ORIGINAL ARTICLE

Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

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ABSTRACT

BACKGROUND

Lenvatinib, an oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, RET, and KIT, showed clinical activity in a phase 2 study involving patients with differentiated thyroid cancer that was refractory to radioiodine (iodine-131).

METHODS

In our phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131, we randomly assigned 261 patients to receive lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and 131 patients to receive placebo. At the time of disease progression, patients in the placebo group could receive open-label lenvatinib. The primary end point was progression-free survival. Secondary end points included the response rate, overall survival, and safety.

RESULTS

The median progression-free survival was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups. The response rate was 64.8% in the lenvatinib group (4 complete responses and 165 partial responses) and 1.5% in the placebo group (P<0.001). The median overall survival was not reached in either group. Treatment-related adverse effects of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (in 59.4%), fatigue or asthenia (in 59.0%), decreased appetite (in 50.2%), decreased weight (in 46.4%), and nausea (in 41.0%). Discontinuations of the study drug because of adverse effects occurred in 37 patients who received lenvatinib (14.2%) and 3 patients who received placebo (2.3%). In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related.

CONCLUSIONS

Lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival and the response rate among patients with iodine-131–refractory thyroid cancer. Patients who received lenvatinib had more adverse effects. (Funded by Eisai; SELECT ClinicalTrials.gov number, NCT01321554.)

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The 10-year survival rate among patients with differentiated thyroid cancer that is refractory to radioiodine (iodine-131) therapy is 10% from the time of detection of metastasis.[1-3] Although treatment options have historically been limited, efforts have first targeted vascular endothelial growth factor (VEGF) and its receptor (VEGFR), since this signaling network has been associated with the aggressiveness and metastasis of thyroid cancer.[4-6] However, other molecular pathways of tumor growth and maintenance beyond VEGF-driven angiogenesis contribute to the pathogenesis of thyroid cancer, including BRAF, NRAS, HRAS, RET/PTC, fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR).[7-16] Because of the involvement of these multiple pathways, multitargeted tyrosine kinase inhibitors are being investigated for the treatment of thyroid cancer that is refractory to iodine-131.[17-22] Recently, sorafenib, a tyrosine kinase inhibitor that inhibits VEGFRs 1, 2, and 3, PDGFR β, Raf-1, RET, and BRAF, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of iodine-131–refractory thyroid cancer on the basis of results of a phase 3 trial showing a 5-month improvement in median progression-free survival.[17]

Lenvatinib is an oral, multitargeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3, FGFRs 1 through 4, PDGFR α, RET, and KIT signaling networks.[23,24] On the basis of results observed in a phase 2 study involving patients with iodine-131–refractory thyroid cancer,[25] we conducted the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) to assess progression-free survival among patients with iodine-131–refractory thyroid cancer who received lenvatinib as compared with those who received placebo.

Methods

Patients

Patients were eligible for enrollment if they were 18 years of age or older and had measurable, pathologically confirmed differentiated thyroid cancer, evidence of iodine-131–refractory disease (according to at least one of the following criteria: at least one measurable lesion without iodine uptake on any iodine-131 scan, at least one measurable lesion that had progressed according to the Response Evaluation Criteria In Solid Tumors [RECIST], version 1.1, criteria within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment, or cumulative activity of iodine-131 that was >600 mCi), and independently reviewed radiologic evidence of progression within the previous 13 months. Eligible patients had received no prior therapy with a tyrosine kinase inhibitor or had received one prior treatment regimen with a tyrosine kinase inhibitor. Additional inclusion and exclusion criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Oversight

All patients provided written informed consent, and the study protocol was approved by all relevant institutional review bodies. The study was conducted in accordance with the provisions of the Declaration of Helsinki and local laws. The study was funded by Eisai and designed in collaboration with the principal investigators. Data collection and management were performed by Pharmaceutical Product Development (a contract research organization), and independent radiologic review was performed by VirtualScopics. Eisai statisticians performed the statistical analyses. All parties vouch for the accuracy and completeness of the data and analyses and for adherence to the study protocol. The first author wrote the manuscript with assistance from professional medical writers funded by Eisai. The study protocol, including the statistical analysis plan, is available at NEJM.org.

Study Design

In this phase 3, randomized, double-blind, placebo-controlled, multicenter study, we recruited patients across the Americas, Europe, Asia, and Australia from August 5, 2011, through October 4, 2012. Eligible patients were stratified according to age, geographic region, and receipt or nonreceipt of prior tyrosine kinase inhibitor treatment, and they were randomly assigned in a 2:1 ratio to receive oral lenvatinib (at a dose of 24 mg once daily) or placebo in 28-day cycles. Block randomization was performed centrally by means of an interactive voice-response and Web-response system.

Study drugs were administered by clinicians who remained unaware of the study-drug assignments until the occurrence of unacceptable toxic effects or disease progression as assessed by independent radiologic review. Dose interrup-

tions and incremental reductions in the dose (to 20 mg, 14 mg, or 10 mg per day) because of toxic effects were permitted (see the Supplementary Appendix). If independent radiologic review confirmed disease progression, the patients who were receiving placebo could elect to enter the open-label lenvatinib phase.

EFFICACY

The primary end point was progression-free survival, which was defined as the time from randomization to the first documentation of disease progression by independent radiologic review or to death, in the intention-to-treat population (all patients who underwent randomization). Secondary end points were the response rate (defined as the best objective response [complete or partial]) according to RECIST, version 1.1 (Table S1 in the Supplementary Appendix),[26] and overall survival, which was defined as the time from randomization until death from any cause. Exploratory efficacy assessments included the rate of disease control (defined as a complete or partial response or stable disease) and the rate of clinical benefit (defined as a complete or partial response or durable stable disease for ≥23 weeks). Progression-free survival and response-rate outcomes in the optional open-label lenvatinib phase were also assessed.

Tumor assessments, consisting of computed tomographic or magnetic resonance imaging of the neck, chest, abdomen, pelvis, and all other known sites of disease, were evaluated in a blinded fashion by a central imaging laboratory, according to RECIST, version 1.1, criteria, every 8 weeks in the randomization phase. Tumor assessments were performed every 12 weeks in the extension phase, but they were not independently reviewed. Data on patients who were lost to follow-up and on patients who were alive at the time of the primary analysis were censored on the latest date on which the patient was known to be alive.

SAFETY AND ADVERSE EFFECTS

Safety assessments were performed throughout the study and included recording of symptoms and vital signs, electrocardiography, echocardiography (including left ventricular ejection fraction), hematologic and biochemical laboratory testing, and urinalysis. Adverse effects were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[27] Specific management plans were required for hypertension and proteinuria (see the Supplementary Appendix).

BIOMARKER ANALYSES

Exploratory biomarker analyses were performed to investigate potential markers of lenvatinib efficacy. Available archival formalin-fixed, paraffin-embedded tissues were obtained and analyzed for *BRAF* and *RAS* mutation hotspots with the use of Ion Torrent Personal Genome Machine amplicon sequencing.

STATISTICAL ANALYSIS

The study was designed to have 90% power to detect a 75% improvement in progression-free survival with lenvatinib versus placebo (hazard ratio for progression or death, 0.57) at a two-sided alpha level of 0.01, assuming a median progression-free survival of 14 months in the lenvatinib group and 8 months in the placebo group. At least 214 progression events or deaths in 392 enrolled patients were required for the primary analysis of progression-free survival. The rates of progression-free and overall survival in the intention-to-treat population for the primary analysis were estimated and plotted with the use of the Kaplan–Meier method and compared with the use of the stratified log-rank test. The hazard ratio and 99% (and 95%) confidence intervals were estimated with the use of stratified Cox proportional-hazards regression. The rates of response, clinical benefit, and disease control were compared with the use of Cochran–Mantel–Haenszel tests at a two-sided alpha level of 0.05.

The analysis of progression-free survival was based on the FDA guidance for progression-free survival,[28] and prespecified sensitivity analyses for progression-free survival were performed. These analyses included investigator assessment and the treatment of all cases of progressive disease, deaths, crossovers, and the subsequent use of anticancer therapy as events. Subgroup analyses were performed according to age (≤65 years vs. >65 years), sex, geographic region (Europe, North America, or other), histologic findings (papillary, poorly differentiated, follicular, or Hürthle-cell thyroid cancer), thyrotropin level (≤0.5, >0.5 to 2.0, or >2.0 to 5.5 mIU per liter), and receipt or nonreceipt of one prior tyrosine kinase inhibitor treatment. The analysis of overall survival was reported both as unadjusted and as adjusted for a potential crossover bias with the use of the rank-preserving structural failure time (RPSFT) mod-

el (see the Supplementary Appendix).[29] Hazard ratios and 95% confidence intervals were estimated with the use of the bootstrap method, with the survival time corrected for crossover in the placebo group.

RESULTS

PATIENTS

Overall, 392 patients from 21 countries were randomly assigned to receive lenvatinib (261 patients) or placebo (131 patients) (Fig. 1). All the patients received treatment and were included in the efficacy and safety analyses. The baseline characteristics of the patients were similar in the two groups (Table 1). At the time of data cutoff (November 15, 2013), the median duration of follow-up was 17.1 months (95% confidence interval [CI], 16.0 to 17.6; interquartile range, 14.4 to 20.4) in the lenvatinib group and 17.4 months (95% CI, 15.9 to 19.0; interquartile range, 14.8 to 20.4) in the placebo group, and 130 patients were still continuing to receive blinded treatment (122 patients who were randomly assigned to lenvatinib [46.7%] and 8 patients who were randomly assigned to placebo [6.1%]). Among 114 eligible patients who received placebo and had tumor progression confirmed by independent review, 109 (95.6%) elected to receive open-label lenvatinib. Of the patients who were randomly assigned to lenvatinib, 41 (15.7%) subsequently received additional anticancer therapies after disease progression.

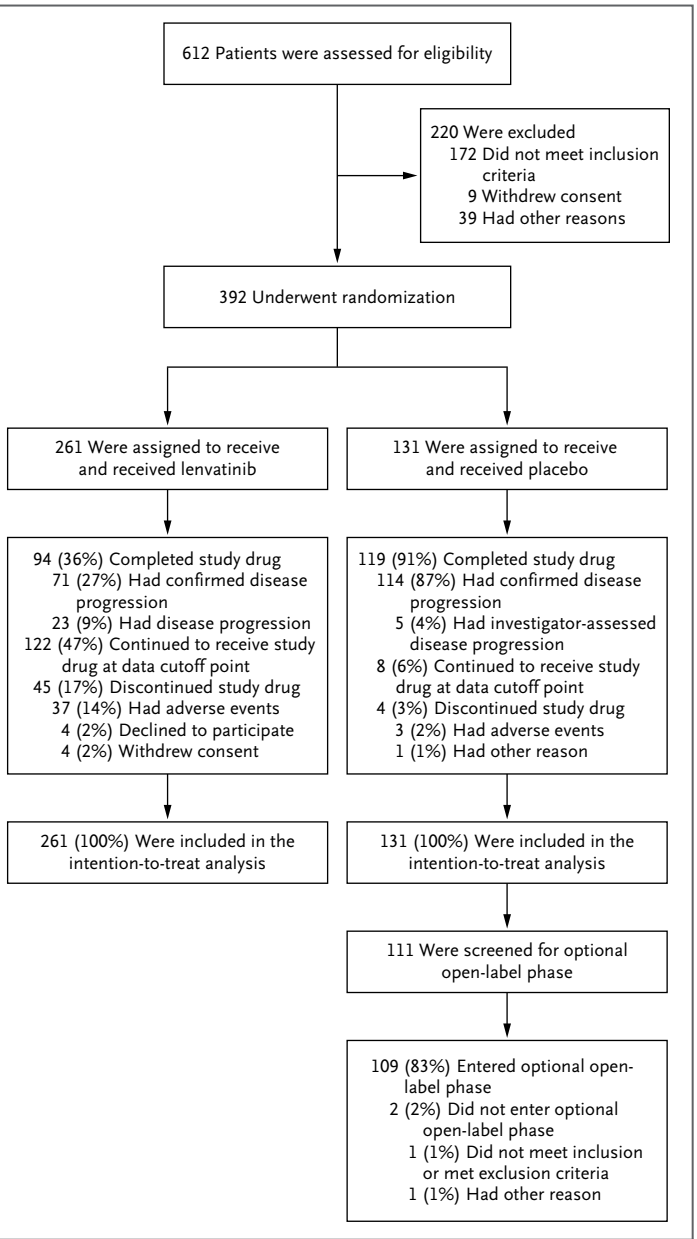

Figure 1. Enrollment, Randomization, and Treatment.

EFFICACY

At the time of the primary analysis of progression-free survival, there were 220 primary events: 202 patients had disease progression (93 [35.6%] in the lenvatinib group and 109 [83.2%] in the placebo group), and 18 patients had died before disease progression (14 in the lenvatinib group and 4 in the placebo group). The median progression-free survival was 18.3 months (95% CI, 15.1 to not estimable) with lenvatinib as compared with 3.6 months (95% CI, 2.2 to 3.7) with placebo (hazard ratio for progression or death, 0.21; 99% CI, 0.14 to 0.31; P<0.001) (Fig. 2). The 6-month progression-free survival rates were 77.5% in the lenvatinib group and 25.4% in the placebo group. Sensitivity analyses showed that a progression-free survival benefit associated with lenvatinib was maintained in all prespecified subgroups (i.e., subgroups defined according to age, sex, race or ethnic group, prior treatment or no prior treatment with a tyrosine kinase inhibitor, geographic region, histologic findings, and baseline thyrotropin levels) (Table 2, and Fig. S1 in the Supplementary Appendix). The median progression-free survival with lenvatinib was 18.7 months among patients who had not received previous treatment with a tyrosine kinase inhibitor and 15.1 months among those who had received one prior treatment regimen with a tyrosine kinase inhibitor (Fig. S1 and S2 in the Supplementary Appendix). A progression-free survival benefit

was observed in patients with thyroid cancer of all histologic types examined (papillary, poorly differentiated, follicular, and Hürthle-cell). Overall, 77 of 152 of patients (38 in the lenvatinib group and 39 in the placebo group) with baseline bone lesions (50.7%) had progressive disease at the time of data-collection cutoff. Progression of existing bone disease occurred in 9 of 38 patients in the lenvatinib group (23.7%) and in 23 of 39 patients in the placebo group (59.0%). Finally, the progression-free survival benefit associated with lenvatinib, as compared with placebo, was maintained regardless of the patient's *BRAF* or *RAS* mutation status (Fig. S1 in the Supplementary Appendix).

Lenvatinib was associated with significant improvement in the response rate (64.8% in the lenvatinib group vs. 1.5% in the placebo group; odds ratio, 28.87; 95% CI, 12.46 to 66.86; P<0.001) (Table 2, and Fig. S3 in the Supplementary Appendix). Complete responses occurred in 4 patients (1.5%) in the lenvatinib group as compared with no patients in the placebo group; partial responses occurred in 165 patients (63.2%) and 2 patients (1.5%), respectively; and durable stable disease for 23 weeks or longer occurred in 40 patients (15.3%) and 39 patients (29.8%), respectively. Progressive disease occurred in 18 patients (6.9%) in the lenvatinib group as compared with 52 patients (39.7%) in the placebo group. In all 4 patients who had a complete response, the response was maintained through the last time point assessed (range, 84 to 124 weeks). Lenvatinib was associated with a median time to objective response of 2 months (95% CI, 1.9 to 3.5). The difference in overall survival between the groups was not significant (hazard ratio for death, 0.73; 95% CI, 0.50 to 1.07; P=0.10 by a stratified log-rank test); this difference became larger when a potential crossover bias was considered (RPSFT model; hazard ratio, 0.62; 95% CI, 0.40 to 1.00; P=0.05 when calculated with the bootstrap method) (Fig. S4 in the Supplementary Appendix). The median progression-free survival among patients entering the open-label phase for whom data could be evaluated was 10.1 months (95% CI, 8.3 to not estimable), and the overall response rate was 52.3% (1 complete response and 56 partial responses).

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Variable	Lenvatinib (N=261)	Placebo (N=131)
Median age — yr	64	61
Male sex — no. (%)	125 (47.9)	75 (57.3)
Region — no. (%)		
Europe	131 (50.2)	64 (48.9)
North America	77 (29.5)	39 (29.8)
Other†	53 (20.3)	28 (21.4)
ECOG performance status — no. (%)‡		
0 or 1	248 (95.0)	129 (98.5)
2 or 3	13 (5.0)	2 (1.5)
One prior treatment regimen with a tyrosine kinase inhibitor — no. (%)§	66 (25.3)	27 (20.6)
Histologic subtype of differentiated thyroid cancer — no. (%)¶		
Papillary	132 (50.6)	68 (51.9)
Poorly differentiated	28 (10.7)	19 (14.5)
Follicular, not Hürthle cell	53 (20.3)	22 (16.8)
Hürthle cell	48 (18.4)	22 (16.8)
Metastatic lesions — no. (%)		
With bony metastases	104 (39.8)	48 (36.6)
With pulmonary metastases	226 (86.6)	124 (94.7)

* There were no significant differences between the groups in any of the characteristics listed in this table.
† Other regions include Brazil, Chile, Japan, South Korea, Russia, and Thailand.
‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating increasing disability.
§ Further information is provided in Table S4 in the Supplementary Appendix.
¶ Histologic findings were determined from investigators' reports.

SAFETY AND SIDE-EFFECT PROFILE

The median duration of treatment was 13.8 months among patients who received lenvatinib and 3.9 months among patients who received placebo. The incidence of treatment-related adverse effects (of all grades) as assessed by the investigator was 97.3% in the lenvatinib group and 59.5% in the placebo group, and the incidence of treatment-related adverse effects of grade 3 or higher was 75.9% in the lenvatinib group and 9.9% in the placebo group (Table 3, and Table S2 in the Supplementary Appendix). Adverse effects of special interest that developed in the lenvatinib group during treatment were hypertension (any grade, 69.3%; grade ≥3, 42.9%), proteinuria (any grade, 32.2%; grade ≥3, 10.0%), arterial thromboembolic effects (any grade, 5.4%; grade ≥3, 2.7%), venous thromboembolic effects (any grade, 5.4%; grade ≥3, 3.8%), renal failure, including acute renal failure (any grade, 4.2%; grade ≥3, 1.9%), hepatic failure (grade ≥3, 0.4%), gastrointestinal fistula (any grade, 1.5%; grade ≥3,

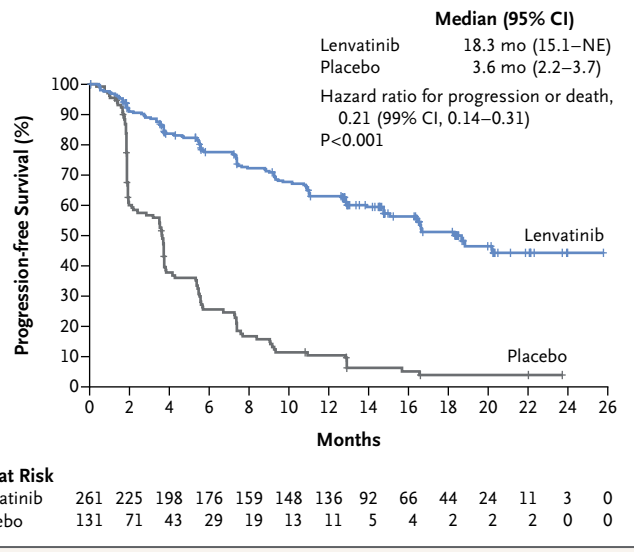

Figure 2. Kaplan–Meier Estimate of Progression-free Survival in the Intention-to-Treat Population.

Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review. Tumor responses were calculated as the maximum percentage change from baseline in the sum of the diameters of target lesions. CI denotes confidence interval, and NE not estimable.

0.8%), corrected QT prolongation (any grade, 8%; grade ≥3, 1.5%), and the posterior reversible encephalopathy syndrome (any grade, 0.4%; grade ≥3, 0). In patients who received lenvatinib, the median serum thyrotropin levels increased from baseline levels in cycle 1 and peaked by cycle 2. The post-baseline levels of serum thyrotropin increased to more than 0.5 mIU per liter in 158 patients in the lenvatinib group (61.5%).

A total of 118 deaths occurred before data cutoff: 71 in the lenvatinib group (27.2%) and 47 in the placebo group (35.9%) (P=0.08). The majority of these deaths were due to disease progression (53 [74.6%] and 35 [74.5%] in the lenvatinib and placebo groups, respectively); the remaining deaths were either not due to progressive disease or were due to an unknown cause. In 20 patients in the lenvatinib group (7.7%), adverse effects that developed during treatment were fatal (Table S3 in the Supplementary Appendix). Of these, 6 deaths (2.3%) were considered by the investigator to be treatment-related, including 1 case each of pulmonary embolism, hemorrhagic stroke, and general deterioration of physical health; 3 cases were reported as deaths or sudden deaths (not otherwise specified). In 6 patients in the placebo group (4.6%), adverse effects that occurred during the treatment period were fatal; none were considered to be treatment-related.

Adverse effects that developed during treatment and led to the discontinuation of treatment were reported in 37 patients who were receiving lenvatinib (14.2%) and in 3 patients who were receiving placebo (2.3%). The most frequent effects leading to dose discontinuation were asthenia and hypertension, each of which occurred in 1.1% of patients in the lenvatinib group. More patients in the lenvatinib group than in the placebo group had a dose interruption (82.4% vs. 18.3%) or reduction (67.8% vs. 4.6%), resulting in a mean lenvatinib dose of 17.2 mg per day. The first dose reduction occurred at a median of 3.0 months (95% CI, 2.7 to 3.7). The most common adverse effects developing during treatment that led to a dose interruption or reduction among patients receiving lenvatinib were diarrhea (22.6%), hypertension (19.9%), proteinuria (18.8%), and decreased appetite (18.0%). Four patients in the lenvatinib group (1.5%) required dose adjustments owing to hypocalcemia.

DISCUSSION

Among patients with progressive iodine-131–refractory differentiated thyroid cancer who received lenvatinib, the median progression-free survival was 14.7 months longer than it was among those who received placebo (hazard ratio for disease progression or death, 0.21; 99% CI, 0.14 to 0.31; P<0.001). This improvement is longer than that observed in other placebo-controlled clinical trials involving patients with this disease.[17,18,20-22] One distinguishing feature of lenvatinib that may underlie this observation is the inhibition of unique targets, including FGFRs.[10] The median progression-free survival in the placebo group in this study was shorter than the 8 months expected, indicating that these patients had aggressive thyroid cancer. The 8-month assumption was conservative and was made before results from similar trials were available. This study is unusual in that all patients had independently verified progressive disease at the time of enrollment. In addition, it is unlikely that investigator bias factored into the observed results in the placebo group, since progression also required confirmation by independent review. The

Table 2. Efficacy Measures.*

Outcome	Lenvatinib (N=261)	Placebo (N=131)	Hazard Ratio†	Odds Ratio (95% CI)
Progression-free survival				
Primary analysis, IRR and ITT populations‡				
Median (95% CI) — mo	18.3 (15.1–NE)	3.6 (2.2–3.7)	0.21 (0.14–0.31)§	
Rate — % (95% CI)				
6 mo	77.5 (71.7–82.3)	25.4 (18.0–33.6)		
12 mo	63.0 (56.5–68.9)	10.5 (5.7–16.9)		
18 mo	51.1 (43.3–58.3)	3.8 (1.1–9.2)		
24 mo	44.3 (35.1–53.1)	NE		
Prespecified sensitivity analyses				
Investigator assessment, ITT population — mo			0.24 (0.16–0.35)§	
Median	16.6	3.7		
95% CI	14.8–NE	3.5–5.4		
IRR population — mo¶			0.22 (0.15–0.32)§	
Median	16.6	3.6		
95% CI	14.8–20.3	2.2–3.7		
Secondary efficacy end points				
Overall survival, RPSFT adjusted, ITT population			0.62 (0.40–1.00)‖	
Median (95% CI) — mo	NE (22.0–NE)	NE (14.3–NE)		
Rate, RPSFT adjusted — % (95% CI)				
6 mo	90.7 (86.4–93.7)	85.3 (78.0–90.4)		
12 mo	81.6 (76.2–85.8)	70.0 (57.1–79.7)		
18 mo	72.3 (65.7–77.9)	63.0 (44.3–76.9)		
24 mo	58.2 (46.0–68.6)	NE		
Response rate — no. (%)**	169 (64.8)	2 (1.5)		28.87 (12.46–66.86)§
Complete response	4 (1.5)	0		
Partial response	165 (63.2)	2 (1.5)		
Stable disease	60 (23.0)	71 (54.2)		
Durable stable disease ≥23 wk	40 (15.3)	39 (29.8)		
Progressive disease	18 (6.9)	52 (39.7)		
Could not be evaluated	14 (5.4)	6 (4.6)		
Exploratory efficacy end points				
Disease-control rate — no. (%)††	229 (87.7)	73 (55.7)		5.05 (2.98–8.54)§
Clinical-benefit rate — no. (%)§§	209 (80.1)	41 (31.3)		7.63 (4.55–12.79)§
Time to first objective response — mo				
Median	2.0	5.6		
95% CI	1.9–3.5	1.8–9.4		

* CI denotes confidence interval, IRR independent radiologic review, ITT intention-to-treat, NE not estimable, and RPSFT rank-preserving structural failure time.
† Corresponding confidence intervals were 99%, with the exception of the confidence interval for overall survival, which was 95%.
‡ The analysis involving the per-protocol population yielded identical results.
§ P<0.001 for the comparison between the two groups.
¶ This sensitivity analysis treated all cases of progressive disease, deaths, crossovers, and use of new anticancer therapies (even in patients who were not receiving a study drug) as events.
‖ P=0.05 when calculated with the use of the bootstrap method.
** Tumor responses were assessed with the use of Response Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review.
†† The disease-control rate was calculated as complete response plus partial response plus stable disease.
§§ The clinical-benefit rate was calculated as complete response plus partial response plus durable stable disease.

Table 3. Adverse Effects.

Effect	Lenvatinib (N=261)		Placebo (N=131)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any treatment-related adverse effect — no. of patients (%)	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	
Treatment-related adverse effect of any grade in ≥10% of patients, of grade ≥3 in ≥2%, or both — %				
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8.0	8.4	0
Fatigue or 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
Palmar–plantar erythrodysesthesia syndrome	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
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	0	3.8	0
Abdominal pain	11.5	0.4	0.8	0.8
Peripheral edema	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
Hypocalcemia	6.9	2.7	0	0
Pulmonary embolism	2.7	2.7	1.5	1.5

* A complete list of serious adverse effects is provided in Table S2 in the Supplementary Appendix.
† A complete list of fatal adverse effects that developed during treatment is provided in Table S3 in the Supplementary Appendix.

8.2-month difference in the median progression-free survival between patients who were initially randomly assigned to lenvatinib and those who crossed over to lenvatinib may be attributed in part to the necessary additional progression event in the latter group.

The progression-free survival benefit with lenvatinib was observed across all prespecified sub-

groups, including patients who had received one prior tyrosine kinase inhibitor treatment (Fig. S2 in the Supplementary Appendix). This efficacy after prior treatment with a tyrosine kinase inhibitor is a key clinical consideration given the likely increased use of these therapies in patients with iodine-131–refractory thyroid cancer. The proportion of patients in whom progression of existing bone metastases occurred was lower in the lenvatinib group than in the placebo group (23.7% vs. 59.0%), and this difference indicates that in this small subgroup of patients, lenvatinib is able to curtail these often-intractable metastases. The median overall survival was not reached; the majority of patients who received placebo crossed over to lenvatinib, and a nonsignificant prolongation in overall survival with lenvatinib was observed (adjusted hazard ratio, 0.62).

The proportion of patients who received lenvatinib and who had treatment-related adverse effects was 97.3%, and 75.9% had treatment-related adverse effects that were grade 3 or higher. Previous studies showed an increased risk of hypertension and proteinuria among patients who received lenvatinib; these findings are consistent with those among patients receiving other VEGF and VEGFR inhibitors.[30,31] Overall, 41.8% of the patients who received lenvatinib, as compared with 2.3% of those who received placebo, had treatment-related hypertension of grade 3 or higher. However, hypertension led to discontinuation of the drug in only 1.1% of the patients in the lenvatinib group and dose reduction or interruption in 19.9% of the patients in that group. Most adverse effects were managed with standard clinical interventions or dose modifications.[31,32] The rate of discontinuation of lenvatinib because of adverse effects that developed during treatment was 14.2%, the median duration of treatment was 13.8 months, and patients who received lenvatinib received a mean dose of 17.2 mg per day. The median time to the first dose reduction was 3.0 months, or 1 month after the median time to the first objective response (2.0 months), which was also the time of the first radiologic tumor assessment. There were more fatal adverse effects during treatment in the lenvatinib group than in the placebo group (7.7% vs. 4.6%), and 6 of 20 deaths in the lenvatinib group (2.3%) were considered to be treatment-related, including 1 case each of pulmonary embolism and hemorrhagic stroke. No specific pattern of fatal adverse effects in the lenvatinib group was observed. In patients who receive lenvatinib, serum thyrotropin levels should be measured on a regular basis, and the daily dose of levothyroxine should be increased accordingly if the level rises.

In this placebo-controlled analysis, a progression-free survival benefit associated with lenvatinib was maintained regardless of *BRAF* or *RAS* mutation status; neither mutational status appeared to predict a benefit with lenvatinib. Therefore, further investigation of biomarkers for lenvatinib efficacy is necessary. Limitations of this study include the possibility that crossovers from placebo to lenvatinib could have confounded the survival analysis, a limitation that we attempted to address with adjusted analyses, and a lack of information on the patients' quality of life.

In conclusion, this study showed that lenvatinib, as compared with placebo, was associated with significant prolongation of progression-free survival and an improved response rate (64.8% vs. 1.5%) among patients with iodine-131–refractory differentiated thyroid cancer. Toxic effects of therapy were considerable, and most toxic effects were managed with dose modification and medical therapy.

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APPENDIX

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