

## **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).

**Continue >**

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

#### **Severe and Fatal Immune-Mediated Adverse Reactions**

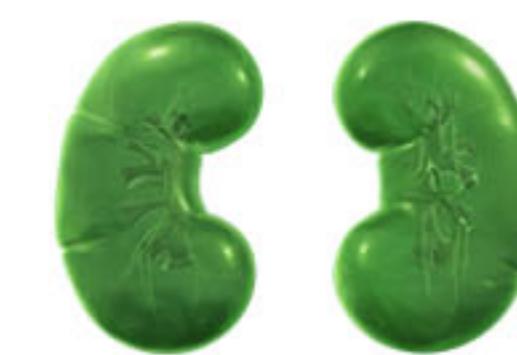
- KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions.

### **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  $\geq 160$  mmHg occurred in 29% of patients, and 21% had diastolic blood pressure  $> 100$  mmHg. In unrespectable



[Indication](#)[Introduction](#)[Efficacy](#)[Safety](#)[Dosing](#)[Access & Support](#)[Selected Safety Information](#)

# In Possibilities

*... 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).

[Continue >](#)

## 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 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.

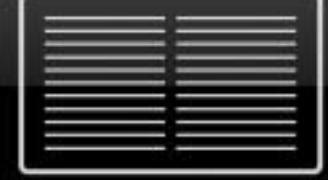
**KEYTRUDA®**  
(pembrolizumab)

**LENVIMA®**  
(lenvatinib)

## Selected Safety Information for LENVIMA® (lenvatinib)

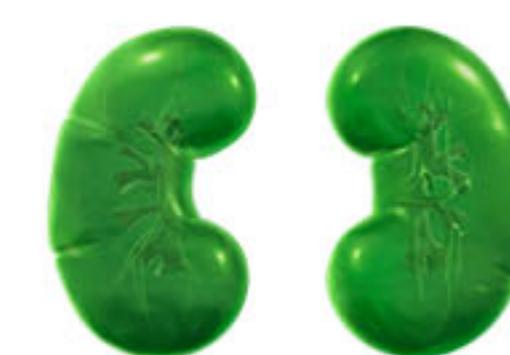
### Hypertension

- 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  $\geq 160$  mmHg occurred in 29% of patients, and 21% had diastolic blood pressure  $> 100$  mmHg. In unrespectable



**KEYTRUDA: PI and MG**  
**LENVIMA: PI and PPI**

**Indications and Selected Safety Information**



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**

Learn about a  
treatment recommendation

**Superior progression-free survival (PFS)  
vs sunitinib (major endpoint)**

- **HR<sup>a</sup>=0.39 (95% CI, 0.32–0.49); P<sup>b</sup><0.0001**
- Number of events<sup>c</sup>: 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

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

**Superior overall survival (OS) vs sunitinib  
(major endpoint)**

- **HR<sup>a</sup>=0.66; 95% CI, 0.49–0.88; P<sup>b</sup>=0.0049**
- Number of deaths<sup>c</sup>: 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

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

**Superior objective response rate (ORR) vs  
sunitinib (additional endpoint)**

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

<b>ORR</b>	<b>CR</b>	<b>PR</b>
<b>71%</b>	<b>16%</b>	<b>55%</b>
<b>with KEYTRUDA + LENVIMA</b>		

<sup>a</sup>Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.

<sup>b</sup>Two-sided P value based on stratified log-rank test.

<sup>c</sup>Tumor assessments were based on RECIST v1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020.

<sup>d</sup>Two-sided P value based upon CMH test.

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HR = hazard ratio; NR = not reached; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

Study Design

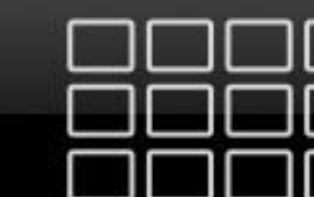
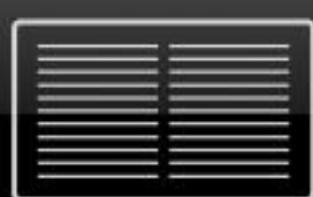
Patient Baseline Characteristics

**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, and complications of allogeneic hematopoietic

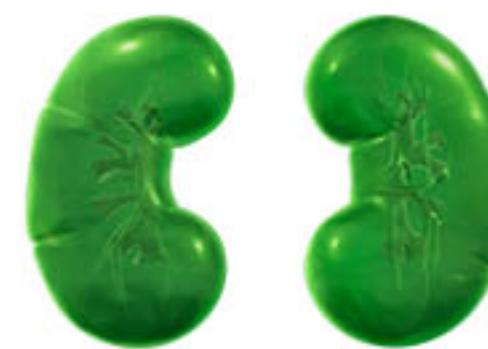
**Summary of Warnings and Precautions for  
LENVIMA® (lenvatinib)**

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



KEYTRUDA: PI and MG  
LENVIMA: PI and PPI

Indications and Selected Safety Information



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**

Learn about a  
treatment recommendation

**Superior progression-free survival (PFS)  
vs sunitinib (major endpoint)**

- **HR<sup>a</sup>=0.39 (95% CI, 0.32–0.49); P<sup>b</sup><0.0001**
- Number of events<sup>c</sup>: 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
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**Median PFS 23.9 months  
with KEYTRUDA + LENVIMA**

**Superior overall survival (OS) vs sunitinib  
(major endpoint)**

- **HR<sup>a</sup>=0.66; 95% CI, 0.49–0.88; P<sup>b</sup>=0.0049**
- Number of deaths<sup>c</sup>: 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

**34% reduced risk of death  
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**Superior objective response rate (ORR) vs  
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- **ORR<sup>c</sup>: 71% (95% CI, 66–76) (n=252/355) with KEYTRUDA + LENVIMA vs 36% (95% CI, 31–41) (n=129/357) with sunitinib; P<sup>d</sup><0.0001**
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<b>ORR</b> <b>71%</b>	<b>CR</b> <b>16%</b>	<b>PR</b> <b>55%</b>
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<sup>a</sup>Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.

<sup>b</sup>Two-sided P value based on stratified log-rank test.

<sup>c</sup>Tumor assessments were based on RECIST v1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020.

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CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HR = hazard ratio; NR = not reached; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

Study Design

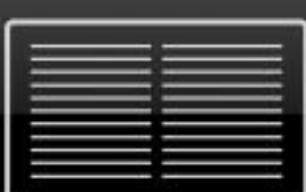
Patient Baseline Characteristics

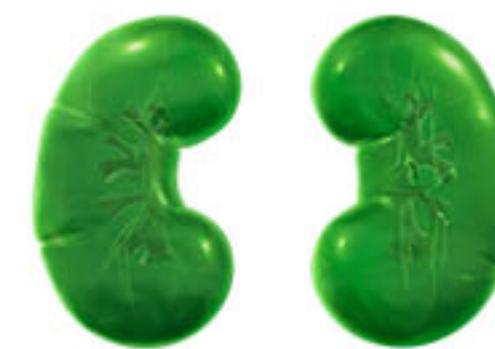
**Summary of Warnings and Precautions for  
KEYTRUDA® (pembrolizumab) (continued)**

transplant 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

**Summary of Warnings and Precautions for  
LENVIMA® (lenvatinib) (continued)**

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





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  
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Learn about a  
treatment recommendation

**Superior progression-free survival (PFS)  
vs sunitinib (major endpoint)**

- **HR<sup>a</sup>=0.39 (95% CI, 0.32–0.49); P<sup>b</sup><0.0001**
- Number of events<sup>c</sup>: 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
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**Median PFS 23.9 months  
with KEYTRUDA + LENVIMA**

**Superior overall survival (OS) vs sunitinib  
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- **HR<sup>a</sup>=0.66; 95% CI, 0.49–0.88; P<sup>b</sup>=0.0049**
- Number of deaths<sup>c</sup>: 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

**34% reduced risk of death  
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**Superior objective response rate (ORR) vs  
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<b>ORR</b> <b>71%</b>	<b>CR</b> <b>16%</b>	<b>PR</b> <b>55%</b>
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<sup>a</sup>Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.

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CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HR = hazard ratio; NR = not reached; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

Study Design

Patient Baseline Characteristics

**Summary of Warnings and Precautions for  
KEYTRUDA® (pembrolizumab) (continued)**

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.

**Summary of Warnings and Precautions for  
LENVIMA® (lenvatinib) (continued)**

Women 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.



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<sup>1</sup>

**Key inclusion criteria:**

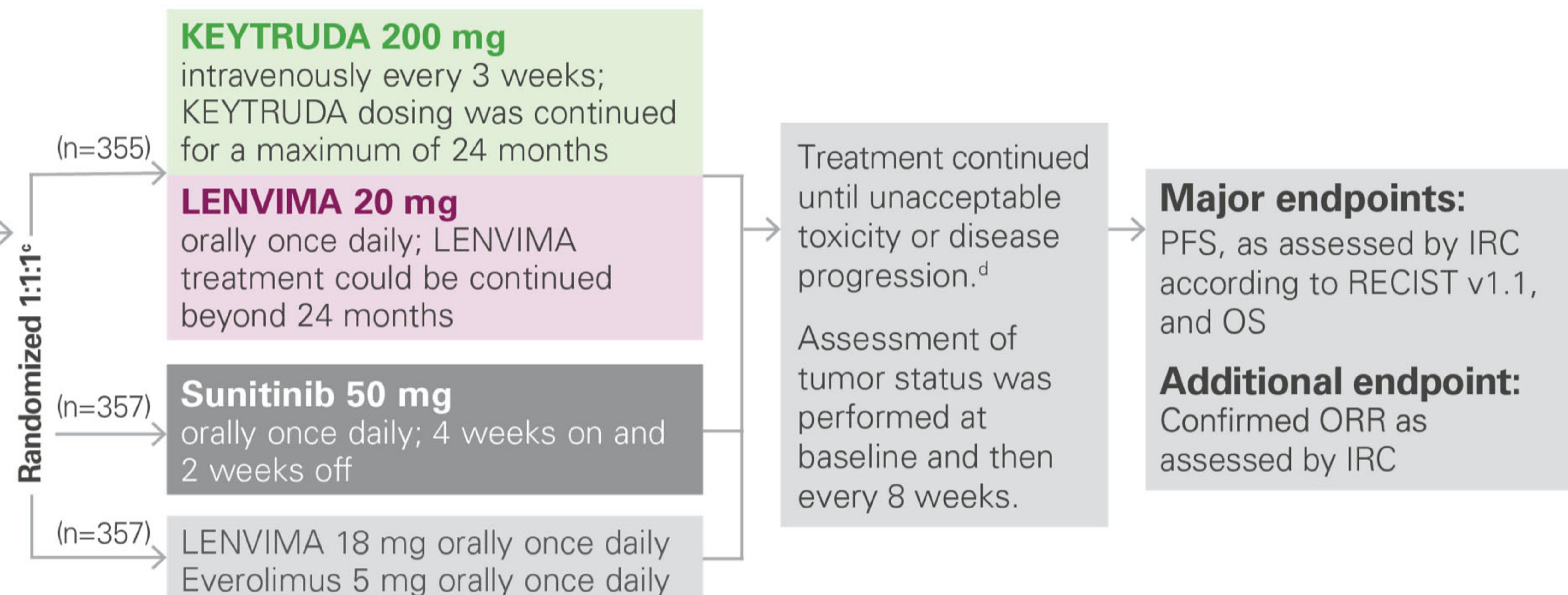
- Advanced RCC in the 1L setting
- Regardless of PD-L1 tumor expression status

**Key exclusion criteria:**

- Active autoimmune disease
- A medical condition that required immunosuppression

**Stratification factors:**

- Geographic region<sup>a</sup>
- MSKCC prognostic groups<sup>b</sup>



<sup>a</sup>North America and Western Europe vs “Rest of the World.”

<sup>b</sup>Randomization was stratified according to Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups: favorable vs intermediate vs poor.

<sup>c</sup>Clinical data are presented from the KEYTRUDA + LENVIMA and sunitinib arms.

<sup>d</sup>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.

## 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, and complications of allogeneic hematopoietic

## 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





Studied in the first-line setting across MSKCC risk groups

**The KEYNOTE-581/CLEAR trial: Baseline characteristics (N=1,069)<sup>1</sup>**

<b>Median age</b>	<b>62 years</b> (range: 29 to 88 years; 42% aged 65 or older)			
<b>Gender</b>	<b>75% Male</b>			
<b>Race</b>	<b>74% White</b>	<b>21% Asian</b>	<b>1% Black</b>	<b>2% Other</b>
<b>Baseline Karnofsky performance status</b>	<b>18% 70 to 80</b> <b>82% 90 to 100</b>			
<b>Common sites of metastases</b>	<b>68% Lung</b>	<b>45% Lymph node</b>	<b>25% Bone</b>	
<b>MSKCC risk category</b>	<b>27% Favorable</b>	<b>64% Intermediate</b>	<b>9% Poor</b>	

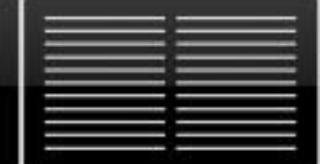
MSKCC = Memorial Sloan Kettering Cancer Center.

### 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, and complications of allogeneic hematopoietic

### 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



## FDA-Approved Indication

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

**Recommended by National Comprehensive Cancer Network® (NCCN®) for advanced clear cell renal cell carcinoma<sup>2</sup>**

**NCCN** recommends pembrolizumab (**KEYTRUDA**) + lenvatinib (**LENVIMA**) as a **PREFERRED** first-line therapy option (**CATEGORY 1**) for advanced clear cell renal cell carcinoma.<sup>2</sup>

### NCCN recommendations according to MSKCC and IMDC risk categories<sup>2</sup>

	Favorable	Intermediate	Poor
<b>Pembrolizumab (KEYTRUDA) + Lenvatinib (LENVIMA)</b>	<b>PREFERRED CATEGORY 1</b>	<b>PREFERRED CATEGORY 1</b>	<b>PREFERRED CATEGORY 1</b>

- Pembrolizumab (KEYTRUDA) + lenvatinib (LENVIMA): A **PREFERRED** first-line option (**CATEGORY 1**) for favorable and intermediate/poor-risk patients with advanced clear cell renal cell carcinoma within NCCN for Kidney Cancer.

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.

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center.

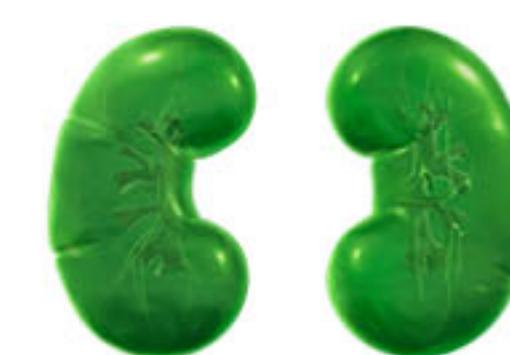
## Summary of Warnings and Precautions for KEYTRUDA® (pembrolizumab)

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, and complications of allogeneic hematopoietic

## 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





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

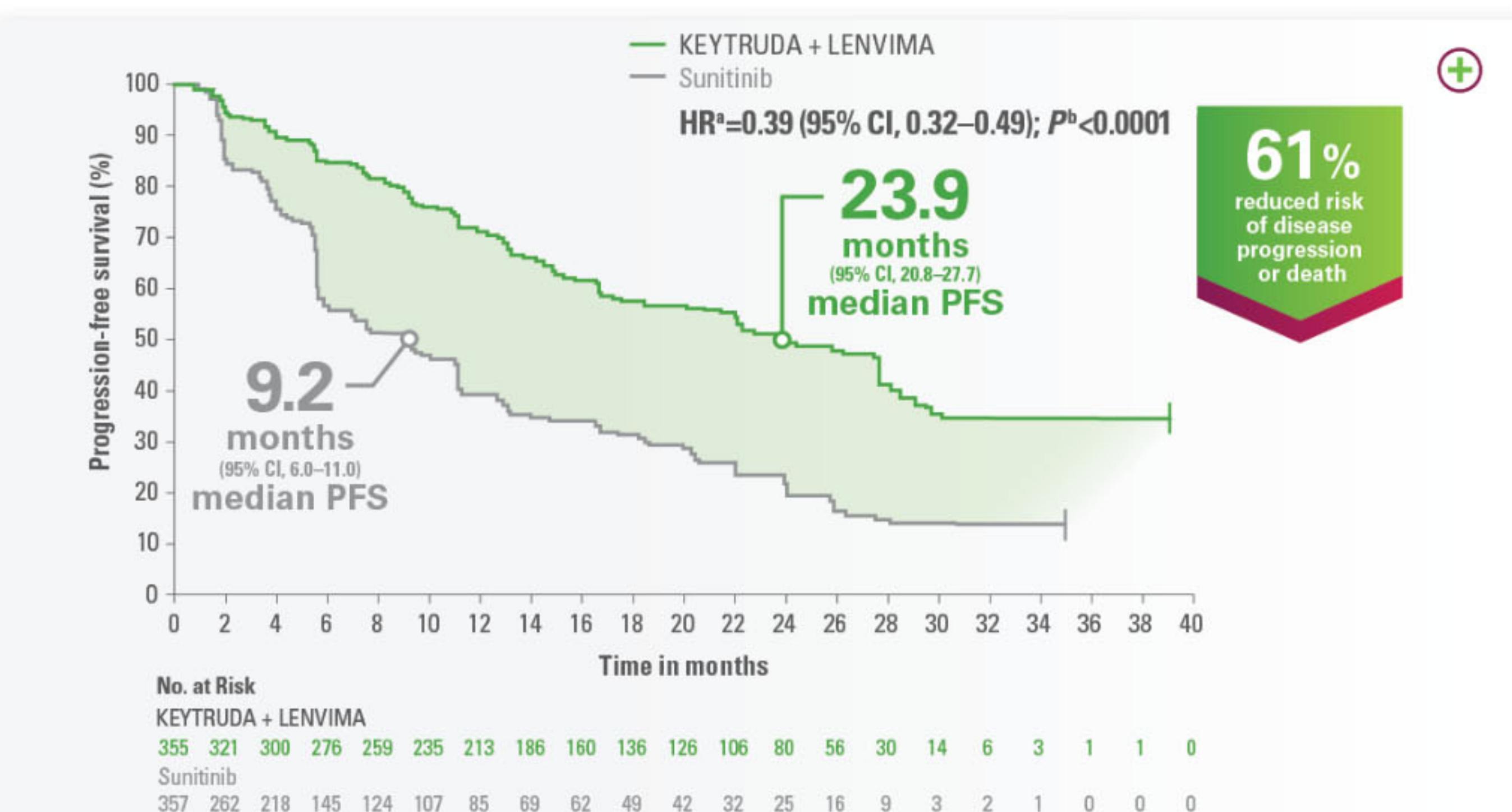
## Superior PFS at protocol-specified interim analysis with KEYTRUDA + LENVIMA vs sunitinib ( $HR^a=0.39$ ; 95% CI, 0.32–0.49; $P^b<0.0001$ )

- Number of events<sup>c</sup>: 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



<sup>a</sup>Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.

<sup>b</sup>Two-sided  $P$  value based on stratified log-rank test.

<sup>c</sup>Tumor assessments were based on RECIST v1.1; data cutoff date = 28 Aug 2020.

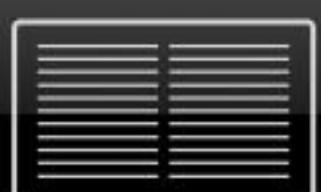
CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

### Selected Safety Information for KEYTRUDA® (pembrolizumab)

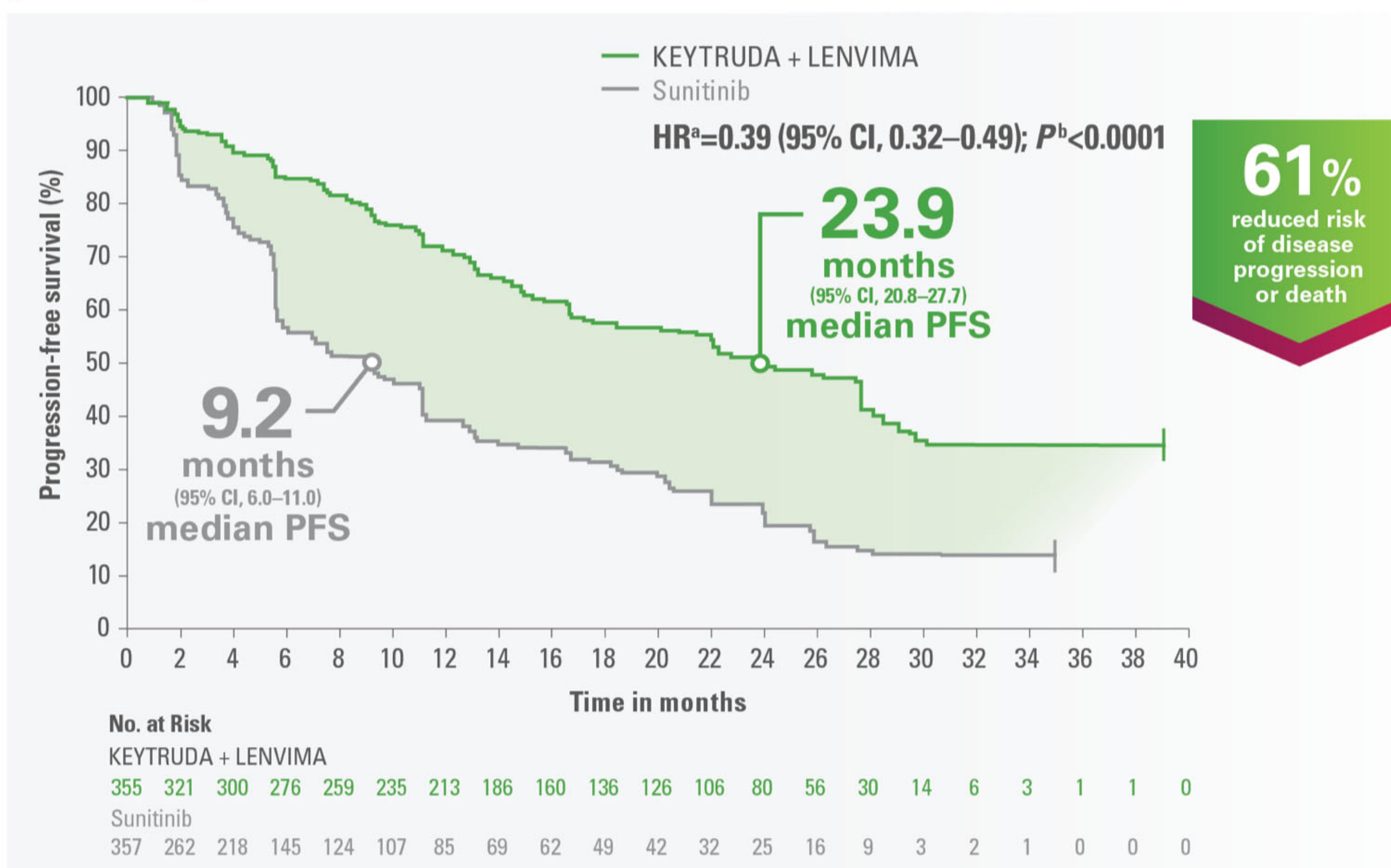
- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to

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

- 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,



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



<sup>a</sup>Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.

<sup>b</sup>Two-sided P value based on stratified log-rank test.

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

### Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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-

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

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



# Exploratory subgroup analysis of PFS for KEYTRUDA + LENVIMA vs sunitinib in patients with advanced RCC based on selected baseline features<sup>3</sup>

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

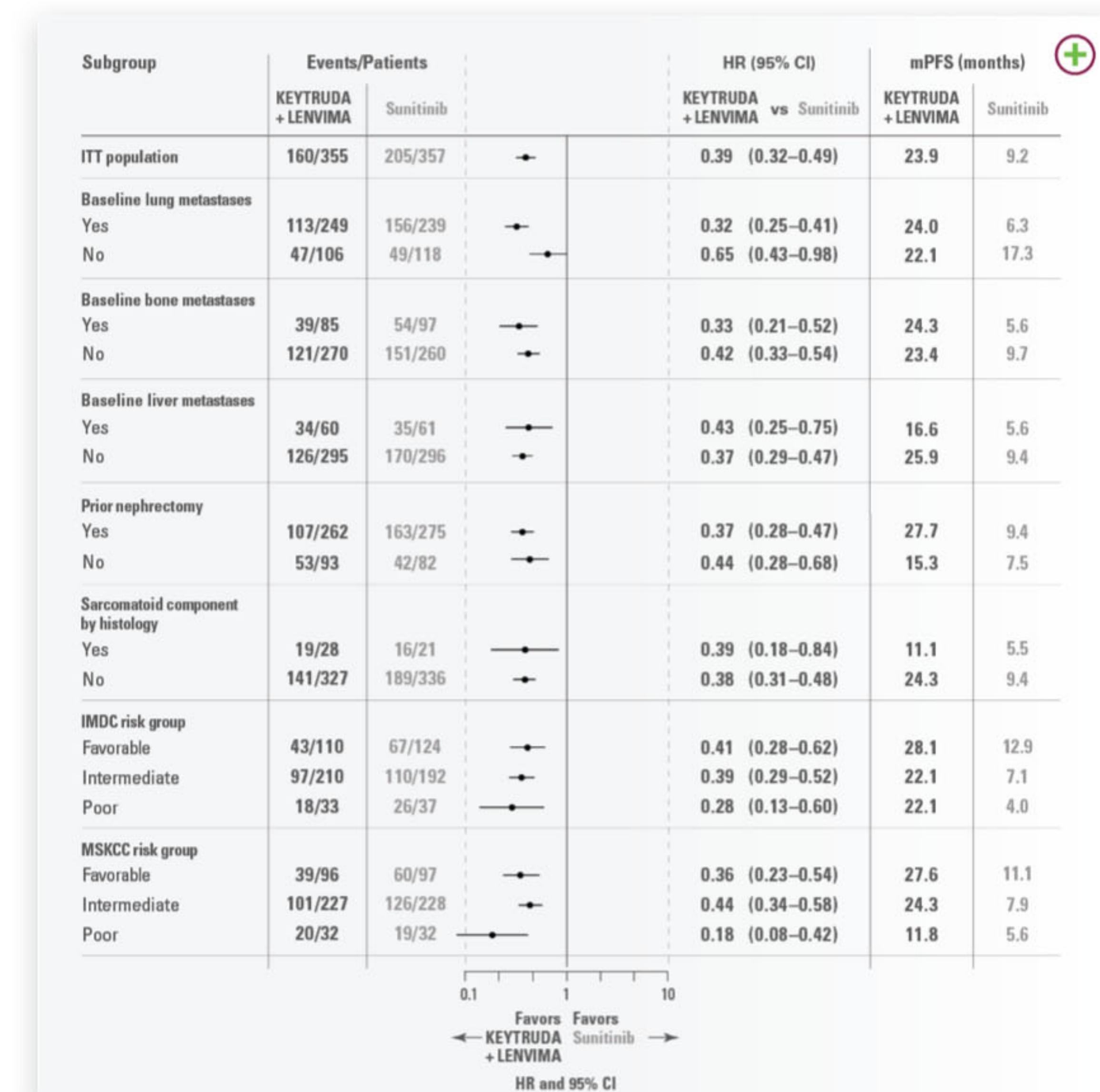
This exploratory analysis of the KEYNOTE-581/CLEAR trial evaluated PFS for KEYTRUDA + LENVIMA vs sunitinib in patients with advanced RCC with or without specific baseline features, including baseline lung metastases, baseline bone metastases, baseline liver metastases, prior nephrectomy, sarcomatoid component by histology, IMDC risk group, and MSKCC risk group.<sup>a</sup>

PFS was assessed by IRC according to RECIST v1.1.

<sup>a</sup>mPFS for the KEYTRUDA + LENVIMA and sunitinib arms was estimated using the Kaplan-Meier method; HR and 95% CIs comparing KEYTRUDA + LENVIMA with sunitinib were estimated by a stratified Cox model. If a stratification factor was itself a subgroup, this factor was removed from the stratified analysis.

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; ITT = intent to treat; mPFS = median progression-free survival; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

From *Frontiers in Oncology*, Grünwald V, et al. Phase 3 CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for the lenvatinib-plus-pembrolizumab and sunitinib arms. *Front Oncol.* 2023;13:1223282. doi:10.3389/fonc.2023.1223282. Copyright © 2023. Reprinted with permission from *Frontiers in Oncology*.

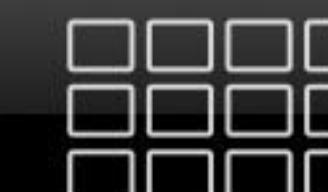


## Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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

## Selected Safety Information for LENVIMA® (lenvatinib)

- 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





# PFS by subgroups by IRC per RECIST v1.1<sup>3,a</sup>

Subgroup	Events/Patients		HR (95% CI)		mPFS (months)	
	KEYTRUDA + LENVIMA	Sunitinib	KEYTRUDA + LENVIMA vs Sunitinib		KEYTRUDA + LENVIMA	Sunitinib
ITT population	160/355	205/357	●	0.39 (0.32–0.49)	23.9	9.2
Baseline lung metastases						
Yes	113/249	156/239	●	0.32 (0.25–0.41)	24.0	6.3
No	47/106	49/118	●	0.65 (0.43–0.98)	22.1	17.3
Baseline bone metastases						
Yes	39/85	54/97	●	0.33 (0.21–0.52)	24.3	5.6
No	121/270	151/260	●	0.42 (0.33–0.54)	23.4	9.7
Baseline liver metastases						
Yes	34/60	35/61	●	0.43 (0.25–0.75)	16.6	5.6
No	126/295	170/296	●	0.37 (0.29–0.47)	25.9	9.4
Prior nephrectomy						
Yes	107/262	163/275	●	0.37 (0.28–0.47)	27.7	9.4

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

<sup>a</sup>mPFS for the KEYTRUDA + LENVIMA and sunitinib arms was estimated using the Kaplan-Meier method; HR and 95% CIs comparing KEYTRUDA + LENVIMA with sunitinib were estimated by a stratified Cox model. If a stratification factor was itself a subgroup, this factor was removed from the stratified analysis.

From *Frontiers in Oncology*, Grünwald V, et al. Phase 3 CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for the lenvatinib-plus-pembrolizumab and sunitinib arms. *Front Oncol.* 2023;13:1223282. doi:10.3389/fonc.2023.1223282. Copyright © 2023. Reprinted with permission from *Frontiers in Oncology*.

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; ITT = intent to treat; mPFS = median progression-free survival; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

## Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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

## Selected Safety Information for LENVIMA® (lenvatinib)

treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

### Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC,



# PFS by subgroups by IRC per RECIST v1.1<sup>3,a</sup>

Subgroup	Events/Patients		HR (95% CI)		mPFS (months)	
	KEYTRUDA + LENVIMA	Sunitinib	KEYTRUDA + LENVIMA vs Sunitinib		KEYTRUDA + LENVIMA	Sunitinib
Prior nephrectomy						
Yes	107/262	163/275	—	0.37 (0.28–0.47)	27.7	9.4
No	53/93	42/82	—	0.44 (0.28–0.68)	15.3	7.5
Sarcomatoid component by histology						
Yes	19/28	16/21	—	0.39 (0.18–0.84)	11.1	5.5
No	141/327	189/336	—	0.38 (0.31–0.48)	24.3	9.4
IMDC risk group						
Favorable	43/110	67/124	—	0.41 (0.28–0.62)	28.1	12.9
Intermediate	97/210	110/192	—	0.39 (0.29–0.52)	22.1	7.1
Poor	18/33	26/37	—	0.28 (0.13–0.60)	22.1	4.0
MSKCC risk group						
Favorable	39/96	60/97	—	0.36 (0.23–0.54)	27.6	11.1

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

<sup>a</sup>mPFS for the KEYTRUDA + LENVIMA and sunitinib arms was estimated using the Kaplan-Meier method; HR and 95% CIs comparing KEYTRUDA + LENVIMA with sunitinib were estimated by a stratified Cox model. If a stratification factor was itself a subgroup, this factor was removed from the stratified analysis.

From *Frontiers in Oncology*, Grünwald V, et al. Phase 3 CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for the lenvatinib-plus-pembrolizumab and sunitinib arms. *Front Oncol.* 2023;13:1223282. doi:10.3389/fonc.2023.1223282. Copyright © 2023. Reprinted with permission from *Frontiers in Oncology*.

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; ITT = intent to treat; mPFS = median progression-free survival; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

## Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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

## Selected Safety Information for LENVIMA® (lenvatinib)

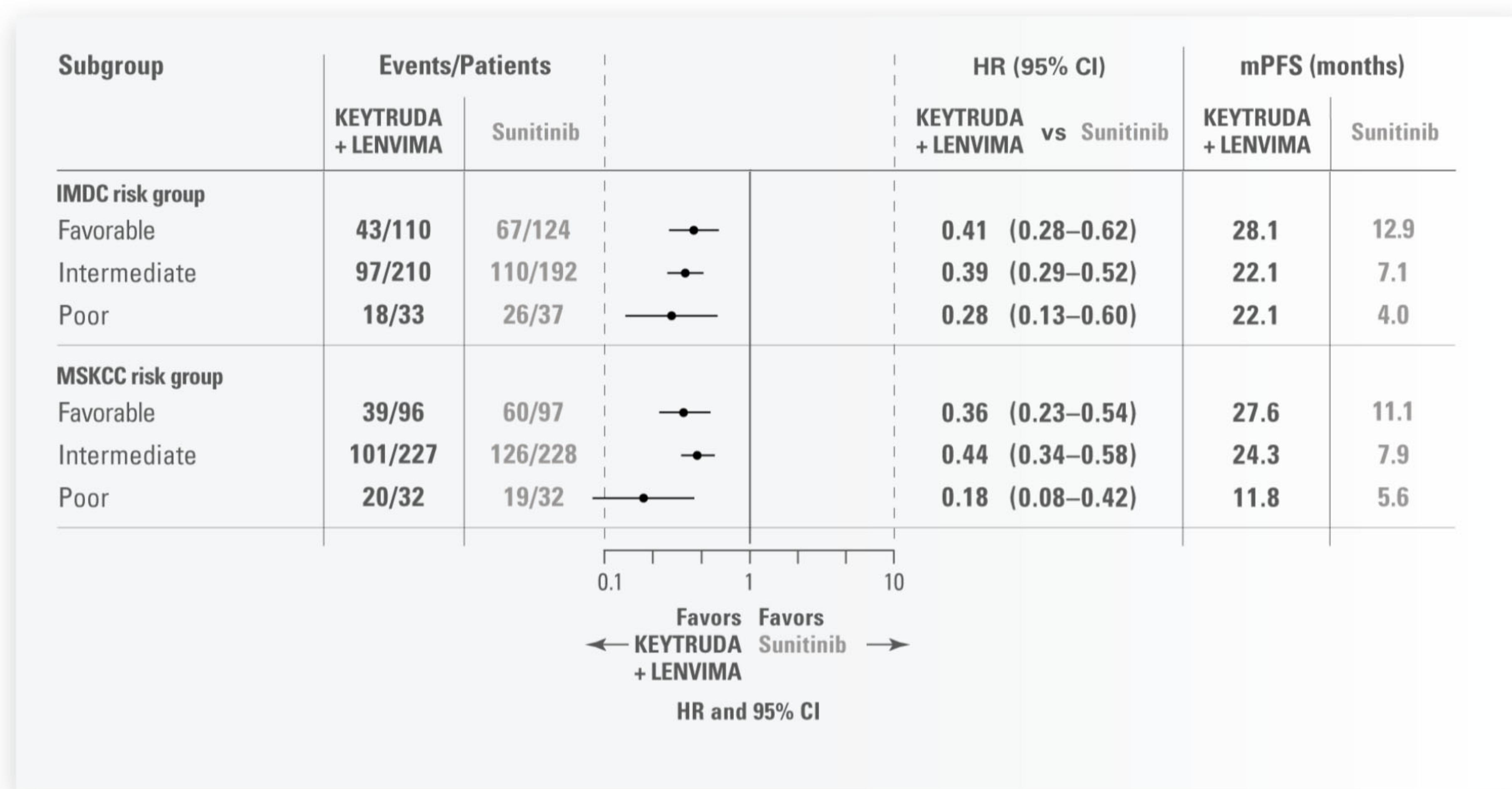
treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

### Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC,



# PFS by subgroups by IRC per RECIST v1.1<sup>3,a</sup>



**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

<sup>a</sup>mPFS for the KEYTRUDA + LENVIMA and sunitinib arms was estimated using the Kaplan-Meier method; HR and 95% CIs comparing KEYTRUDA + LENVIMA with sunitinib were estimated by a stratified Cox model. If a stratification factor was itself a subgroup, this factor was removed from the stratified analysis.

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CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; ITT = intent to treat; mPFS = median progression-free survival; MSKCC = Memorial Sloan Kettering Cancer Center; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

## Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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

## Selected Safety Information for LENVIMA® (lenvatinib)

treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

### Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC,



# Exploratory subgroup analysis of PFS for KEYTRUDA + LENVIMA in patients with advanced RCC<sup>1</sup>

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

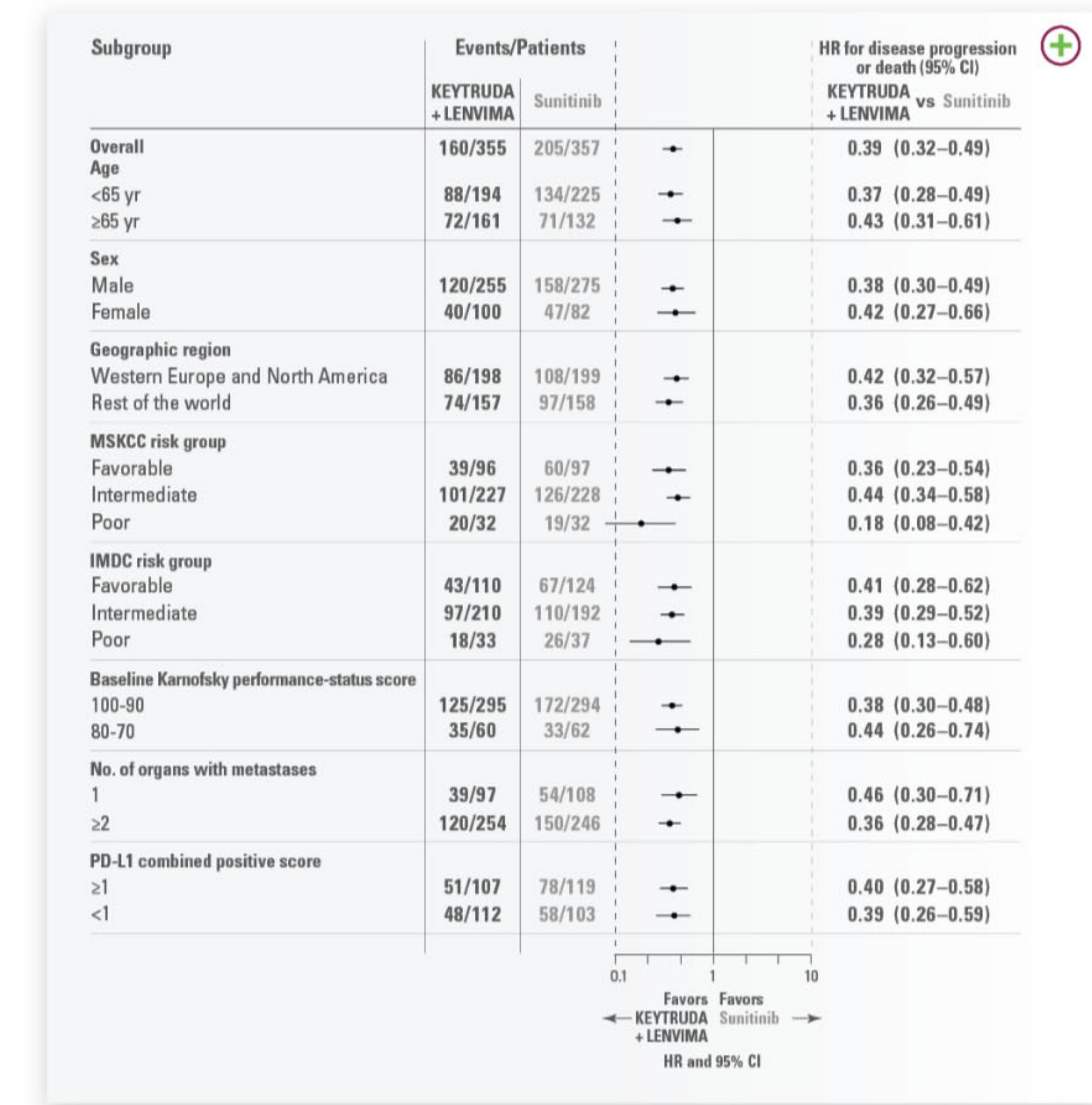
This exploratory analysis of the KEYNOTE-581/CLEAR trial evaluated PFS for KEYTRUDA + LENVIMA vs sunitinib in patients with advanced RCC across geographic region, MSKCC risk group, IMDC risk group, baseline Karnofsky performance-status score, number of metastatic organs, and PD-L1 combined positive score.<sup>a</sup>

PFS was assessed according to RECIST v1.1 by an IRC.

<sup>a</sup>Differences between the treatment groups were evaluated with the stratified log-rank test, stratified according to geographic region, and MSKCC prognostic risk group. A stratified Cox regression model was used to estimate the hazard ratio for disease progression or death and 95% CIs. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. PD-L1 combined positive score is defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; MSKCC = Memorial Sloan Kettering Cancer Center; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

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## Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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

## Selected Safety Information for LENVIMA® (lenvatinib)

treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

### Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC,



# PFS by subgroups by IRC per RECIST v1.1<sup>1,a</sup>

Subgroup	Events/Patients		HR for disease progression or death (95% CI) KEYTRUDA + LENVIMA vs Sunitinib	
	KEYTRUDA + LENVIMA	Sunitinib		
Overall	<b>160/355</b>	<b>205/357</b>	●	<b>0.39 (0.32–0.49)</b>
Age				
<65 yr	<b>88/194</b>	<b>134/225</b>	●	<b>0.37 (0.28–0.49)</b>
≥65 yr	<b>72/161</b>	<b>71/132</b>	●	<b>0.43 (0.31–0.61)</b>
Sex				
Male	<b>120/255</b>	<b>158/275</b>	●	<b>0.38 (0.30–0.49)</b>
Female	<b>40/100</b>	<b>47/82</b>	●	<b>0.42 (0.27–0.66)</b>
Geographic region				
Western Europe and North America	<b>86/198</b>	<b>108/199</b>	●	<b>0.42 (0.32–0.57)</b>
Rest of the world	<b>74/157</b>	<b>97/158</b>	●	<b>0.36 (0.26–0.49)</b>
MSKCC risk group				
Favorable	<b>39/96</b>	<b>60/97</b>	●	<b>0.36 (0.23–0.54)</b>
Intermediate	<b>101/227</b>	<b>126/228</b>	●	<b>0.44 (0.34–0.58)</b>
Poor	<b>20/32</b>	<b>19/32</b>	●	<b>0.18 (0.08–0.42)</b>

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; MSKCC = Memorial Sloan Kettering Cancer Center; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

<sup>a</sup>Differences between the treatment groups were evaluated with the stratified log-rank test, stratified according to geographic region, and MSKCC prognostic risk group. A stratified Cox regression model was used to estimate the hazard ratio for disease progression or death and 95% CIs. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. PD-L1 combined positive score is defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

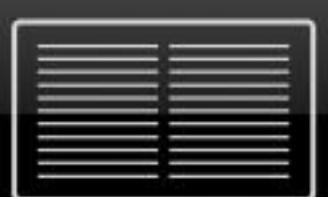
From *The New England Journal of Medicine*, Motzer R, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med*. 2021;384:1289–1300. Copyright © 2021, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

## Selected Safety Information for KEYTRUDA® (pembrolizumab) (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

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

- Patients on LENVIMA + everolimus (100% 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



# PFS by subgroups by IRC per RECIST v1.1<sup>1,a</sup>

Subgroup	Events/Patients		HR for disease progression or death (95% CI) KEYTRUDA + LENVIMA vs Sunitinib
	KEYTRUDA + LENVIMA	Sunitinib	
Poor	20/32	19/32	0.18 (0.08–0.42)
IMDC risk group			
Favorable	43/110	67/124	0.41 (0.28–0.62)
Intermediate	97/210	110/192	0.39 (0.29–0.52)
Poor	18/33	26/37	0.28 (0.13–0.60)
Baseline Karnofsky performance-status score			
100-90	125/295	172/294	0.38 (0.30–0.48)
80-70	35/60	33/62	0.44 (0.26–0.74)
No. of organs with metastases			
1	39/97	54/108	0.46 (0.30–0.71)
≥2	120/254	150/246	0.36 (0.28–0.47)
PD-L1 combined positive score			
≥1	51/107	78/119	0.40 (0.27–0.58)

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; MSKCC = Memorial Sloan Kettering Cancer Center; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

<sup>a</sup>Differences between the treatment groups were evaluated with the stratified log-rank test, stratified according to geographic region, and MSKCC prognostic risk group. A stratified Cox regression model was used to estimate the hazard ratio for disease progression or death and 95% CIs. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. PD-L1 combined positive score is defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

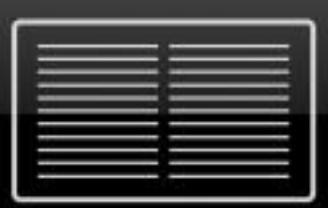
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## Selected Safety Information for KEYTRUDA® (pembrolizumab) (continued)

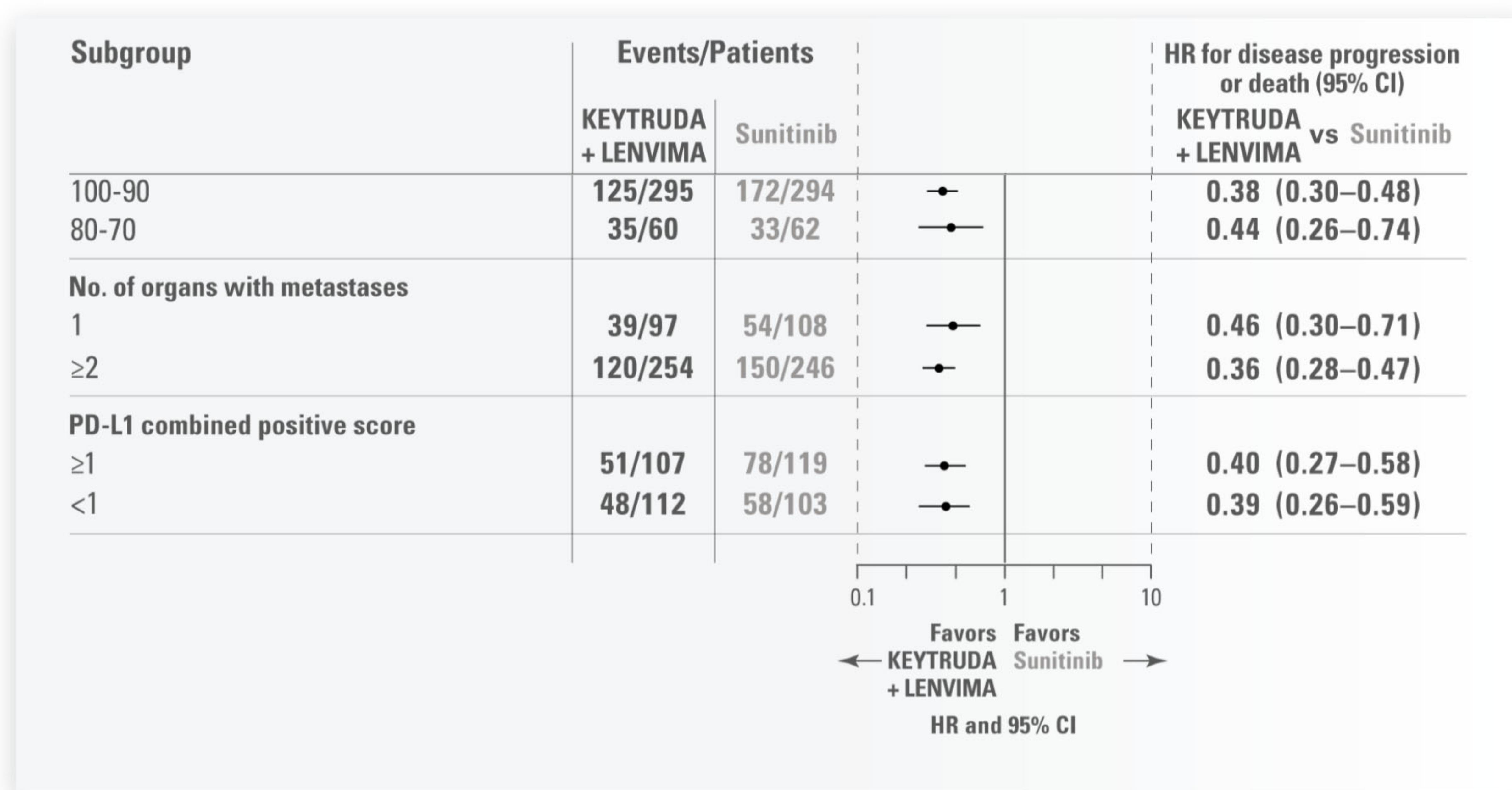
- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to

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

- Patients on LENVIMA + everolimus (100% 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



# PFS by subgroups by IRC per RECIST v1.1<sup>1,a</sup>



CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IRC = independent radiologic review committee; MSKCC = Memorial Sloan Kettering Cancer Center; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RCC = renal cell carcinoma; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

**LIMITATION:** The KEYNOTE-581/CLEAR trial was not powered to detect differences in the treatment effect in these subgroups. No statistical testing was planned for this post hoc analysis, and no adjustment for multiplicity was made, therefore, no conclusions can be drawn.

<sup>a</sup>Differences between the treatment groups were evaluated with the stratified log-rank test, stratified according to geographic region, and MSKCC prognostic risk group. A stratified Cox regression model was used to estimate the hazard ratio for disease progression or death and 95% CIs. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. PD-L1 combined positive score is defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

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## Selected Safety Information for KEYTRUDA® (pembrolizumab)

- 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

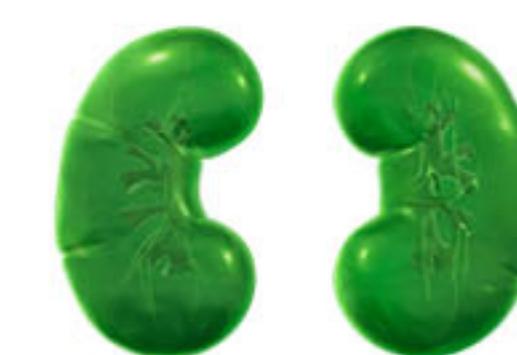
## Selected Safety Information for LENVIMA® (lenvatinib)

treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

### Cardiac Dysfunction

- Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC,





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

## 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<sup>a</sup>=0.66; 95% CI, 0.49–0.88;  $P^b=0.0049$**
- Number of deaths<sup>c</sup>: 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.

Study Design



Patient Baseline Characteristics

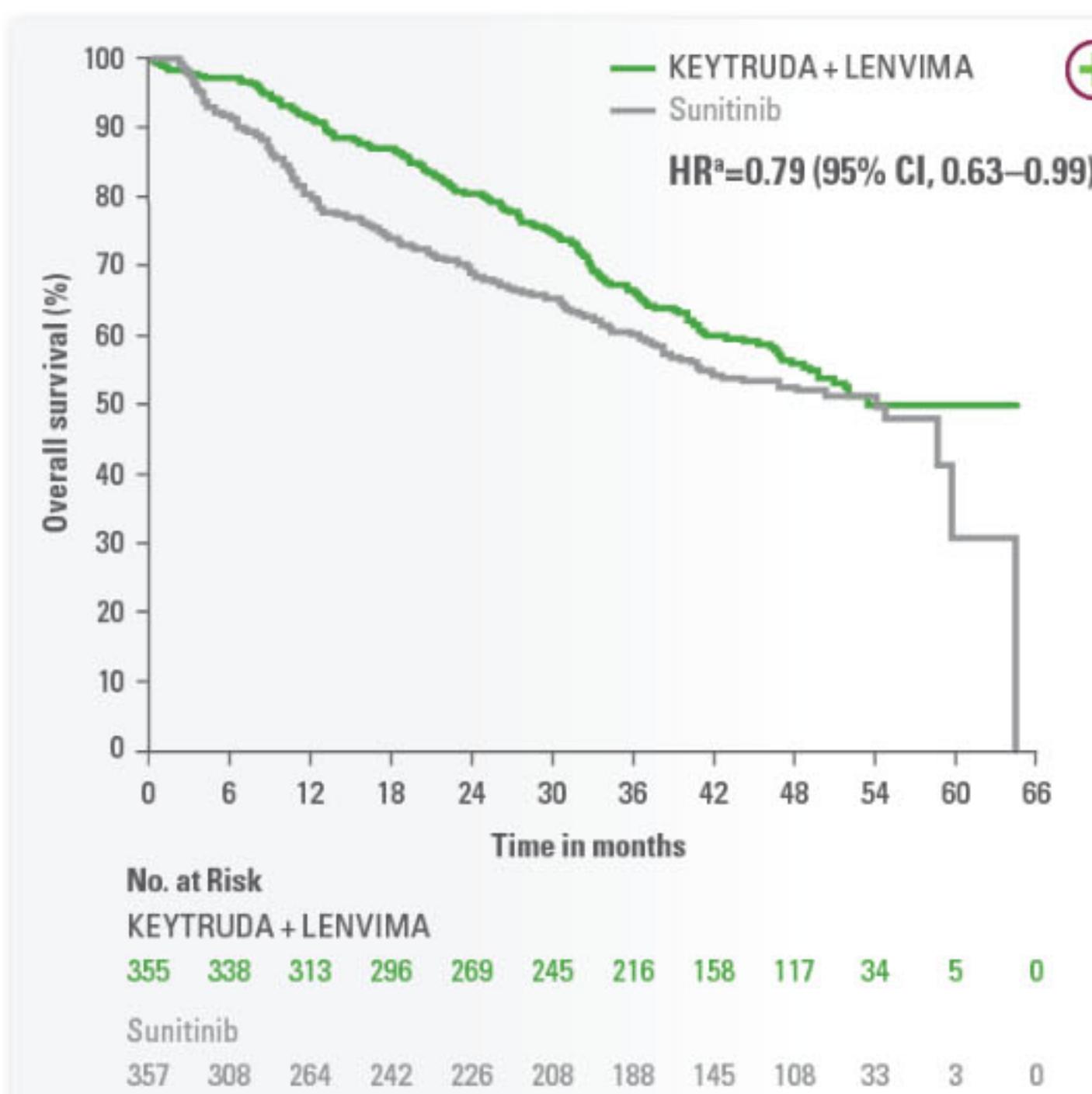


NCCN Recommendations



**Updated OS<sup>d,e</sup> 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<sup>a</sup>=0.79 (95% CI, 0.63–0.99)**
- Number of deaths<sup>e</sup>: 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

<sup>a</sup>Hazard ratio is based on a Cox Proportional Hazards Model. Stratified by geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups.

<sup>b</sup>Two-sided  $P$  value based on stratified log-rank test.

<sup>c</sup>Data cutoff date = 28 Aug 2020.

<sup>d</sup>An updated OS analysis was conducted when 304 deaths were observed based on the planned number of deaths for the prespecified final analysis.

<sup>e</sup>Updated OS cutoff date = 31 July 2022.

CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

## Selected Safety Information for KEYTRUDA® (pembrolizumab) (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

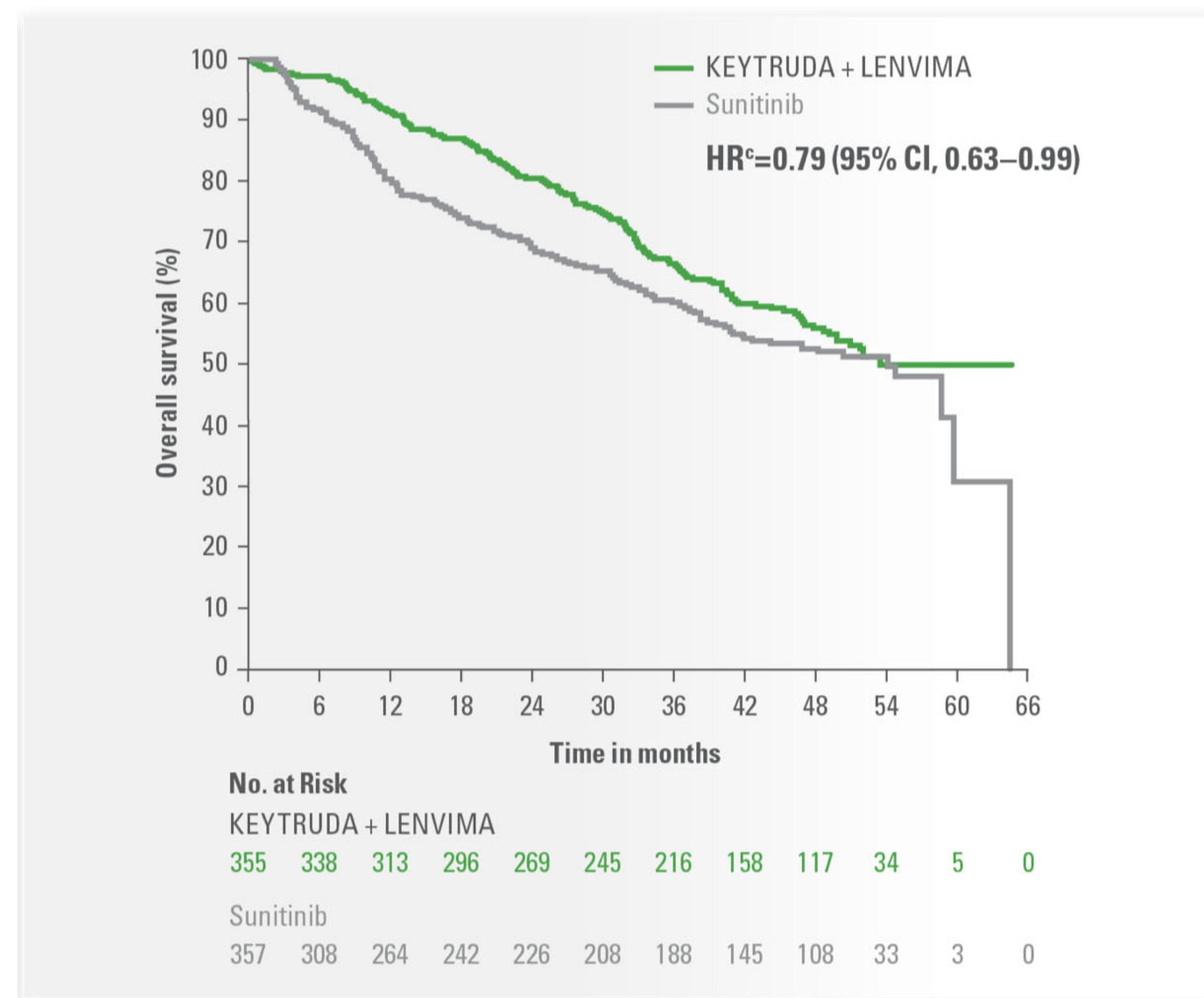
## Selected Safety Information for LENVIMA® (lenvatinib) (continued)

patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure  $\geq 160$  mmHg occurred in 29% of patients, and 21% had diastolic blood pressure  $\geq 100$  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.



## Updated OS<sup>a,b</sup> at protocol-specified final analysis

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



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.

### Selected Safety Information for KEYTRUDA® (pembrolizumab) (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

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

- Hypertension: Hypertension occurred in 70% 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





Efficacy | Safety | Dosing | Access & Support  
PFS | OS | ORR



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

A greater ORRa 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

Nearly **2X** greater ORR demonstrated with **KEYTRUDA + LENVIMA** (71%) vs sunitinib (36%) ( $P^b <0.0001$ ).

ORR was an additional endpoint in the KEYNOTE-581/CLEAR trial.

**CR:** 16% with KEYTRUDA + LENVIMA vs 4% with sunitinib.

**PR:** 55% with KEYTRUDA + LENVIMA vs 32% with sunitinib.

Study Design +

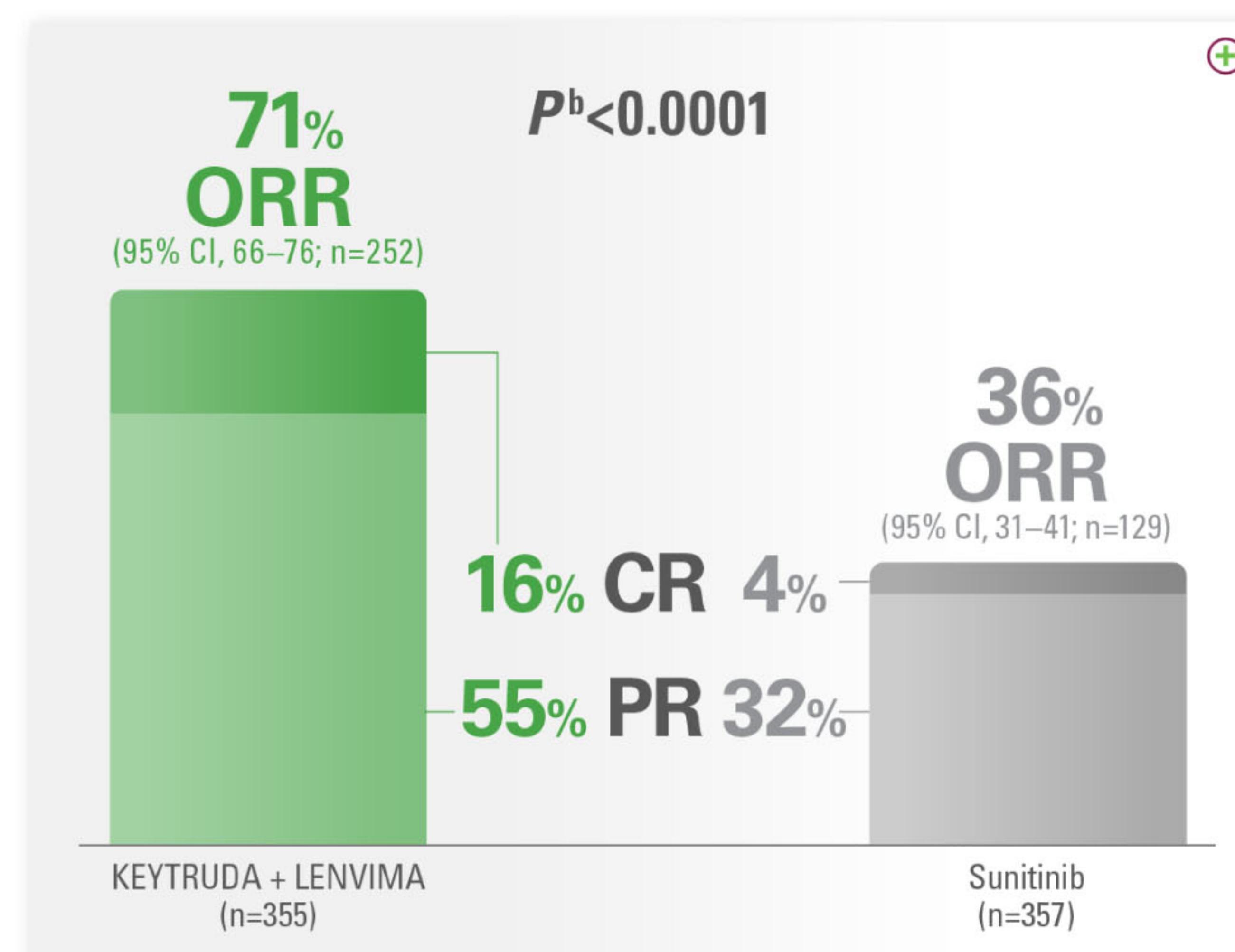
Patient Baseline Characteristics +

NCCN Recommendations +

<sup>a</sup>Tumor assessments were based on RECIST v1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020.

<sup>b</sup>Two-sided P value based upon CMH test.

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ORR = objective response rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1.



## Selected Safety Information for KEYTRUDA® (pembrolizumab)

### Immune-Mediated Pneumonitis

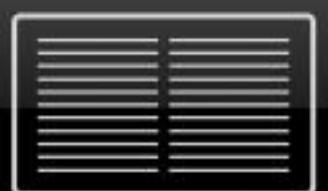
- KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.2%).  
1/201 reactions. Systemic corticosteroids were required in 75% of patients with Grade 3 or 4 pneumonitis.

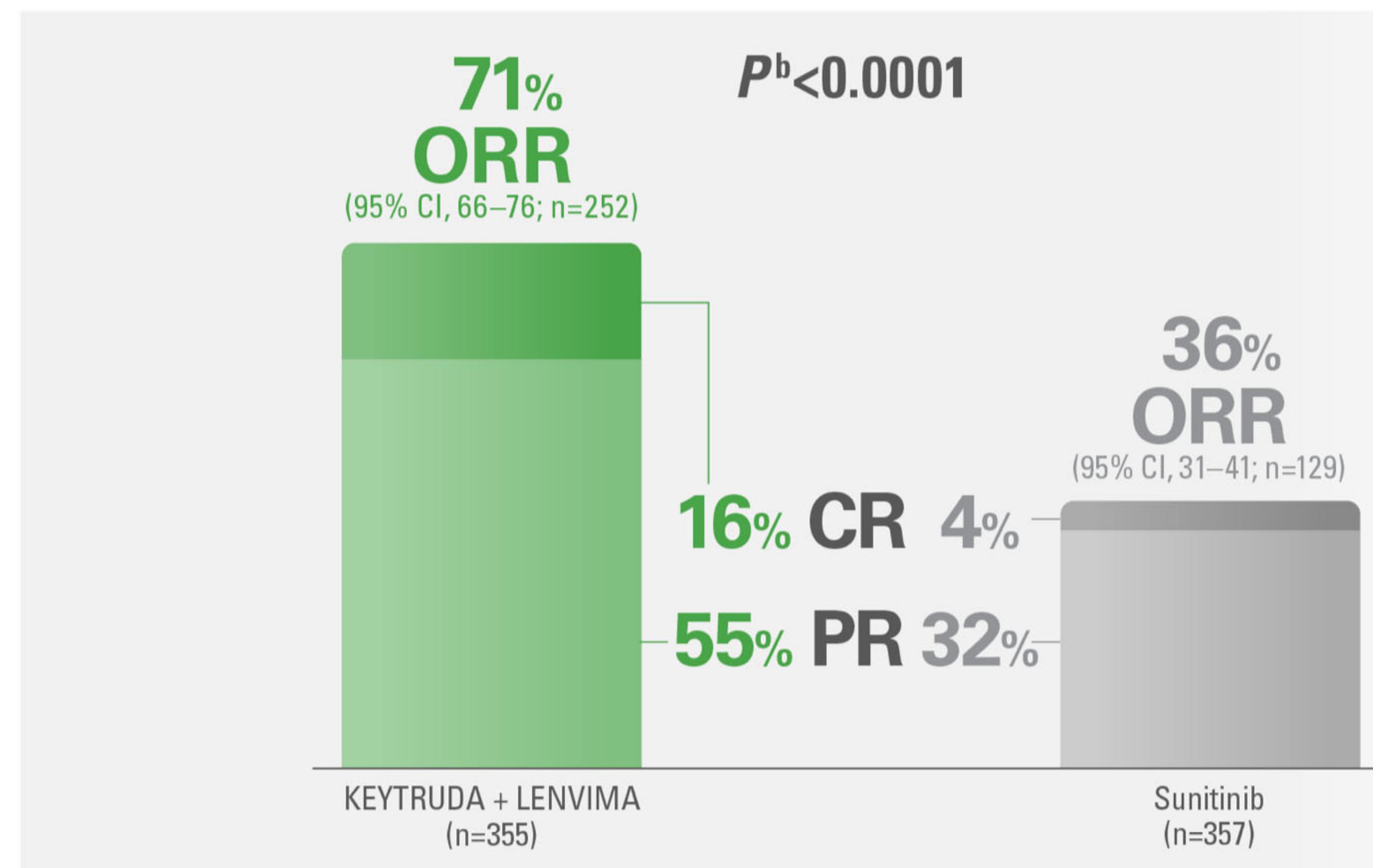
## Selected Safety Information for LENVIMA® (lenvatinib)

The safety of resuming after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

### Hepatotoxicity

- Across clinical studies enrolling 1,327 LENVIMA-treated patients with malignancies other than RCC, adverse hepatic



**ORR with KEYTRUDA + LENVIMA vs sunitinib in the KEYNOTE-581/CLEAR trial<sup>a</sup>**

<sup>a</sup>Tumor assessments were based on RECIST v1.1; only confirmed responses are included for ORR. Data cutoff date = 28 Aug 2020.

<sup>b</sup>Two-sided P value based upon CMH test.

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ORR = objective response rate; PR = partial response; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

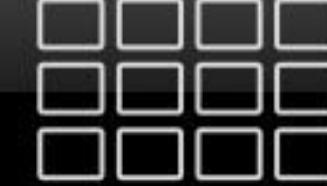
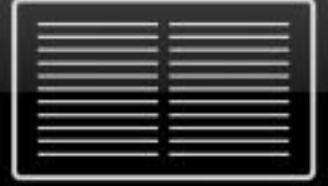
## Selected Safety Information for KEYTRUDA® (pembrolizumab)

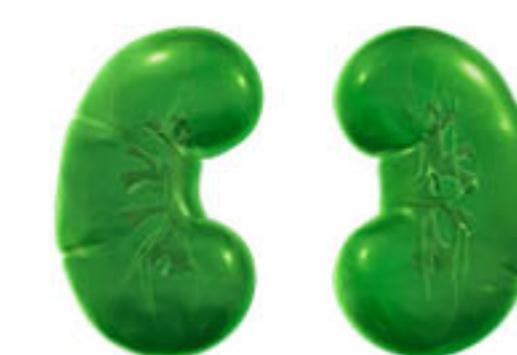
### Immune-Mediated Pneumonitis

- 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 (0.7%).

## Selected Safety Information for LENVIMA® (lenvatinib)

- 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,





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

## Adverse reactions (ARs) 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	
Autoimmune hepatitis	
Dyspnea	
Hypertensive crisis	
Increased blood creatinine	
Multiple organ dysfunction syndrome	

Myasthenic syndrome	
Myocarditis	
Nephritis	
Pneumonitis	
Ruptured aneurysm	
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)

#### 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 associated with KEYTRUDA has been reported in 0.9% of patients.

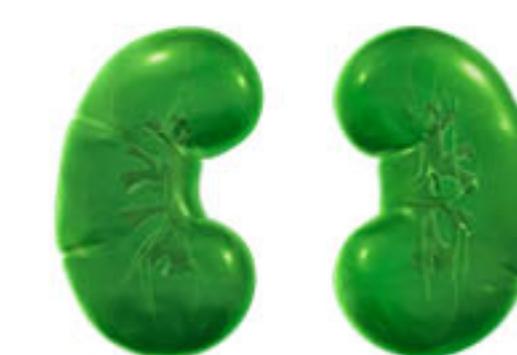
### Selected Safety Information for LENVIMA® (lenvatinib)

The safety of 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.

#### Hepatotoxicity

- Across clinical studies enrolling 1,327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic





## Adverse reactions (ARs) 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**

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

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

Pneumonitis (3%)

Myocardial infarction (3%)

Hepatotoxicity (3%)

Acute kidney injury (3%)

Rash (3%)

Diarrhea (2%)

- No dose reduction for KEYTRUDA is recommended.

### Selected Safety Information for KEYTRUDA® (pembrolizumab)

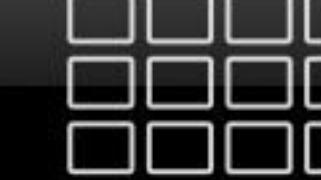
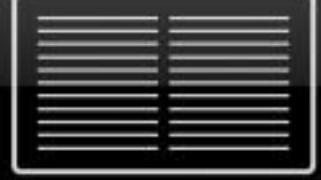
#### Hepatotoxicity and Immune-Mediated Hepatitis

- 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

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

- 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



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

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

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

## Selected Safety Information for KEYTRUDA® (pembrolizumab)

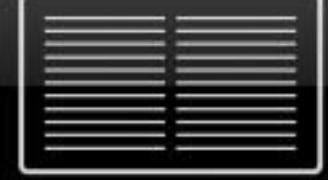
### Hepatotoxicity and Immune-Mediated Hepatitis

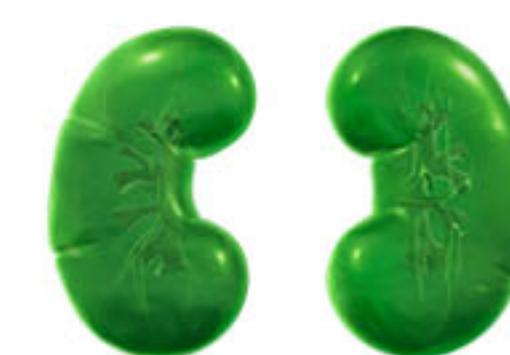
- KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional

## Selected Safety Information for LENVIMA® (lenvatinib)

LENVIMA due to hepatic encephalopathy and/or 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





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

**Most common ( $\geq 3\%$ ) adverse reactions in patients receiving KEYTRUDA + LENVIMA that resulted in interruption of KEYTRUDA**

Adverse Reactions	% of Patients
Diarrhea	10
Hepatotoxicity	8
Fatigue	7
Lipase increased	5
Amylase increased	4
Musculoskeletal pain	3
Hypertension	3
Rash	3
Acute kidney injury	3
Decreased appetite	3

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

Adverse Reactions	% of Patients
Diarrhea	26
Fatigue	18
Hypertension	17
Proteinuria	13
Decreased appetite	12
Palmar-plantar erythrodysesthesia	11
Nausea	9
Stomatitis	9
Musculoskeletal pain	8
Rash	8

Adverse Reactions	% of Patients
Increased lipase	7
Abdominal pain	6
Vomiting	6
Increased ALT	5
Increased amylase	5

ALT = alanine aminotransferase.

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

#### Immune-Mediated Endocrinopathies

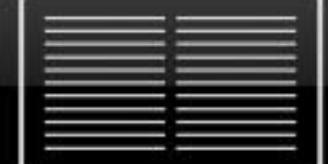
#### Adrenal Insufficiency

- 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

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

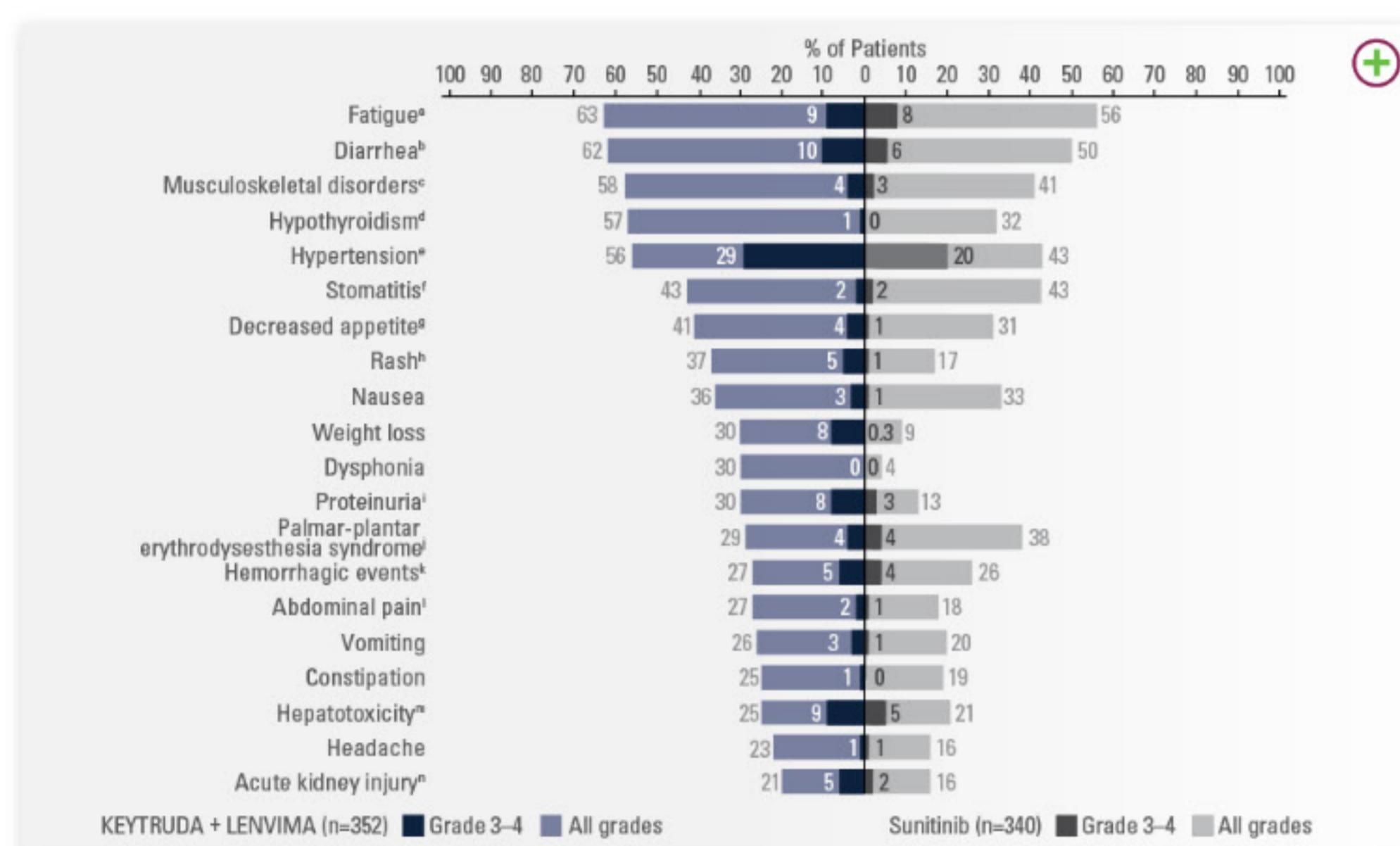
failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).

- 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.





## 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).

<sup>a</sup>Includes asthenia, fatigue, lethargy, and malaise.

<sup>b</sup>Includes diarrhea and gastroenteritis.

<sup>c</sup>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.

<sup>d</sup>Includes hypothyroidism, increased blood thyroid stimulating hormone, and secondary hypothyroidism.

<sup>e</sup>Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure.

<sup>f</sup>Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.

<sup>g</sup>Includes decreased appetite and early satiety.

<sup>h</sup>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.

<sup>i</sup>Includes hemoglobinuria, nephrotic syndrome, and proteinuria.

<sup>j</sup>Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, and plantar erythema.

<sup>k</sup>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.

<sup>l</sup> Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, and upper abdominal pain.

<sup>m</sup> 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.

<sup>n</sup> 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.

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

## Selected Safety Information for KEYTRUDA® (pembrolizumab)

### 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 of hypophysitis.

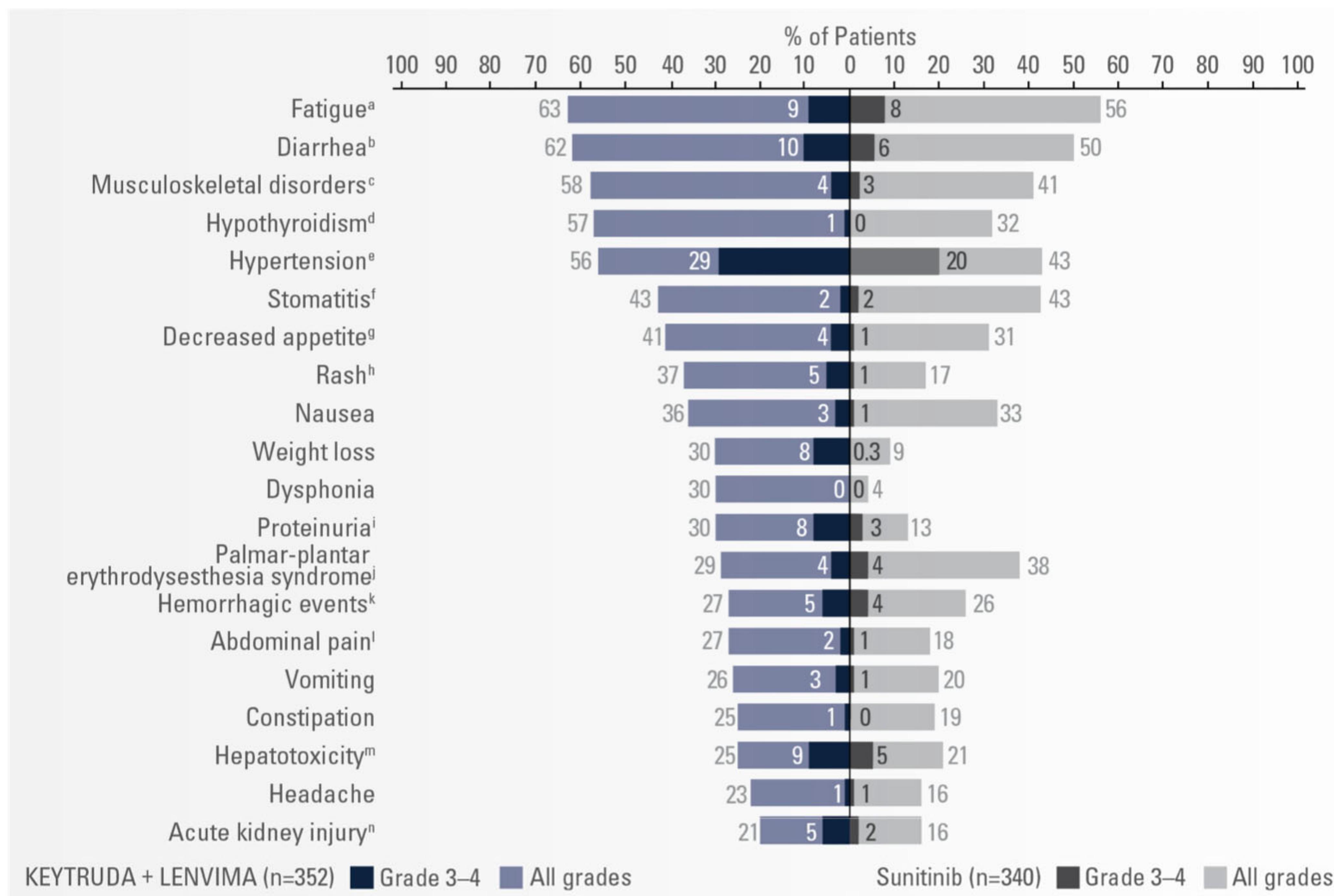
## Selected Safety Information for LENVIMA® (lenvatinib)

### 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

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

<sup>a</sup>Includes asthenia, fatigue, lethargy, and malaise.<sup>b</sup>Includes diarrhea and gastroenteritis.<sup>c</sup>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.<sup>d</sup>Includes hypothyroidism, increased blood thyroid stimulating hormone, and secondary hypothyroidism.<sup>e</sup>Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure.<sup>f</sup>Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.<sup>g</sup>Includes decreased appetite and early satiety.<sup>h</sup>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.<sup>i</sup>Includes hemoglobinuria, nephrotic syndrome, and proteinuria.<sup>j</sup>Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, and plantar erythema.<sup>k</sup>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.<sup>l</sup>Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, and upper abdominal pain.<sup>m</sup>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.<sup>n</sup>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.

### Selected Safety Information for KEYTRUDA® (pembrolizumab)

#### 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

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

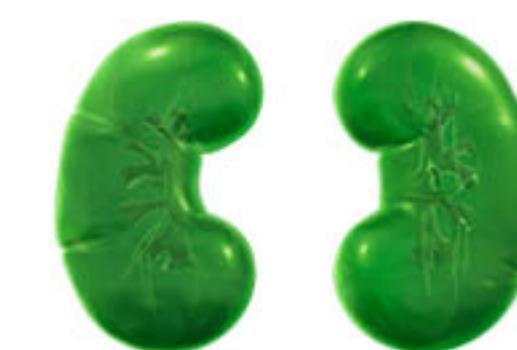
ALT = alanine aminotransferase; CNS = central nervous system; MRI = magnetic resonance imaging; QTc = corrected QT interval.

**Before prescribing LENVIMA® (lenvatinib), please read the accompanying [Prescribing Information and Patient Information](#).**





Efficacy | Safety | **Dosing** | Access & Support



**KEYTRUDA** | **LENVIMA**

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

## 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** or withhold, dose reduce, or discontinue **LENVIMA** in accordance with the instructions in the **KEYTRUDA** Prescribing Information and **LENVIMA** Prescribing Information, respectively. No dose reductions are recommended for **KEYTRUDA**.

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

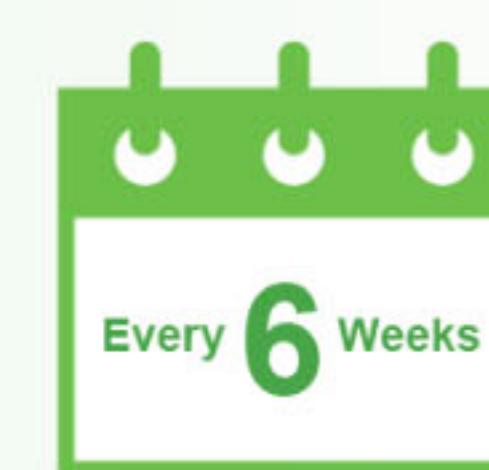
### Dosage and administration for KEYTRUDA



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



Adults: 200 mg



Adults: 400 mg

IV = intravenous.

### Selected Safety Information for KEYTRUDA® (pembrolizumab)

#### Thyroid Disorders

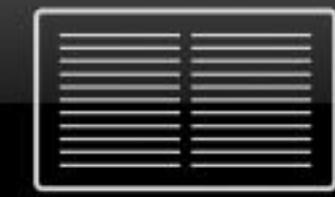
- KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.

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

ALT = alanine aminotransferase; CNS = central nervous system; MRI = magnetic resonance imaging; QTc = corrected QT interval.

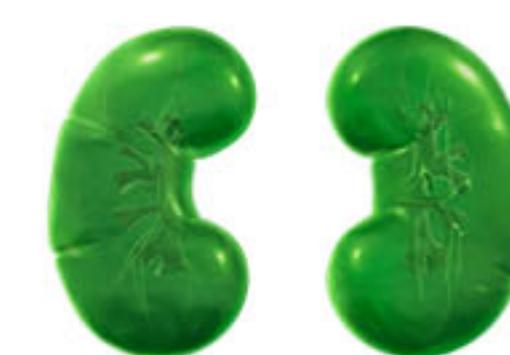
**Before prescribing LENVIMA® (lenvatinib), please read the accompanying [Prescribing Information and Patient Information](#).**

KEYTRUDA® (pembrolizumab) and LENVIMA® (lenvatinib) are trademarks of Merck & Co., Inc. © 2018 Merck & Co., Inc. All rights reserved.



KEYTRUDA: PI and MG  
LENVIMA: PI and PPI

Indications and Selected Safety Information



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

## 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 or withhold, dose reduce, or discontinue LENVIMA in accordance with the instructions in the KEYTRUDA Prescribing Information and LENVIMA Prescribing Information, respectively. No dose reductions are recommended for KEYTRUDA.

### Dosage and administration for LENVIMA<sup>a</sup>



- 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 RCC** 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 RCC** and **severe hepatic impairment** (Child-Pugh C) is **10 mg orally once daily**.

Preparation of Suspension

### Selected Safety Information for KEYTRUDA® (pembrolizumab)

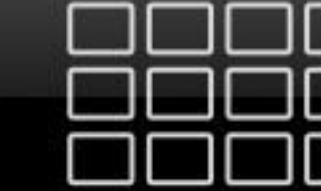
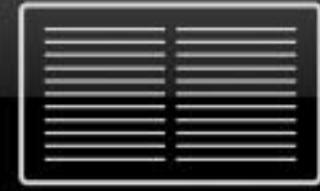
*Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis*

- 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

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

ALT = alanine aminotransferase; CNS = central nervous system; MRI = magnetic resonance imaging; QTc = corrected QT interval.

**Before prescribing LENVIMA® (lenvatinib), please read the accompanying Prescribing Information and Patient Information.**



## LENVIMA 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 °F to 46 °F (2 °C to 8 °C) 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)

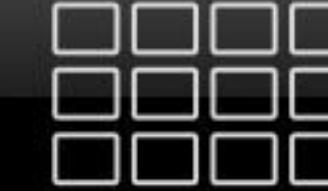
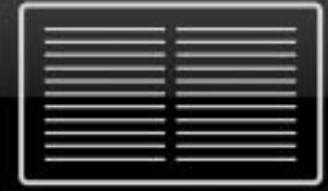
Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis

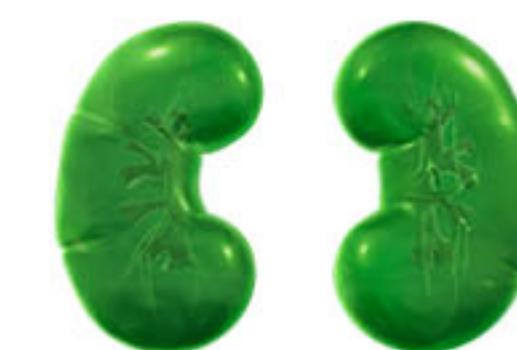
- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients

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

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





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

## Information and support resources for patients



### The Merck Access Program for KEYTRUDA

The Merck Access Program can help answer questions about benefit investigations, billing and coding, co-pay assistance for eligible patients, the prior authorization process, referral to the Merck Patient Assistance Program for eligibility determination (provided through the Merck Patient Assistance Program, Inc), and product distribution.

### KEY+YOU Patient Support Program

Patients can find educational resources to help with the practical and emotional challenges of cancer. Phone support is available for eligible patients 7 days a week, in addition to e-mails, online activities, and more.

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

#### Immune-Mediated Nephritis With Renal Dysfunction

- KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 89% (8/9) of patients. Nephritis led to

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

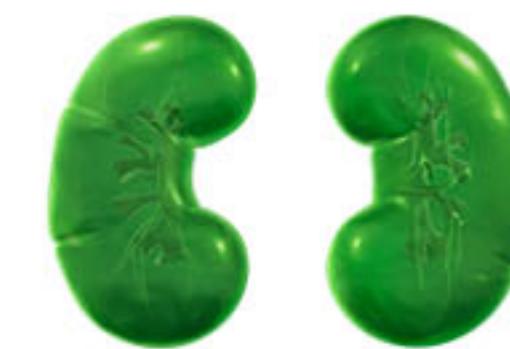
events, or any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received





KEYTRUDA | LENVIMA

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



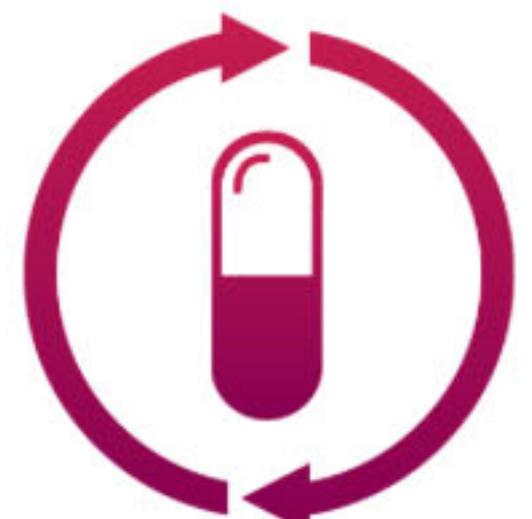
## Information and support resources for patients



### Eisai Patient Support

Eisai Patient Support offers information and resources to help patients get access to LENVIMA, including: Benefit verification, co-pay assistance, the LENVIMA Welcome Kit, the LENVIMA Dose Exchange Program, and the LENVIMA Patient Assistance Program. Eligibility criteria apply. For program and eligibility information, please visit: [www.LENVIMAREIMBURSEMENT.com/hcp](http://www.LENVIMAREIMBURSEMENT.com/hcp) or call 1-866-613-4724.

Eisai cannot guarantee payment of any claim. Coding, coverage, and reimbursement may vary significantly by payor, plan, patient, and setting of care. Actual coverage and reimbursement decisions are made by individual payors following the receipt of claims. For additional information, customers should consult with their payors for all relevant coding, reimbursement, and coverage requirements. It is the sole responsibility of the provider to select the proper code and ensure the accuracy of all claims used in seeking reimbursement. All services must be medically appropriate and properly supported in the patient medical record.



### Dose Exchange Program

For assistance with patients that require a dose reduction, please visit [www.LENVIMAREIMBURSEMENT.com/hcp](http://www.LENVIMAREIMBURSEMENT.com/hcp).



### LENVIMA Co-Pay Program

With the LENVIMA Co-Pay Program, eligible commercially insured patients may pay as little as \$0 per month.\* Annual limits apply. Depending on the insurance plan, patients could have additional financial responsibility. See [www.LENVIMAREIMBURSEMENT.com/hcp](http://www.LENVIMAREIMBURSEMENT.com/hcp) for complete terms and conditions. For assistance, call 1-855-347-2448 or visit [www.LENVIMACopay.com](http://www.LENVIMACopay.com) to enroll eligible patients.

\*Not available to patients enrolled in state or federal healthcare programs, including Medicare, Medigap, VA, DoD, or TRICARE.



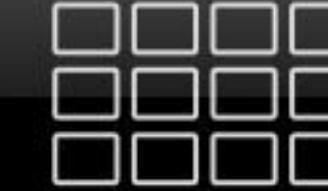
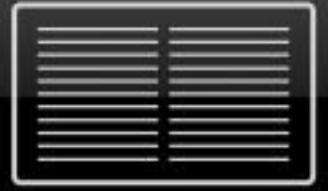
## Selected Safety Information for KEYTRUDA® (pembrolizumab)

### 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

## Selected Safety Information for LENVIMA® (lenvatinib)

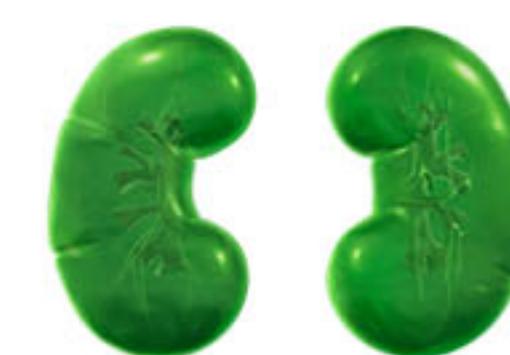
- In differentiated thyroid cancer (DTC), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In advanced renal cell carcinoma (RCC), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In unresectable hepatocellular carcinoma (HCC), hypertension occurred in 45%





KEYTRUDA | LENVIMA

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



## Information and support resources for patients (*continued*)



### Accessing LENVIMA

#### Specialty Pharmacies

LENVIMA is available through certain Specialty Pharmacies, which will mail the medication directly to patients. Please visit [www.LENVIMASpecialtyPharmacy.com](http://www.LENVIMASpecialtyPharmacy.com) for a complete list of the mail-order Specialty Pharmacies that dispense LENVIMA.

#### Physician Office/Clinic or Hospital Pharmacies

LENVIMA can also be dispensed through eligible physician offices, clinics or hospital pharmacies. Please contact your preferred distributor for more information, including eligibility requirements.



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

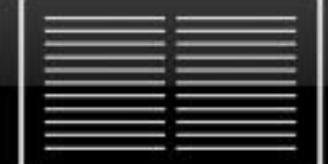
#### Other Immune-Mediated Adverse Reactions

- 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. Cardiovascular Myocarditis pericarditis

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

ALT = alanine aminotransferase; CNS = central nervous system; MRI = magnetic resonance imaging; QTc = corrected QT interval.

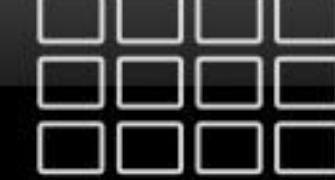
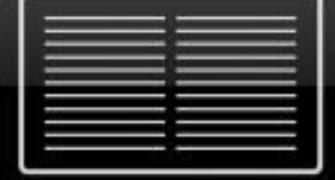
**Before prescribing LENVIMA® (lenvatinib), please read the accompanying [Prescribing Information and Patient Information](#).**





## References:

1. 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
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed January 5, 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.
3. Grünwald V, Powles T, Eto M, et al. Phase 3 CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for the lenvatinib-plus-pembrolizumab and sunitinib arms. *Front Oncol.* 2023;13:1223282. doi:10.3389/fonc.2023.1223282





## Abbreviations

1L = first line  
ALT = alanine aminotransferase  
AR = adverse reaction  
AST = aspartate aminotransferase  
ATC = anaplastic thyroid carcinoma  
CI = confidence interval  
CMH = Cochran-Mantel-Haenszel  
CNS = central nervous system  
CR = complete response  
DM = diabetes mellitus  
DTC = differentiated thyroid cancer  
GVHD = graft-versus-host disease  
HCC = hepatocellular carcinoma  
HR = hazard ratio  
HSCT = hematopoietic stem cell transplantation  
IMDC = International Metastatic Renal Cell Carcinoma Database Consortium  
IRC = independent radiologic review committee  
ITT = intent to treat  
IV = intravenous  
mPFS = median progression-free survival  
MRI = magnetic resonance imaging  
MSKCC = Memorial Sloan Kettering Cancer Center  
NCCN = National Comprehensive Cancer Network® (NCCN®)  
NR = not reached





## Abbreviations

ONJ = osteonecrosis of the jaw

ORR = objective response rate

OS = overall survival

PD-1 = programmed death receptor-1

PD-L1 = programmed death ligand 1

PFS = progression-free survival

PR = partial response

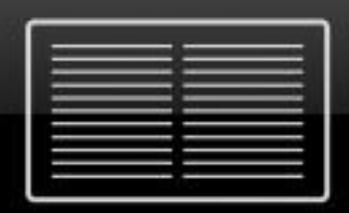
QTc = corrected QT interval

RCC = renal cell carcinoma

RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1

RPLS = reversible posterior leukoencephalopathy syndrome

TSH = thyroid stimulating hormone



## Selected Safety Information for KEYTRUDA® (pembrolizumab)

### Severe and Fatal Immune-Mediated Adverse Reactions

- KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.
- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.
- Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in

## Selected Safety Information for LENVIMA® (lenvatinib)

### Hypertension

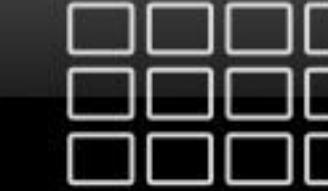
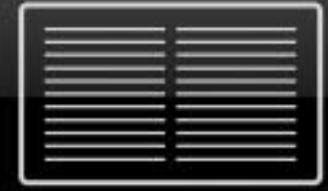
- In differentiated thyroid cancer (DTC), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In advanced renal cell carcinoma (RCC), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure  $\geq$ 160 mmHg occurred in 29% of patients,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

### Cardiac Dysfunction

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

### Arterial Thromboembolic Events

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



patients whose adverse reactions are not controlled with corticosteroid therapy.

#### Immune-Mediated Pneumonitis

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

#### Immune-Mediated Colitis

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

#### Hepatotoxicity and Immune-Mediated Hepatitis

- KEYTRUDA 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

- Among patients receiving LENVIMA with KEYTRUDA, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).
- Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

#### **Hepatotoxicity**

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

#### **Renal Failure or Impairment**

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



were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients.

#### Immune-Mediated Endocrinopathies

##### *Adrenal Insufficiency*

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

##### *Hypophysitis*

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

- Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

#### **Proteinuria**

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

#### **Diarrhea**

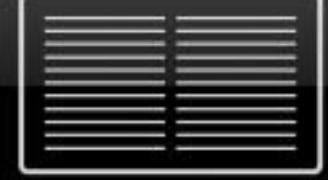
- Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus-treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly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

#### **Fistula Formation and Gastrointestinal Perforation**

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

#### **QT Interval Prolongation**

- In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval



KEYTRUDA after symptom improvement.

#### *Thyroid Disorders*

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

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

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

*Immune-Mediated Nephritis With Renal Dysfunction*

and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

- Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

#### **Hypocalcemia**

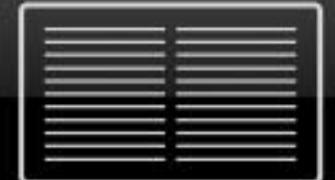
- In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus-treated patients.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

#### **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

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

#### **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



לעומת מושגיהם של מושגים

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

# Immune-Mediated Dermatologic Adverse Reactions

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

## Other Immune-Mediated Adverse Reactions

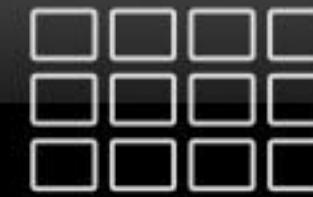
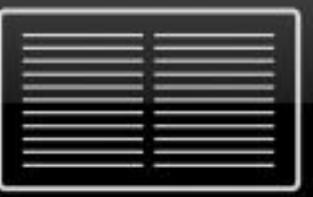
- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other anti-PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions.  
*Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis;  
*Nervous System:* Meningitis, encephalitis, myelitis

(all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

- Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

# **Impairment of Thyroid Stimulating Hormone Suppression/ Thyroid Dysfunction**

- LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level  $\leq 0.5$  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



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.

### **Infusion-Related Reactions**

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

### **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti-PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced

medical practice.

### **Impaired Wound Healing**

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

### **Osteonecrosis of the Jaw (ONJ)**

- ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ. Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

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

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

### **Embryo-Fetal Toxicity**

- Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of 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



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 ( $\geq 2\%$ ) were hemorrhagic events (5%), diarrhea (4%), hypertension, myocardial infarction, pneumonitis, and vomiting (3% each), acute kidney injury, adrenal insufficiency, dyspnea, and pneumonia (2% each). Permanent discontinuation of KEYTRUDA, LENVIMA, or both due to an adverse reaction occurred in 37% of patients; 29% KEYTRUDA only, 26% LENVIMA only, and 13% both. The most common adverse reactions ( $\geq 2\%$ ) resulting in permanent discontinuation of KEYTRUDA, LENVIMA, or the combination

and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

### **Adverse Reactions**

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

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

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

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



discontinuation of KEYTRUDA, LENVIMA, or the combination were pneumonitis, myocardial infarction, hepatotoxicity, acute kidney injury, rash (3% each), and diarrhea (2%).

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

### 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.

**Before prescribing KEYTRUDA® (pembrolizumab), please read the accompanying [Prescribing Information](#). The [Medication Guide](#) also is available.**

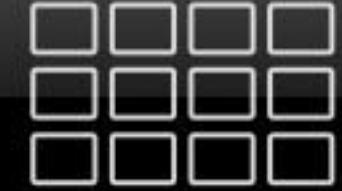
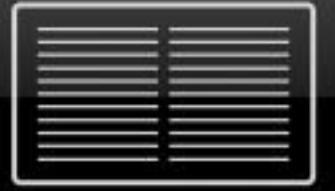
diarrhea (2%).

Dose interruptions of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with KEYTRUDA. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients.

The most common adverse reactions ( $\geq 5\%$ ) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (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



# KEYTRUDA® (pembrolizumab) + LENVIMA® (lenvatinib)

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; CNS = central nervous system; MRI = magnetic resonance imaging; QTc = corrected QT interval.

**Before prescribing LENVIMA® (lenvatinib), please read the accompanying [Prescribing Information and Patient Information](#).**



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## Selected Safety Information for KEYTRUDA® (pembrolizumab)

### Severe and Fatal Immune-Mediated Adverse Reactions

- KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

- Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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

### Immune-Mediated Pneumonitis

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

### Immune-Mediated Colitis

- KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating corticosteroid 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 immunosuppressive therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients.

### Hepatotoxicity and Immune-Mediated Hepatitis

- KEYTRUDA 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 immunosuppressive 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. Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity. Adrenal insufficiency occurred in 0.6% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

#### Hypophysitis

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

#### Thyroid Disorders

- KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.5%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Thyroiditis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (6) 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 7% 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%), polymyopathy/rheumatism; **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.

#### Infusion-Related Reactions

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

#### Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

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

#### Increased Mortality in Patients With Multiple Myeloma

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

#### 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, dysuria, and pneumonia (2% each).

Permanent discontinuation of KEYTRUDA in 37% of patients; 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, dysphoria and proteinuria (30% each), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain and hemorragic events (27% each), vomiting (26%), constipation and hepatotoxicity (25% each), headache (23%), and acute kidney injury (2%).

#### 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.

Before prescribing KEYTRUDA® (pembrolizumab), please read the accompanying [Prescribing Information](#). The [Medication Guide](#) also is available.

## 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.

### Cardiac Dysfunction

- 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. Withdraw and resume at reduced dose when hypertension is controlled 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 had an arterial thromboembolic event within the previous 6 months.

### Hepatotoxicity

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

### Diarrhea

- Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus-treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withdraw 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, QTcTc interval prolongation occurred in 9% of LENVIMA-treated patients and QTc interval prolongation of >50 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >50 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >50 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, bradycardia, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withdraw and resume at reduced dose upon recovery based on severity.

### Hypocalcemia

- In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 0.6% 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. Withdraw 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. Withdraw 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). Withdraw 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