# Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer

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**Context:** Lenvatinib improved the progression-free survival (PFS) and overall response rate of patients with radioiodine-refractory differentiated thyroid cancer vs placebo in the Phase 3 *S*tudy of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT).

**Objective:** The objective of the study was to characterize tumor size changes with lenvatinib treatment.

**Design:** SELECT was a phase 3, randomized, double-blind, multicenter study.

**Setting:** In this clinical trial, tumor assessments of lenvatinib (n = 261) and placebo-treated (n = 131) patients were performed by independent radiological review per Response Evaluation Criteria in Solid Tumors version, 1.1 at 8-week intervals.

**Patients:** Patients with complete or partial response were defined as responders to lenvatinib (n = 169). Of the 92 nonresponders, 76 had at least one postbaseline tumor assessment and were included in this analysis.

**Interventions:** Lenvatinib (24 mg once daily) or placebo in 28-day cycles until unacceptable toxicity, disease progression, or death.

**Main Outcome Measures:** This was an exploratory analysis of key end points from SELECT, including PFS, overall response rate, and tumor reduction.

**Results:** The median maximum percentage change in tumor size was −42.9% for patients receiving lenvatinib (responders, −51.9%; nonresponders, −20.2%). Tumor size reduction was most pronounced at first assessment (median, −24.7% at 8 wk after randomization); thereafter, the rate of change was slower but continuous (−1.3% per mo). In a multivariate model, percentage change in tumor size at the first assessment was a marginally significant positive predictor for PFS ($P = .06$).

**Conclusions:** The change in tumor size conferred by lenvatinib was characterized by two phases: an initial, rapid decline, followed by slower, continuous shrinkage. **(*J Clin Endocrinol Metab* 101: 4103–4109, 2016)**



Lenvatinib is an oral multikinase inhibitor of vascular endothelial growth factor (VEGF) receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor-α, ret protooncogene (RET), and stem cell factor receptor (KIT) (1–3). In the Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT), a phase 3, randomized, double-blind, multicenter study of 392 patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC), treatment with lenvatinib significantly prolonged progression-free

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Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; RET, ret protooncogene; RR-DTC, radioiodine-refractory differentiated thyroid cancer; SELECT, Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid; Tg, Thyroglobulin; VEGF, vascular endothelial growth factor.

survival (PFS; hazard ratio [HR] 0.21; 99% confidence interval [CI] 0.14–0.31; $P < .001$) by 14.7 months (lenvatinib median PFS, 18.3 mo) compared with placebo (median PFS, 3.6 mo) (4).

Notably, lenvatinib treatment also resulted in an overall response rate (ORR) of 64.8%, which included four patients who achieved complete responses (CR), compared with an ORR of 1.5% in placebo-treated patients (all partial responses) (4). ORR is a key end point in oncology clinical trials and has been correlated with improved overall survival in several studies, including metastatic breast cancer (5) and a meta-analysis of mixed tumor types, but not yet in RR-DTC (6). In a recent meta-analysis of metastatic nonsmall cell lung cancer clinical trials submitted to the US Food and Drug Administration, ORR was found to be strongly associated with PFS. An association between ORR or PFS with overall survival, however, was not established, possibly because of the crossover study designs and post-study interventions (7). Because the change in tumor volume is central to measuring patient response to therapy, this exploratory analysis examines the rate, magnitude, and duration of tumor size changes in SELECT.

## Patients and Methods

### The SELECT trial

This phase 3, randomized, double-blind, multicenter study enrolled male or female patients with RR-DTC, measurable disease, and independently reviewed radiological evidence of progression (by computed tomography or magnetic resonance imaging scans per Response Evaluation Criteria in Solid Tumors, version 1.1) within the prior 13 months. All patients provided written informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Patients could have previously been treated with up to one prior VEGF or VEGF receptor-targeted therapy. Further details of the SELECT study design, including relevant protocol approvals, have been previously published (4). Briefly, patients with RR-DTC were randomized 2:1 to receive oral lenvatinib (24 mg once daily) or placebo in 28-day cycles until unacceptable toxicity, independently reviewed radiological-confirmed disease progression, unacceptable toxicity, or death. Blinded, central radiological tumor assessments were performed using Response Evaluation Criteria in Solid Tumors version, 1.1 criteria every 8 weeks. Dose interruptions and incremental, sequential reductions due to adverse events were permitted (from 24 mg/d to 20, 14, and 10 mg/d).

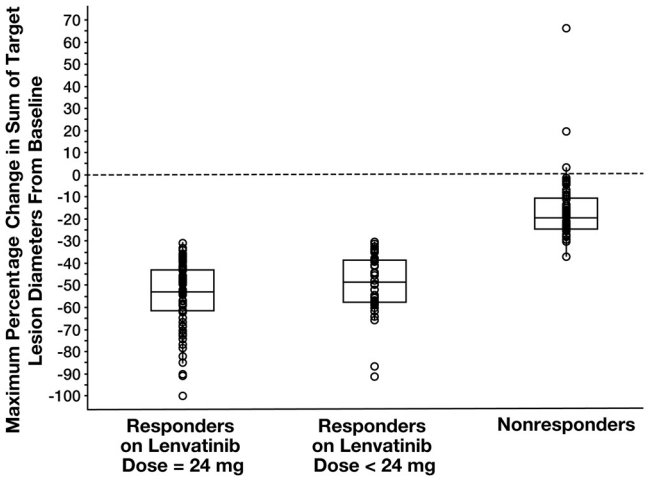


**Figure 1.** Maximum percentage change in sum of target lesion diameters from baseline in patients with RR-DTC who were randomized to receive lenvatinib in SELECT. Patients with best overall response of partial or complete response were considered responders. Patients whose earliest responses occurred within 30 days of receiving 24 mg/d lenvatinib were defined as responders at 24-mg lenvatinib; otherwise, patients were considered responders at less than 24-mg lenvatinib. Nonresponders shown include the 76 patients who had at least one postbaseline target lesion measurement.

Blood samples were collected at baseline, cycle 1/day 15, day 1 of subsequent cycles, and at the end of randomized study treatment. Serum was isolated from blood samples using standard techniques and frozen at −20°C and then shipped overnight on dry ice from the clinical site to the analytical laboratory and stored at −80°C. Thyroglobulin (Tg) levels were analyzed using the Elecsys 2010 kit by Cobas (Roche Diagnostics).

### Statistical analysis

Patients who responded to lenvatinib treatment (responders) were defined as those patients who had a CR or partial response as their best overall response. Patients were considered responders at 24 mg if their earliest responses occurred within 30 days of receiving 24 mg/d; otherwise, patients were considered responders at less than 24 mg lenvatinib. The rate of change in tumor size over time was analyzed using a two-segment linear regression model, in which the first segment was from baseline to the first radiological tumor assessment at 8 weeks, and the second segment was from the first radiological tumor assessment onward. The associations between PFS and variables of interest were analyzed by univariate analyses; variables with a univariate $P < .2$ were then included in a multivariate Cox regression model.

## Results

### Patient characteristics

SELECT randomized 392 (male, n = 200; female, n = 192) patients to receive lenvatinib (n = 261) or placebo

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**Table 1.** Percentage Change From Baseline in Sum of Target Lesion Diameter by Metastasis Site

| Metastasis Site | Lenvatinib n | Lenvatinib Mean Maximum Change, % | Placebo n | Placebo Mean Maximum Change, % | *P* Value |
|---|---|---|---|---|---|
| Lung | 189 | −45.9 | 103 | 2.7 | <.0001 |
| Liver | 14 | −35.6 | 12 | 5.1 | <.0001 |
| Lymph node | 119 | −47.5 | 55 | −2.9 | <.0001 |
| Bone | 34 | −10.7 | 16 | 6.5 | .0021 |

(n = 131). Baseline demographics and patient characteristics are summarized in Supplemental Table 1. The primary analysis of SELECT, including an examination of the safety of lenvatinib, has already been published. At baseline, the median tumor size as measured by the sum of diameters of target lesions for all patients receiving lenvatinib was 59.1 mm (range, 15.1–331.2). Of the 261 patients who received lenvatinib, 169 were responders and 92 were nonresponders (defined above). Of the nonresponders, 60 had stable disease, 16 had progressive disease, and 16 were not included in the analysis.

### Tumor reduction with lenvatinib treatment

At the time of primary data cutoff (November 15, 2013), the median maximum percentage change in tumor size was −42.9% for all patients receiving lenvatinib

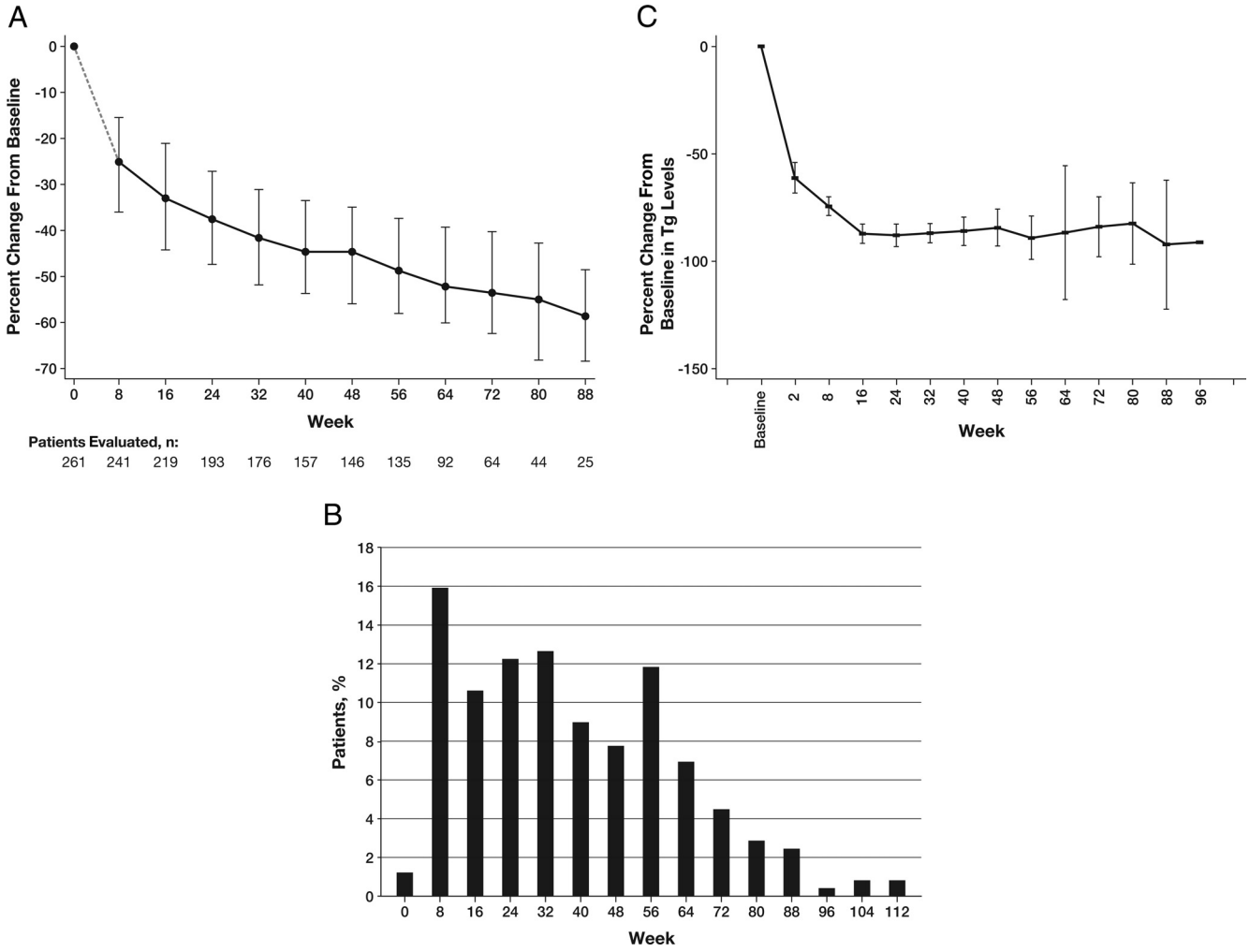


**Figure 2.** A, Change in tumor size over time (median and interquartile range of the percentage change in the sum of target lesion diameters) for patients with RR-DTC who were randomized to receive lenvatinib in SELECT. B, Percentage of lenvatinib-treated patients with observed nadir in tumor size over time. C, Change from baseline in Tg levels (median and SE) for lenvatinib-treated patients from SELECT. A straight dotted line is used to connect time points between 0 and 8 weeks because the real curve during this period is actually unknown. The connected lines are intended to highlight the general tumor shrinkage pattern over 88 weeks. The data are based on patients with both baseline and postbaseline tumor assessments. SE, standard error.

(range, −100.0 to 65.6), and the median time to first objective response was 2.0 months (95% CI 1.9, 3.5). Among the responders to lenvatinib treatment (patients with CR or partial response, n = 169), 75% had an objective response duration that was longer than 9.4 months; however, the median duration of objective response was not yet reached at the time of analysis. Overall, responders had a median target lesion reduction of −51.9% (range, −100 to −30.3). Target lesion size reduction was also experienced by nonresponders to lenvatinib treatment (n = 92; Figure 1). Of the 92 nonresponders, 76 patients had at least one postbaseline target lesion measurement and were included in this analysis, with a median target lesion reduction of −20.2% (range, −37.8 to 65.6). Median target lesion reduction was −20.3% (range, −37.4 to −2.9) and −15.7% (range, −37.8 to 65.6) for patients with stable disease (n = 60) and progressive disease (n = 16) receiving lenvatinib, respectively. Among the 16 remaining patients who were not included in the analysis, seven discontinued treatment due to an adverse event, five experienced unconfirmed disease progression prior to discontinuing treatment, and four discontinued by choice.

Tumor reduction was significantly greater in patients receiving lenvatinib compared with those receiving placebo in all specific target lesion metastasis sites examined. Mean percentage change from baseline was −45.9% for lenvatinib vs 2.7% for placebo ($P < .0001$) in lung, −35.6% vs 5.1% ($P < .0001$) in liver, −47.5% vs −2.9% ($P < .0001$) for lymph node, and −10.7% vs 6.5% ($P < .01$) for bone metastases (Table 1).

Notably, lenvatinib-induced tumor size reduction appeared to occur in two phases (Figure 2A). First, a rapid initial decline in average tumor size (−25.2%; median −25.0%) was observed by 8 weeks, which was the time of the first radiological tumor assessment. Thereafter, a slower, continuous decrease in tumor size was observed at an average rate of −1.3% per month. As demonstrated by the proportion of patients who reached nadir tumor size, tumor regression continued throughout the course of the treatment period, even after the rapid decline at the first tumor assessment (Figure 2B). Median percentage change from baseline in tumor size decreased 22.1% at week 8, 28.9% at week 16, and greater than 50% by week 88 (Figure 2A). This reduction in tumor size occurred concurrently with a decrease in Tg levels that was also observed with lenvatinib treatment. The maximum decrease in Tg levels occurred at 88 weeks (median 92.3%), with a corresponding median percentage change from baseline in tumor size of 57.0% (Figure 2, A and C).

## Tumor size reduction, lenvatinib exposure, and PFS

Increased lenvatinib exposure (area under the curve) was correlated with greater tumor size reduction during the first 8 weeks ($R^2 = 0.355$; Figure 3A). Tumor size reduction was also correlated with treatment duration (Figure 3B). Based on the first radiological tumor assessment on treatment, the initial mean tumor size reduction for patients who had received 1 or more years of lenvatinib treatment compared with those who had received less than 1 year of treatment was 27.4% and 21.9%, respectively. The rates of change in tumor size after subsequent assessments were similar for all patients. For patients with smaller lesions at baseline (less than median baseline tumor size), the percentage change in tumor size from baseline at week 8 was −30.3% (range, −57.9 to 4.3) compared with a change of −20.8% (range, −49.2 to 65.6) for

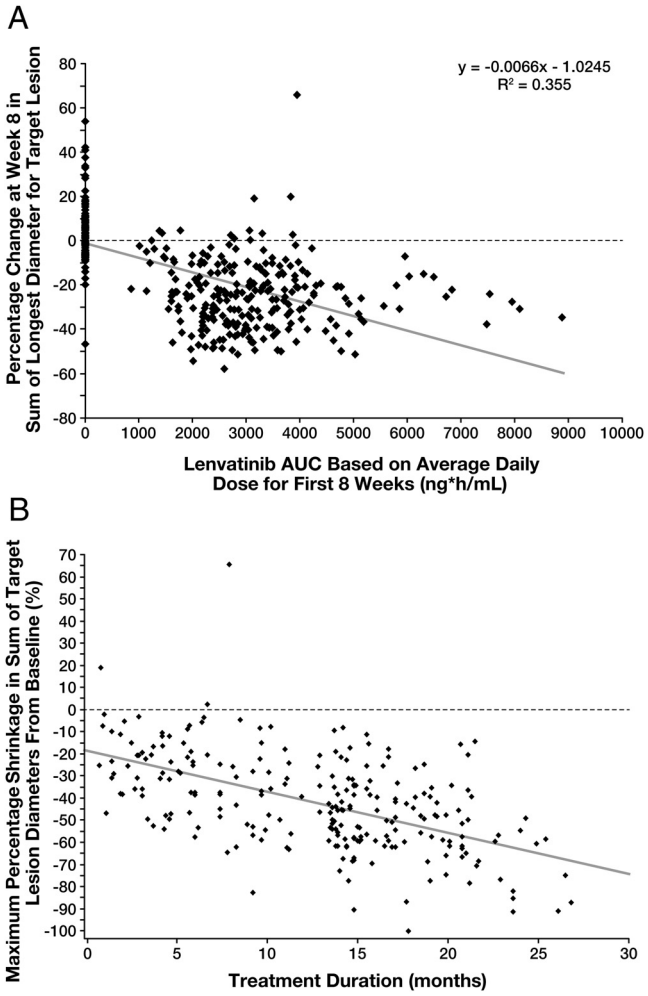


**Figure 3.** A, Percentage change in tumor size at first postdose assessment and lenvatinib exposure during the first 8 weeks of treatment (at time of first tumor assessment). B, The relationship between lenvatinib treatment duration and maximum percentage tumor size change from baseline. AUC, area under the curve.

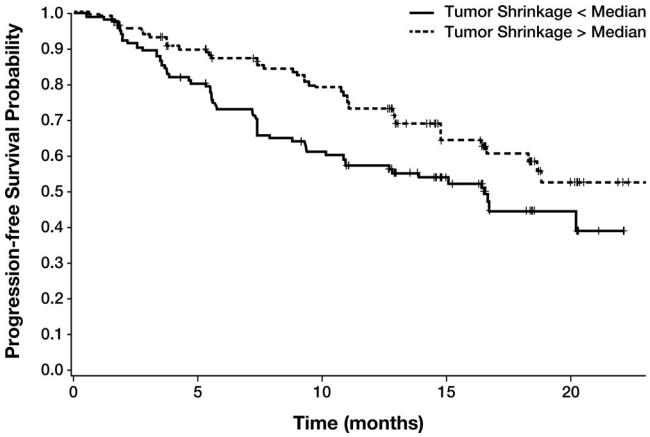


**Figure 4.** Kaplan-Meier estimate of PFS of lenvatinib-treated patients with RR-DTC stratified by tumor size reduction (above vs below the median at wk 8, −24.7%).

patients with larger lesions at baseline (median baseline tumor size or greater).

Patients with greater tumor size reduction during the first 8 weeks (defined as greater than the median of −24.7%) had significantly prolonged PFS compared with patients whose tumor size reduction was less than the median (HR 0.61; 95% CI 0.41–0.91; log rank $P = .014$; Figure 4). Because many variables may influence PFS, a multivariate Cox regression analysis was planned to further evaluate the possible relationship between tumor size reduction during the first 8 weeks of lenvatinib treatment and PFS (Table 2). Of the tested variables, baseline body weight, histology, baseline Eastern Cooperative Oncology Group (ECOG) performance status, baseline tumor size, and percentage change in tumor size at the first radiological tumor assessment (all $P < .05$) were found to be associated with PFS in univariate analyses. When these variables were included in the multivariate Cox regression model, several factors remained significantly associated with PFS, including baseline body weight, baseline ECOG performance status, and baseline tumor size. Percentage tumor size reduction at the first radiological tumor assessment was determined to be a marginally significant positive predictor for PFS in the multivariate model ($P = .06$; Table 2). Median PFS for patients with smaller tumors (less than the median baseline tumor size) at baseline was not estimable (95% CI 16.7 to not estimable), but patients with larger tumors (median baseline tumor size or greater) at baseline had a median PFS of 13.9 months (95% CI 9.3–18.3).

**Table 3.** Univariate and Multivariate Analyses of Potential Factors Associated With Tumor Size Reduction

| | Univariate Analysis *P* Value | Multivariate Analysis *P* Value |
|---|---|---|
| Age (≤ vs > 65 y) | .027 | .055 |
| Sex (male vs female) | .432 | |
| Baseline body weight (< vs ≥ median) | .075 | .035 |
| Baseline ECOG performance status (< vs ≥ 1) | <.001 | .007 |
| Histology (follicular vs papillary) | .359 | |
| Prior VEGF-targeted therapy (0 vs 1) | .168 | .459 |
| Baseline tumor size (< vs ≥ median) | <.001 | <.001 |

*P* values were estimated with linear regression model. Factors with univariate $P < .2$ were included in the multivariate model.

A similar analysis to examine potential variables that may influence tumor size change with lenvatinib treatment was also performed (Table 3). In univariate linear regression analyses, age, baseline ECOG performance status, and baseline tumor size were associated with maximum percentage change in tumor size (all $P < .05$). In the multivariate model, factors that remained significantly associated with percentage tumor size reduction were those also associated with PFS, namely baseline body weight, baseline ECOG performance status, and baseline tumor size.

**Table 2.** Univariate and Multivariate Analyses of Potential Factors Associated With PFS

| | Univariate Analysis | | | Multivariate Analysis[a] | | |
|---|---|---|---|---|---|---|
| **Parameter** | **HR[b]** | **95% CI** | ***P* Value[b]** | **HR** | **95% CI** | ***P* Value[a,b]** |
| Age (≤ vs > 65 y) | 0.79 | 0.54–1.17 | .24 | | | |
| Sex (male vs female) | 1.26 | 0.86–1.84 | .24 | | | |
| Baseline body weight (< vs ≥ median) | 1.59 | 1.08–2.33 | .02 | 1.55 | 1.03–2.32 | 004 |
| Baseline ECOG performance status (< vs ≥ 1) | 0.50 | 0.34–0.74 | <.01 | 0.63 | 0.41–0.96 | .03 |
| Histology (follicular vs papillary) | 0.64 | 0.43–0.97 | .04 | 0.69 | 0.45–1.07 | .10 |
| Prior VEGF-targeted therapy (0 vs 1) | 0.75 | 0.49–1.14 | .18 | 0.86 | 0.55–1.34 | .49 |
| Baseline tumor size (< vs ≥ median) | 0.49 | 0.33–0.72 | <.01 | 0.61 | 0.40–0.94 | .03 |
| Percentage tumor reduction, wk 8 (< vs ≥ median) | 1.67 | 1.11–2.50 | .01 | 1.49 | 0.98–2.26 | .06 |

[a] Multivariate analysis includes only factors with $P < .2$ from univariate analyses.

[b] HRs and *P* values were estimated with Cox proportional hazard models.

## Discussion

In the phase 3 SELECT study, lenvatinib treatment in patients with RR-DTC resulted in an early and pronounced reduction in tumor size in many patients, as assessed by the first post-treatment radiological evaluation at 8 weeks. Because 8 weeks was the earliest assessment time point, it is unclear whether the response might have been even more rapid. It is important that clinicians are aware of the important clinical value that can be attained due to this rapid response, especially because patients with advanced disease are likely to experience pain or other complications because of tumor bulk or burden; therefore, the substantial tumor debulking may delay or abrogate the need for surgical intervention in some patients or make surgery easier.

After the first radiological evaluation, the tumors of patients treated with lenvatinib demonstrated a slower but continuous decrease in size. A concern regarding most anticancer or antiangiogenic therapies is that tumors often circumvent treatment by up-regulating escape or resistance mechanisms, thus becoming refractory to therapy (8). The ongoing tumor reduction observed with lenvatinib treatment is, therefore, especially noteworthy. It may be because of the multitargeted nature of lenvatinib inhibition, specifically inhibition of the fibroblast growth factor receptor signaling network and RET, which have shown to play key roles in thyroid cancer development and progression (9, 10). The unique binding mode of lenvatinib as a type V multikinase inhibitor could also explain the rapid and prolonged response observed with lenvatinib treatment (11).

The magnitude of lenvatinib-induced tumor reduction was correlated both to lenvatinib exposure during the first 8 weeks of treatment and treatment duration. Further, the tumor reduction observed was also associated with a decline in Tg levels, which is often used as a measure of successful thyroid tumor treatment. Although we do not know whether there is a causal relationship, this may provide supporting evidence that the starting dose of lenvatinib should not be lowered, contrary to the practice by some clinicians to try to limit drug-associated toxicities (12). Lenvatinib-induced tumor size reduction at 8 weeks was significantly correlated with PFS, although this correlation was diminished once other baseline patient characteristics were considered. This analysis had several limitations, including the lack of quality-of-life assessments and the collection of symptom data, which would provide additional context to the benefit of reducing tumor burden. The lack of data prior to the first 8-week radiological scan also limits the ability to more precisely determine when the reduction in tumor burden is truly occurring.

In conclusion, lenvatinib treatment in patients with RR-DTC in the phase 3 SELECT trial not only significantly prolonged PFS but also significantly reduced tumor burden, compared with placebo. Further investigation is warranted to confirm these findings.

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