#1 PRESCRIBED
first-line therapy for
RAI-refractory DTC patients[1,2*]

See a spectrum of results

Lenvatinib (LENVIMA®) is the preferred first-line treatment by the National Comprehensive Cancer Network® (NCCN®) for locally recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer[†‡]

NCCN **PREFERRED** FIRST-LINE THERAPY

- 18.3-month (95% CI: 15.1-NE) median PFS was observed with LENVIMA vs 3.6 months (95% CI: 2.2-3.7) with placebo (HR: 0.21 [95% CI: 0.16-0.28]; *P*<0.001; primary endpoint)[2,3]

RAI=radioactive iodine; DTC=differentiated thyroid cancer; CI=confidence interval; NE=not estimable; PFS=progression-free survival; HR=hazard ratio.
*Ipsos Healthcare US Oncology Monitor (August 2018 to July 2019, 349 physicians reporting on 1,701 Stage 4 patients, all data collected online) © Ipsos 2019, all rights reserved.
†Lenvatinib (LENVIMA)[1] has a category 2A recommendation. Category 2A recommendation is based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. All recommendations are category 2A unless otherwise indicated.
‡Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma V.2.2019. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 15, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. The National Comprehensive Cancer Network 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 for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC).

SELECTED SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC, hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In 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 HCC, hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

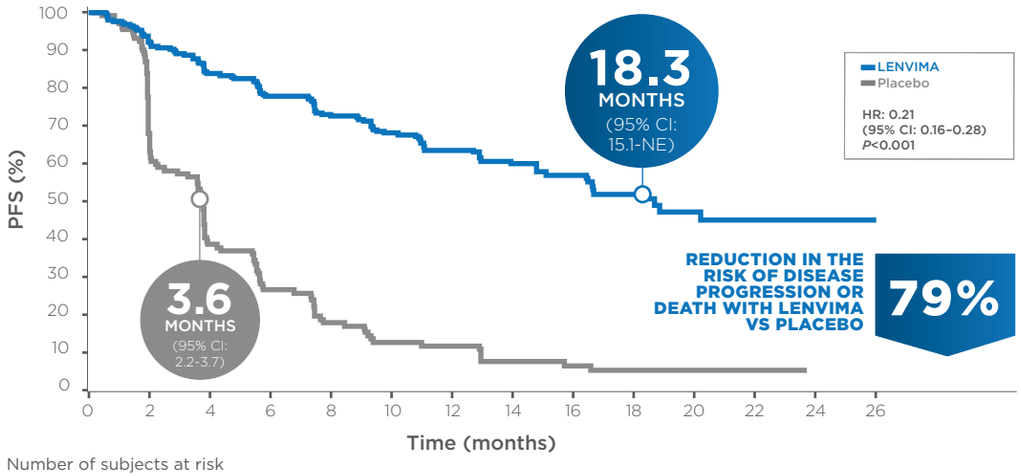
Please see Selected Safety Information throughout and full Prescribing Information.

LENVIMA®
(lenvatinib) capsules 10 mg and 4 mg
RESULTS THAT MATTER

Superior PFS benefit

MAJOR EFFICACY OUTCOME

Median PFS: 18.3 months with LENVIMA® vs 3.6 months with placebo[2,3]



Number of subjects at risk

LENVIMA	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

SELECT study results based on a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients with locally recurrent or metastatic RAI-refractory DTC (N=392) who have had radiographic evidence of disease progression within 12 months prior to randomization as confirmed by independent radiologic review.[2,3]

- 107 events (41%) occurred in the LENVIMA arm vs 113 events (86%) in the placebo arm[2]
  - 93 patients (36%) who received LENVIMA progressed vs 109 patients (83%) who received placebo
  - Death occurred in 14 patients (5%) who received LENVIMA vs 4 patients (3%) who received placebo

SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

SELECTED SAFETY INFORMATION

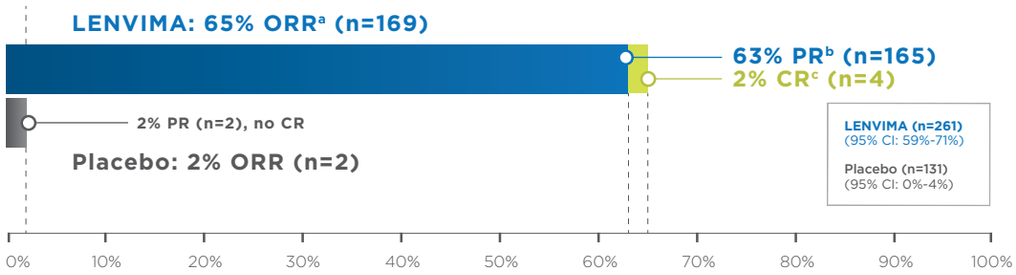
Warnings and Precautions (cont'd)

Hypertension (cont'd). 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.

Superior response

OTHER EFFICACY OUTCOME

65% ORR[a] with LENVIMA® (including 2% CR) vs 2% ORR with placebo[2-4]



LENVIMA IS THE FIRST TKI TO DEMONSTRATE A COMPLETE RESPONSE IN A PHASE 3 TRIAL FOR LOCALLY RECURRENT OR METASTATIC, PROGRESSIVE RAI-REFRACTORY DTC[2,3,5]

- **Median OS was not estimable** due to crossover from placebo at disease progression (HR: 0.73 [95% CI: 0.50-1.07]; *P*=0.10)[2]

TKI=tyrosine kinase inhibitor; OS=overall survival; RECIST=Response Evaluation Criteria In Solid Tumors.
Responses evaluated using RECIST 1.1.[2,3]
P<0.001, according to the Cochran–Mantel–Haenszel chi-square test.[2]
[a]Objective response rate (ORR)=sum of CR and PR.[2,4]
[b]Partial response (PR)=30% or greater decrease in the sum of diameters of target lesions.[4]
[c]Complete response (CR)=disappearance of all target and nontarget lesions.[4]

SELECTED SAFETY INFORMATION

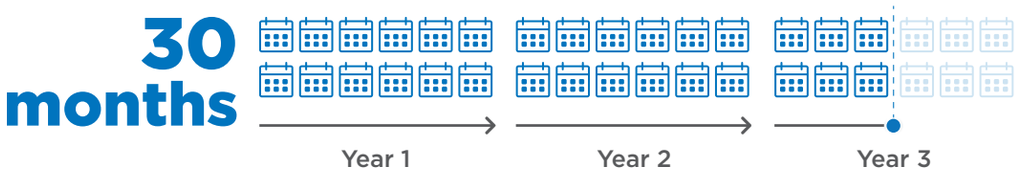
Warnings and Precautions (cont'd)

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. 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.

Duration of response analysis

30-month (95% CI: 18.4-36.7) median duration of response among patients who responded to LENVIMA®[6]



- Post hoc analysis (n=261) was conducted based on investigator-assessed response; 157 patients (60.2%) in the LENVIMA arm responded per investigator assessment[6]

Limitations: the post hoc exploratory subgroup analysis (data cutoff: September 1, 2016) was not a prespecified study endpoint. Patients who did not respond were not evaluated. No conclusions can be drawn.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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).

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.

Selected Safety Information

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.

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.

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

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

Warnings and Precautions (cont'd)

Hemorrhagic Events (cont'd).
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 ≤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 at least 30 days after the last dose.

Adverse Reactions

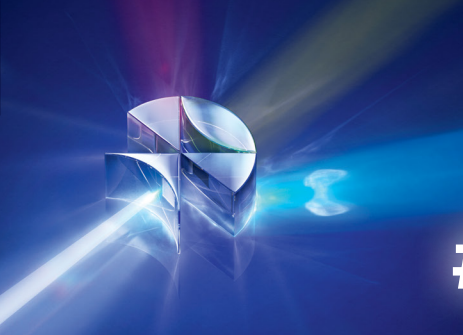
In DTC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions (≥2%) were pneumonia (4%), hypertension (3%), and dehydration (3%). Adverse reactions led to dose reductions in 68% of LENVIMA-treated patients; 18% discontinued LENVIMA. The most common adverse reactions (≥10%) resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 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 or RCC and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with RCC or DTC 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.

References: 1. Data on file. Eisai Inc. **2.** LENVIMA [package insert]. Woodcliff Lake, NJ: Eisai Inc. **3.** Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-630. **4.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. **5.** NEXAVAR [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2018. **6.** Gianoukakis AG, Dutcus CE, Batty N, Guo M, Baig M. Prolonged duration of response in lenvatinib responders with thyroid cancer. *Endocr Relat Cancer*. 2018;25(6):699-704.



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NCCN **PREFERRED** FIRST-LINE THERAPY

Superior PFS benefit

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Superior response

65% ORR[a] with LENVIMA (including 2% CR[b]) vs 2% ORR with placebo (no CR)[2,4]

Visit **www.LENVIMA.com/hcp** to learn more

[a]ORR=sum of CR and PR.[2,4]
[b]CR=disappearance of all target and nontarget lesions.[4]
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Price disclosure information for prescribers available here: https://us.eisai.com/RequiredPriceDisclosures

SELECTED SAFETY INFORMATION

Use in Specific Populations (cont'd)

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 or RCC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe hepatic impairment. Reduce the dose for patients with DTC or RCC and severe hepatic impairment.

Please see Selected Safety Information throughout and full Prescribing Information.

Eisai

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RESULTS THAT MATTER