warnings and Precautions]*	• Monitor thyroid function prior to initiation and at least monthly during treatment. • Treat hypothyroidism according to standard medical practice.		
Impaired wound healing *[see Warnings and Precautions]*	• The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.		• **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.
Osteonecrosis of the jaw (ONJ) *[see Warnings and Precautions]*	• 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 LENVIMA treatment, particularly in patients at higher risk. • For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.		• **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 judgement of adequate resolution.
Other adverse reactions *[see Warnings and Precautions for Diarrhea, Hypocalcemia, Hemorrhagic events]*		• Persistent or intolerable Grade 2 or 3 adverse reaction • Grade 4 laboratory abnormality	• **Withhold** until improves to Grade 0 to 1 or baseline. • **Resume** at a reduced dose.
		• Grade 4 adverse reaction	• Permanently **discontinue**.

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

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.

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 (*continued*)

reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

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

Other Immune-Mediated Adverse Reactions

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

Infusion-Related Reactions

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

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

Hemorrhagic Events (*continued*)

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.

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.

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.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Selected Safety Information (*continued*)

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

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

Increased Mortality in Patients With Multiple Myeloma

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

Embryofetal Toxicity

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

Adverse Reactions

- In KEYNOTE-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*)

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.

  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%).

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.

ALT = alanine aminotransferase.

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.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

For the first-line treatment of adult patients with advanced renal cell carcinoma

Monitor and help manage adverse reactions

KEYTRUDA + LENVIMA: Adverse reaction management

When administering KEYTRUDA in combination with LENVIMA for the treatment of adult patients with advanced renal cell carcinoma, modify the dosage of one or both drugs as appropriate. Withhold or discontinue KEYTRUDA. Withhold, dose reduce, or discontinue LENVIMA as appropriate.

Monitor for adverse reactions and consult the Prescribing Information for KEYTRUDA and for LENVIMA as appropriate for management.

Manage adverse reactions for KEYTRUDA by withholding or discontinuing treatment. No dose reductions of KEYTRUDA are recommended.

Manage adverse reactions for LENVIMA by withholding, reducing the dose, or discontinuing LENVIMA.

Indication for KEYTRUDA + LENVIMA

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

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

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*)

Use in Specific Populations (*continued*)

- 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 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.

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

For more information, please visit KeytrudaLenvimaHCP.com.

MERCK Eisai

KEYTRUDA® (pembrolizumab) Injection 100 mg

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