LENVIMA®: Efficacy that drives results

LENVIMA with everolimus is the only approved 2L TKI-mTOR inhibitor combination for the treatment of adults with aRCC[1,2]

- **14.6-month median PFS** (95% CI: 5.9-20.1) with LENVIMA + everolimus vs 5.5 months (95% CI: 3.5-7.1) with everolimus alone (HR: 0.37 [95% CI: 0.22-0.62]); major efficacy endpoint[1]
  - Number of events: 26 events (51%) with LENVIMA + everolimus vs 37 events (74%) with everolimus alone

NCCN RECOMMENDED OPTION

Lenvatinib (LENVIMA) + everolimus has a National Comprehensive Cancer Network® (NCCN®) category 2A other recommended regimen as a subsequent therapy option for patients with relapse or stage IV clear cell RCC*†

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

†Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.4.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed January 18, 2023. To view the most recent and complete version of the guideline, 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.

INDICATION

LENVIMA is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

SUMMARY OF WARNINGS AND PRECAUTIONS

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

NCCN=National Comprehensive Cancer Network® (NCCN®).
TKI=tyrosine-kinase inhibitor; mTOR=mammalian target of rapamycin; 2L=second line; aRCC=advanced renal cell carcinoma; PFS=progression-free survival; CI=confidence interval; HR=hazard ratio.

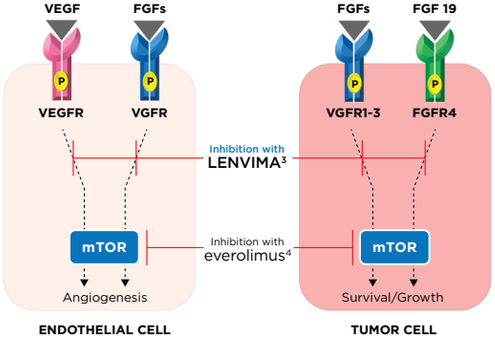
Please see Selected Safety Information throughout and full Prescribing Information.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Consider the MOA of LENVIMA® + everolimus

LENVIMA in combination with everolimus is a TKI-mTOR in 2L aRCC[1]

- LENVIMA is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor receptors (VEGFR): VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)[1]
- LENVIMA inhibits other kinases (including FGFR1, 2, 3, and 4; PDGFRα, KIT, and RET) that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression, in addition to their normal cellular functions[1]



LENVIMA + everolimus inhibits multiple cellular steps (RTK and mTOR) involved in tumor cell survival and proliferation in addition to angiogenesis[1]

The combination of lenvatinib and everolimus showed increased anti-angiogenic and antitumor activity as demonstrated by decreases in[1,4]:

- human endothelial cell proliferation
- tube formation
- both VEGF and FGF signaling in vitro
- tumor volume in mouse xenograft models of human renal cell cancer that were greater than those with either drug alone

MOA=mechanism of action; TKI=tyrosine kinase inhibitor; mTOR=mammalian target of rapamycin; 2L=second line; aRCC=advanced renal cell carcinoma; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; FGF=fibroblast growth factor; FGFR=fibroblast growth factor receptor; FLT=Fms-related tyrosine kinase 1; KDR=kinase insert domain receptor; PDGFRα=platelet-derived growth factor receptor alpha; RET=rearranged during transfection; RTK=receptor tyrosine kinase.

SELECTED SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), 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 HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

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

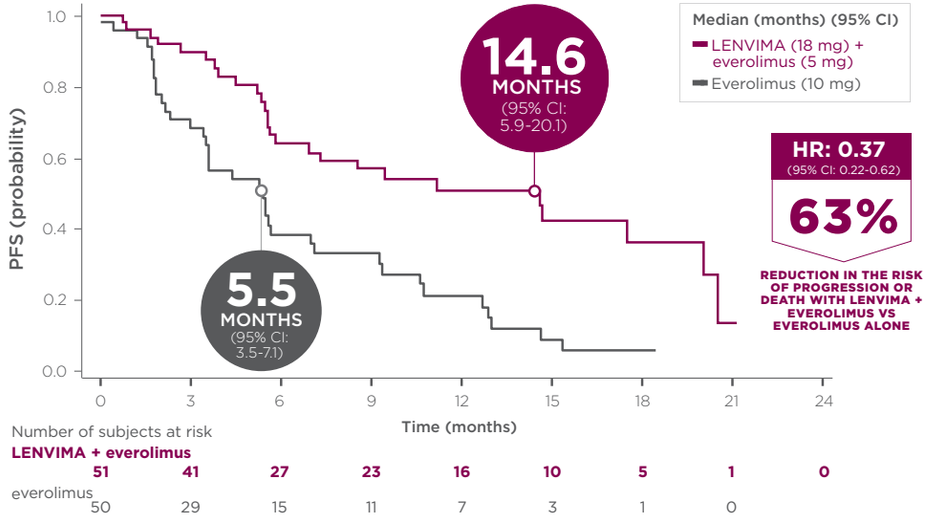
Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, 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.

MAJOR EFFICACY OUTCOME

14.6 months median PFS with the combination[1]



- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm
  - 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus
  - Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus
- The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs with an observed HR of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm

Study design
Study 205 randomized 153 patients with advanced or metastatic RCC who had previously received anti-angiogenic therapy 1:1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24-mg monotherapy, or everolimus 10-mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST version 1.1. Other efficacy outcome measures included overall survival and objective response rate. The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs.[1]

PFS=progression-free survival; HR=hazard ratio; CI=confidence interval; RECIST=Response Evaluation Criteria in Solid Tumors.

SELECTED SAFETY INFORMATION

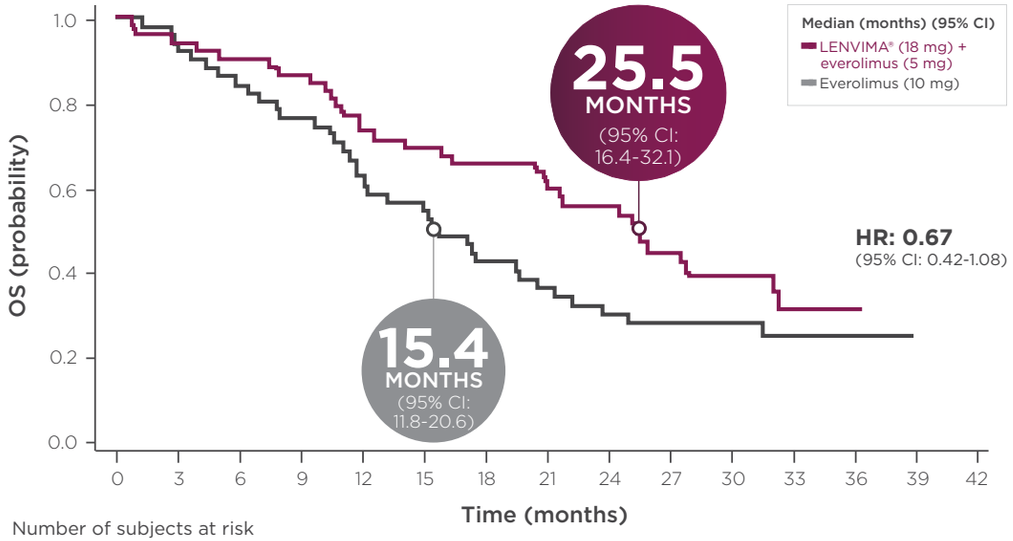
Warnings and Precautions (cont'd)

Hepatotoxicity. Across clinical studies enrolling 1327 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.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Greater than 2 years median OS with the combination[1]



Number of subjects at risk

LENVIMA + everolimus	**51**	**48**	**46**	**44**	**37**	**35**	**32**	**30**	**26**	**17**	**11**	**7**	**2**	**0**	**0**
everolimus	50	46	42	38	30	27	20	17	13	10	9	5	1	0	0

- At the time of analysis, 63% of deaths (32 patients) had occurred in the LENVIMA + everolimus arm and 74% of deaths (37 patients) had occurred in the everolimus arm

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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

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

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

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.

37% response rate with the combination[1]

[a]Evaluated according to RECIST 1.1.

6x more patients responded to LENVIMA + everolimus[1]

- The ORR was supported by a retrospective, blinded, independent radiologic review of scans[1,5]
- Tumor assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR[1]

OS=overall survival; CI=confidence interval; HR=hazard ratio; ORR=objective response rate; PR=partial response; CR=complete response; RECIST=Response Evaluation Criteria In Solid Tumors.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

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

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Recognize, monitor, and manage ARs with LENVIMA® + everolimus

Recognize ARs | Monitor ARs | Manage ARs

Adverse reactions in Study 205

Most common ARs (≥30%) observed in LENVIMA + everolimus–treated patients

- Diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis/oral inflammation (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%)[1]

Most common serious ARs (≥5%) in LENVIMA + everolimus-treated patients

- Renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%)[1]

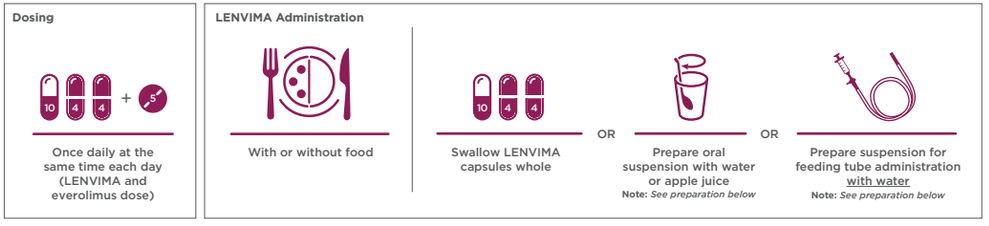
Most common grade 3-4 ARs (≥5%)[1]

Adverse reaction	LENVIMA 18 mg + everolimus 5 mg (n=62)	everolimus 10 mg (n=50)
Diarrhea	19%	2%
Fatigue[a]	18%	2%
Hypertension/increased blood pressure	13%	2%
Renal failure event[b]	10%	2%
Proteinuria/urine protein present	8%	2%
Vomiting	7%	0%
Hemorrhagic events[c]	6%	2%
Nausea	5%	0%
Decreased appetite	5%	0%
Arthralgia/myalgia[d]	5%	0%
Dyspnea/exertional dyspnea	5%	8%

Study 205 was not designed to demonstrate a statistically significant difference in AR rates for LENVIMA in combination with everolimus, as compared to everolimus alone.[1]

AR=adverse reaction.
[a]Includes asthenia, fatigue, lethargy, and malaise.
[b]Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment.
[c]Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele.
[d]Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia.

Once a day. Every day. With or without food[1]



Capsules pictured are not actual size.
Refer to the everolimus prescribing information for recommended everolimus dosing information.

Recommended dose: **18 mg LENVIMA (one 10-mg capsule and two 4-mg capsules) + one 5-mg tablet of everolimus.[1]**

The approved combination contains **half** of the 10-mg dose that was used in the everolimus monotherapy arm of Study 205. The half-life of LENVIMA is approximately 28 hours.

Preparation of LENVIMA 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).

Everolimus is not distributed by Eisai Inc.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 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.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Once a day. Every day. With or without food[1]

Continue LENVIMA® until disease progression or unacceptable toxicity.[1]

Recommended dose of LENVIMA for renal or hepatic impairment[1]

In patients with:	Recommended dose:
Severe renal impairment (CrCl <30 mL/min)[a]	**10 mg (one 10-mg capsule) once daily**
Severe hepatic impairment (Child-Pugh C)	**10 mg (one 10-mg capsule) once daily**

- No dose adjustment is recommended in patients with mild or moderate renal or hepatic impairment. Patients with end-stage renal disease were not studied

[a]As calculated by the Cockcroft-Gault equation.

Missed doses of LENVIMA[1]

- LENVIMA should be taken at the same time each day
- 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

Please see Table 1 in the full Prescribing Information for LENVIMA for Recommended Dose Modifications for adverse reactions.

Review the full prescribing information for everolimus for recommended dose modifications.

CrCl=creatinine clearance.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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

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

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

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

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

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

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

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

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

Adverse Reactions

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus–treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

Selected Safety Information

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 the last dose. LENVIMA® may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC (endometrial carcinoma) and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC 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 EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

References: 1. LENVIMA [package insert]. Nutley, NJ; Eisai Inc. **2.** Afinitor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022. **3.** Tohyama O, Matsui J, Kodama K, et al. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. *J Thyroid Res.* 2014;2014:638747. doi:10.1155/2014/638747 **4.** Matsuki M, Adachi Y, Ozawa Y, et al. Targeting of tumor growth and angiogenesis underlies the enhanced antitumor activity of lenvatinib in combination with everolimus. *Cancer Sci.* 2017;108(4):763-771. **5.** Motzer RJ, Hutson TE, Ren M, Dutcus C, Larkin J. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. *Lancet Oncol.* 2016;17(1):e4-e5.

LENVIMA® + everolimus: A treatment option for adult patients with aRCC following one prior anti-angiogenic therapy[1]

LENVIMA with everolimus is the only approved 2L TKI-mTOR inhibitor combination for the treatment of adults with aRCC[1,2]

14.6 months median PFS[1*]

14.6 months median PFS: (95% CI: 5.9-20.1) with LENVIMA + everolimus vs 5.5 months (95% CI: 3.5-7.1) with everolimus alone; HR: 0.37 (95% CI: 0.22-0.62)

- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm

Greater than 2 years median OS[1†]

Greater than 2 years median OS: **25.5-month median OS** (95% CI: 16.4-32.1) with LENVIMA + everolimus vs 15.4 months (95% CI: 11.8-20.6) with everolimus alone; HR: 0.67 (95% CI: 0.42-1.08)

37% response rate[1†]

37% response rate: **35% PR (n=18/51) and 2% CR (n=1/51)** with LENVIMA + everolimus (95% CI: 24%-52%) vs 6% PR (n=3/50) and 0% CR with everolimus alone (95% CI: 1%-17%)

SUMMARY OF WARNINGS AND PRECAUTIONS

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

Take a closer look at LENVIMA

lenvimahcp.com/2nd-line-advanced-renal-cell-carcinoma

aRCC=advanced renal cell carcinoma; PFS=progression-free survival; CI=confidence interval; HR=hazard ratio; OS=overall survival; PR=partial response; CR=complete response.

*Major efficacy outcome.

†Other efficacy outcome.

Please see Selected Safety Information throughout and full Prescribing Information.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg