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Impact of baseline tumor burden on overall survival in patients with radioiodine-refractory differentiated thyroid cancer treated with lenvatinib in the SELECT global phase 3 trial

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BACKGROUND: Radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) is an aggressive form of thyroid cancer. Lenvatinib is a multikinase inhibitor approved for treatment of RAI-R DTC. The impact of tumor response and tumor burden on overall survival (OS) after lenvatinib treatment in patients with RAI-R DTC was assessed. **METHODS:** Data from patients treated with lenvatinib (N = 261) in SELECT were retrospectively analyzed. Patients were divided into lenvatinib responder or nonresponder subgroups and into low (≤40 mm) or high (>40 mm) tumor burden subgroups based on baseline sums of diameters of target lesions using Response Evaluation Criteria in Solid Tumors, version 1.1 (cutoff values were determined by receiver-operating characteristic analyses). Associations of tumor response and tumor burden with OS were assessed. **RESULTS:** Median OS was prolonged in lenvatinib responders versus nonresponders (52.2 vs 19.0 months; hazard ratio [HR], 0.32; 95% CI, 0.23-0.46). Patients with a lower tumor burden who received lenvatinib had prolonged OS versus those with a higher tumor burden (median OS, not reached vs 29.1 months, respectively; HR, 0.42; 95% CI, 0.28-0.63). Baseline tumor burden was associated with OS by multivariate analysis (HR, 0.56; 95% CI, 0.35-0.89; $P = .0138$). **CONCLUSIONS:** Patients with a lower tumor burden receiving lenvatinib had prolonged OS compared with those with a higher tumor burden receiving lenvatinib. Baseline tumor burden may be a prognostic factor for OS in patients with RAI-R DTC treated with lenvatinib. ***Cancer* 2022;128:2281-2287**.

KEYWORDS: lenvatinib, prognosis, survival rate, thyroid neoplasms, tumor burden.

INTRODUCTION

Patients with differentiated thyroid cancer (DTC) generally experience good outcomes; however, patients with radioiodine-refractory DTC (RAI-R DTC) have a 10-year survival rate of approximately 10% and a median survival of only 3 to 5 years after discovery of metastases.[1-5] Lenvatinib is an oral multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1 through 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, RET, and KIT.[6-9] Lenvatinib is approved for treating patients with locally recurrent or metastatic, progressive RAI-R DTC based on the results of the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT), which demonstrated significantly longer progression-free survival (PFS) in patients with RAI-R DTC treated with lenvatinib (18.3 months) versus placebo (3.6 months).[10,11] A post hoc analysis of SELECT showed that patients with a low (<median) tumor burden at baseline had a longer median PFS than those with a high (≥median) tumor burden.[12] Additionally, patients with a lower tumor burden at baseline had a longer median duration of response than those with a higher tumor burden.[13]

Although disease burden appears to be associated with PFS and duration of response in patients treated with lenvatinib, the relationship between disease burden and overall survival (OS) after lenvatinib treatment is less clear. Real-world studies from Japan, with small numbers of patients with RAI-R DTC, suggested that tumor burden at baseline and tumor shrinkage after treatment initiation may influence OS in patients receiving lenvatinib.[14-16] Because some but

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not all patients with RAI-R DTC may experience rapid disease progression[2] and many patients have asymptomatic or slow-growing disease,[5] it is important to identify patients who are most likely to benefit from lenvatinib and to determine the optimal time to initiate therapy, particularly because lenvatinib can engender treatment-related adverse events.[11] Clarifying the relationship between tumor characteristics (eg, baseline tumor burden, tumor shrinkage) and OS may help predict the potential benefits of earlier lenvatinib treatment.

This post hoc analysis of the SELECT trial assessed the impact of tumor burden at baseline and tumor response on OS in patients with RAI-R DTC treated with lenvatinib.

MATERIALS AND METHODS

Patients

Full details of the phase 3 international, randomized, double-blind, multicenter SELECT trial have been previously published (ClinicalTrials.gov number NCT01321554).[11] SELECT compared lenvatinib to placebo in patients ≥18 years of age with RAI-R DTC who had evidence of disease progression within the previous 13 months (verified via independent radiologic review [IRR]).[11]

All patients provided written informed consent and the study protocol was approved by all relevant institutional review bodies. SELECT was conducted in accordance with the provisions of the Declaration of Helsinki and local laws.

Study Design

Patients were randomly assigned 2:1 to receive lenvatinib 24 mg/day or placebo in 28-day cycles. Dose interruptions and reductions were permitted. Tumor assessments were conducted by a centralized imaging laboratory using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) every 8 weeks in the randomization phase. Treatment continued until IRR-verified disease progression according to RECIST v1.1. Following disease progression, patients in the placebo group could receive optional open-label lenvatinib treatment. The primary endpoint was PFS; secondary endpoints included objective response rate, OS, and safety.

Post Hoc Tumor Response, Tumor Burden, and OS Analyses

This post hoc analysis was conducted using updated OS data from SELECT (data cutoff: September 1, 2016).[17] To explore the association between OS and best overall response, patients from the lenvatinib group were divided into responder (those with complete or partial response) or nonresponder (those with stable or progressive disease) subgroups; OS for each group was summarized using Kaplan-Meier estimates. Hazard ratios (HRs) and CIs were derived using the Cox proportional hazards model. To further explore and confirm the association between OS and best overall response, landmark analyses comparing the OS of lenvatinib responders with nonresponders at 4, 8, and 12 months were also conducted using this method.

To clarify the relationship between baseline tumor burden and OS, patients in the lenvatinib group were subdivided based on baseline sums of diameters of target lesions per IRR using RECIST v1.1. The 4 baseline tumor burden subgroups, based on quartiles of all patients (n = 392) in SELECT, were ≤35, >35 to 60, >60 to 92, and >92 mm. These cutoffs were previously used to determine the impact of baseline tumor burden on PFS in SELECT.[11] On the basis of these initially defined categories, we conducted 2 receiver-operating characteristic analyses (Kaplan-Meier and Nearest Neighbor Estimation) to determine the appropriate baseline tumor burden cutoff value for further analyses. Patients in the lenvatinib and placebo groups were divided into low and high baseline tumor burden subgroups according to this value.

OS in patients randomized to receive lenvatinib was compared in low versus high baseline tumor burden subgroups using Kaplan-Meier estimates; HRs and CIs were derived using the Cox proportional hazards model. A multivariate analysis was also conducted in the lenvatinib group to explore associations between baseline variables and OS. Variables included in the model were sums of diameters of target lesions (low vs high baseline tumor burden), age (≤65 vs >65 years), sex (male vs female), body weight (<median vs ≥median), Eastern Cooperative Oncology Group performance status (ECOG PS; 0 vs ≥1), number of previous VEGF-targeted therapies (0 vs 1), histology (papillary or follicular), and number of metastatic sites (<2 vs ≥2). Two additional analyses were conducted: one to compare OS in patients with low baseline tumor burden receiving lenvatinib versus placebo and another to compare OS in patients with high baseline tumor burden receiving lenvatinib versus placebo. To address potential bias resulting from the high crossover rate from placebo to open-label lenvatinib, an adjusted OS analysis using the rank-preserving structural failure time model was also conducted. HRs were estimated using the Cox proportional hazards model; 95% CIs were estimated using the bootstrap method.

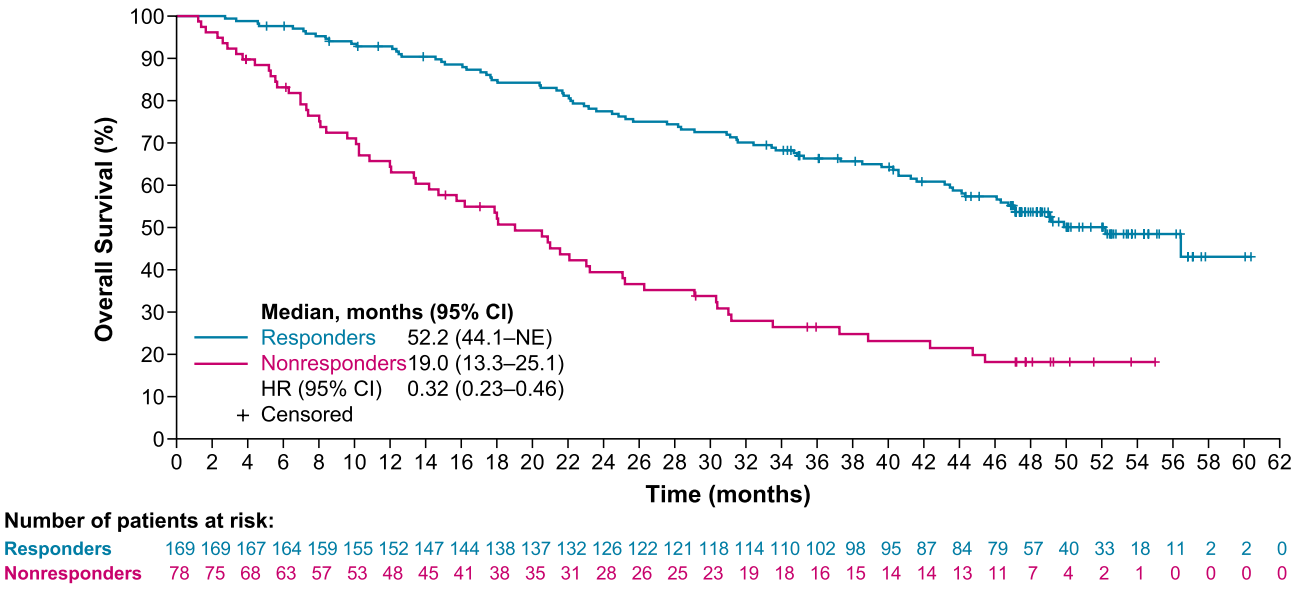


FIGURE 1. Overall survival by objective response in patients randomly assigned to the lenvatinib group. CI indicates confidence interval; HR, hazard ratio; NE, not estimable.

RESULTS

OS in Lenvatinib Responders Versus Nonresponders

Of the 261 patients randomly assigned to the lenvatinib group, 247 were included in this post hoc analysis of OS by tumor response (14 patients were not evaluable or unknown). The median OS in lenvatinib responders (those with complete or partial responses) was 52.2 months (95% CI, 44.1 to not estimable [NE] months) versus 19.0 months (95% CI, 13.3-25.1 months) in nonresponders (HR, 0.32; 95% CI, 0.23-0.46) (Fig. 1). Results of the landmark analyses were consistent with the overall OS by tumor response analysis (Supporting Fig. 1).

Baseline Tumor Burden and OS

All 261 patients who were randomly assigned to the lenvatinib group were included in the OS analysis by baseline tumor burden. Results of the analysis per the 4 initially defined tumor burden categories demonstrated that the subgroup with the smallest sum of diameters of target lesions had longer median OS than the 3 subgroups with larger sums of diameters of target lesions (Supporting Fig. 2). Based on these findings, results of receiver-operating characteristic analyses suggested that the optimal cutoff value was approximately 40 mm (Supporting Fig. 3). Patients in the lenvatinib group were subdivided into ≤40-mm (n = 79) and >40-mm (n = 182) subgroups. Patients in the placebo group were also subdivided based on this cutoff value (36 patients in the low tumor burden subgroup; 95 patients in the high tumor burden subgroup).

Baseline characteristics per tumor burden subgroup in the lenvatinib and placebo groups are displayed in Table 1 and Supporting Table 1, respectively. Baseline characteristics for the lenvatinib group were generally similar across subgroups; however, the low tumor burden subgroup had a larger percentage of patients with an ECOG PS of 0 and fewer metastatic sites (0 or 1). In the placebo group, the low tumor burden subgroup had a larger percentage of patients ≤65 years of age; additionally, the low tumor burden subgroup had a larger percentage of patients with an ECOG PS of 0, 0 previous VEGF-targeted therapies, and 1 metastatic site. The most frequent site of metastasis was lung and its percentage was generally similar across subgroups. As expected, the high tumor burden subgroups (both lenvatinib and placebo) had a larger percentage of patients with other metastases (including bone and lymph node metastases) than the low tumor burden subgroups.

When comparing OS in the lenvatinib group between patients with baseline sums of diameters of target lesions ≤40 and >40 mm, the median OS was not reached (95% CI, 47.1 months to NE) in the ≤40-mm subgroup and 29.1 months (95% CI, 23.2-38.5 months) in the >40-mm subgroup (HR, 0.42; 95% CI, 0.28-0.63) (Fig. 2).

TABLE 1. Baseline demographic and disease characteristics per baseline tumor burden[a] subgroup (≤40 and >40 mm) in patients randomly assigned to the lenvatinib group

	Lenvatinib (n = 261)	
Baseline Characteristic	≤40 mm (n = 79)	>40 mm (n = 182)
Age group, years, n (%)		
≤65	47 (59.5)	108 (59.3)
>65	32 (40.5)	74 (40.7)
Male, n (%)	33 (41.8)	92 (50.5)
Race, n (%)		
White	60 (75.9)	148 (81.3)
Asian	19 (24.1)	27 (14.8)
Other	0	7 (3.8)
Median body weight, kg (range)	72.2 (42-136)	73.5 (33-155)
ECOG PS, n (%)		
0	56 (70.9)	88 (48.4)
≥1	23 (29.1)	94 (51.6)
Prior VEGF-targeted therapies, n (%)		
0	63 (79.7)	132 (72.5)
1	16 (20.3)	50 (27.5)
Number of metastatic sites, n (%)		
0	3 (3.8)	1 (0.5)
1	40 (50.6)	22 (12.1)
≥2	36 (45.6)	159 (87.4)
Histology, n (%)		
Papillary thyroid cancer	54 (68.4)	115 (63.2)
Follicular thyroid cancer	25 (31.6)	67 (36.8)
Type of metastases, n (%)		
Lung	70 (88.6)	156 (85.7)
Lymph node	25 (31.6)	113 (62.1)
Bone	10 (12.7)	94 (51.6)
Pleural	6 (7.6)	40 (22.0)
Liver	8 (10.1)	35 (19.2)
Pericardium/intra-abdominal mass	5 (6.3)	19 (10.4)
Musculoskeletal (nonbone)/skin	0	10 (5.5)
Brain	2 (2.5)	7 (3.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; VEGF, vascular endothelial growth factor.
[a]Tumor burden was defined as the sums of diameters of target lesions, per RECIST v1.1.

Results of the multivariate analysis of patients in the lenvatinib group showed that baseline sums of diameters of target lesions (≤40 vs >40 mm) was significantly associated with OS (HR, 0.56; 95% CI, 0.35-0.89; $P = .0138$) after adjusting for other baseline characteristics. Body weight (<median vs ≥median), histology (papillary vs follicular DTC), number of metastatic sites at baseline (<2 vs ≥2), and ECOG PS (0 vs ≥1) also significantly affected OS. Age, sex, and number of previous VEGF-targeted therapies were not significantly associated with OS (Table 2). An ad hoc multivariate analysis with baseline sums of diameters of target lesions as a continuous variable yielded similar results (Supporting Table 2).

Similar percentages of patients in the placebo group crossed over to the optional open-label lenvatinib phase in the low tumor burden (n = 33; 91.7%) and high tumor burden (n = 82; 86.3%) subgroups. The median time between randomization and crossover was 170 days in patients with low baseline tumor burden and 132 days in those with high baseline tumor burden. An ad hoc analysis of OS in the lenvatinib versus placebo groups by baseline tumor burden showed that median OS in patients with lower sums of diameters of target lesions (≤40 mm) was not reached (95% CI, 47.1 months to NE) in the lenvatinib group and 41.0 months (95% CI, 23.2 months to NE) in the placebo group (HR, 0.39; 95% CI, 0.21-0.73). Median OS in patients with sums of baseline tumor diameters of >40 mm was 29.1 months (95% CI, 23.2-38.5 months) in the lenvatinib group and 31.6 months (95% CI, 17.9-44.3 months) in the placebo group (HR, 1.07; 95% CI, 0.78-1.48) (Fig. 3). Furthermore, the adjusted rank-preserving structural failure time model analysis showed that patients with high baseline tumor burden who received lenvatinib versus those who received placebo had a median OS of 29.1 months (95% CI, 23.2-38.5 months) and 14.3 months (95% CI, 8.5-50.0 months), respectively (HR, 0.49; 95% CI, 0.30-0.74).

DISCUSSION

In SELECT, lenvatinib significantly improved PFS in patients with RAI-R DTC versus placebo[11]; an updated analysis of SELECT also showed longer PFS in lenvatinib responders versus nonresponders (median difference = 25.2 months).[13] Our results, showing longer OS in lenvatinib responders versus nonresponders (median difference = 33.2 months), are consistent with this finding and demonstrate that tumor response is associated with longer OS in addition to longer PFS (Fig. 1).

Ad hoc univariate and multivariate analyses of potential factors associated with PFS in SELECT showed that lower (<median) baseline tumor burden was significantly associated with longer PFS.[12] Our study sought to clarify the relationship between baseline tumor burden and OS in patients receiving lenvatinib, which has previously only been explored in real-world studies with relatively small participant numbers.[14-16] A retrospective multivariate analysis of 26 patients with RAI-R DTC who received lenvatinib showed that the sums of diameters of target lesions was an independent prognostic factor for both OS and PFS: patients with larger sums of diameters of target lesions (>70 mm) had worse OS outcomes than those with smaller sums of diameters of target lesions (≤70 mm) (relative risk, 9.54; 95% CI, 1.20-75.8;

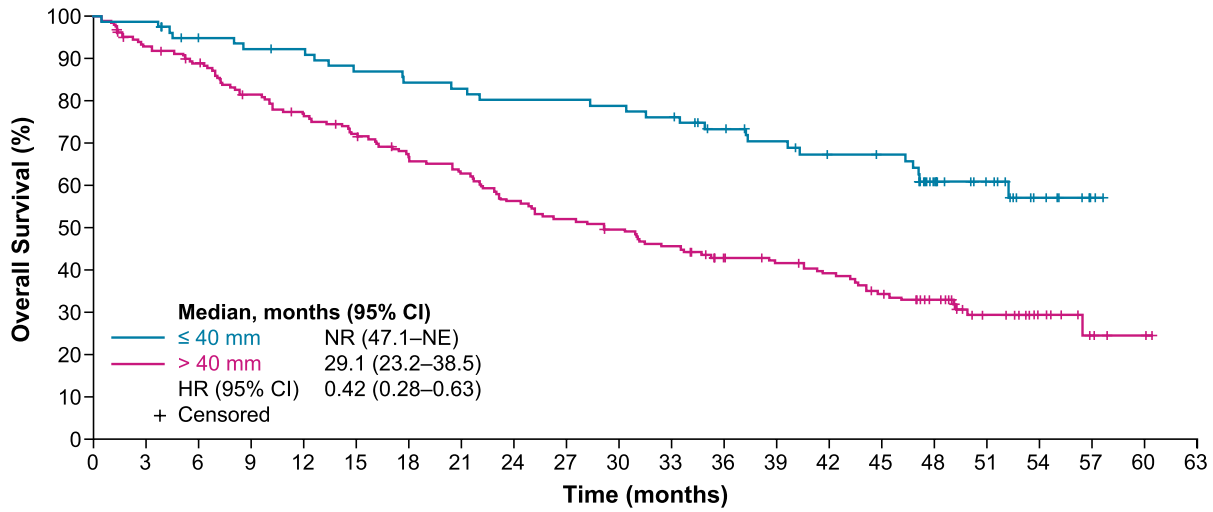


FIGURE 2. Overall survival by baseline tumor burden[a] (≤40 and >40 mm) in patients randomly assigned to the lenvatinib group
[a]Tumor burden was defined as the sums of diameters of target lesions per RECIST v1.1.
CI indicates confidence interval; NE, not estimable; NR, not reached; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

TABLE 2. Multivariate analysis of overall survival in patients randomly assigned to the lenvatinib group

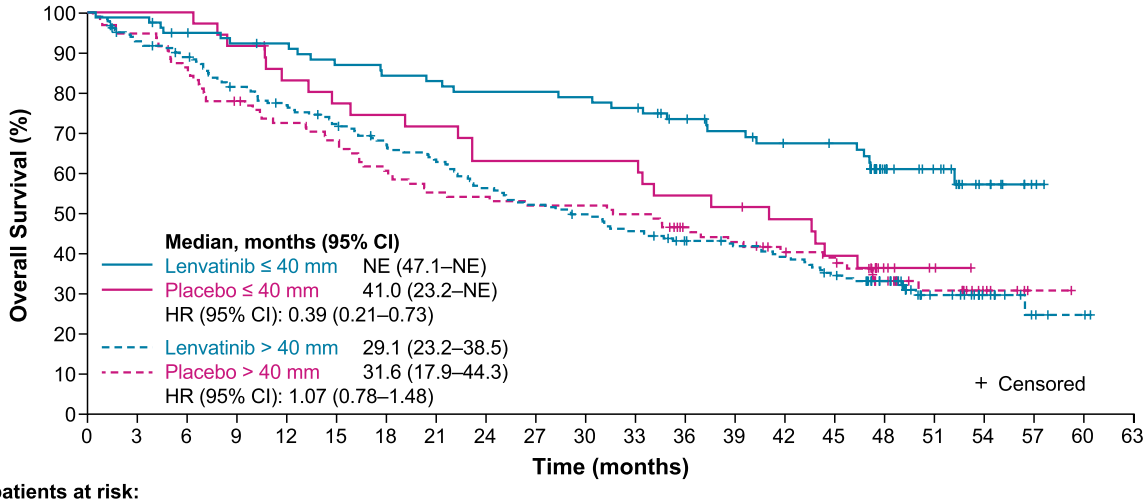
Parameter	*P* value	Hazard Ratio (95% CI)
Baseline sums of diameters of target lesions, ≤40 vs >40 mm	.0138	0.56 (0.35-0.89)
Age, ≤65 vs >65, years	.1027	0.76 (0.54-1.06)
Sex, male vs female	.2174	1.26 (0.87-1.80)
Baseline body weight, kg, <median vs ≥median	.0051	1.69 (1.17-2.45)
Baseline ECOG PS, 0 vs ≥1	.0196	0.67 (0.48-0.94)
Previous VEGF-targeted therapy, 0 vs 1	.4914	0.88 (0.61-1.27)
Histology, papillary vs follicular	.0242	1.50 (1.05-2.14)
Number of metastatic sites at baseline, <2 vs ≥2)	.0295	0.56 (0.34-0.94)

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF, vascular endothelial growth factor.

$P = .03$).[16] Our comparison of OS in patients receiving lenvatinib showed that those with lower baseline tumor burden had prolonged OS versus those with higher burden (median not reached vs 29.1 months, respectively) (Fig. 2). Because PFS prolongation was observed regardless of tumor burden, this result does not indicate that lenvatinib is ineffective in patients with RAI-R DTC with high tumor burden.[11] Additionally, our multivariate analysis demonstrated that baseline sums of diameters of target lesions (≤40 vs >40 mm) was significantly associated with OS (HR, 0.56; 95% CI, 0.35-0.89; $P = .0138$) (Table 2). These results are consistent with a previous post hoc analysis of patients from SELECT with lung metastases ≥1 cm who received lenvatinib and had prolonged OS, even though 89% of those given placebo eventually crossed over to lenvatinib,[17] as both analyses underscore the importance of early treatment initiation.

Interestingly, a similar number of patients in the low versus the high tumor burden groups who received placebo (91.7% vs 86.3%) crossed over to open-label lenvatinib after disease progression with placebo. However, patients in the placebo group with higher tumor burden had a shorter median duration from randomization to initiation of open-label lenvatinib versus those with lower tumor burden (132 vs 170 days). Because the high crossover rate and earlier initiation of open-label lenvatinib likely contributed to the similar OS between patients with a high tumor burden receiving lenvatinib and those receiving a placebo, an adjusted analysis was conducted to attempt to correct for this potential confounder. The results of the adjusted analysis showed that, similar to the results of the low tumor burden subgroup, patients in the high tumor burden subgroup who received lenvatinib had an OS advantage over patients who received placebo (median 29.1 vs 14.3 months, respectively).

Results of our post hoc analysis of SELECT suggest that sum of diameters of target lesions may be used as a prognostic marker of OS in patients receiving lenvatinib.



Number of patients at risk:

Lenvatinib ≤ 40 mm	79	78	73	70	69	65	63	62	60	60	59	57	51	47	43	42	26	19	9	2	0	0
Placebo ≤ 40 mm	36	36	36	33	29	27	26	25	22	22	22	22	19	18	16	13	5	2	0	0	0	0
Lenvatinib > 40 mm	182	166	157	142	133	124	114	106	95	88	83	76	68	64	59	51	39	19	11	4	2	0
Placebo > 40 mm	95	90	82	73	67	63	56	51	50	48	48	46	38	35	31	29	20	13	6	1	0	0

FIGURE 3. Overall survival by baseline tumor burden[a] (≤40 and >40 mm) in patients randomly assigned to the lenvatinib or placebo groups. [a]Tumor burden was defined as the sums of diameters of target lesions per RECIST v1.1. CI indicates confidence interval; HR, hazard ratio; NE, not estimable; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Limitations

Because of the post hoc nature of these analyses, conclusions about the association between baseline tumor burden and tumor response with OS in patients receiving lenvatinib should be made with caution. OS was defined as time from randomization until death of any cause; thus, our results do not speak to the associations between tumor burden and tumor response with cancer-specific survival. Furthermore, differences in baseline characteristics aside from tumor burden (eg, the higher percentage of patients with an ECOG PS of 0 and fewer metastatic sites in patients with low tumor burden) may have affected survival outcomes. Notably, our multivariate analysis showed that ECOG PS and number of metastatic sites significantly affected OS after adjusting for other factors. Additionally, patients with high tumor burden who received placebo had a shorter median duration from randomization to initiation of open-label lenvatinib than did patients with low tumor burden. Although we attempted to correct for crossover bias by adding the adjusted analysis (a similar adjusted OS analysis was conducted for the intent-to-treat population in SELECT[11]), our comparisons of OS in lenvatinib and placebo subgroups by baseline tumor burden should be interpreted with caution. Additionally, we did not evaluate quality of life in our study. Another potential limitation of our analysis is the use of target lesions of RECIST v1.1 selected by independent reviewers for the measurement of tumor burden, which did not take nontarget lesions into account. Although RECIST v1.1 is not routinely used for disease evaluation in clinical practice, multiple lesions are typically evaluated before and after treatment, which is consistent with the approach used in these analyses. Last, the observation that patients with lower tumor burdens had longer OS than patients with higher tumor burdens regardless of whether they were randomized to the lenvatinib or placebo cohorts should be considered when interpreting our results. Given these limitations, additional studies, including those that include the relationship between baseline tumor burden and OS as a prespecified analysis, should be conducted to clarify the utility of tumor burden as a prognostic factor for OS in patients with RAI-R DTC who are potential candidates for tyrosine kinase inhibitor treatment.

CONCLUSION

RAI-R DTC is an aggressive and often rapidly progressing disease,[1,2,5] and only approximately 36% to 53% of patients with RAI-R DTC receive a second-line therapy.[18] Thus, timely and precise treatment selection is crucial to maximize efficacy outcomes. Our results showed prolonged OS in patients who received lenvatinib and had a lower tumor burden versus those with a higher tumor burden, suggesting that earlier initiation of lenvatinib

in patients with RAI-R DTC may optimize survival outcomes.

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CONFLICT OF INTEREST DISCLOSURES

Naomi Kiyota reports grants from Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb, AstraZeneca Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., and Rakuten Medical Inc., and honoraria from Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb, Merck Biopharma, AstraZeneca Co., Ltd., Merck Sharp & Dohme Corp., Eisai Co., Ltd., and Bayer AG. **Makoto Tahara** reports grants and personal fees from Eisai, MSD, Bristol Myers Squibb, Rakuten Medical, Pfizer, AstraZeneca, Bayer, and Ono Pharmaceutical, and personal fees from Merck, Serono, and Loxo. **Bruce Robinson** reports a leadership role with Cochlear and Mayne Pharma, stock and other ownership interests with Cochlear and Mayne Pharma, a consulting or advisory role with Loxo and Eisai, serving on a speakers' bureau for Eisai, and receiving travel/accommodations/expenses from Eisai. **Steven I. Sherman** reports honoraria from Eisai, a consulting or advisory role with Exelixis, Loxo, and Lilly, and research funding from Exelixis. **Sophie Leboulleux** reports participation on tumor boards for Eisai Co., Ltd., and Lilly. **Takuya Suzuki** is an employee of Eisai Co., Ltd. **Min Ren** is an employee of Eisai Inc. **Kazuma Fushimi** is an employee of Eisai Co., Ltd. **Lori J. Wirth** reports a consulting/advisory role with Bayer HealthCare Pharmaceuticals, Blueprint Medicines, Lilly, Eisai, Exelixis, Genentech, Loxo Oncology, and Merck, and data safety monitoring committees for Iovance Biotherapeutics and PDS Biotechnology Corporation. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Naomi Kiyota: Conceptualization, investigation, writing–original draft, and writing–review and editing. **Makoto Tahara:** Investigation and writing–review and editing. **Bruce Robinson:** Investigation and writing–review and editing. **Martin Schlumberger:** Investigation and writing–review and editing. **Steven I. Sherman:** Investigation and writing–review and editing. **Sophie Leboulleux:** Investigation and writing–review and editing. **Eun Kyung Lee:** Investigation and writing–review and editing. **Takuya Suzuki:** Conceptualization, investigation, writing–original draft, and writing–review and editing. **Min Ren:** Formal analysis and writing–review and editing. **Kazuma Fushimi:** Investigation and writing–review and editing. **Lori J. Wirth:** Investigation and writing–review and editing.

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