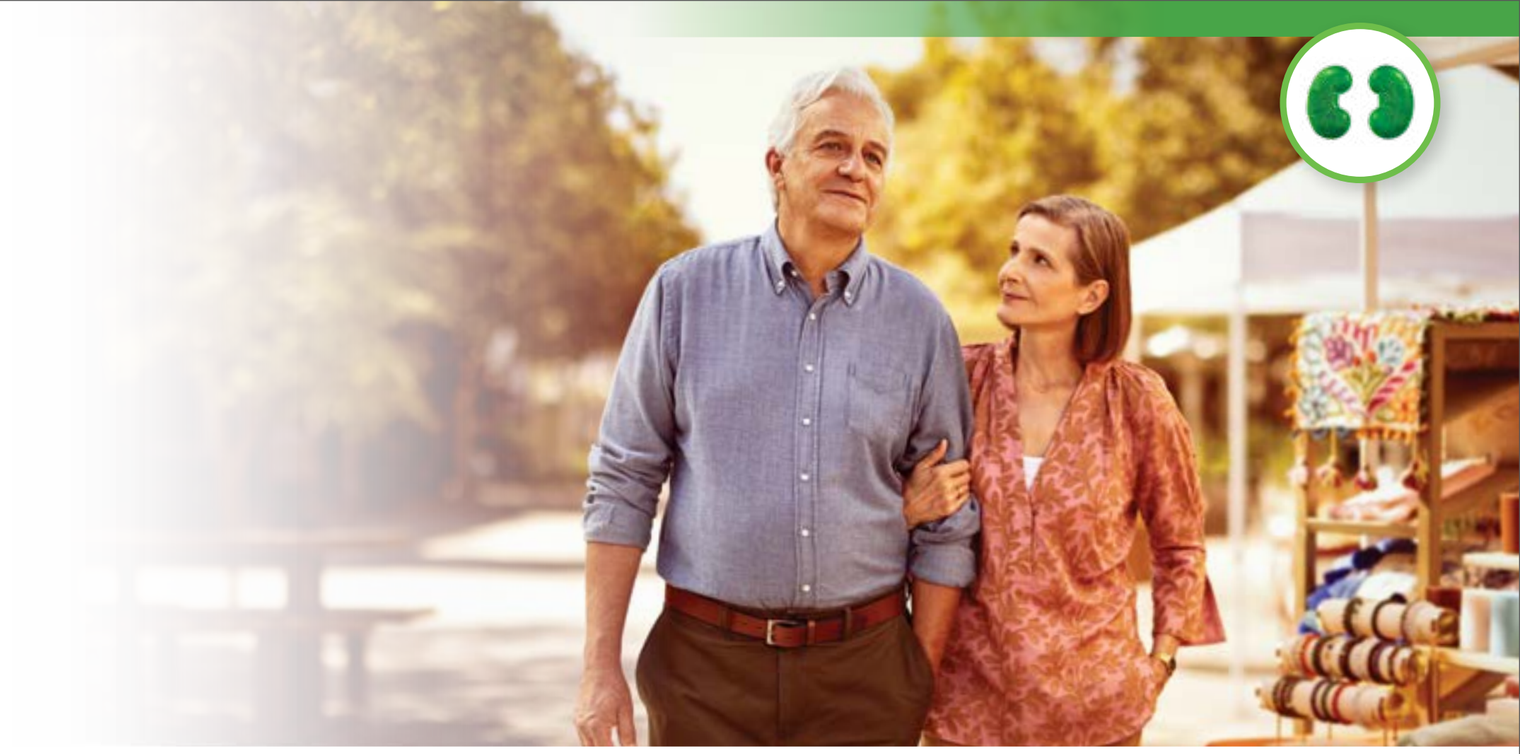
Focus On Possibilities

FOR TREATING YOUR PATIENTS WITH ADVANCED RCC



Actor Portrayal

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).

National Comprehensive Cancer Network® (NCCN®) recommends pembrolizumab (**KEYTRUDA**) + lenvatinib (**LENVIMA**) as a **CATEGORY 1, PREFERRED** first-line therapy option for advanced clear cell renal cell carcinoma.[1]

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[1]

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.

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Studied in the first-line setting across MSKCC risk groups

The KEYNOTE-581/CLEAR trial: A multicenter, randomized, open-label, phase 3 trial with 1,069 patients[2]

Key inclusion criteria:
- Advanced RCC in the 1L setting
- Regardless of PD-L1 tumor expression status

Key exclusion criteria:
- Active autoimmune disease
- A medical condition that required immunosuppression

Stratification factors:
- Geographic region[a]
- MSKCC prognostic groups[b]

Randomized 1:1:1[c]

(n=355) **KEYTRUDA 200 mg** intravenously every 3 weeks; KEYTRUDA dosing was continued for a maximum of 24 months
LENVIMA 20 mg orally once daily; LENVIMA treatment could be continued beyond 24 months

(n=357) **Sunitinib 50 mg** orally once daily; 4 weeks on and 2 weeks off

(n=357) LENVIMA 18 mg orally once daily Everolimus 5 mg orally once daily

Treatment continued until unacceptable toxicity or disease progression.[d]

Assessment of tumor status was performed at baseline and then every 8 weeks.

Major endpoints:
PFS, as assessed by IRC according to RECIST v1.1, and OS

Additional endpoint:
Confirmed ORR as assessed by IRC

[a]North America and Western Europe vs "Rest of the World."
[b]Randomization was stratified according to Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups: favorable vs intermediate vs poor.
[c]Clinical data are presented from the KEYTRUDA + LENVIMA and sunitinib arms.
[d]Administration of KEYTRUDA with LENVIMA was permitted beyond RECIST-defined disease progression, if the patient was clinically stable and considered by the investigator to be deriving clinical benefit.
1L = first-line; IRC = independent radiologic review committee; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

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.

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

Hypertension (*continued*)

- 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 included throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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

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

Baseline characteristics in the KEYNOTE-581/CLEAR trial

Age

Median age of **62 years** (range: 29–88)

42% age 65 or older

Gender

75% Male

Race

74% White

21% Asian

1% Black

2% Other

KEYNOTE-581/CLEAR trial: Baseline characteristics (N=1,069)

Baseline Karnofsky performance status

18% 70 to 80

82% 90 to 100

Common sites of metastases

68% Lung

45% Lymph node

25% Bone

MSKCC risk category

27% Favorable

64% Intermediate

9% Poor

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

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

- Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

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

Cardiac Dysfunction

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

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.

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

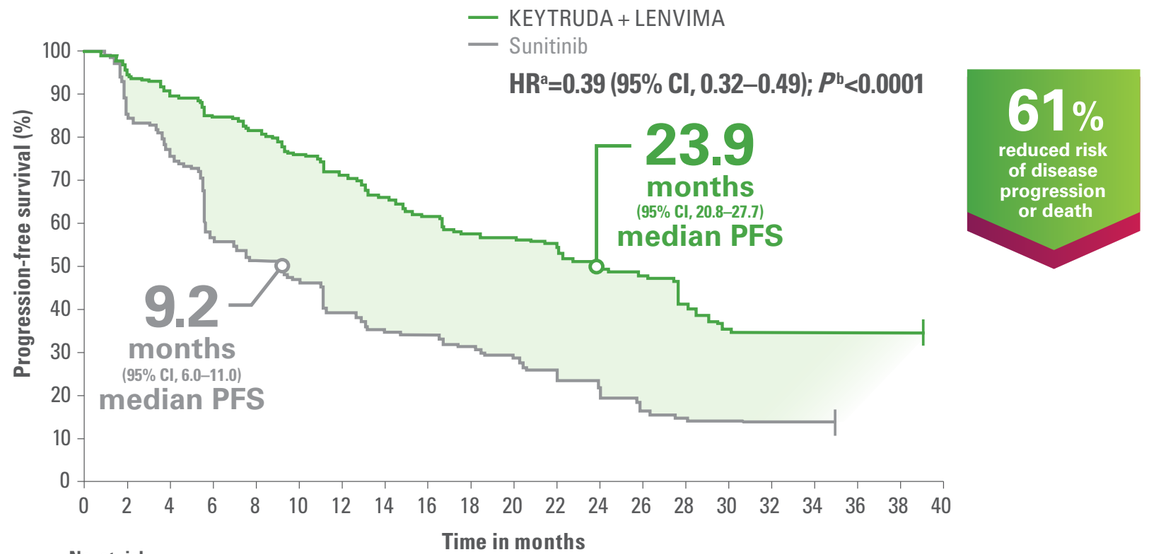
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

Superior PFS with KEYTRUDA + LENVIMA vs sunitinib (HR[a]=0.39; 95% CI, 0.32–0.49; *P*[b]<0.0001) at protocol-specified interim analysis

- Number of events[c]: 160/355 (45%) with KEYTRUDA + LENVIMA vs 205/357 (57%) with sunitinib; Progressive disease: 145/355 (41%) vs 196/357 (55%), respectively; Death: 15/355 (4%) vs 9/357 (3%), respectively.
- **Median PFS: 23.9 months** (95% CI, 20.8–27.7) with KEYTRUDA + LENVIMA vs **9.2 months** (95% CI, 6.0–11.0) with sunitinib.
- PFS and OS were major endpoints in the KEYNOTE-581/CLEAR trial.

2.5x greater median PFS observed with **KEYTRUDA + LENVIMA** (23.9 months) vs sunitinib (9.2 months).

Kaplan-Meier estimates of PFS with KEYTRUDA + LENVIMA (n=355) vs sunitinib (n=357) in the KEYNOTE-581/CLEAR trial



[a]Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
[b]Two-sided *P* value based on stratified log-rank test.
[c]Tumor assessments were based on RECIST v1.1; data cutoff date = 28 Aug 2020.
HR = hazard ratio; CI = confidence interval.

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

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

Immune-Mediated Pneumonitis

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

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

Arterial Thromboembolic Events (*continued*)

- 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 included throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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

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

Durable overall survival with KEYTRUDA + LENVIMA vs sunitinib

Superior OS with KEYTRUDA + LENVIMA demonstrated at protocol-specified interim analysis

34%
reduced risk of death

- **HR[a]=0.66, 95% CI, 0.49–0.88; *P*[b]=0.0049.**
- Number of deaths[c]: 80/355 (23%) with KEYTRUDA + LENVIMA vs 101/357 (28%) with sunitinib.
- **Median OS was not reached (NR) in either arm:** KEYTRUDA + LENVIMA (95% CI, 33.6–NR) and sunitinib (95% CI, NR–NR).
- OS and PFS were major endpoints in the KEYNOTE 581/CLEAR trial.

[a]Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
[b]Two-sided *P* value based on stratified log-rank test.
[c]Data cutoff date = 28 Aug 2020.

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

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

Immune-Mediated Colitis

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

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

Hepatotoxicity

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

Renal Failure or Impairment

- Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).

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

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

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

Overall survival with KEYTRUDA + LENVIMA vs sunitinib *(continued)*

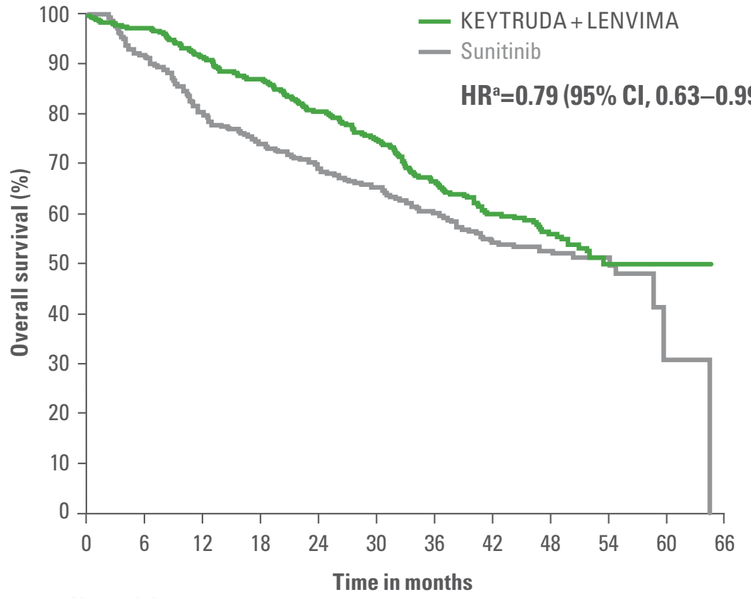
Updated OS[b,c] at protocol-specified final analysis

This protocol-specified final analysis occurred after the interim analysis, which demonstrated the superiority of OS with KEYTRUDA + LENVIMA vs sunitinib. No statistical testing was planned for the protocol-specified final OS analysis.

- **HR[a]=0.79 (95% CI, 0.63–0.99).**
- Number of deaths[b]: 149/355 (42%) with KEYTRUDA + LENVIMA vs 159/357 (45%) with sunitinib.
- **Median OS: 53.7 months** (95% CI, 48.7–NR) with KEYTRUDA + LENVIMA vs **54.3 months** (95% CI, 40.9–NR) with sunitinib.

[a]Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
[b]Updated OS cutoff date = 31 July 2022.
[c]An updated OS analysis was conducted when 304 deaths were observed based on the planned number of deaths for the prespecified final analysis.

Kaplan-Meier estimates of updated OS with KEYTRUDA + LENVIMA (n=355) vs sunitinib (n=357) in the KEYNOTE-581/CLEAR trial



No. at risk

KEYTRUDA + LENVIMA	355	338	313	296	269	245	216	158	117	34	5	0
Sunitinib	357	308	264	242	226	208	188	145	108	33	3	0

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.

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.

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

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

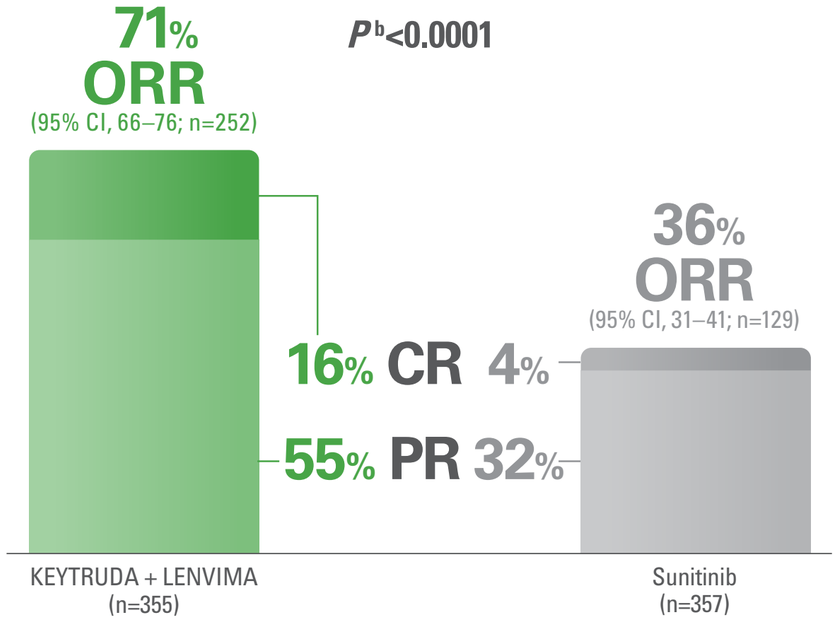
KEYTRUDA® (pembrolizumab) Injection 100 mg
LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

A **greater ORR**[a] was demonstrated with **KEYTRUDA + LENVIMA: 71% (95% CI, 66–76)** vs **36% (95% CI, 31–41)** with sunitinib **(*P*[b]<0.0001)** at protocol-specified interim analysis

- **CR: 16%** with KEYTRUDA + LENVIMA vs **4%** with sunitinib.
- **PR: 55%** with KEYTRUDA + LENVIMA vs **32%** with sunitinib.
- ORR was an additional endpoint in the KEYNOTE-581/CLEAR trial.

Nearly 2x greater ORR demonstrated with **KEYTRUDA + LENVIMA** (71%) vs sunitinib (36%) (*P*[b]<0.0001).

ORR with KEYTRUDA + LENVIMA vs sunitinib in the KEYNOTE-581/CLEAR trial[a]



[a]Tumor assessments were based on RECIST v1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020.
[b]Two-sided *P* value based upon CMH test.
CR = complete response; PR = partial response; CMH = Cochran-Mantel-Haenszel.

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

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

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*)

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 included throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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

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

Adverse reactions in the KEYNOTE-581/CLEAR trial

The safety of KEYTRUDA + LENVIMA was investigated in the KEYNOTE-581/CLEAR trial in patients treated with KEYTRUDA + LENVIMA (n=352) compared to sunitinib (n=340) at the protocol-specified interim analysis.

The median duration of exposure to KEYTRUDA + LENVIMA was 17 months (range: 0.1 to 39).

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

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

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

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

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

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.

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.

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Adverse reactions in 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%)	Hepatotoxicity (3%)	Rash (3%)
Myocardial infarction (3%)	Acute kidney injury (3%)	Diarrhea (2%)

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

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

Immune-Mediated Endocrinopathies (*continued*)

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.

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

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.

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

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

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

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

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

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

ALT = alanine aminotransferase.

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

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

Immune-Mediated Endocrinopathies (*continued*)

Thyroid Disorders (continued)

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

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.

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

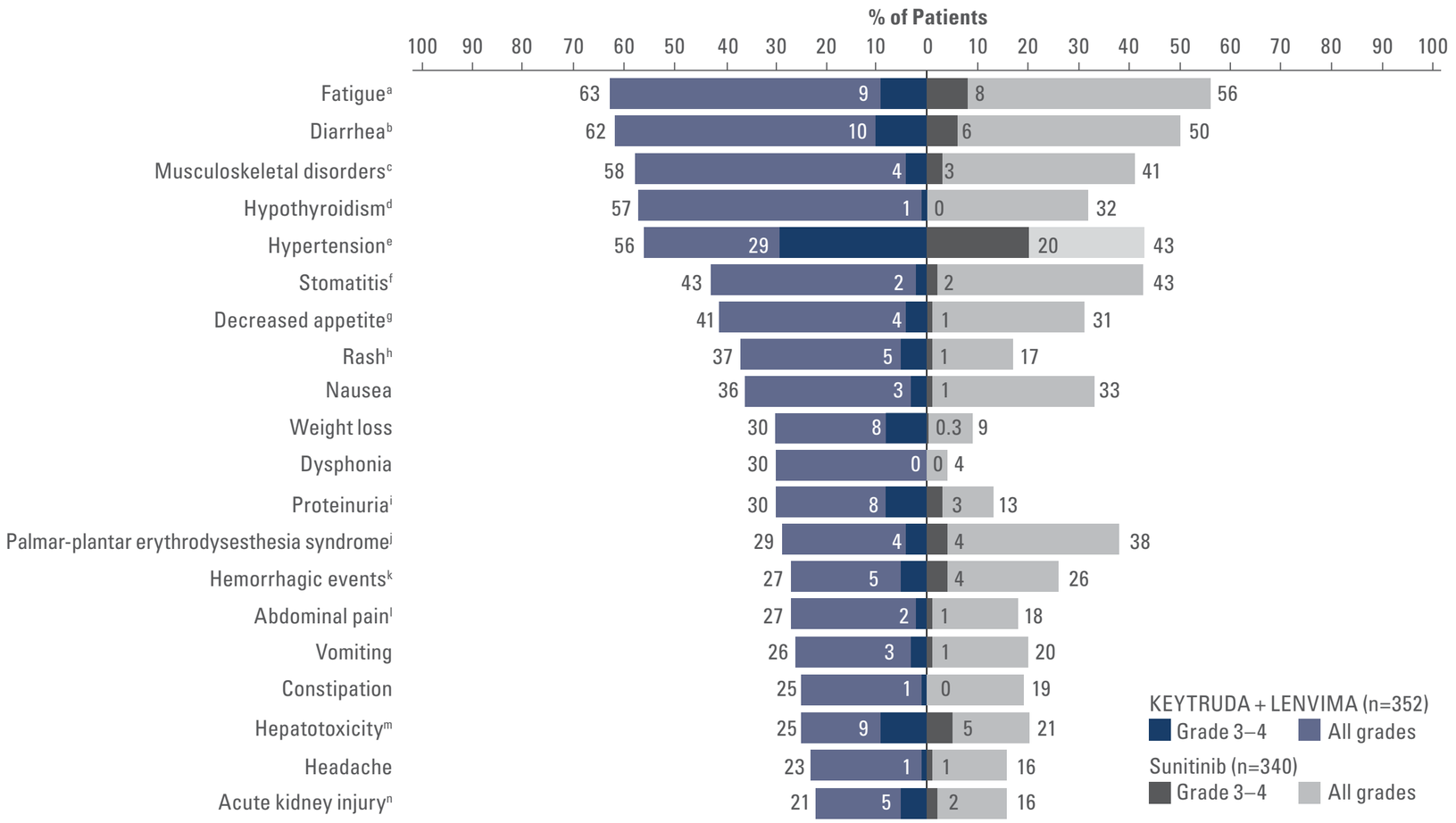
Before prescribing LENVIMA, please read the additional Selected Safety Information included throughout this document and the accompanying Prescribing Information and Patient Information.

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

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

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



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

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

AST = aspartate aminotransferase.

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

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

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

Selected Safety Information (*continued*)

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

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

Immune-Mediated Endocrinopathies (*continued*)

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 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.

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

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.

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Selected Safety Information (*continued*)

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

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

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*)

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 included throughout this document and the accompanying Prescribing Information. The Medication Guide also is available.

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Selected Safety Information (*continued*)

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

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.

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%).

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

Selected Safety Information (*continued*)

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

Adverse Reactions

- 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%).

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*)

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.
- 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.

ALT = alanine aminotransferase.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed March 12, 2024. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. **2.** Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med.* 2021;384(14):1289–1300. doi:10.1056/NEJMoa2035716

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

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

KEYTRUDA® (pembrolizumab) Injection 100 mg

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

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

In the protocol-specified interim analysis for the KEYNOTE-581/CLEAR trial:

KEYTRUDA + LENVIMA demonstrated superiority in PFS, OS, and ORR vs sunitinib

SUPERIOR PFS
vs sunitinib (major endpoint)

- **HR[a]=0.39; 95% CI, 0.32–0.49; *P*[b]<0.0001**
- Number of events[c]: 160/355 (45%) with KEYTRUDA + LENVIMA vs 205/357 (57%) with sunitinib; Progressive disease: 145/355 (41%) vs 196/357 (55%), respectively; Death: 15/355 (4%) vs 9/357 (3%), respectively
- **Median PFS: 23.9 months** (95% CI, 20.8–27.7 months) vs **9.2 months** (95% CI, 6.0–11.0 months) with sunitinib

Median PFS 23.9 months
with **KEYTRUDA + LENVIMA**

SUPERIOR OS
vs sunitinib (major endpoint)

- **HR[a]=0.66; 95% CI, 0.49–0.88; *P*[b]=0.0049**
- Number of deaths[c]: 80/355 (23%) with KEYTRUDA + LENVIMA vs 101/357 (28%) with sunitinib
- **Median OS** for KEYTRUDA + LENVIMA was NR (95% CI, 33.6–NR) vs NR (95% CI, NR–NR) with sunitinib

[a]Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and MSKCC prognostic groups.
[b]Two-sided *P* value based on stratified log-rank test.

34% reduced risk of death
with **KEYTRUDA + LENVIMA**

SUPERIOR ORR
vs sunitinib (additional endpoint)

- **ORR[c]: 71%** (95% CI, 66–76) (n=252/355) with KEYTRUDA + LENVIMA vs **36%** (95% CI, 31–41) (n=129/357) with sunitinib; ***P*[d]<0.0001**
  - **CR: 16%** vs **4%** with sunitinib
  - **PR: 55%** vs **32%** with sunitinib

[c]Tumor assessments were based on RECIST v1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020.
[d]Two-sided *P* value based upon CMH test.

ORR 71% | CR 16% | PR 55%
with **KEYTRUDA + LENVIMA**

Summary of Warnings and Precautions for KEYTRUDA® (pembrolizumab)

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time during or after treatment with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection, other transplant (including corneal graft) rejection, and complications of allogeneic hematopoietic stem cell transplantation. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or permanently discontinued and corticosteroids administered if appropriate. KEYTRUDA can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman.

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

Summary of Warnings and Precautions for LENVIMA® (lenvatinib)

Adverse reactions, some of which can be serious or fatal, may occur with LENVIMA, including hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid stimulating hormone suppression/thyroid dysfunction, impaired wound healing, osteonecrosis of the jaw, and embryo-fetal toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception. Based on the severity of the adverse reaction, LENVIMA should be interrupted, reduced, and/or discontinued.

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

For references cited in this brochure, see the previous page.

For more information, visit KeytrudaLenvimaHCP.com.

MERCK Eisai

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