Response that matters with the power of LENVIMA® (lenvatinib) in RAI-R DTC

[EACH REGION TO FILL IN LOCAL PRODUCT LABELLING AND APPROPRIATE CONTACT INFORMATION. PLEASE REPORT ADVERSE EVENTS OR REQUEST MEDICAL INFORMATION FROM YOUR EISAI MEDICAL DEPARTMENT]

LENVIMA® is indicated as monotherapy for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine (RAI-R DTC).[1]

Product labelling is available here.[1]

Reference: 1. LENVIMA® product labelling.

GL-LENA-23-00009 March 2023

LENVIMA® (lenvatinib) capsules

RESPONSE THAT MATTERS

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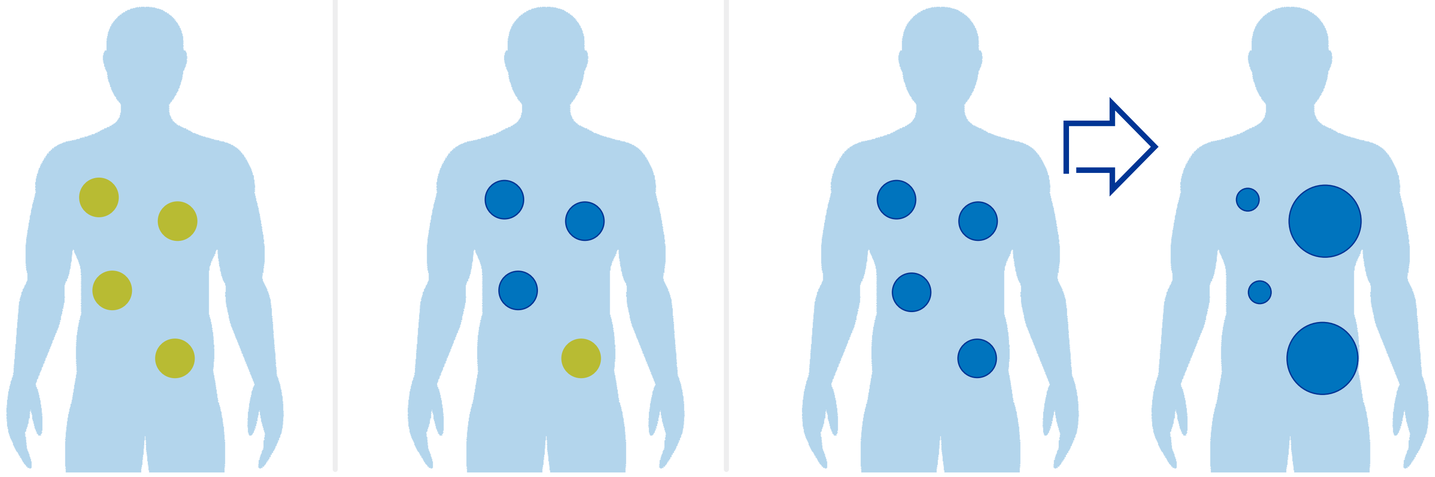
Identifying appropriate patients for systemic therapy

Patients refractory to RAI exhibit at least 1 of the following:[1–3]

1. Metastatic lesions that have no RAI-R uptake
2. One or more lesions that do not have RAI uptake
3. Tumour progression of lesions that do have RAI uptake

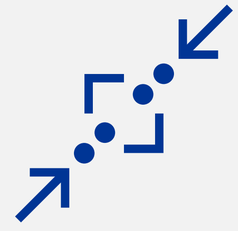


● No uptake ● Uptake

Most definitions also include patients who have received greater than 600 mCi (22 GBq) cumulative dose of RAI.[2] This is because those patients do not seem to benefit from additional treatment.

Patients who experience structural signs of progression, as determined by:[4]

Tumour size



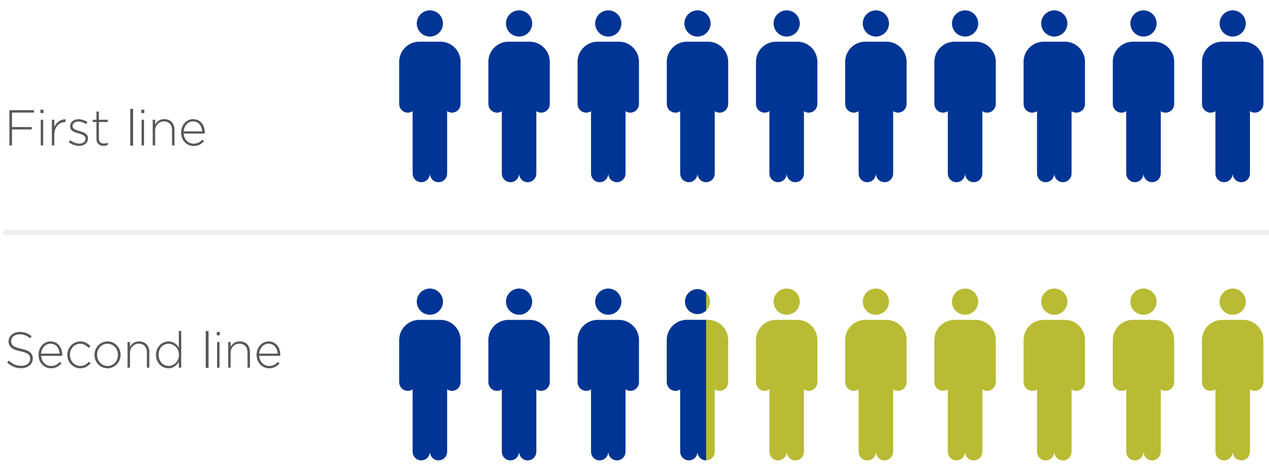
Location of metastases

Growth rate

Symptoms

References: 1. Cabanillas ME *et al. Lancet* 2016;388(10061):2783-2795. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630. **3.** Brose MS, *et al. Lancet* 2014;384(9940):319-328. **4.** Brose MS and Tuttle MR, *Clinical Advances in Hematology & Oncology*. 2016;14(5):Supplement 9.

Deliver your best treatment first as you may not get a second chance[1–3]



Up to 65%
of patients receiving systemic therapy will never receive a second treatment*[2]

Patients with slow-growing tumours may experience rapid disease progression[3]

10% ten-year survival rate in patients with RAI-R DTC[2,3]

~2.5 to 3.5-year median survival in RAI-R DTC patients with metastases[1]

*In this real-world analysis of small molecule kinase inhibitor therapies used in the first, second and third line, approximately 36–53% of patients received a second-line treatment.

References: 1. Cooray SD and Topliss DJ, *Endocrinol Diabetes Metab Case Rep* 2017 doi: 10.1530/EDM-16-0089. **2.** Dacosta Byfield SA, *et al. Adv Ther* 2019;36(4):896–915. **3.** Tuttle RM, *et al. Best Pract Res Clin Endocrinol Metab* 2017;31(3):295–305.

Guideline recommended[1]

LENVIMA® is recommended by the NCCN guidelines based on superior efficacy, safety and evidence

NCCN

Preferred first-line therapy

- **LENVIMA®** is the **preferred** first-line therapy for clinically progressive or symptomatic RAI-R DTC
  - NCCN Categories of Preference: preferred interventions are based on superior efficacy, safety and evidence; and, when appropriate, affordability (US guidelines)
- **LENVIMA®** has a **category 1 recommendation** based on the results from the SELECT study
  - Category 1 recommendations are based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Make **LENVIMA® your first-line TKI treatment of choice** for your RAI-R DTC patients[2]

NCCN: National Comprehensive Cancer Network, **TKI:** tyrosine kinase inhibitor.

References: 1. NCCN. Thyroid carcinoma. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (accessed March 2023). **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

SELECT study design[1]

An international, multicentre, randomised, double-blind, placebo-controlled phase 3 study

392 patients with RAI-R DTC

Inclusion criteria

- ≥18 years of age
- Measurable, pathologically confirmed RAI-R DTC
- ≥1 measurable lesion without iodine uptake on any ^{131}I scan
- 1 measurable lesion that had progressed according to RECIST
- Independently reviewed radiologic evidence of progression within the previous 13 months
- ≤1 prior treatment with a TKI
- Adequate renal, bone marrow, coagulation and liver function

Exclusion criteria

- Anaplastic or medullary thyroid cancer
- Any other malignancy within the past 24 months
- Anticancer treatment 21 days before randomisation
- Proteinuria ≥1 g/24 hours
- Significant cardiovascular or gastrointestinal dysfunction

Stratification

Region: Europe, North America, Asia and Australia

Age: ≤65 or >65 years

Prior VEGF-targeted treatment: (0 or 1)

Randomisation 2:1

LENVIMA®
24 mg
Once daily orally

Placebo
Patients could cross over to LENVIMA® (open-label) at disease progression

Endpoints

Primary
PFS

Secondary
Response rate
OS

Safety

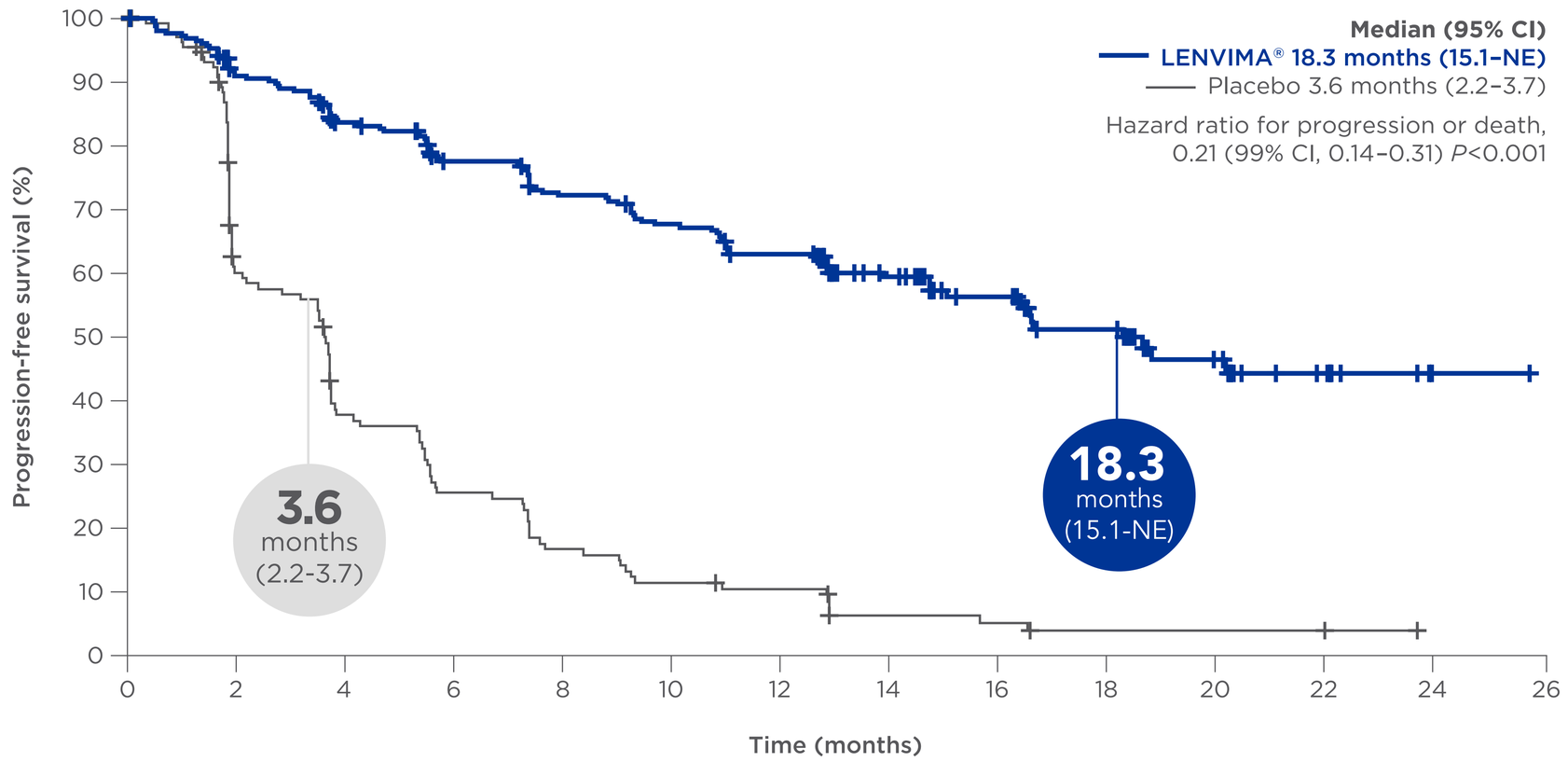
Response rate defined as sum of CR + PR.

CR: complete response, **OS:** overall survival, **PFS:** progression-free survival, **PR:** partial response, **RECIST:** response evaluation criteria in solid tumours, **TKI:** tyrosine kinase inhibitor, **VEGF:** vascular endothelial growth factor.

Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

LENVIMA® delivers superior PFS benefit compared to placebo[1]

18.3-month median PFS vs 3.6 months with placebo[1]



79%
reduction in the risk of progression or death
with LENVIMA® vs placebo[1]

Number of patients 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

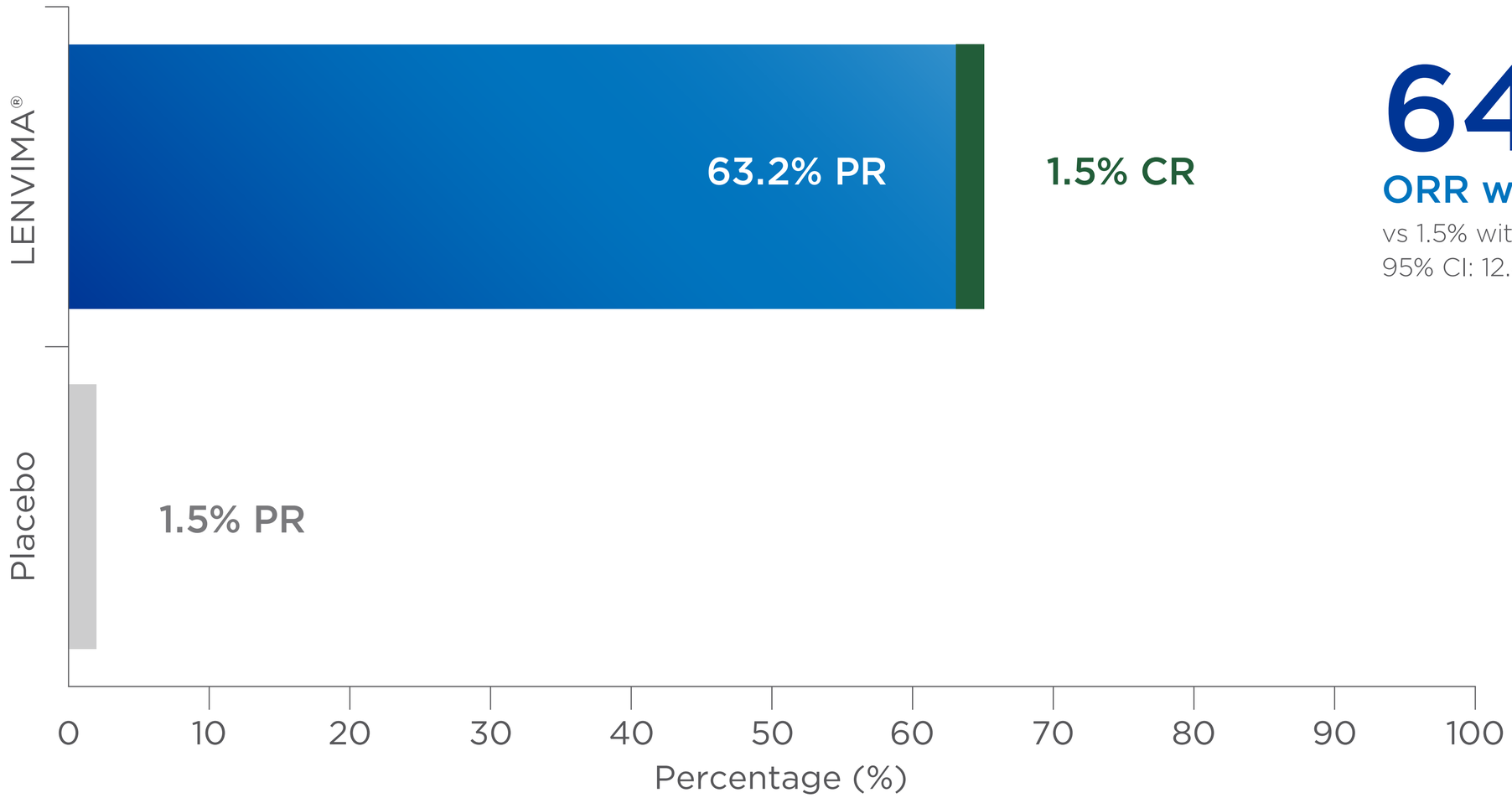
Tumour responses were assessed with the use of RECIST, version 1.1, and were confirmed by independent centralised radiologic review. Tumour responses were calculated as the maximum percentage change from baseline in the sum of the diameters of target lesions.

CI: confidence interval, **NE:** not estimable, **PFS:** progression-free survival, **RECIST:** response evaluation criteria in solid tumours.

Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

LENVIMA® delivers superior responses compared to placebo[1]

The first and only TKI to demonstrate complete responses in a phase 3 trial for locally recurrent or metastatic, progressive RAI-R DTC[1–3]



64.8%
ORR with LENVIMA®
vs 1.5% with placebo (OR: 28.87, 95% CI: 12.46–66.86; *P*<0.001)[1]

ORR defined as sum of CR + PR.

CI: confidence interval, **CR:** complete response, **OR:** odds ratio, **ORR:** objective response rate, **PR:** partial response, **TKI:** tyrosine kinase inhibitor.

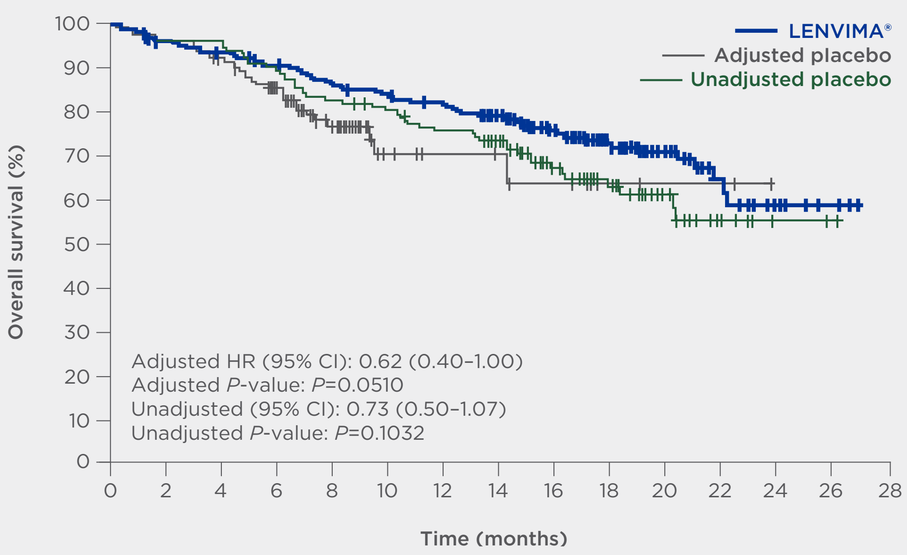
References: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630. **2.** Brose MS, *et al. Lancet.* 2014;384(9940):319-328. **3.** Brose MS *et al. Lancet Oncol.* 2021;22(8):1126-1138.

47% reduction in the risk of death with **LENVIMA®** vs placebo in RAI-R DTC patients over 65[1]

In this prespecified subgroup analysis patients were stratified by age (≤65 or >65 years)

OS in the ITT population[2]

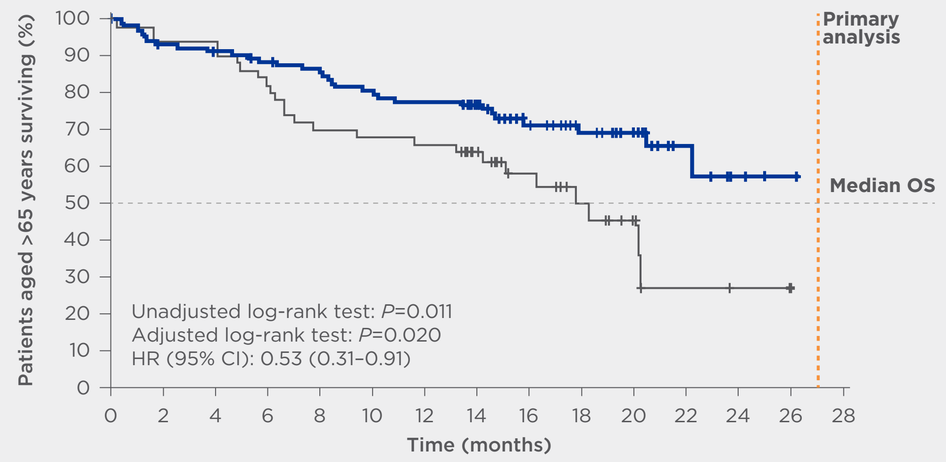
Median OS was not reached in the overall population



OS in patients >65 years[1]

Median OS was NE with LENVIMA® vs 18.4 months with placebo (HR: 0.53, 95% CI: 0.31–0.91; adjusted *P*=0.020)

Treatment	Total	Treatment failure	Censored	Median, months (95% CI)
LENVIMA®	106	31	75	NE (22.1–NE)
Placebo	50	25	25	18.4 (13.3–20.3)



The median age of patients in the LENVIMA® group of the SELECT study was 64 years of age[2]

CI: confidence interval, **HR:** hazard ratio, **ITT:** intention to treat, **NE:** not estimable, **OS:** overall survival, **TKI:** tyrosine kinase inhibitor.

References: 1. Brose MS, *et al. J Clin Oncol* 2018;36: erratum DOI 10.1200/JCO.2018.78.0940. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

LENVIMA® patients with small lung metastases had long survival[1]

44.7-month median OS vs 33.1 months with placebo with lung metastases ≥1.0 cm[1]

	≥1.0 cm	≥1.5 cm	≥2.0 cm
LENVIMA® median OS (months)	**44.7**	**44.1**	**34.7**
Placebo median OS (months)	33.1	22.3	19.3
HR (95% CI)	0.63 (0.47–0.85) *P*=0.0025	0.63 (0.45–0.89) *P*=0.0082	0.65 (0.44–0.98) *P*=0.0383
LENVIMA® median PFS (months)	**20.2**	**18.7**	**16.6**
Placebo median PFS (months)	3.7	3.5	3.5
HR (95% CI)	0.20 (0.15–0.28) *P*<0.0001	0.20 (0.14–0.29) *P*<0.0001	0.17 (0.11–0.28) *P*<0.0001

In the SELECT study:[1,2]

89.3%
of patients had lung metastases

78.1%
of patients had lung metastases ≥1.0 cm

In patients with lung metastases over 1 cm, **start LENVIMA® early** before tumour progression

Post hoc, exploratory, subgroup analysis.[1]

In the overall population, there was no significant difference in overall survival between LENVIMA® and placebo.[1]

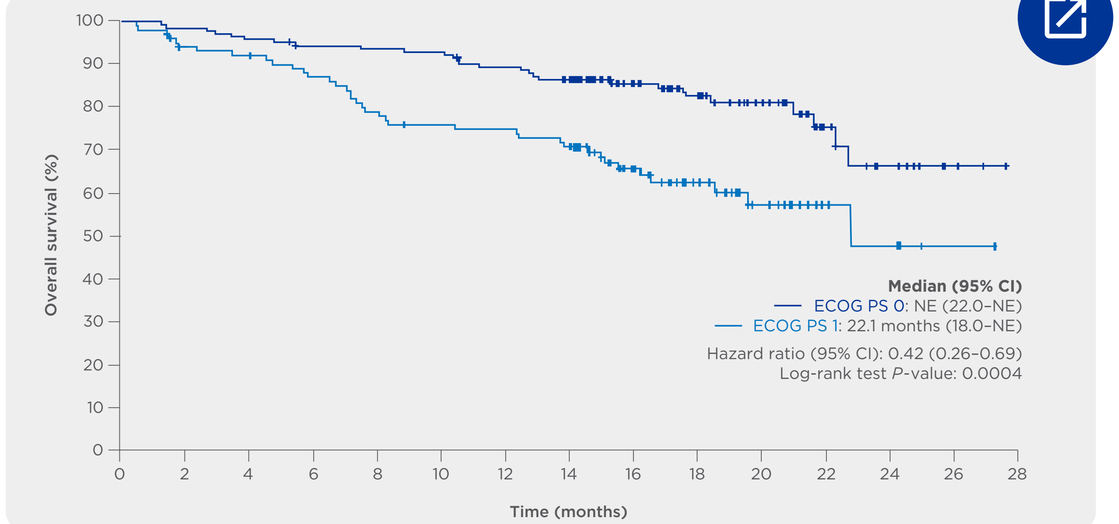
CI: confidence interval, **HR:** hazard ratio, **OS:** overall survival, **PFS:** progression-free survival.

References: 1. Tahara M, *et al. Eur J Cancer* 2021;147:51–57. **2**. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

LENVIMA® demonstrated improved PFS and OS in patients with a low ECOG performance status[1]

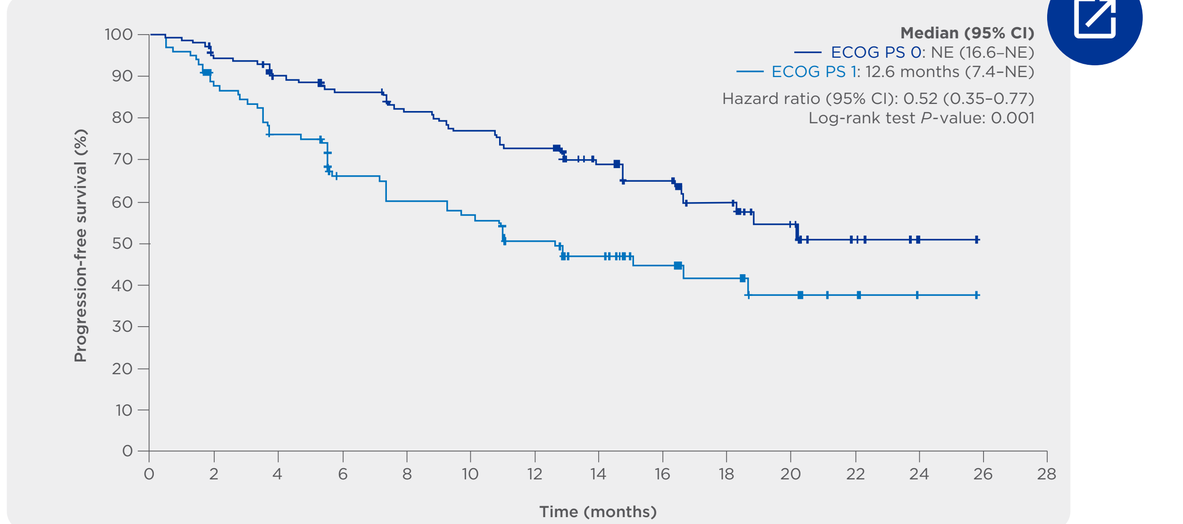
Longer median OS and PFS in patients with an ECOG performance status of 0 compared to 1[1]

OS in patients treated with LENVIMA®[1]



Median OS for patients with an ECOG performance status of 0 was NE vs 22.1 months in patients with an ECOG performance status of 1 (HR: 0.42, 95% CI: 0.26–0.69; *P*=0.0004)

PFS in patients treated with LENVIMA®[1]



Median PFS for patients with an ECOG performance status of 0 was NE vs 12.6 months in patients with an ECOG performance status of 1 (HR: 0.52, 95% CI: 0.35–0.77; *P*=0.001)

Start LENVIMA® at ECOG performance status 0 to maximise the therapeutic effect

This *post hoc,* exploratory, subgroup analysis of the SELECT study examined the effect of baseline ECOG performance status and tumour size (sum of all targeted lesions) on the efficacy (PFS, OS, ORR, and time to ECOG performance status ≥2) of LENVIMA®. AEs according to patients' ECOG performance status at baseline were also analysed.[1]

AE: adverse event, **CI:** confidence interval, **ECOG:** Eastern Cooperative Oncology Group, **HR:** hazard ratio, **NE:** not estimable, **OR:** odds ratio, **ORR:** objective response rate, **OS:** overall survival, **PFS:** progression-free survival.

Reference: 1. Taylor MH, *et al. Thyroid.* 2021;31(8):1226-1234.

Real-world clinical outcomes of **LENVIMA®**

Two key studies have analysed the effectiveness of LENVIMA® in real-world patients[1,2]

SUBSEQUENT THERAPY

LENVIMA® and subsequent therapy for RAI-R DTC: A real-world study of clinical effectiveness in the United States[1]

CLINICAL EFFECTIVENESS

Real-world treatment patterns and clinical outcomes in RAI-R DTC patients treated with LENVIMA® monotherapy[2]

References: 1. Kish JK, *et al*. *Adv Ther* 2020;37(6):2841–2852. **2.** Rajkovic-Hooley O, *et al*. Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

RWD study design

Retrospective observational study in the US[1]

The aim of this study was to explore real-world clinical outcomes of first-line LENVIMA® in addition to treatment patterns and outcomes in the second line post-LENVIMA®[1]

181 patients with RAI-R DTC	Treatments received as second line following discontinuation of first-line LENVIMA®
Inclusion criteria • Physician confirmed RAI-R DTC • 18 years of age at the initiation of first-line LENVIMA® therapy • Initiated first-line LENVIMA® between 01/01/2016 and 31/05/2017 • Documented radiographic evidence of best disease response to first-line LENVIMA® • Initiated any second-line therapy **Exclusion criteria** • Patients treated with first-line LENVIMA® as part of a clinical trial • Synchronous anaplastic histology	sorafenib (n=90) cabozantinib (n=35) pazopanib (n=15) sunitinib (n=10) vandetanib (n=8) paclitaxel (n=7) axitinib (n=6) dabrafenib/trametinib (n=5) pembrolizumab (n=2)

Adapted from Kish JK, *et al*. 2020.[1]

RWD: real-world data.

Reference: 1. Kish JK, *et al*. *Adv Ther* 2020;37(6):2841–2852.

Patient demographics and clinical characteristics

Patient baseline demographics and clinical characteristics were similar to the SELECT study[1,2]

	First-line LENVIMA® (n=181)*	
Sex (n, %)		
Male	77	42.5
Female	104	57.5
Race/ethnicity (n, %)		
White	138	76.2
Asian	9	5.0
Black/African American	26	14.4
Native Hawaiian or other Pacific Islander	0	0.0
American Indian or Alaska Native	0	0.0
Other	8	4.4
Histological subtype of DTC (n, %)		
Follicular	74	40.9
Papillary	102	56.4
Hürthle cell	5	2.8
Tumour characteristics at initial diagnosis (n, %)*		
Extra-thyroid extension	42	23.2
Multi-focality	42	23.2
Vascular invasion	67	37.0
Genetic mutations (% tested, % abnormal of those tested)*		
BRAF	43.1%	48.1
RAS	39.2%	50.0
RET	44.8%	41.8
PI3K	32.6%	9.1
PTEN	29.3%	2.0
Sites of metastatic disease at first-line initiation of LENVIMA® (n, %)†		
Bone	64	35.4
Central nervous system	0	0.0
Distant lymph nodes	40	22.1
Kidney	4	2.2
Lung	124	68.5
Mediastinum	26	14.4
Liver	34	18.8
Any other	2	1.1
Age at initiation of first-line therapy, years (mean, SD)	60.2	11.8
ECOG performance status at first-line initiation (n, %)		
0/1	167	92.3
≥2	14	7.7
Months of follow-up from initiation of first-line LENVIMA® (mean, SD)	20.6	6.0

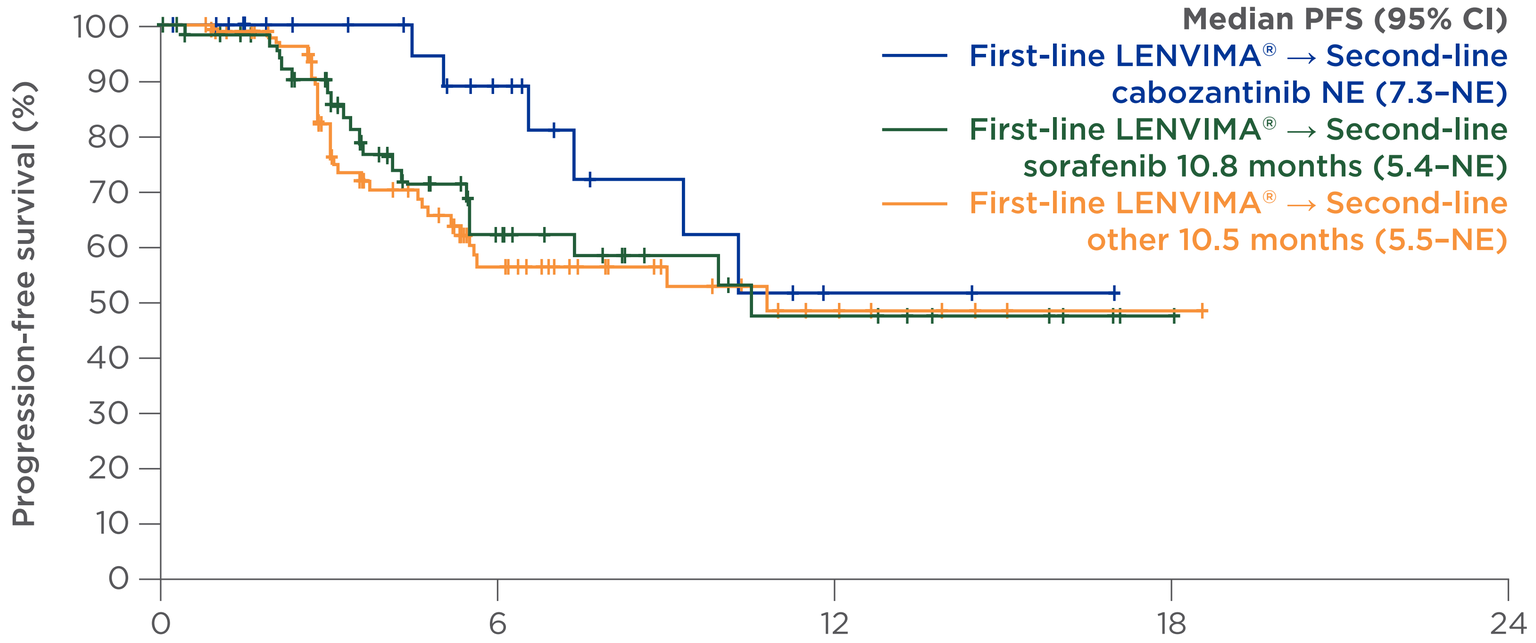
Adapted from Kish JK, *et al.* 2020.[1]

*Proportions may not sum to 100% due to rounding.
†Categories are not mutually exclusive and proportions may not sum to 100%.

BRAF: rapidly accelerated fibrosarcoma B-type, **ECOG:** Eastern Cooperative Oncology Group, **PI3K:** phosphatidylinositol 3-kinase, **PTEN:** phosphatase and tensin homolog, **RAS:** rat sarcoma, **RET:** rearranged during transfection, **SD:** standard deviation.

References: 1. Kish JK, *et al. Adv Ther* 2020;37(6):2841–2852. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

Real-world evidence supports first-line use of **LENVIMA®** **in RAI-R DTC patients**[1]



Number of patients at risk:

LENVIMA® → Second-line cabozantinib	35		13		2		0	0
LENVIMA® → Second-line sorafenib	90		30		7		1	0
LENVIMA® → Second-line other	56		19		8		1	0

Adapted from Kish JK, *et al.* 2020.[1]

With **LENVIMA®**

14.0-month
median PFS with LENVIMA® in the first line[1]

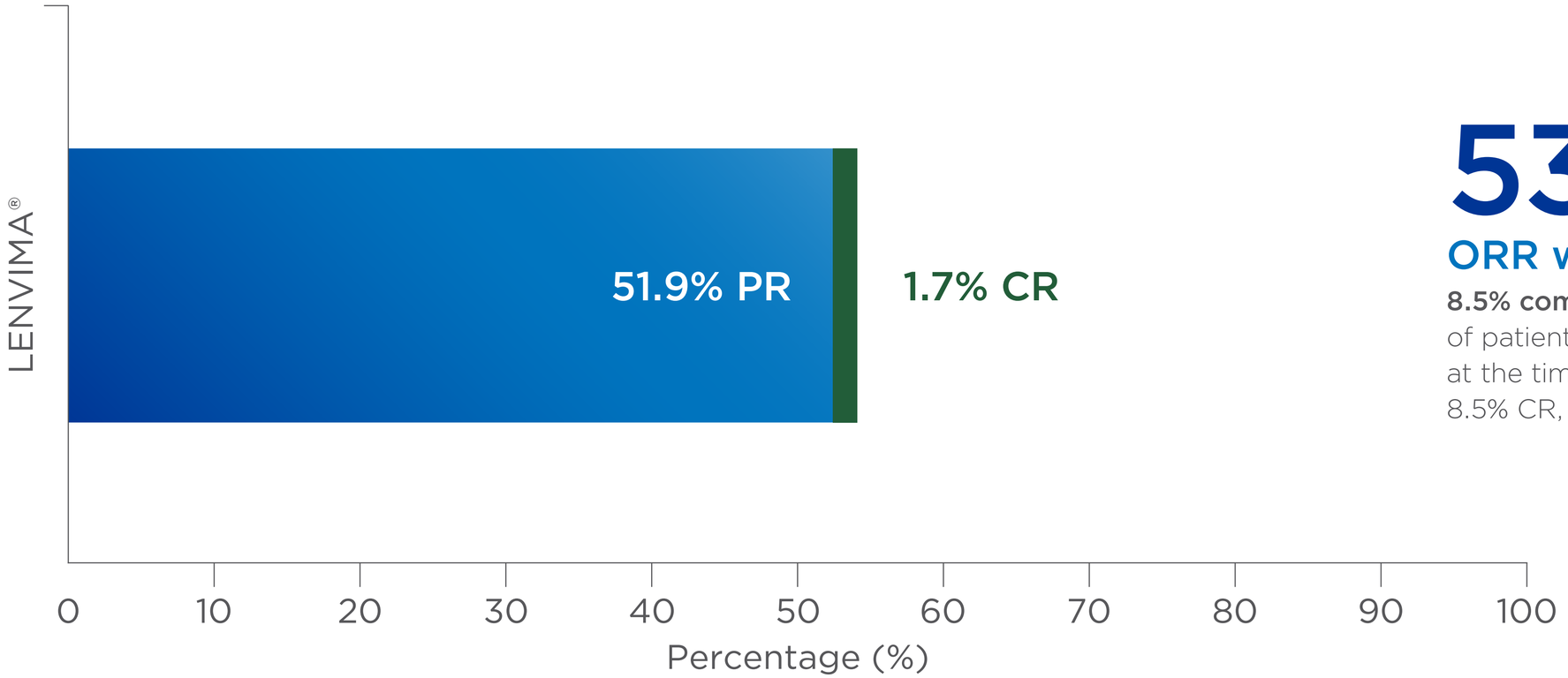
10.5-month
median PFS with other common TKIs in the second line[1]

CI: confidence interval, **NE:** not evaluable, **PFS:** progression-free survival, **TKI:** tyrosine kinase inhibitor.

Reference: 1. Kish JK, *et al. Adv Ther* 2020;37:2841–2852.

Real-world evidence supports first-line use of **LENVIMA®** **in RAI-R DTC patients**[1]

53.6% ORR with LENVIMA® in the first line. 15.5% ORR with other common TKIs in the second line[1]



53.6%

ORR with LENVIMA®[1]*

8.5% complete responses in the cohort of patients receiving first-line LENVIMA® at the time of data cut-off (64.8% ORR: 8.5% CR, 56.3% PR)[1†]

*The purpose of this study was to assess the effectiveness of LENVIMA® first line followed by second-line therapy. Patients were required to have initiated second-line therapy by the time of data cut-off, which could have downwardly biased the selection criterion to patients with more advanced disease.[1]

†Data cut-off: 17 October 2018.

ORR defined as sum of CR + PR.

CR: complete response, **ORR:** objective response rate, **PR:** partial response, **TKI:** tyrosine kinase inhibitor.

Reference: 1. Kish JK, *et al. Adv Ther* 2020;37:2841–2852.

RWD study design[1]

Retrospective observational study in the US[1]

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

308 patients with RAI-R DTC treated with LENVIMA® monotherapy

Inclusion criteria

- Had a histologically confirmed diagnosis of DTC
- Had a clear physician-reported diagnosis of RAI-R status prior to initiation of LENVIMA® monotherapy
- Age ≥18 years at the initiation of LENVIMA® monotherapy
- Initiated LENVIMA® monotherapy for RAI-R DTC in the 1L between February 13, 2015 and September 30, 2020
- Had complete treatment history available from initiation of 1L treatment to last follow-up

Exclusion criteria

- Received LENVIMA® for RAI-R DTC as part of a clinical trial
- Received any systemic treatments for other primary tumours than DTC during the study period
- Synchronous anaplastic histology at diagnosis

The licensed starting dose of **LENVIMA®** in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day

Endpoints

PFS

OS

BOR

Once daily orally

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

No direct comparisons between results from the pivotal clinical trial and real-world data study should be made, as there could be potential differences in patient populations, patient characteristics, follow-up duration, response assessment timing, frequency and criteria that are used in clinical trials versus real-world settings and provider selection bias. Because this is a single cohort study, no data on comparative therapies were included.

1L: first-line, **BOR:** best overall response, **OS:** overall survival, **PFS:** progression-free survival, **RWD:** real-world data.

Reference: 1. Rajkovic-Hooley O, *et al*. Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

Patient baseline demographics and clinical characteristics[1]

Baseline patient demographics and clinical characteristics were representative of the overall RAI-R DTC patient population[1]

	Overall (%) n=308*
Age at LENVIMA® initiation (years)	
Median	60
Gender	
Male	48.4
Female	51.6
Race	
White/Caucasian	73.4
African American	15.6
Asian	4.9
Other/not reported	6.1
ECOG score at LENVIMA® initiation	
0/1	72.4
≥2	25.9
Histology	
Locally-reported FTC	48.4
Locally-reported PTC	48.4
Locally-reported HTC	3.2
Metastases at LENVIMA® initiation	89.6

Adapted from Rajkovic-Hooley O, *et al.* 2022.[1]

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

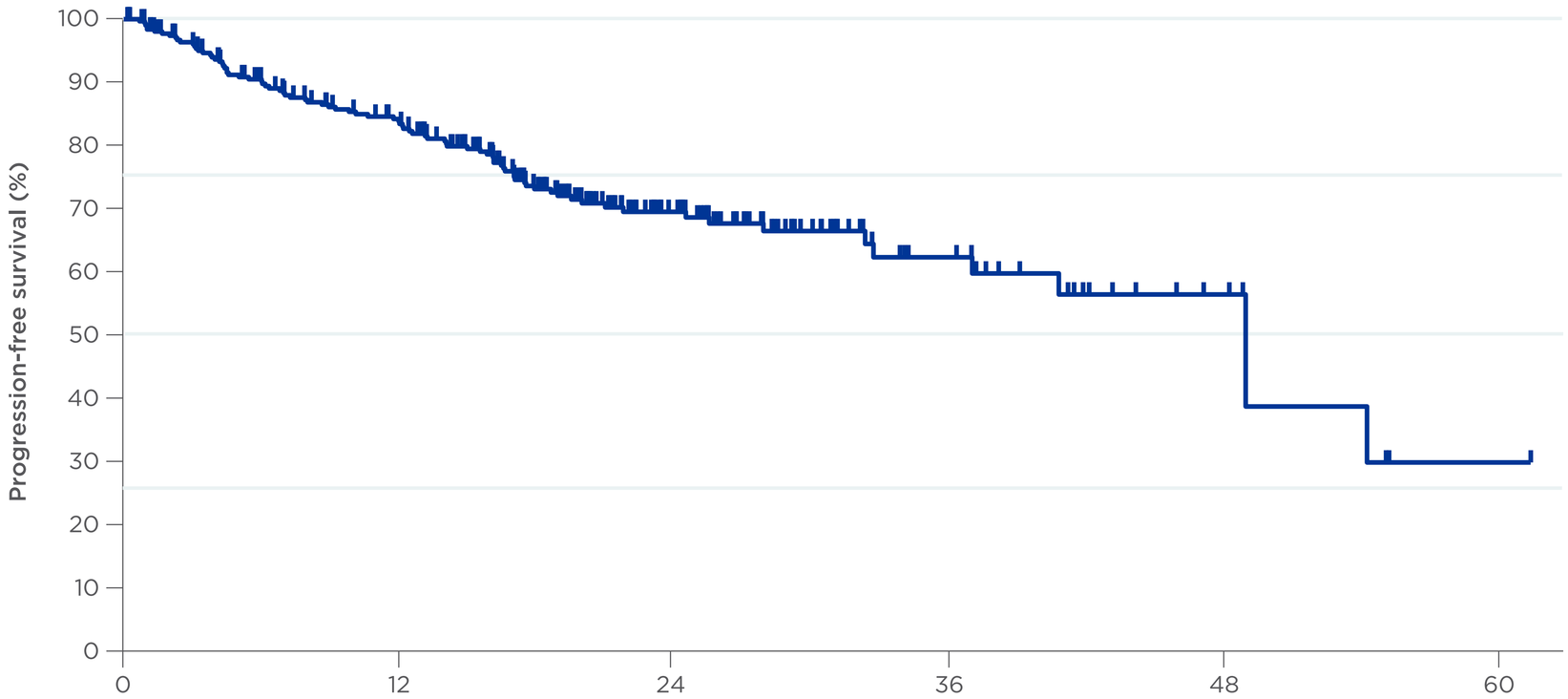
Limitations: The results of this real-world study should be interpreted with caution because of the potential for selection bias, since the study patient cohort represents only practices of physicians who agreed to participate in the study, and potential loss to follow-up during study period. Differences in outcome assessment schedules and criteria used among participating oncologists were expected in real-world clinical practice. No final conclusions for the overall US DTC population should be drawn.

ECOG: Eastern Cooperative Oncology Group, **FTC:** follicular thyroid cancer, **HTC:** Hürthle cell thyroid cancer, **PTC:** papillary thyroid cancer.

Reference: 1. Rajkovic-Hooley O, *et al.* Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

Real-world PFS with **LENVIMA®** treatment in RAI-R DTC patients[1]

49-month median PFS (CI: 37.0-54.2)[1]



Number of patients at risk:

308	209	80	25	8	1

54.2%
estimated PFS rate at 4 years

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

Adapted from Rajkovic-Hooley O, *et al.* 2022.[1]

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

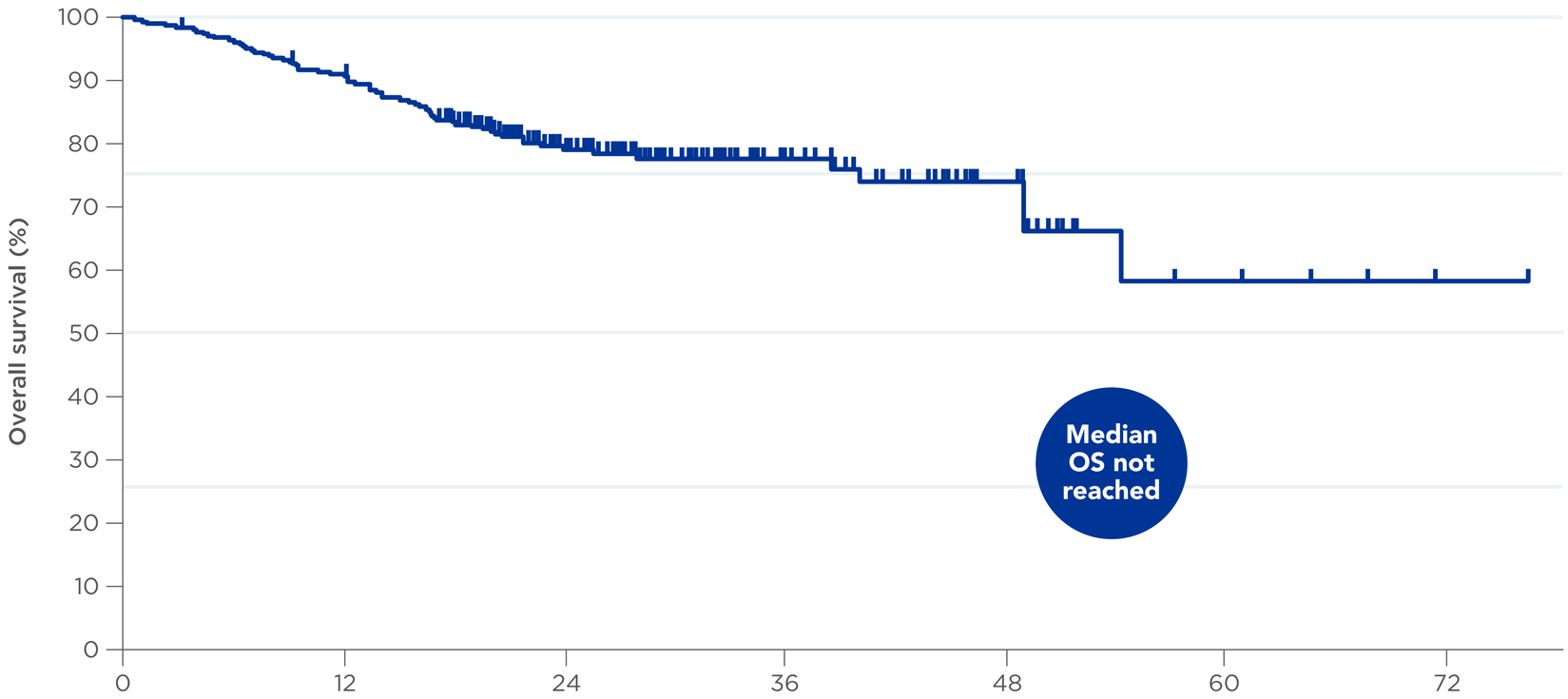
Limitations: The results of this real-world study should be interpreted with caution because of the potential for selection bias, since the study patient cohort represents only practices of physicians who agreed to participate in the study, and potential loss to follow-up during study period. Differences in outcome assessment schedules and criteria used among participating oncologists were expected in real-world clinical practice. No final conclusions for the overall US DTC population should be drawn.

CI: confidence interval, **PFS:** progression-free survival.

Reference: 1. Rajkovic-Hooley O, *et al.* Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

Real-world OS with **LENVIMA®** treatment in RAI-R DTC patients[1]

Median OS was not-reached[1]



Number of patients at risk:

306	276	132	49	21	5	1

57.0%
estimated OS rate at 6 years

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

Adapted from Rajkovic-Hooley O, *et al.* 2022.[1]

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

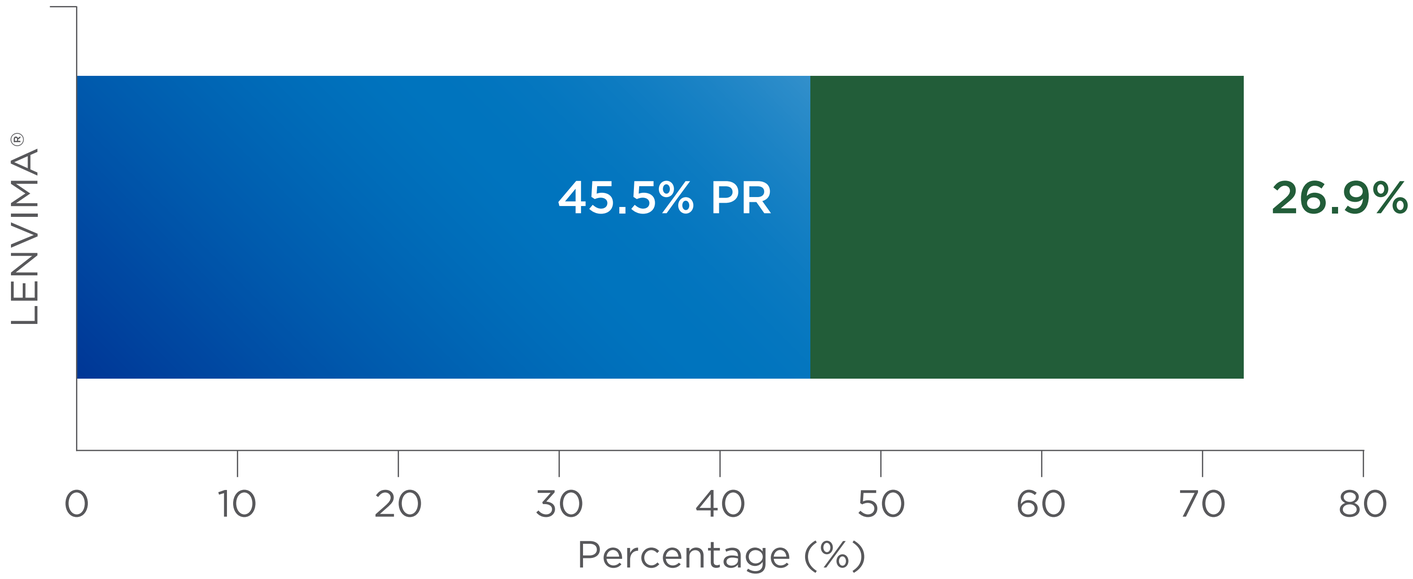
Limitations: The results of this real-world study should be interpreted with caution because of the potential for selection bias, since the study patient cohort represents only practices of physicians who agreed to participate in the study, and potential loss to follow-up during study period. Differences in outcome assessment schedules and criteria used among participating oncologists were expected in real-world clinical practice. No final conclusions for the overall US DTC population should be drawn.

OS: overall survival.

Reference: 1. Rajkovic-Hooley O, *et al.* Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

Real-world physician-reported best overall responses with **LENVIMA®** treatment in RAI-R DTC patients[1]

Real-world disease control rate: 90.6% of patients achieved physician-reported CR, PR or SD[1]



72.4%
physician-reported BOR LENVIMA®[1]

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

BOR defined as sum of CR + PR.

BOR and progression were based on the physician-reported information available in the patient's medical record.

Limitations: The results of this real-world study should be interpreted with caution because of the potential for selection bias, since the study patient cohort represents only practices of physicians who agreed to participate in the study, and potential loss to follow-up during study period. Differences in outcome assessment schedules and criteria used among participating oncologists were expected in real-world clinical practice. No final conclusions for the overall US DTC population should be drawn.

BOR: best overall response, **CR:** complete response, **PR:** partial response, **RECIST:** Response Evaluation Criteria in Solid Tumours, **SD:** stable disease.

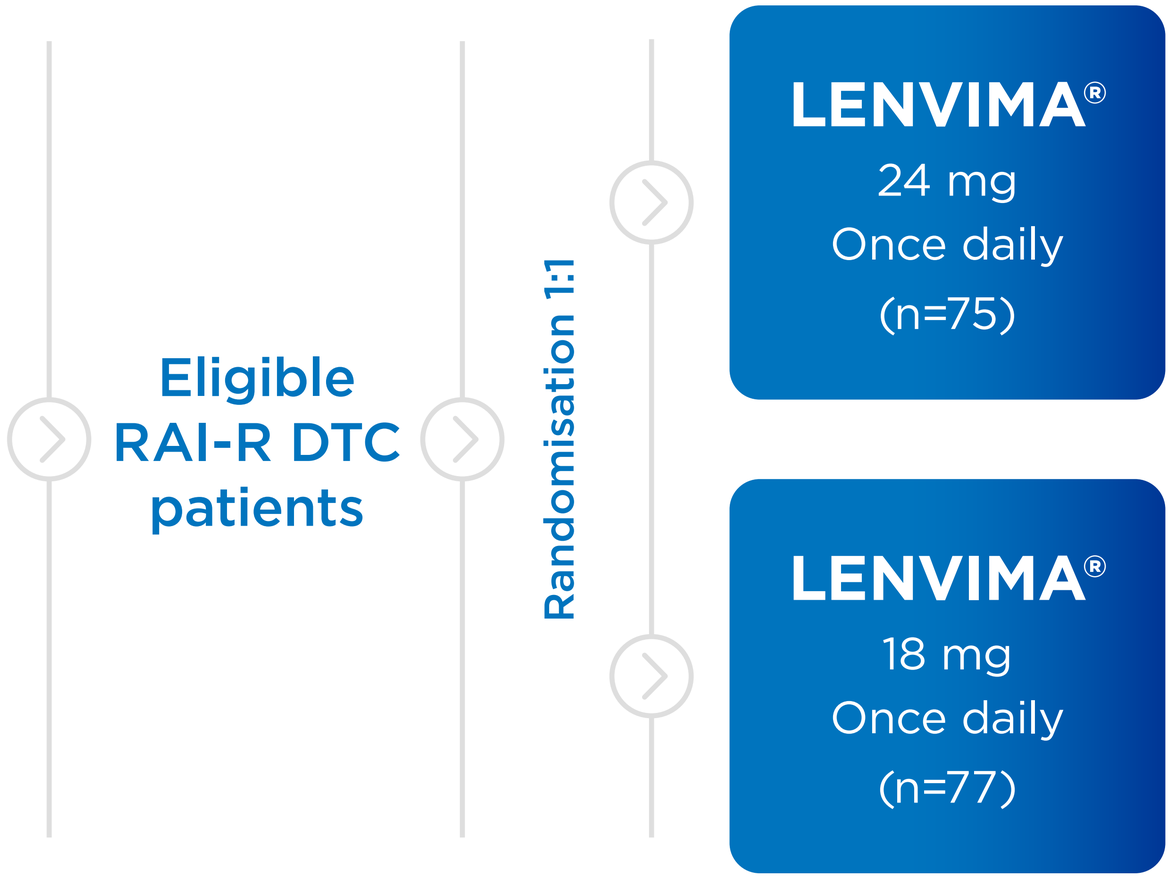
Reference: 1. Rajkovic-Hooley O, *et al.* Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

LENVIMA® 24 mg/day confirmed as the appropriate starting dose[1]

Study 211 was a randomised, double-blind, multicentre trial to compare the efficacy and safety of LENVIMA® at a starting dose of 24 mg vs 18 mg in RAI-R DTC patients

Study background

- This dose confirmation, non-inferiority study evaluated whether a starting dose of LENVIMA® 18 mg once daily provided comparable efficacy to the licensed 24 mg starting dose, but had a better safety profile
- Post-marketing requirement for the FDA, Canada, EMA, South Korea
- All tumour assessments were per investigator assessment



Study 211 included a non-approved dosing regimen (18 mg), which is included in this section for context and to confirm licensed dosing (24 mg).

ORR defined as sum of CR + PR.

CR: complete response, **EMA:** European Medicines Agency, **FDA:** Food and Drug Administration, **ORR:** objective response rate, **PFS:** progression-free survival, **PFS2:** progression-free survival after next line of anticancer treatment, **PR:** partial response, **TEAEs:** treatment-emergent adverse events.

Reference: 1. Brose MS, *et al. J Clin Endocarinol Metab* 2022;107(3):776–787.

LENVIMA® dosing

The recommended daily dose of LENVIMA® is **24 mg taken once daily**[1]

Recommended daily dose	First dose reduction	Second dose reduction	Third dose reduction
24 mg orally once daily	*20 mg orally once daily*	*14 mg orally once daily*	*10 mg orally once daily*
			

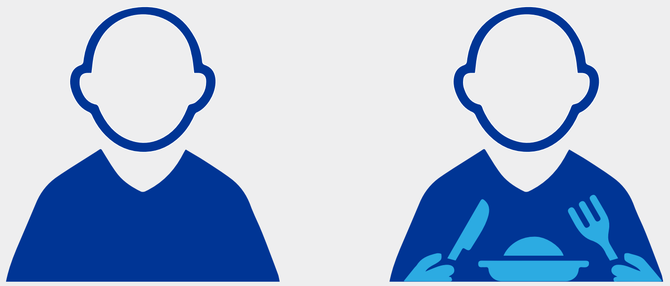
Dose reductions are an important part of maintaining therapy:[2]

- Most patients (68%) in the SELECT study required a dose reduction
- Mean dose of LENVIMA® throughout the study was 17.2 mg per day

References: 1. LENVIMA® product labelling. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

LENVIMA® administration

Orally, once daily, at the same time each day[1]



With or without food[1]

Swallowed whole with water or dissolved in a tablespoon of water or apple juice[1]

For patients with difficulty swallowing the capsules whole:[1]

LENVIMA® capsules can be dissolved in a small glass of liquid. Patients should measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. The capsules should be left in the liquid for at least 10 minutes. Patients should stir for at least 3 minutes, then they may drink the mixture. After drinking, patients should add 1 tablespoon of water or apple juice to the glass and stir the contents a few times before swallowing the additional liquid.

Reference: 1. LENVIMA® product labelling.

[Local markets to adapt per local label]

Adverse events[1]

- The most frequently reported adverse reactions (occurring in ≥30% of patients) are hypertension (68.6%), diarrhoea (62.8%), decreased appetite (51.5%), decreased weight (49.1%), fatigue (45.8%), nausea (44.5%), proteinuria (36.9%), stomatitis (35.8%), vomiting (34.5%), dysphonia (34.1%), headache (34.1%) and PPES (32.7%)[1]
- The most important serious adverse reactions were renal failure and impairment (2.4%), arterial thromboembolisms (3.9%), cardiac failure (0.7%), intracranial tumour haemorrhage (0.7%), PRES/RPLS (0.2%), hepatic failure (0.2%), and arterial thromboembolisms (cerebrovascular accident (1.1%)), transient ischaemic attack (0.7%), and myocardial infarction (0.9%)[1]

LENVIMA® -related AEs were predictable and manageable[2]

SELECT study AEs[2]

AEs[1,2]	LENVIMA® (n=261)		Placebo (n=131)	
Any treatment-related adverse event–no. of patients (%)	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
	254 (97.3)	198 (75.9)	78 (59.5)	13 (9.9)
Adverse effect developing during treatment–no. of patients (%)				
Serious Total Treatment-related	130 (49.8) 79 (30.3)		30 (22.9) 8 (6.1)	
Fatal Total Treatment-related	20 (7.7) 6 (2.3)		6 (4.6) 0	
Adverse effect developing during treatment–no. of patients (%)				
Hypertension	67.8	41.8	9.2	2.3
Diarrhoea	59.4	8.0	8.4	0
Fatigue/asthenia	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
PPES	31.8	3.4	0.8	0
Proteinuria	31.0	10.0	1.5	0
Vomiting	28.4	1.9	6.1	0
Headache	27.6	2.7	6.1	0
Dysphonia	24.1	1.1	3.1	0
Arthralgia	18.0	0	0.8	0
Dysgeusia	16.9	0	1.5	0
Rash	16.1	0.4	1.5	0

Click here to see the SELECT study AE table in more detail

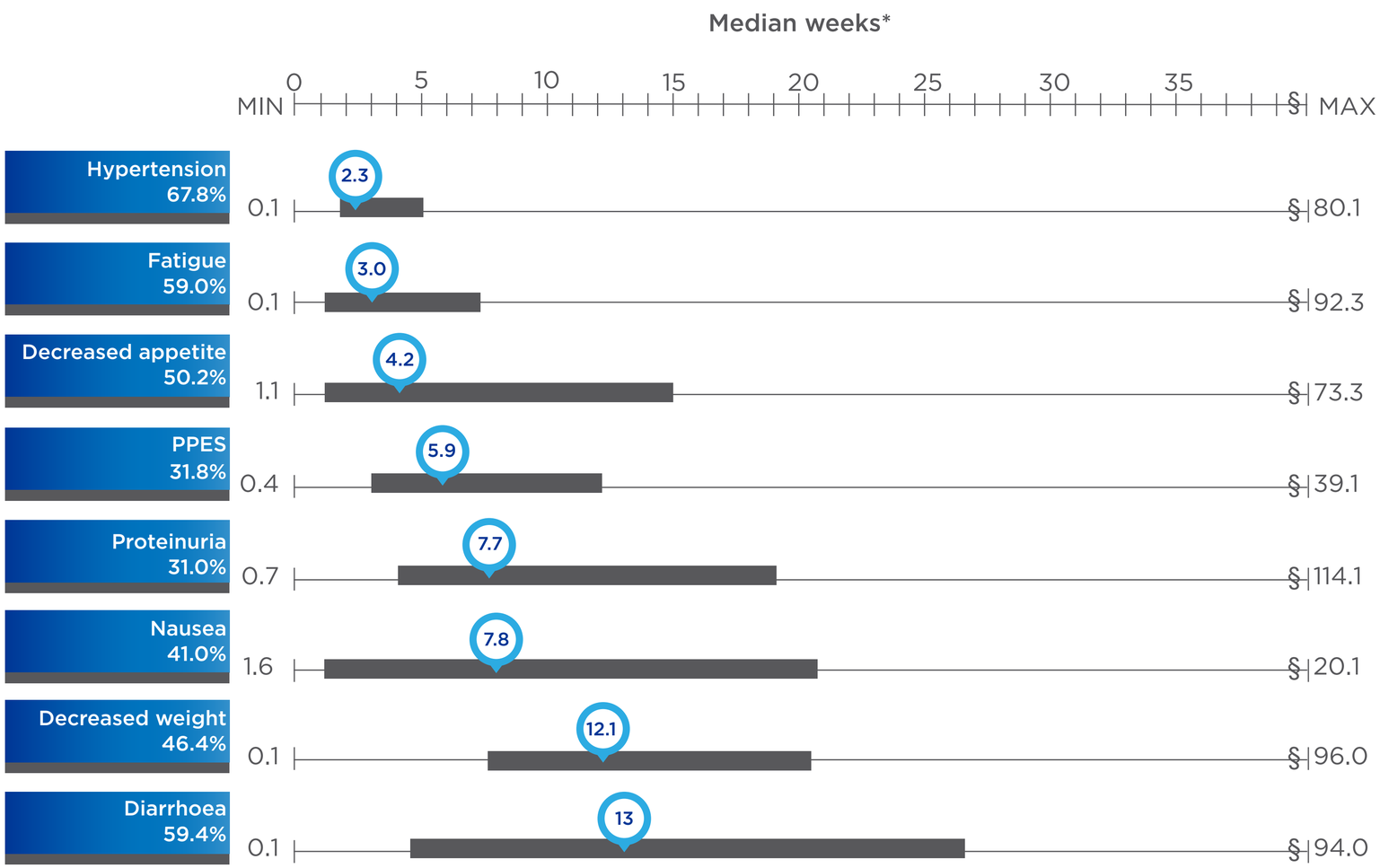
- The most common AEs (≥1%) resulting in discontinuation of **LENVIMA®** were hypertension (1.1%) and fatigue/asthenia (1.1%).[1] The median treatment duration was 13.8 months for **LENVIMA®**[2]

AE: adverse event, **PPES:** palmar-plantar erythrodysesthesia syndrome, **PRES:** posterior reversible encephalopathy syndrome, **RPLS:** reversible posterior leukoencephalopathy syndrome.

References: 1. LENVIMA® product labelling. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

Post hoc analysis of time to first onset of select AEs[1,2]

Monitor patients for AEs throughout treatment with LENVIMA®



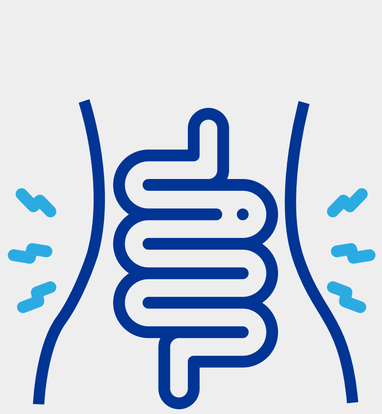
Limitation: This is a *post hoc* exploratory analysis for descriptive purposes only; no conclusions can be drawn.

*The bar represents the time to first onset of select AEs for the middle 50% of patients who experienced the AE from quartile 1 to 3.
AE: adverse event, **PPES:** palmar-plantar erythrodysesthesia syndrome.
References: 1. Eisai data on file. Lenvatinib AR Management Message Lexicon. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

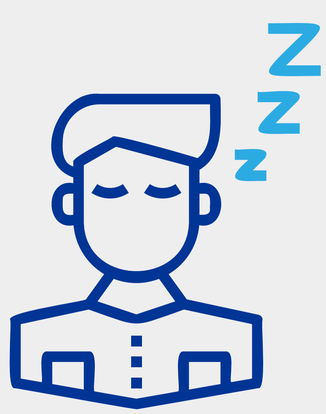
LENVIMA®-related AEs require anticipation and appropriate planning[1]

Appropriate supportive care, including timely identification of AEs, is essential to manage AEs associated with LENVIMA®, avoid longer dose interruptions, and maximise efficacy[2]

Hypertension



Diarrhoea



Fatigue

Each region to fill in appropriate AE management strategies relevant to their market

AE: adverse event.

References: 1. LENVIMA® product labelling. **2.** Wirth L, *et al. Oncologist* 2022;27(7):565–572.

Hypertension
Diarrhoea
Fatigue

Strategies to help manage hypertension[1]

Hypertension

- Hypertension occurred in 67.8% of patients receiving LENVIMA®[2]
- Grade ≥3 hypertension occurred in 41.8% of LENVIMA®-treated patients[2]

Hypertension Management Strategies

Control

- Control blood pressure prior to initiating LENVIMA®
- Educate patients on the importance of self-monitoring blood pressure

Monitor

- Monitor after 1 week of therapy
- Then every 2 weeks for the first 2 months
- Then at least monthly thereafter during treatment

Withhold

- Withhold for grade 3 that persists despite optimal antihypertensive therapy

Permanently discontinue

- Permanently discontinue for grade 4 hypertension

Resume

- Resume at reduced dose when hypertension is controlled at less than or equal to grade 2

AE: adverse event.

References: 1. LENVIMA® product labelling. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

How severity of hypertension is defined by grade[1]*

Grade 1	Systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg
Grade 2	Systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg; monotherapy indicated
Grade 3	Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

*As per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
BP: blood pressure, **WNL:** within normal limits.
References: 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed March 2023).

Strategies to help manage diarrhoea[1]

Diarrhoea

- Diarrhoea occurred in 59.4% of patients receiving LENVIMA®[2]
- Grade ≥3 diarrhoea occurred in 8.0% of LENVIMA®-treated patients[2]

Diarrhoea Management Strategies

Withhold

For persistent or intolerable grade 2 or 3 diarrhoea

- Withhold until improves to grade 0 to 1 or baseline

Resume

- Resume at reduced dose

Permanently discontinue

- Permanently discontinue for grade 4 diarrhoea

References: 1. LENVIMA® product labelling. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

How severity of diarrhoea is defined by grade[1]*

Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living
Grade 3	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated

*As per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

References: 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed March 2023).

Strategies to help manage fatigue[1]

Fatigue

- Fatigue occurred in 59.0% of patients receiving LENVIMA®[2]
- Grade ≥3 fatigue occurred in 9.2% of LENVIMA®-treated patients[2]

Fatigue Management Strategies

Withhold

For persistent or intolerable grade 2 or 3 fatigue

- Withhold until improves to grade 0 to 1 or baseline

Resume

- Resume at reduced dose

References: 1. LENVIMA® product labelling. **2.** Schlumberger M, *et al*. *N Engl J Med* 2015;372:621–630.

Hypertension
Diarrhoea
Fatigue

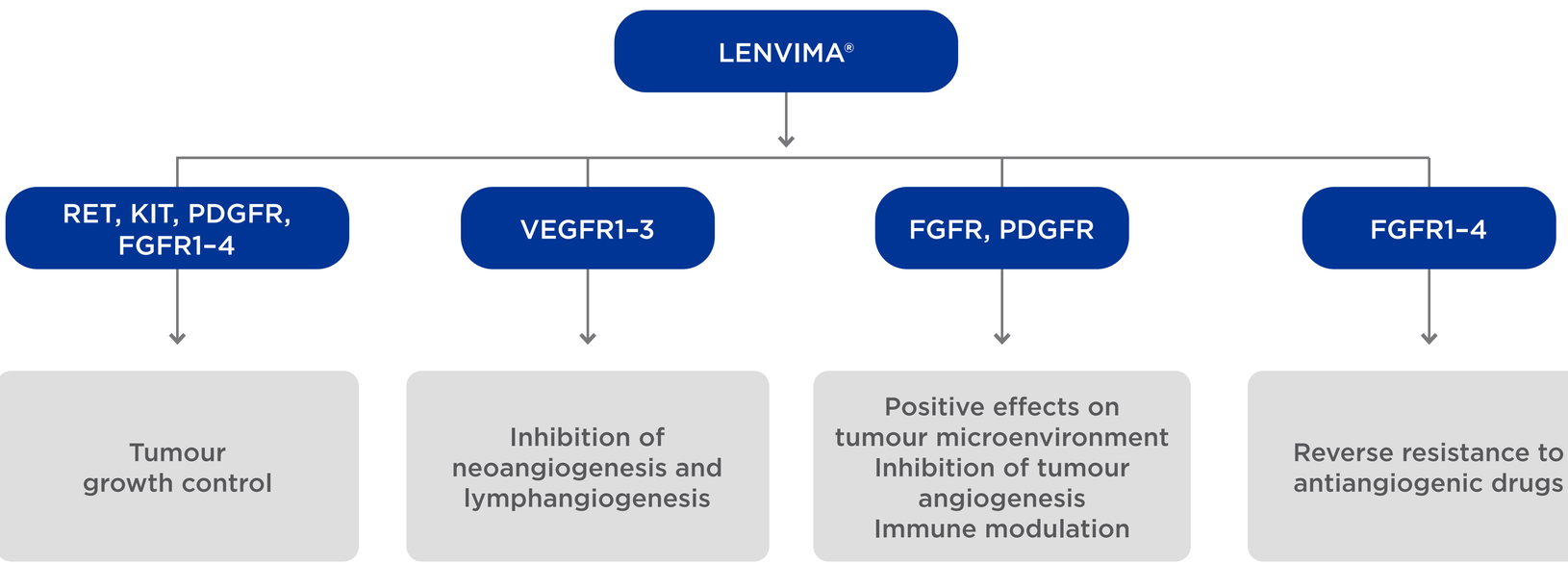
How severity of fatigue is defined by grade[1]*

Grade 1	Fatigue that can be relieved by rest
Grade 2	Fatigue not relieved by rest; limiting instrumental activities of daily living
Grade 3	Fatigue not relieved by rest, limiting self-care activities of daily living

*As per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

References: 1. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed March 2023).

LENVIMA®: the only approved TKI with FGFR1–4 and VEGFR1–3 inhibition[1–5]



LENVIMA®

has demonstrated a broad spectrum of antitumour activity including inhibition of FGFRs, VEGFRs and RET[1,2]

ATP: adenosine triphosphate; **FGFR:** fibroblast growth factor receptor; **PDGFR:** platelet-derived growth factor receptor; **RET:** rearranged during transfection, **TKI:** tyrosine kinase inhibitor, **VEGFR:** vascular endothelial growth factor receptor.

References: 1. LENVIMA® product labelling. **2.** Stjepanovic N, *et al. Biologics* 2014;8:129–139. **3.** Okamoto K, *et al. ACS Med Chem Lett* 2015;6:89–94. **4.** Matsuki M, *et al. Cancer Med* 2018;7:2641–2653. **5.** Tohyama O, *et al. J Thyroid Res* 2014; 2014:638747.

LENVIMA®: your TKI treatment of choice

LENVIMA® is the preferred systemic therapy option for the treatment of patients with RAI-R DTC by the NCCN[1]

- **Superior PFS benefit vs placebo[2]**
  18.3 months vs 3.6 months, HR: 0.21, 99% CI: 0.14–0.31; *P*<0.001
- **Superior response vs placebo[2]**
  64.8% ORR (including a 1.5% CR) vs 1.5% ORR (no CR), OR: 28.7, 95% CI: 12.46–66.86; *P*<0.001
- **OS improvement in patients aged over 65 years with RAI-R DTC[3]***
- **Long survival in patients with an ECOG performance status of 0 or small lung metastases[4,5]**
- **24 mg/day is the appropriate starting dose[6]**
- **Predictable and manageable AE profile[2]**
- **Findings from phase 3 trials are supported by real-world data[7,8]**

*Prespecified subgroup analysis.

ORR defined as sum of CR + PR.

AE: adverse event, **CI:** confidence interval, **CR:** complete response, **ECOG:** Eastern Cooperative Oncology Group, **HR:** hazard ratio, **ITT:** intention to treat, **NCCN:** National Comprehensive Cancer Network, **NE:** not estimable, **ORR:** objective response rate, **OS:** overall survival, **TKI:** tyrosine kinase inhibitor.

References: 1. NCCN. Thyroid carcinoma. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (accessed March 2023). **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630. **3.** Brose MS, *et al. J Clin Oncol* 2018;36: erratum DOI 10.1200/JCO.2018.78.0940. **4.** Tahara M, *et al. Ann Oncol* 2019;30 (suppl 5):v756–v759. **5.** Wirth LJ, *et al. J Clin Oncol* 2019;37 (suppl 15):6081–6081. **6.** Brose MS, *et al.* J *Clin Endocrinol Metab* 2022;107(3):776–787. **7.** Kish JK, *et al. Adv Ther* 2020;37(6):2841–2852. **8.** Rajkovic-Hooley O, *et al.* Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

[Each region to fill in local product labelling and appropriate contact information]

Please report Adverse Events or request
Medical Information from your
Medical Department

Definition of RAI-R DTC in SELECT

In the SELECT study, patients were eligible for enrolment if they had measurable, pathologically confirmed DTC and evidence of RAI-R disease according to at least 1 of the following criteria:[1]

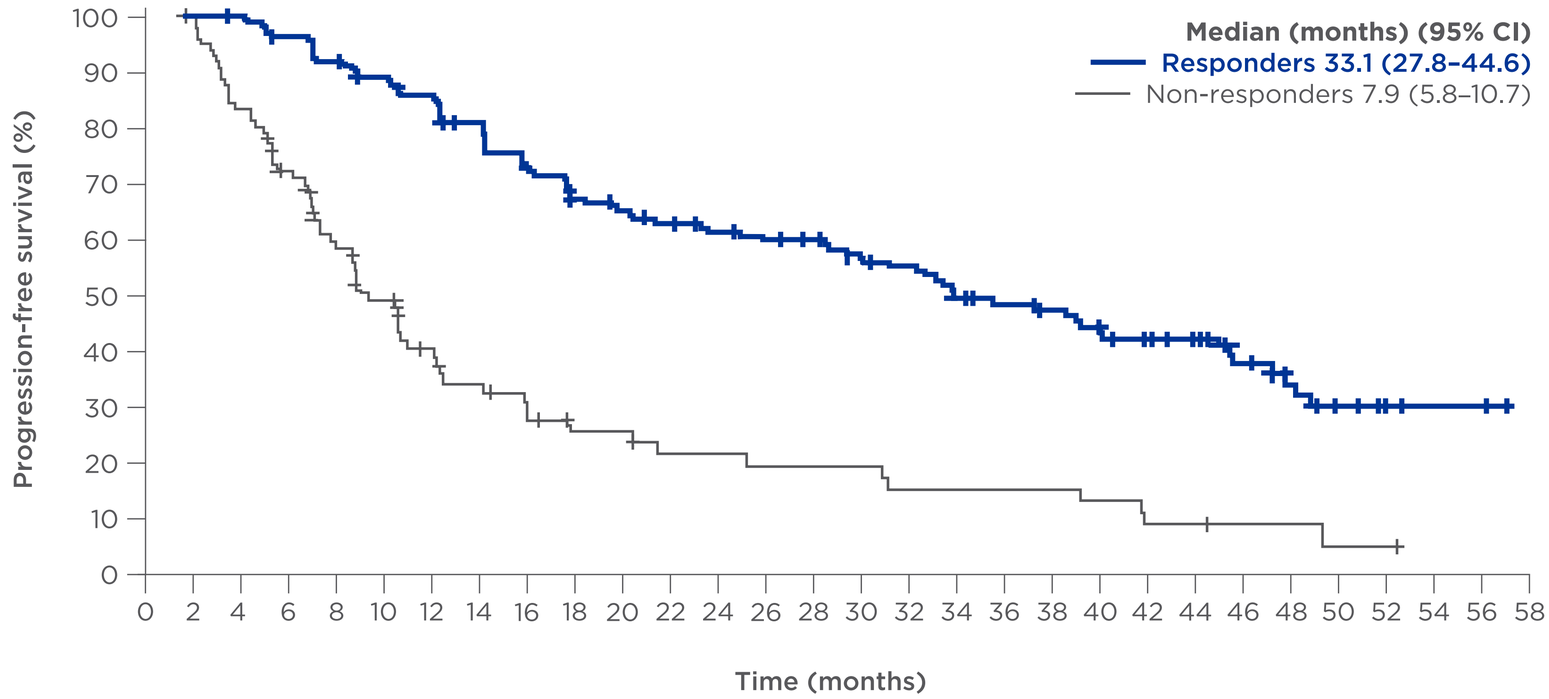
- At least 1 measurable lesion without iodine uptake on any ^{131}I scan
- At least 1 measurable lesion that had progressed according to RECIST version 1.1 criteria within 12 months after ^{131}I therapy despite ^{131}I avidity at the time of treatment
- Or cumulative activity of ^{131}I that was >600 mCi

RECIST: response evaluation criteria in solid tumours.

Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

SELECT STUDY DESIGN

LENVIMA® delivers a durable PFS in responders[1]



Number of patients at risk:

Responders

157	**155**	**148**	**141**	**132**	**126**	**117**	**109**	**102**	**93**	**86**	**84**	**79**	**77**	**73**	**68**	**66**	**53**	**50**	**47**	**41**	**37**	**33**	**23**	**16**	**9**	**6**	**2**	**2**	**0**

Non-responders

104	77	60	47	36	27	21	19	15	13	11	10	10	9	9	9	7	7	7	7	6	3	3	2	2	1	1	0	0	0

With **LENVIMA®**

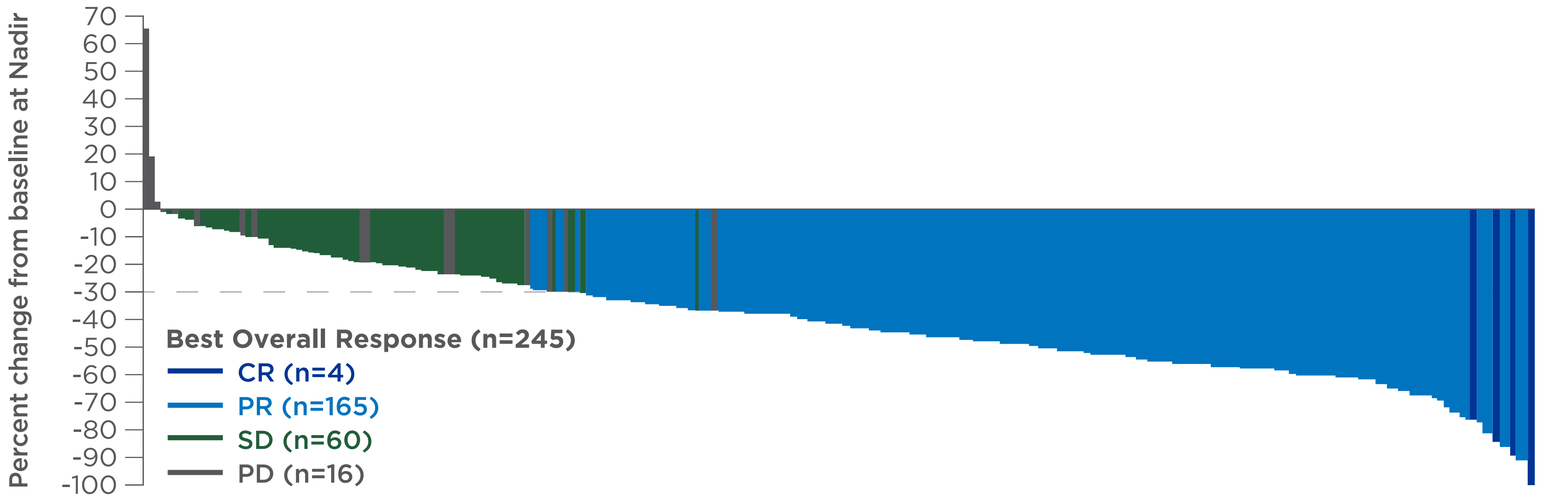
33.1-month
median PFS in LENVIMA® responders vs 7.9 months in non-responders[1]

60.2%
ORR with LENVIMA® in this analysis
vs 2.3% with placebo[1]

Post hoc, exploratory, subgroup analysis.[1]
Responders were defined as patients who had a CR or PR as their best overall response.
CI: confidence interval, **CR:** complete response, **ORR:** objective response rate, **PFS:** progression-free survival, **PR:** partial response.
Reference: 1. Gianoukakis AG, *et al. Endocrine-Related Cancer* 2018;25:699–704.

LENVIMA® delivers tumour shrinkage[1]

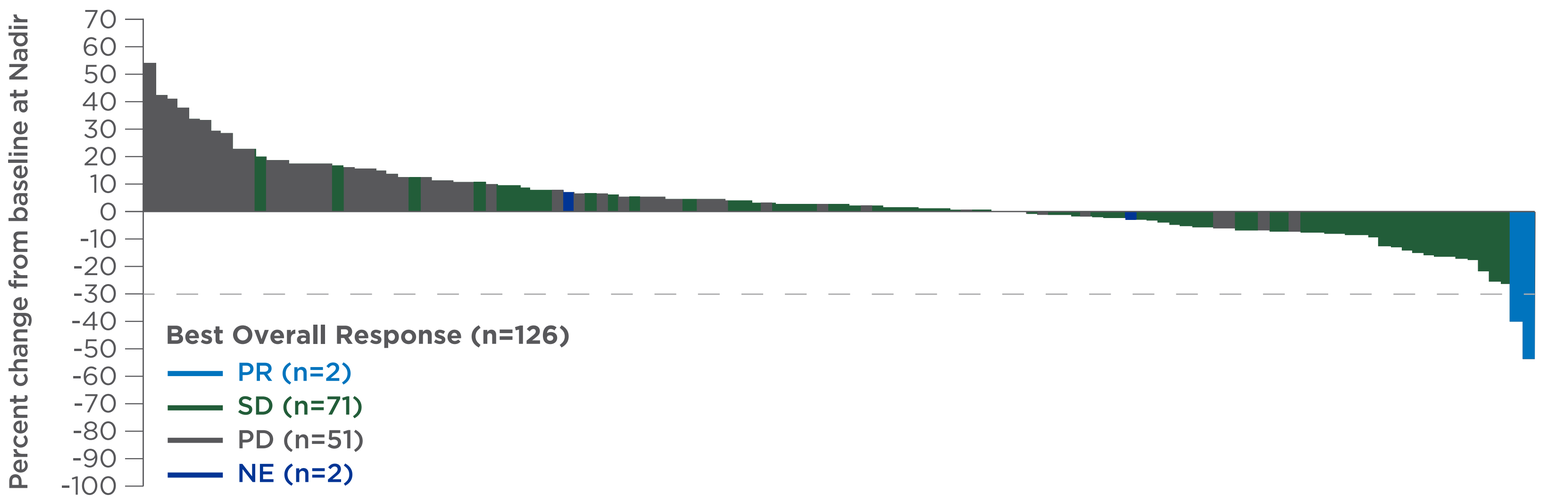
Treatment group: LENVIMA®



With **LENVIMA®**

~9 out of 10
patients experienced tumour shrinkage[1,2]

Treatment group: Placebo



169 patients
achieved an objective response
with LENVIMA® vs 2 patients with placebo[1]

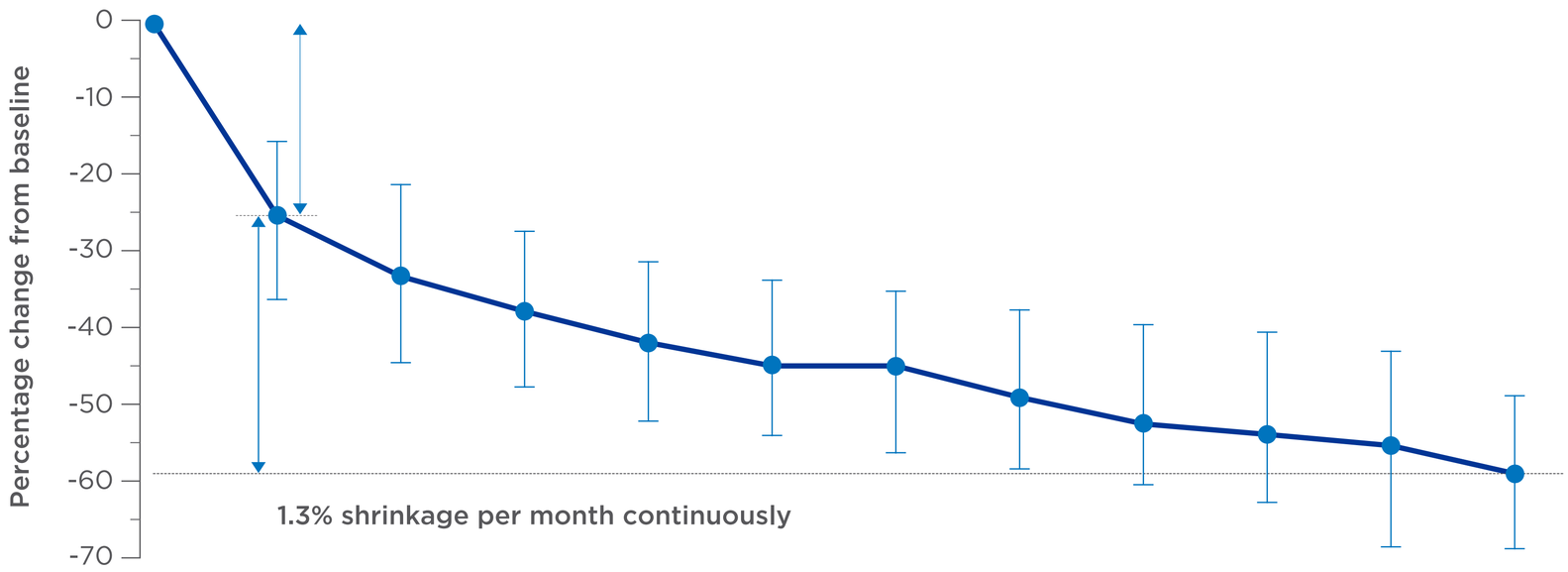
ORR defined as sum of CR + PR.

CR: complete response, **NE:** not estimable, **ORR:** objective response rate, **PD:** progressive disease, **PR:** partial response, **SD:** stable disease.

References: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630 (supplementary appendix). **2.** Brose MS, *et al. J Clin Oncol* 2018;36: erratum DOI 10.1200/JCO.2018.78.0940.

LENVIMA® demonstrated continuous tumour shrinkage over 88 weeks[1]

Average change in tumour size over time



Week

0	8	16	24	32	40	48	56	64	72	80	88

Patients evaluated, n:

261	241	219	193	176	157	146	135	92	64	44	25

With **LENVIMA®**

42.9%

median maximum percentage change in tumour size in all patients treated with LENVIMA® (responders and non-responders)[1]

25.2%

initial average reduction in tumour size at week 8 in all patients treated with LENVIMA®[1]

1.3%

per month average continuous reduction in tumour size after week 8 in all patients treated with LENVIMA®[1]

Post hoc, exploratory analysis.[1]

Responders were defined as patients who had a complete response or partial response as their best overall response.

Reference: 1. Robinson B, *et al. J Clin Endocrinol Metab* 2016;101(11):4103–4109.

30-month median duration of response among patients with an objective response on **LENVIMA®**[1]

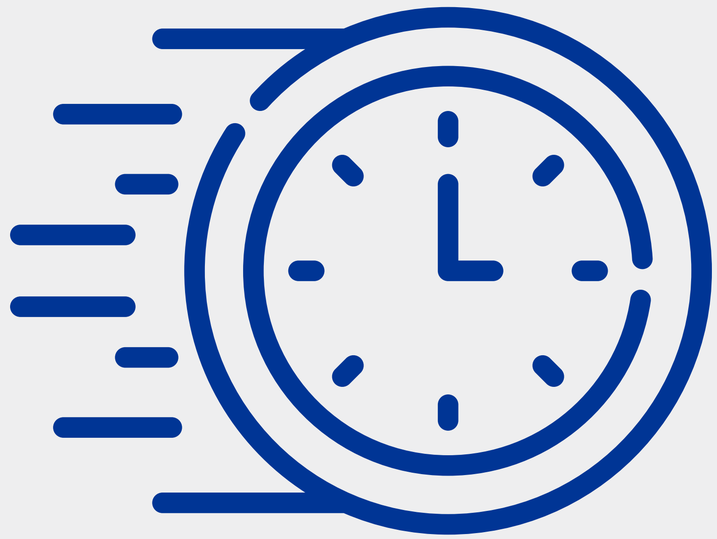
30 months

Post hoc, exploratory, subgroup analysis.[1]

Reference: 1. Gianoukakis AG, *et al. Endocr Relat Cancer.* 2018;25(6):699–704.

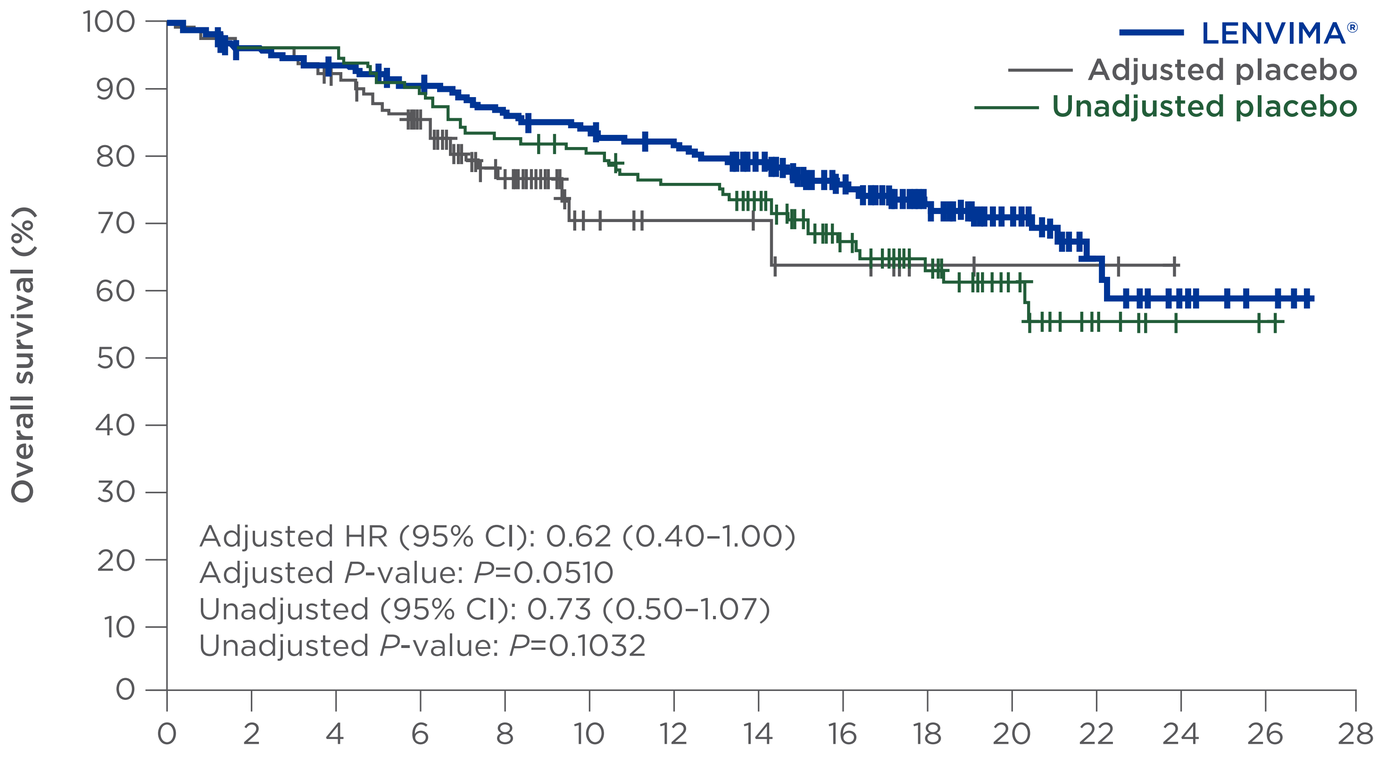
2-month median time to first objective response for patients on **LENVIMA®**[1]

2 months



Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

OS in the ITT population[1]



Number of subjects at risk:

LENVIMA®	261	248	239	230	219	211	203	169	114	78	55	22	10	3	0
Adjusted placebo	131	126	119	98	55	16	13	11	8	3	2	2	0	0	0
Unadjusted placebo	131	126	126	118	108	103	96	78	53	39	23	8	2	1	0

At the time of the primary analysis of SELECT, OS for LENVIMA® was not significantly prolonged in the ITT population[1]

83%
of patients crossed over from placebo to **LENVIMA®** which could have confounded the OS analysis[1]

In the overall population, there was no significant difference in overall survival between LENVIMA® and placebo.

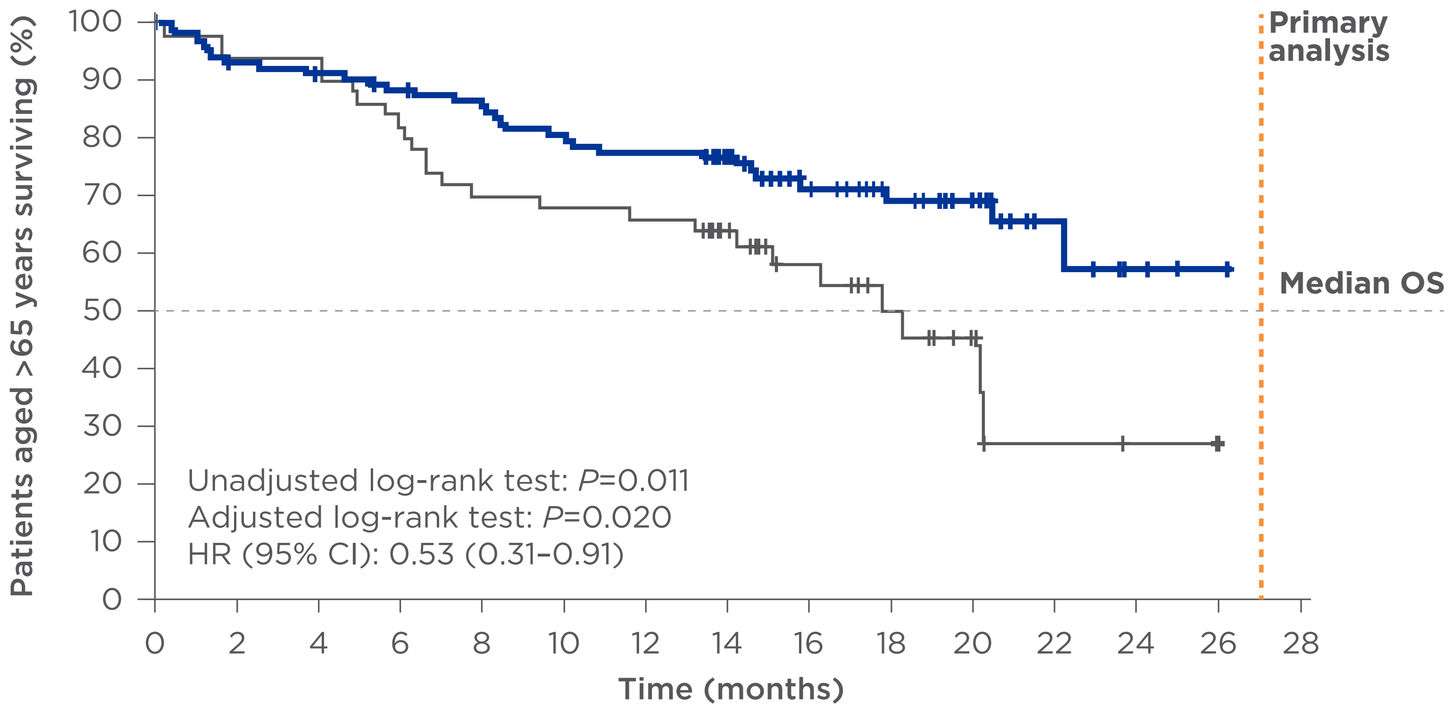
CI: confidence interval, **HR:** hazard ratio, **ITT:** intention to treat, **OS:** overall survival.

Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630 (supplementary appendix).

OS in patients >65 years[1]

47% reduction in the risk of death with LENVIMA® vs placebo[1]

Treatment	Total	Treatment failure	Censored	Median, months (95% CI)
LENVIMA®	106	31	75	NE (22.1–NE)
Placebo	50	25	25	18.4 (13.3–20.3)



Number of patients at risk:

LENVIMA®	106	98	95	91	88	82	79	67	42	31	24	8	4	1	0
Placebo	50	47	47	42	35	34	33	26	16	11	7	2	1	1	0

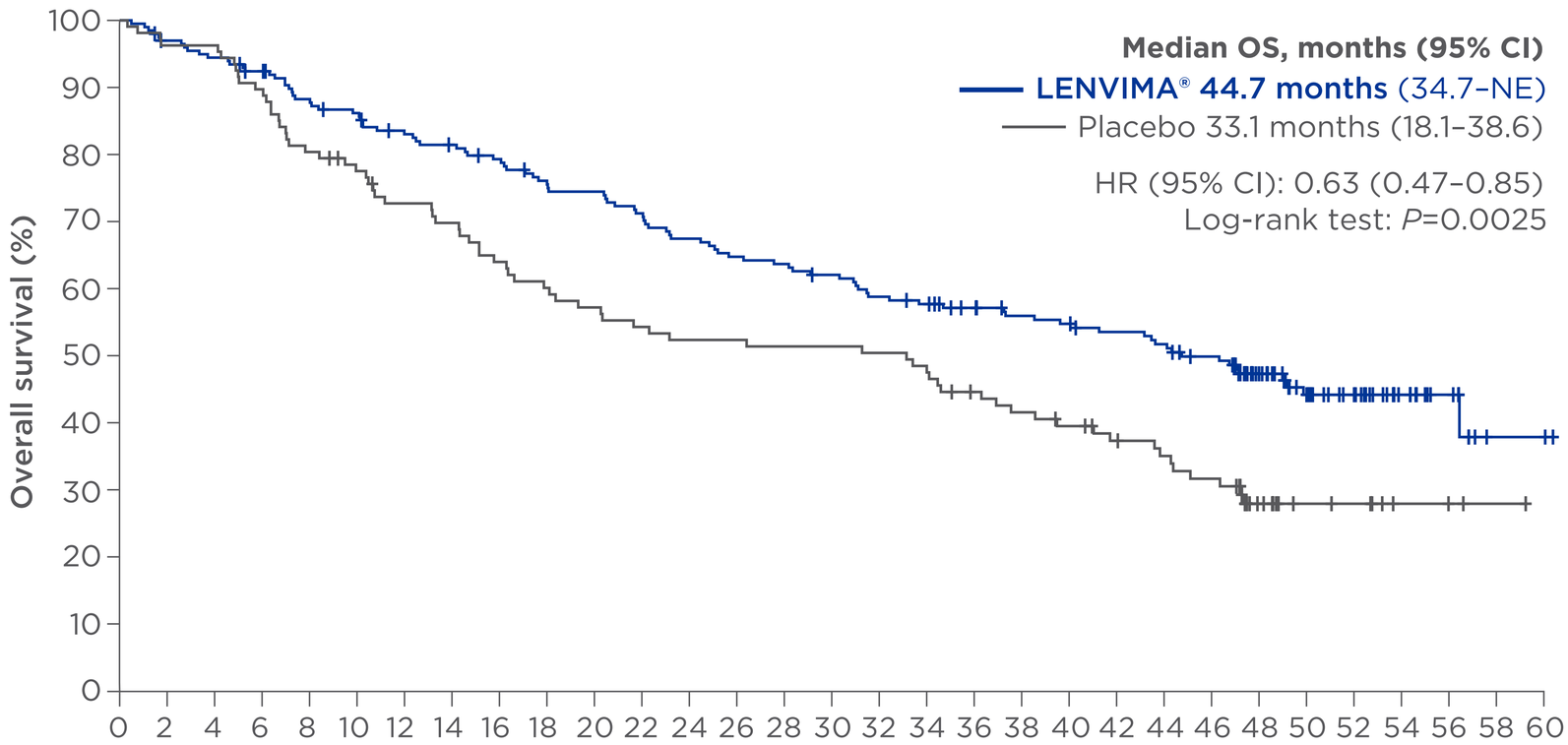
In the overall population, there was no significant difference in overall survival between LENVIMA® and placebo.

CI: confidence interval, **HR:** hazard ratio, **ITT:** intention to treat, **NE:** not evaluable, **OS:** overall survival.

Reference: 1. Brose MS, *et al. J Clin Oncol* 2018;36: erratum DOI 10.1200/JCO.2018.78.0940.

LENVIMA® demonstrated long OS in patients with lung metastases ≥1.0 cm[1]

Kaplan–Meier estimate of OS



Number of patients at risk:

LENVIMA®	199	191	186	180	170	165	157	153	148	141	138	132	125	120	118	114	108	105	99	94	92	88	85	79	55	40	31	18	10	2	2
Placebo	107	103	103	96	86	81	75	72	66	62	59	56	54	54	53	53	52	50	44	41	38	34	31	28	14	8	7	3	2	1	0

LENVIMA®

median OS
44.7 months
(95% CI: 34.7-NE)

vs placebo
median OS
33.1 months
(95% CI: 18.1-38.6)
11.7 additional months

Post hoc, exploratory, subgroup analysis.[1]

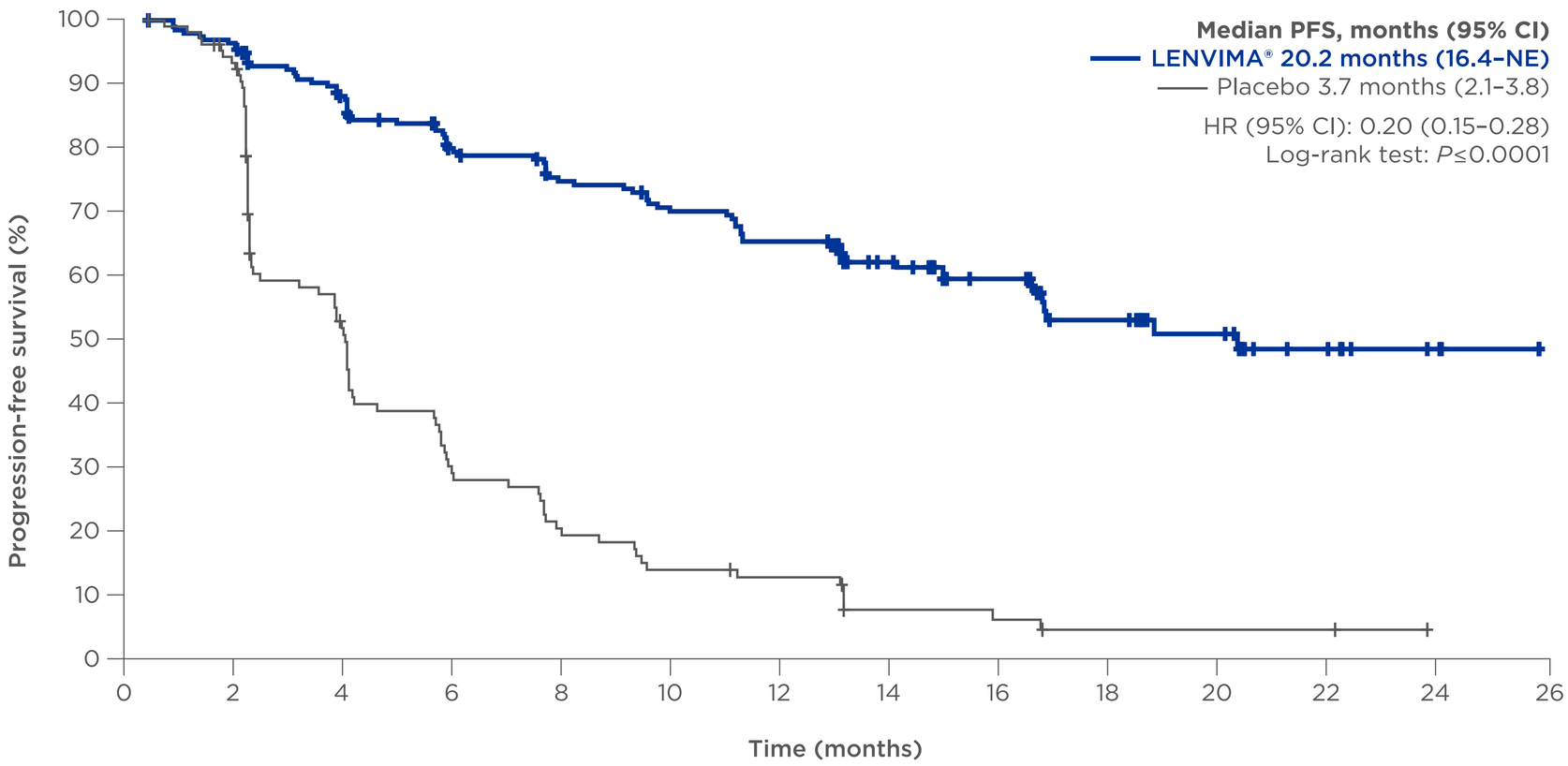
In the overall population, there was no significant difference in overall survival between LENVIMA® and placebo.[1]

CI: confidence interval, **HR:** hazard ratio, **NE:** not evaluable, **OS:** overall survival.

Reference: 1. Tahara M, *et al. Ann Oncol* 2019;30 (suppl 5):v756–v759.

LENVIMA® demonstrated long PFS in patients with lung metastases ≥1.0 cm[1]

Kaplan–Meier estimate of PFS



LENVIMA®

median PFS
20.2 months
(95% CI: 16.4–NE)

vs placebo
median PFS
3.7 months
(95% CI: 2.1–3.8)
16.5 additional months

Number of patients at risk:

LENVIMA®

199	176	154	137	125	117	109	74	55	36	22	9	3	0

Placebo

107	57	37	26	18	13	11	5	4	2	2	2	0	0

Post hoc, exploratory, subgroup analysis.[1]

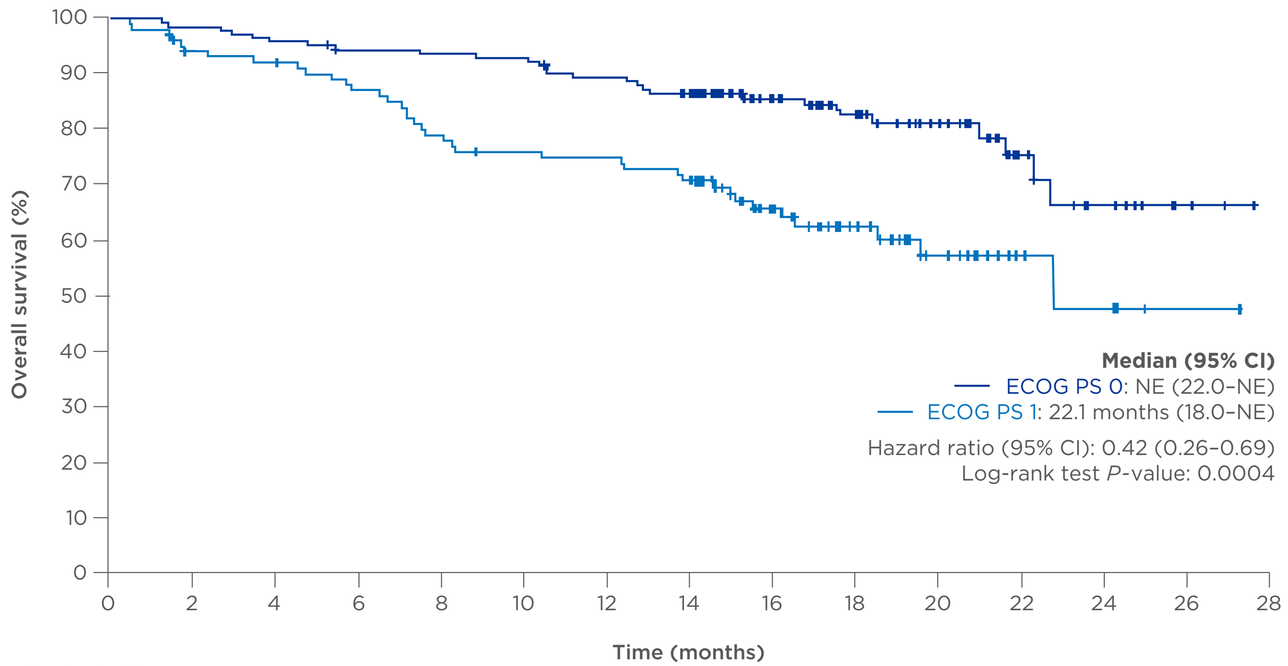
In the overall population, there was no significant difference in overall survival between LENVIMA® and placebo.[1]

CI: confidence interval, **HR:** hazard ratio, **ITT:** intention to treat, **NE:** not evaluable, **PFS:** progression-free survival.

Reference: 1. Tahara M, *et al. Ann Oncol* 2019;30 (suppl 5):v756–v759.

LENVIMA® patients with an ECOG performance status of 0 had longer median OS compared to patients with an ECOG performance status of 1[1]

Kaplan–Meier estimate of OS



Number of patients at risk:

ECOG PS 0	144	142	138	134	133	131	126	103	68	48	36	15	8	2
ECOG PS 1	104	95	91	86	133	131	72	61	42	27	16	6	2	1

These results may indicate that it is beneficial to start **LENVIMA®** early, before ECOG performance status worsens and tumour size increases[1]

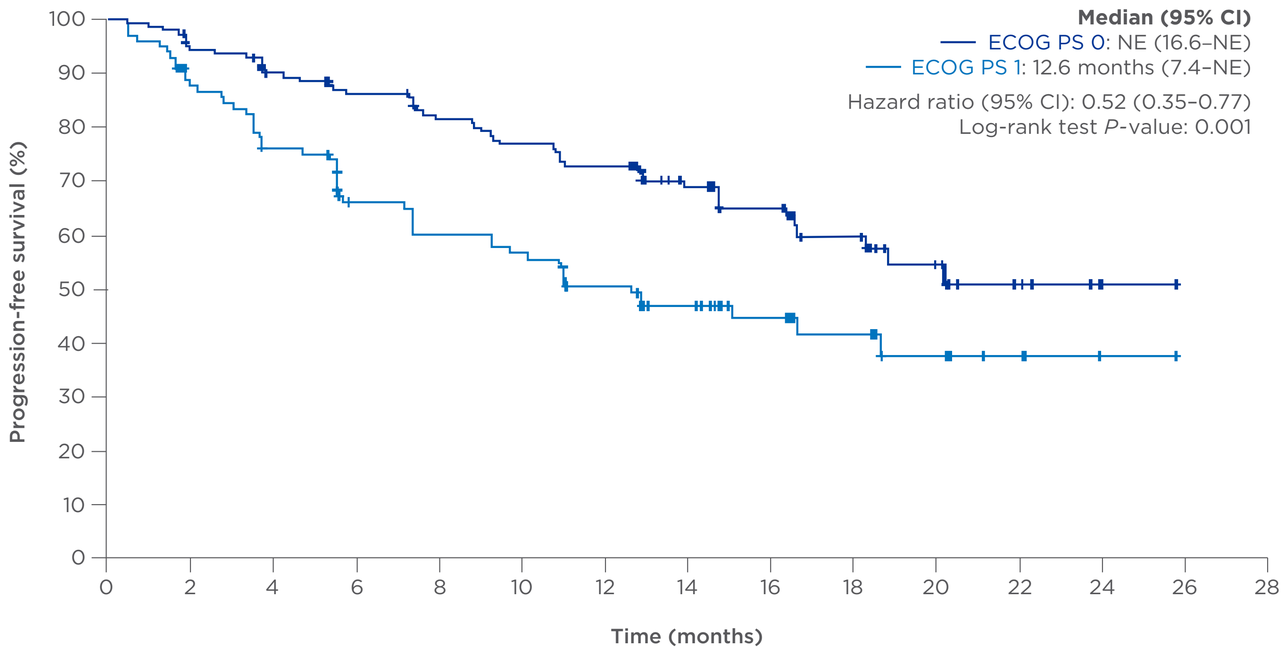
This post hoc, exploratory, subgroup analysis of the SELECT study examined the effect of baseline ECOG performance status and tumour size (sum of all targeted lesions) on the efficacy (PFS, OS, ORR, and time to ECOG ≥2) of LENVIMA®. AEs according to patients' ECOG performance status at baseline were also analysed.[1]

CI: confidence interval, **ECOG PS:** Eastern Cooperative Oncology Group performance status, **NE:** not estimable, **OS:** overall survival.

Reference: 1. Taylor MH, *et al. Thyroid.* 2021;31(8):1226–1234.

LENVIMA® patients with an ECOG performance status of 0 had longer median PFS compared to patients with an ECOG performance status of 1[1]

Kaplan–Meier estimate of PFS



Number of patients at risk:

ECOG PS 0	144	132	121	114	103	97	92	60	44	30	16	7	2	
ECOG PS 1	104	83	70	56	51	48	41	30	21	14	8	4	1	

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CI: confidence interval, **ECOG PS:** Eastern Cooperative Oncology Group performance status, **NE:** not estimable, **PFS:** progression-free survival.

Reference: 1. Taylor MH, *et al. Thyroid.* 2021;31(8):1226–1234.

Study limitations[1]

- As a retrospective observational study of secondary data from multiple sites, biases in provider participation, patient selection, and information may exist and impact the findings. Providers were not required to submit all patients treated by them or at their site; however, given the rarity of RAI-R DTC, the specificity of the selection criteria, and limiting providers to submitting a maximum of 10 cases, it is believed that this bias is minimal
- Second, radiology reports and images were not evaluated by an independent reviewer and inaccurate recording of tumour lesions by the patient's treating provider may have occurred
- Finally, the design inherently may create downwardly biased estimates of first-line PFS (requirement of failure of first-line therapy within the study period) and upwardly biased estimates of PFS for second-line therapy following first-line LENVIMA® (high rate of early censoring)
- In addition, although it is not included in this current study given the small sample size for most second-line agents, more data is warranted to assess the impact of patients' characteristics on the selection of second-line treatments

OS: overall survival, **PFS:** progression-free survival.

Reference: 1. Kish JK, *et al. Adv Ther* 2020;37:2841–2852.

Study limitations[1]

Potential provider selection bias: only oncologists who met the study eligibility criteria and consented to participate provided data for this study

- Efforts were made to minimise selection bias by recruiting a physician sample across all regions in the US and limiting the maximum number of providers per oncology practice

Potential patient selection bias: providers selected the eligible patients; they may not have included all the patients who could be eligible

- Efforts were made to minimise patient selection bias by allowing each physician to provide data for approximately 5 randomly selected patients

Differences in outcome assessment schedules and criteria used among participating oncologists were expected in real-world clinical practice

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

Reference: 1. Rajkovic-Hooley O, *et al*. Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

LENVIMA® treatment patterns in a real-world study in RAI-R DTC patients[1]

- By the end of follow-up, 32.1% of patients had discontinued LENVIMA® treatment, while 67.9% were still on therapy
- Median duration of LENVIMA® treatment was 17.5 months overall, 9.0 months in those who discontinued, and 20.2 months in those still on therapy
- Median time to discontinuation of LENVIMA® was 49.0 months (95% CI: 38.5–54.2) by Kaplan-Meier analyses
- Among the 99 patients who discontinued LENVIMA® treatment, the most common reasons were disease progression (36.4%) and death (32.3%)
- Among patients who discontinued LENVIMA®, 19 initiated a 2nd line treatment (sorafenib and cabozantinib were the most common)
- 10.4% of patients required dose change or interruption (increase, decrease, or treatment break) during LENVIMA® treatment

[This real-world data set includes 62% of patients initiated LENVIMA® at the recommended starting dose of 24 mg/day whilst 38% of patients received a lower starting dose between 14–20 mg/day. The 14–20 mg starting dose is not aligned to the Product Label. Countries will need to check with local compliance to see if this data set can be used in promotional materials.]

The licensed starting dose of LENVIMA® in RAI-R DTC is 24 mg/day. This study included patients who were initiated LENVIMA® at a lower starting dose. In this study, 38% of patients were initiated on a starting dose of 14–20 mg/day.

Limitations: The results of this real-world study should be interpreted with caution because of the potential for selection bias, since the study patient cohort represents only practices of physicians who agreed to participate in the study, and potential loss to follow-up during study period. Differences in outcome assessment schedules and criteria used among participating oncologists were expected in real-world clinical practice. No final conclusions for the overall US DTC population should be drawn.

CI: confidence interval.

Reference: 1. Rajkovic-Hooley O, *et al*. Real-world treatment patterns and clinical outcomes in radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) patients treated with lenvatinib monotherapy. Poster presentation at ATA; 19th–23rd October 2022; Montreal, Canada; Poster no. 359.

LENVIMA® 24 mg/day confirmed as the appropriate starting dose[1]

A lower starting dose of 18 mg once daily failed to demonstrate non-inferiority by ORR_{wk24} vs 24 mg[1]

	LENVIMA® starting dose	
	24 mg (n=75)	18 mg (n=77)
Best overall response as of week 24, n (%)		
CR	0 (0.0)	0 (0.0)
PR	43 (57.3)	31 (40.3)
SD	27 (36.0)	36 (46.8)
PD	2 (2.7)	4 (5.2)
NE	3 (4.0)	6 (7.8)
ORR as of week 24, n (%)	43 (57.3)	31 (40.3)
(95% CI)	(46.1, 68.5)	(29.3, 51.2)
Difference [18 mg–24 mg] (%) (95% CI)	-17.1 (-32.7, -1.4)	
OR [18 mg/24 mg] (95% CI)	0.50 (0.26, 0.96)	

Significant

17.1%

improvement in ORR_{wk24} for LENVIMA® dose starting of 24 mg vs 18 mg[1]

57.3% vs 40.3% (OR: 0.50, 95% CI: 0.26–0.96)[1]

- ORR for 24 mg arm (57.3% as of week 24; 64% overall) was consistent with that seen in the SELECT trial[1,2]
- PFS for the 24 mg arm was numerically better than the 18 mg arm[1]

Study 211 included a non-approved dosing regimen (18 mg), which is included in this section for context and to confirm licensed dosing (24 mg).

ORR defined as sum of CR + PR.

CI: confidence interval, **CR:** complete response, **NE:** not estimable, **OR:** odds ratio, **ORR:** objective response rate, **PD:** progressive disease, **PR:** partial response, **SD:** stable disease.

References: 1. Brose MS, *et al. J Clin Endocrinol Metab* 2022;107(3):776–787. **2.** Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

LENVIMA® 24 mg/day confirmed as the appropriate starting dose[1]

The safety profiles of LENVIMA® at 24 mg once daily and 18 mg were comparable[1]

	LENVIMA® starting dose	
	24 mg (n=75) n (%)	18 mg (n=77) n (%)
Grade ≥3 TEAEs as of week 24	46 (61.3)	44 (57.1)
Hypertension	19 (25.3)	15 (19.5)
Proteinuria	5 (6.7)	4 (5.2)
Asthenia	2 (2.7)	4 (5.2)
Diarrhoea	2 (2.7)	2 (2.6)
Hyponatraemia	1 (1.3)	3 (3.9)
Lipase increased	2 (2.7)	2 (2.6)
Myalgia	1 (1.3)	3 (3.9)
Stomatitis	2 (2.7)	2 (2.6)
Vomiting	2 (2.7)	2 (2.6)

Similar incidence of grade ≥3 TEAEs at week 24 with 18 mg starting dose vs 24 mg[1]

61.3% vs 57.1% (difference: -4.2%, 95% CI: -19.8%–11.4%)[1]

- Dose reductions were higher in the 24 mg arm (69.3% vs 59.7%) compared to the 18 mg arm[1]
- Dose interruptions were similar between groups (64.0% in the 24 mg arm vs 66.2% in the 18 mg arm)[1]

Study 211 included a non-approved dosing regimen (18 mg), which is included in this section for context and to confirm licensed dosing (24 mg).

CI: confidence interval, **TEAEs:** treatment-emergent adverse events.

Reference: 1. Brose MS, *et al. J Clin Endocrinol Metab* 2022;107(3):776–787.

Study 211 - HRQoL was measured by patient-reported outcome instruments[1]

Summary of instruments used to measure HRQoL[1]

EQ-5D-3L instrument	FACT-G instrument
Subscales are HUI and VAS	**Includes a total score and 4 subscales**
5 Dimensions 1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression	**Subscales** 1. Physical well-being 2. Social/family well-being 3. Functional well-being 4. Emotional well-being
3 Levels 1. No problems 2. Some problems 3. Extreme problems	
Recall period: 'Today'	**Recall period: 7 days**
HUI is derived from the 5 dimensions using country-specific weights[a] • Calculated values range from 1 (perfect health) to <0 (worst health/death)[b] **VAS measures global health status** • Scale from 0 to 100, in which 100 is the 'best imaginable health state'	• Physical, social/family, and functional well-being scales are measured on a scale of 0 (worst) to 28 (best) • Emotional well-being scale is measured on a scale of 0 (worst) to 24 (best) • Total score is on a scale from 0 (worst) to 108 (best) • Higher values indicate better quality of life

Adapted from Taylor *et al.* 2023.[1]

[a]Country weights used in Study 211 were UK (patients from Belgium, Germany, Italy, France, and Russia), US (patients from Australia, Canada, and the US), and South Korea (patients from South Korea).

[b]The predictive value for HUI using the United States algorithm is -0.109 (worst health) to 1 (perfect health).

EQ-5D-3L: EuroQol 5-dimension 3-level scale, **FACT-G:** Functional Assessment of Cancer Therapy–General, **HUI:** health utilities index, **VAS:** visual analog scale.

Reference: 1. Taylor MH, *et al. Cancer Med* 2023;12(4):4332–4342.

HRQoL was similar between **LENVIMA®** 24 mg/day and 18 mg/day[1]

No statistically significant differences in mean scores between treatment arms for either EQ-5D or FACT-G HRQoL scores

- This is the first double-blind, randomised, multicentre trial to assess QoL outcomes with LENVIMA® in DTC[1]

Longitudinal change from baseline in overall least squares mean scores in HRQoL[1]

Scale	LS mean difference (95% CI)	LS mean difference *p*-value
	LENVIMA® 18 mg vs 24 mg	
EQ-5D-3L		
VAS	-0.42 (-4.88, 4.03)	0.8507
HUI	-0.02 (-0.07, 0.03)	0.4589
FACT-G		
Total score	0.47 (-3.45, 4.39)	0.8132
Physical well-being	0.48 (-0.95, 1.92)	0.5058
Social/family well-being	-0.10 (-1.54, 1.34)	0.8886
Emotional well-being	0.57 (-0.32, 1.46)	0.2076
Functional well-being	-0.28 (-1.74, 1.19)	0.7076

Adapted from Taylor *et al.* 2023.[1]

P-values for mean differences between least squares scores did not reach statistical significance

No significant differences were observed between the dosing arms in time to first deterioration or time to definitive deterioration for a HRQoL outcome. However, EQ-5D-VAS showed a trend in favour of the 24 mg arm (HR [18 mg/24 mg] 1.72; 95% CI 0.99–3.01)[1]

Study 211 included a non-approved dosing regimen (18 mg), which is included in this section for context and to confirm licensed dosing (24 mg).

CI: confidence interval, **EQ-5D-3L:** EuroQol 5-dimension 3-level scale, **FACT-G:** Functional Assessment of Cancer Therapy-General, **HRQoL:** health-related quality of life, **HUI:** health utilities index, **LS:** least squares, **VAS:** visual analog scale.

Reference: 1. Taylor MH, *et al. Cancer Med* 2023;12(4):4332–4342.

LENVIMA® dosing for special populations

Patients with **severe hepatic impairment** and **severe renal impairment** require an alternative starting dose[1]

Alternative starting dose
14 mg orally once daily

Severe hepatic impairment[1]

- In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily

Severe renal impairment[1]

- In patients with severe renal impairment, the recommended starting dose is 14 mg taken once daily

Further dose adjustments may be necessary on the basis of individual tolerability

Reference: 1. LENVIMA® product labelling.

Adverse events[1]

AEs	LENVIMA® (n=261)		Placebo (n=131)	
Any treatment-related adverse effect–no. of patients (%)	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
	254 (97.3)	198 (75.9)	78 (59.5)	*13 (9.9)*
Adverse effect developing during treatment–no. of patients (%)				
Serious				
Total	130 (49.8)		30 (22.9)	
Treatment-related	79 (30.3)		8 (6.1)	
Fatal				
Total	20 (7.7)		6 (4.6)	
Treatment-related	6 (2.3)		0	
Adverse effect developing during treatment–no. of patients (%)				
Hypertension	67.8	41.8	9.2	2.3
Diarrhoea	59.4	8.0	8.4	0
Fatigue/asthenia	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
PPES	31.8	3.4	0.8	0

AE: adverse event, **PPES:** palmar-plantar erythrodysesthesia syndrome.

Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.

Adverse events[1]

AEs	LENVIMA® (n=261)		Placebo (n=131)	
Any treatment-related adverse effect–no. of patients (%)	**Any Grade (%)**	**Grade ≥3 (%)**	**Any Grade (%)**	**Grade ≥3 (%)**
Proteinuria	31.0	10.0	1.5	0
Vomiting	28.4	1.9	6.1	0
Headache	27.6	2.7	6.1	0
Dysphonia	24.1	1.1	3.1	0
Arthralgia	18.0	0	0.8	0
Dysgeusia	16.9	0	1.5	0
Rash	16.1	0.4	1.5	0
Constipation	14.6	0.4	8.4	0
Myalgia	14.6	1.5	2.3	0
Dry mouth	13.8	0.4	3.8	0
Upper abdominal pain	13	0	3.8	0
Abdominal pain	11.5	0.4	0.8	0.8
Peripheral oedema	11.1	0.4	0	0
Alopecia	11.1	0	3.8	0
Dyspepsia	10.0	0	0	0
Oropharyngeal pain	10.0	0.4	0.8	0
Hypocalcaemia	6.9	2.7	0	0
Pulmonary embolism	2.7	2.7	1.5	1.5

AE: adverse event.

Reference: 1. Schlumberger M, *et al. N Engl J Med* 2015;372:621–630.