

Defining Radioiodine-Refractory Differentiated Thyroid Cancer: Efficacy and Safety of Lenvatinib by Radioiodine-Refractory Criteria in the SELECT Trial

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Background: While there is a clear consensus for defining radioiodine-refractory differentiated thyroid cancer (RR-DTC), it is unknown whether these criteria are equally valid for determining when radioiodine (RAI) therapy is no longer beneficial and systemic treatment should be considered. Lenvatinib, a multikinase inhibitor, significantly prolonged progression-free survival (PFS) compared to placebo in a Phase 3 trial in RR-DTC (SELECT; hazard ratio [HR]: 0.21 [99% confidence interval (CI) 0.14–0.31]; $p < 0.001$). This sub-analysis compared clinical outcomes of lenvatinib-treated patients in SELECT stratified by RR-DTC inclusion criteria.

Methods: In SELECT, patients with measurable RR-DTC and radiologic evidence of disease progression ≤ 13 months prior to study entry were randomized 2:1 to lenvatinib (24 mg/day; 28-day cycle) or placebo. In this analysis, patients were stratified based on the following RR-DTC inclusion criteria: no RAI uptake, disease progression within 12 months of RAI therapy despite RAI avidity at the time of treatment, and extensive (>600 mCi) cumulative RAI exposure. All had disease progression as an inclusion criterion for SELECT.

Results: Of 392 patients (261 lenvatinib; 131 placebo) enrolled, 275, 235, and 73 patients met the inclusion criteria for no RAI uptake, disease progression despite RAI avidity, and extensive RAI exposure, respectively. There was significant overlap between the patient groups, with 167 (42.6%) patients meeting more than one inclusion criterion. Lenvatinib improved median PFS compared to placebo in all groups (“no RAI uptake”: lenvatinib not quantifiable [NQ; CI 14.8–NQ] vs. placebo, 3.7 months [CI 2.5–5.3]; “disease progression despite RAI avidity”: lenvatinib 16.5 months [CI 12.8–NQ] vs. placebo, 3.7 months [CI 1.9–5.4]; “extensive RAI exposure”: lenvatinib 18.7 months [CI 10.7–NQ] vs. placebo, 3.6 months [CI 1.9–5.5]). Objective response rates were 71.8%, 60.0%, and 56.0% for patients with no RAI uptake, disease progression despite RAI avidity, and extensive RAI exposure, respectively. Lenvatinib-related adverse events were similar across groups.

Conclusions: Comparable efficacy and safety profiles were observed in lenvatinib-treated patients regardless of RR-DTC criteria, possibly because of a large overlap among patients fulfilling each criterion. However, differing definitions for RR-DTC may be equally valid because both lenvatinib and placebo arms exhibited similar PFS outcomes across groups.

Keywords: lenvatinib, thyroid cancer, multitargeted kinase inhibitor, Phase 3, radioiodine therapy

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Introduction

APPROXIMATELY 90% OF ALL thyroid cancers are differentiated thyroid cancer, which is typically treated with surgery in the first instance, followed by ablation of the thyroid remnant with radioiodine (RAI) (1). Approximately four cases per million of the population are refractory to RAI therapy (2). Life expectancy for patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC) is three to six years, with a 10-year survival rate of 10% from the time metastatic lesions are detected (2–4).

Patients with RR-DTC have few options if further treatment is needed for metastatic disease, and novel therapeutic strategies are therefore required (3). Tyrosine kinase inhibitors (TKIs) have demonstrated promising results in the treatment of RR-DTC (3,5). Lenvatinib is an oral multi-kinase inhibitor that targets vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors (FGFR) 1–4, platelet-derived growth factor receptor- α , and RET and KIT proto-oncogenes (6–8). Lenvatinib has been approved for the treatment of patients with RR-DTC in Japan, Europe, and the United States (9), based on the results of the randomized, double-blind, multicenter, Phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial, in which lenvatinib significantly increased progression-free survival (PFS) in patients with RR-DTC compared to placebo (hazard ratio [HR]=0.21 [99% confidence interval (CI) 0.14–0.31]; $p < 0.001$) (10).

Patients with RR-DTC often present with clinically heterogeneous lesions (5,10–12). Based on clinical presentation and tumor imaging scans, most patients with RR-DTC fall into one or more of the following categories (13,14): those with metastatic disease that does not take up RAI at the time of initial treatment; those with tumors that have previously taken up RAI but have lost the ability to do so; those with tumors that retain RAI uptake in only some lesions; those with metastatic disease that progresses despite substantial RAI uptake; and those with disease progression despite receiving >600 mCi (22.3 GBq) of RAI.

In clinical studies in accordance with the prescribed criteria for RR-DTC, TKIs showed efficacy, but the correlation between each of these categories of RR-DTC and a patient's response to RAI therapy is unclear. Therefore, establishing a common definition for RR-DTC has become increasingly important because clinicians need to recognize the point at which RAI therapy is no longer beneficial to a patient and when to initiate the use of emerging systemic treatment options for this disease setting. This analysis examines the efficacy and safety of lenvatinib in patients with RR-DTC according to the three definitions of RR-DTC used as inclusion criteria in SELECT.

Materials and Methods

Study design

The full details of SELECT (ClinicalTrials.gov number NCT01321554) have been previously published (10). Briefly, patients with RR-DTC, measurable disease, and independently reviewed radiologic evidence of disease progression within 13 months prior to study entry were randomized 2:1 to receive lenvatinib (24 mg/day in a 28-day cycle) or placebo until disease progression or unacceptable toxicity. Patients were stratified by age (≤ 65 or >65 years), geographic region (Europe, North America, or other), and prior TKI treatment (yes or no).

Up to one prior TKI treatment was allowed. The trial had a crossover design that allowed patients who progressed on placebo to be offered open-label treatment with lenvatinib (10).

For the current analysis, patients in SELECT were stratified according to the three RR-DTC inclusion criteria. Patients with one or more measurable lesion that did not demonstrate RAI uptake on any RAI scan were included in the “no RAI uptake” group. Patients with measurable lesions that had progressed within 12 months of RAI therapy per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (15) despite demonstration of RAI avidity at the time of treatment by pretreatment or posttreatment scanning (these patients were not eligible for possible curative surgical therapy) were included in the “disease progression despite RAI avidity” group. Finally, patients who had received a cumulative activity of RAI >600 mCi (22 GBq), with the last treatment administered less than six months prior to study entry were included in the “extensive RAI exposure” group (10). It is important to note that patients could be included in multiple categories, and this could obscure differences among the three RR-DTC inclusion criteria groups.

Endpoints and assessments

The primary endpoint of SELECT was PFS determined by independent radiologic review in the intent-to-treat population. Secondary endpoints included the objective response rate (ORR) comprising complete or partial response according to RECIST v1.1, and overall survival (OS). Survival endpoints were calculated using Kaplan–Meier product-limit estimates and a stratified log-rank test. Calculation of HRs and associated CIs used a Cox proportional hazards regression model stratified by the randomization factors. Response rates were compared using stratified Cochran–Mantel–Haenszel tests at a two-sided alpha level of 0.05 (10).

Adverse events (AEs) were recorded and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (16). Other safety assessments included symptom and vital signs reporting, hematologic and biochemical laboratory testing, urinalysis, electrocardiography, and echocardiography (including left ventricular ejection fraction) (10).

Results

SELECT enrolled 392 eligible patients from 21 countries (the Americas, Europe, Asia, and Australia) between August 2011 and October 2012 (10,17). The cutoff date for the primary data analysis was November 15, 2013. The median follow-up at this time was 17.1 months for patients who received lenvatinib and 17.4 months for patients on placebo.

Patient groups and characteristics

Of the 392 patients enrolled in SELECT (261 lenvatinib, 131 placebo), 275 patients met the inclusion criteria for “no RAI uptake,” 235 for “disease progression despite RAI avidity,” and 73 for “extensive RAI exposure” (Table 1). All patients had disease progression as an inclusion criterion in SELECT. Baseline characteristics were similar across groups, with the exception of median RAI activity received, which was higher in the “extensive RAI exposure” group (Table 1). A total of 167 (42.6%) patients met more than one RR-DTC criterion and were therefore included in multiple groups (Fig. 1). The greatest

TABLE 1. BASELINE AND DEMOGRAPHIC CHARACTERISTICS BY RR-DTC INCLUSION CRITERIA

	<i>No RAI uptake</i>		<i>Disease progression despite RAI avidity</i>		<i>Extensive RAI exposure</i>	
	<i>Lenvatinib (n=174)</i>	<i>Placebo (n=101)</i>	<i>Lenvatinib (n=155)</i>	<i>Placebo (n=80)</i>	<i>Lenvatinib (n=50)</i>	<i>Placebo (n=23)</i>
Age, years, median (range)	63 (27–89)	62 (21–81)	64 (27–89)	62 (40–81)	63 (27–83)	60 (46–74)
Sex, <i>n</i> (%)						
Male	91 (52.3)	57 (56.4)	76 (49.0)	48 (60.0)	19 (38.0)	13 (56.5)
Female	83 (47.7)	44 (43.6)	79 (51.0)	32 (40.0)	31 (62.0)	10 (43.5)
Region, <i>n</i> (%)						
Europe	99 (56.9)	52 (51.5)	88 (56.8)	45 (56.2)	25 (50.0)	9 (39.1)
North America	46 (26.4)	29 (28.7)	44 (28.4)	18 (22.5)	14 (28.0)	6 (26.1)
Asia ^a	27 (15.5)	14 (13.8)	18 (11.6)	12 (15.0)	7 (14.0)	6 (26.1)
Baseline TSH (μ IU/mL), <i>n</i> (%)						
≤ 0.5	149 (85.6)	93 (92.1)	132 (85.2)	74 (92.5)	46 (92.0)	23 (100.0)
>0.5 – 2.0	17 (9.8)	8 (7.9)	18 (11.6)	5 (6.3)	2 (4.0)	0
>2.0 – 5.5	8 (4.6)	0	5 (3.2)	1 (1.3)	2 (4.0)	0
ECOG PS, <i>n</i> (%)						
0	106 (60.9)	56 (55.4)	78 (50.3)	38 (47.5)	24 (48.0)	13 (56.5)
1	64 (36.8)	43 (42.6)	65 (41.9)	42 (52.5)	25 (50.0)	9 (39.1)
2	4 (2.3)	2 (2.0)	11 (7.1)	0	1 (2.0)	1 (4.3)
3	0	0	1 (0.6)	0	0	0
Prior VEGF therapy, <i>n</i> (%)						
0	128 (73.6)	80 (79.2)	117 (75.5)	64 (80.0)	40 (80.0)	17 (73.9)
1	46 (26.4)	21 (20.8)	38 (24.5)	16 (20.0)	10 (20.0)	6 (26.1)
Histology, <i>n</i> (%)						
Papillary	108 (62.1)	72 (71.3)	95 (61.3)	57 (71.3)	30 (60.0)	17 (73.9)
Poorly differentiated	17 (9.8)	16 (15.8)	14 (9.0)	11 (13.8)	4 (8.0)	3 (13.0)
Follicular, not Hürthle cell	66 (37.9)	29 (28.7)	60 (38.7)	23 (28.8)	20 (40.0)	6 (26.1)
Hürthle cell	31 (17.8)	14 (13.9)	26 (16.8)	11 (13.8)	4 (8.0)	3 (13.0)
Mean tumor burden at baseline, mm (range)	68 (15–226)	69 (15–236)	73 (15–331)	74 (15–267)	72 (15–331)	82 (20–143)
Time from most recent disease progression to randomization, <i>n</i> (%)						
<3 months	142 (81.6)	74 (73.3)	122 (78.7)	54 (67.5)	43 (86.0)	14 (60.9)
≥ 3 months	28 (16.1)	24 (23.8)	31 (20)	22 (27.5)	7 (14.0)	8 (34.8)
Missing	4 (2.3)	3 (3.0)	2 (1.3)	4 (5.0)	0	1 (4.3)
Median radioiodine activity received, GBq	11.1 ^b	13.0 ^c	11.8 ^d	11.4 ^e	30.6	30.1

^aAsia including Japan, Republic of Korea, and Thailand.

^bData available for 162 patients.

^cData available for 96 patients.

^dData available for 154 patients.

^eData available for 79 patients.

ECOG PS, Eastern Cooperative Oncology Group performance status; GBq, gigabecquerel (1 GBq=27.0 mCi); RAI, radioiodine; RR-DTC, radioiodine-refractory differentiated thyroid cancer; TSH, thyrotropin; VEGF, vascular endothelial growth factor.

overlap was in the “no RAI uptake” and “disease progression despite RAI avidity” groups, in which 117 (29.8%) patients qualified for both groups. There was only minor overlap between the “no RAI uptake” and “extensive RAI exposure” groups ($n=6$; 1.5%). The number of patients categorized into both the “disease progression despite RAI avidity” and “extensive RAI exposure” groups was slightly higher ($n=19$; 4.8%). There were 25 (6.4%) patients who met all three RR-DTC group criteria. Of the patients enrolled, 224 (57.1%) met only one RR-DTC inclusion criterion. For the 106 total lenvatinib-treated patients across all groups, 65 (61.3%) were ≤ 65 years old, 59 (55.7%) had papillary histology, 47 (44.3%) had follicular histology, 27 (25.5%) had disease progression or death within six months of randomization, and the median tumor size at baseline was 60.9 mm (range 15.1–331.2 mm). For

the 61 total placebo-treated patients, 39 (63.9%) were ≤ 65 years old, 48 (78.7%) had papillary histology, 13 (21.3%) had follicular histology, 41 (67.2%) had disease progression or death within six months of randomization, and the median tumor size at baseline was 59.9 mm (range 15.2–236.1 mm).

Efficacy

The efficacy of lenvatinib was maintained in all three groups regardless of the RR-DTC criteria used, with lenvatinib treatment resulting in significantly longer PFS compared to placebo in all three RR-DTC criteria groups (Figs. 2A–C). Notably, in the placebo arms, PFS was similar regardless of RR-DTC inclusion criteria. Median PFS, in months, in the “no RAI uptake” group was not quantifiable (NQ [CI 14.8–NQ]) versus

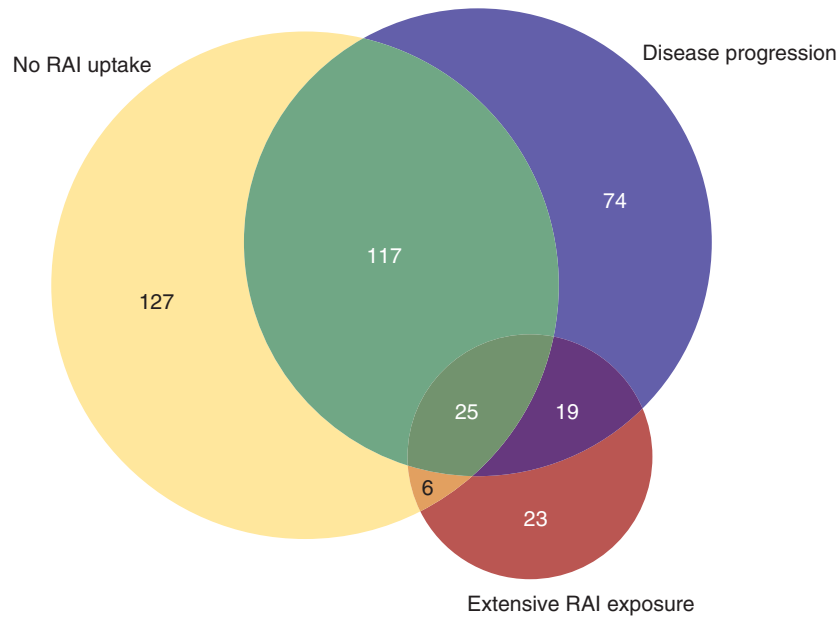


FIG. 1. Venn diagram of patients in SELECT by RR-DTC criteria group. Information is not available for one patient. RAI, radioiodine; RR-DTC, radioiodine-refractory differentiated thyroid cancer; SELECT, Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid.

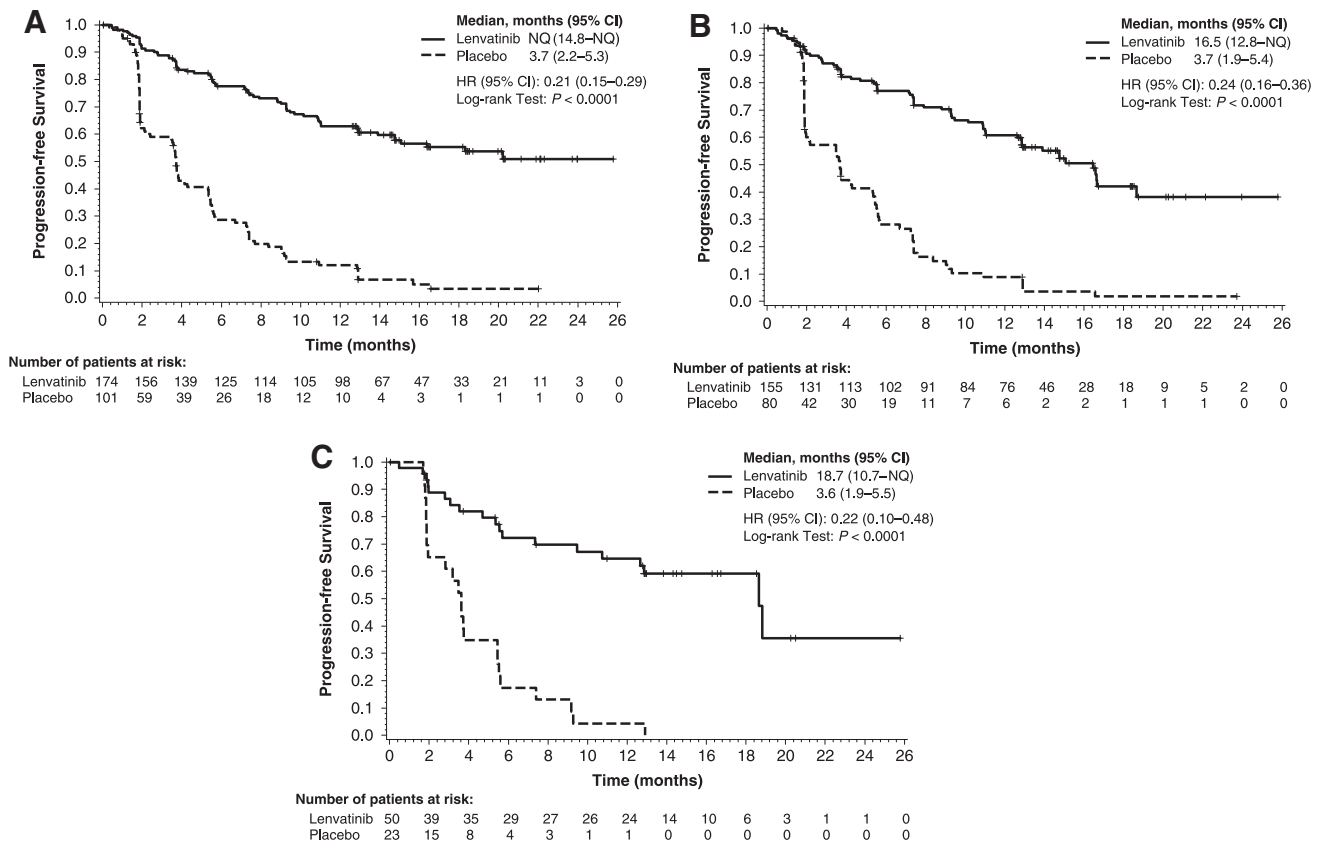


FIG. 2. Kaplan–Meier estimates of progression-free survival by RR-DTC inclusion criteria: (A) no RAI uptake, (B) disease progression, (C) extensive RAI exposure. CI, confidence interval; HR, hazard ratio; NQ, not quantifiable.

TABLE 2. SUMMARY OF TUMOR RESPONSE BY RR-DTC CRITERIA

Response, n (%)	No RAI uptake		Disease progression despite RAI avidity		Extensive RAI exposure	
	Lenvatinib (n=174)	Placebo (n=101)	Lenvatinib (n=155)	Placebo (n=80)	Lenvatinib (n=50)	Placebo (n=23)
ORR	125 (71.8)	2 (2.0)	93 (60.0)	1 (1.3)	28 (56.0)	0
Best overall response						
Complete response	3 (1.7)	0	2 (1.3)	0	0	0
Partial response	122 (70.1)	2 (2.0)	91 (58.7)	1 (1.3)	28 (56.0)	0
Stable disease	30 (17.2)	57 (56.4)	41 (26.5)	43 (53.8)	13 (26.0)	13 (56.5)
Progressive disease	13 (7.5)	38 (37.6)	13 (8.4)	33 (41.3)	3 (6.0)	10 (43.5)
Not evaluable	1 (0.6)	1 (1.0)	1 (0.6)	1 (1.3)	0	0
Unknown	5 (2.9)	3 (3.0)	7 (4.5)	2 (2.5)	6 (12.0)	0

ORR, objective response rate.

3.7 months [CI 2.5–5.3] in the lenvatinib and placebo arms, respectively. In the “disease progression despite RAI avidity” group, median PFS was 16.5 months [CI 12.8–NQ] for lenvatinib versus 3.7 months [CI 1.9–5.4] for placebo. The median PFS in the “extensive RAI exposure” group also favored lenvatinib (18.7 months [CI 10.7–NQ]) compared to placebo (3.6 months [CI 1.9–5.5]).

The ORRs were 71.8%, 60.0%, and 56.0% for patients receiving lenvatinib in the “no RAI uptake,” “disease progression despite RAI avidity,” and “extensive RAI exposure” groups, respectively, compared to 2.0%, 1.3%, and 0%, respectively, for patients receiving placebo (Table 2). Complete responses were reported for three patients in the “no RAI uptake” group and two patients in the “disease progression, despite RAI avidity” group. No patients receiving placebo reported a complete response (Table 2). At data cutoff, median OS was NQ for any group.

Safety

Patients in all three overlapping RR-DTC criteria groups received comparable numbers of cycles of lenvatinib treatment (range 14–16 cycles). Dose intensity and duration of lenvatinib treatment were also similar across groups (Table 3). The safety profiles were generally comparable between the three RR-DTC criteria groups (Table 4). Almost all patients (>96%) experienced a lenvatinib-related treatment-emergent adverse event

(TEAE) in each criteria group. The proportions of patients who experienced lenvatinib-related TEAEs of grade ≥ 3 were also similar across groups, ranging from 73.6% in the “no RAI uptake” group to 76.0% in the “extensive RAI exposure” group. Likewise, the proportion of patients who required lenvatinib dose reductions because of TEAEs was comparable between groups at 69.0% in the “no RAI uptake” group, 63.9% in the “disease progression despite RAI avidity” group, and 56.0% in the “extensive RAI exposure” group. Serious AEs were experienced by 44.3% of patients in the “no RAI uptake” group, 54.2% of patients in the “disease progression despite RAI avidity” group, and 58.0% of patients in the “extensive RAI exposure” group. Fatal treatment-related AEs occurred in 1.1% of patients in the “no RAI uptake” group, 1.3% of patients in the “disease progression despite RAI avidity” group, and 2.0% of patients in the “extensive RAI exposure” group.

Discussion

This analysis demonstrates that the efficacy and safety of lenvatinib was similar regardless of the RR-DTC criteria used to select patients for enrollment in SELECT. PFS, the primary efficacy measure in the original trial, was significantly longer in patients receiving lenvatinib compared to placebo in all three RR-DTC criteria groups. The comparable outcomes observed among the RR-DTC criteria groups suggest that lenvatinib may be effective in treating RR-DTC, irrespective

TABLE 3. LENVATINIB EXPOSURE AND DOSE MODIFICATION BY RR-DTC CRITERIA

Median (range)	No RAI uptake		Disease progression despite RAI avidity		Extensive RAI exposure	
	Lenvatinib (n=174)	Placebo (n=101)	Lenvatinib (n=155)	Placebo (n=80)	Lenvatinib (n=50)	Placebo (n=23)
Number of cycles received	16.0 (1–30)	5.0 (1–25)	15.0 (1–30)	5.0 (1–26)	14.0 (1–29)	5.0 (2–16)
Duration of treatment, months	13.9 (0–27)	4.6 (0–22)	13.6 (0–27)	4.2 (1–24)	12.3 (0–26)	4.1 (2–14)
Dose intensity, mg/day/patient	17.2 (6–24)	24.0 (18–24)	17.0 (6–25)	24.0 (15–24)	17.0 (8–24)	24.0 (22–24)
Received percentage of planned dose	71.8 (24–100)	100.0 (75–100)	70.6 (26–106)	100.0 (61–100)	70.7 (31–100)	100.0 (92–100)

TABLE 4. TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS (AS ASSESSED BY INVESTIGATOR) OCCURRING IN $\geq 20\%$ OF PATIENTS IN ANY TREATMENT GROUP

Related TEAE, %	No RAI uptake				Disease progression despite RAI avidity				Extensive RAI exposure			
	Lenvatinib (n=174)		Placebo (n=101)		Lenvatinib (n=155)		Placebo (n=80)		Lenvatinib (n=50)		Placebo (n=23)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any related TEAE	96.6	73.6	58.4	9.9	96.8	74.8	56.3	10.0	98.0	76.0	34.8	0
Hypertension	66.7	41.4	10.9	2.0	67.7	40.0	10.0	3.8	66.0	38.0	4.3	0
Diarrhea	65.5	8.0	7.9	0	53.5	7.7	10.0	0	46.0	2.0	0	0
Decreased weight	44.8	6.3	8.9	0	49.7	11.0	10.0	0	56.0	12.0	0	0
Decreased appetite	47.1	2.9	11.9	0	52.9	6.5	11.3	0	48.0	6.0	4.3	0
Nausea	39.1	1.7	13.9	1.0	45.2	2.6	13.8	0	38.0	0	4.3	0
Fatigue	38.5	2.3	19.8	1.0	38.1	6.5	16.3	1.3	34.0	4.0	8.7	0
Stomatitis	36.2	2.9	5.0	0	34.2	5.8	5.0	0	38.0	10.0	0	0
Proteinuria	33.3	10.3	2.0	0	30.3	9.0	1.3	0	14.0	4.0	0	0
Vomiting	28.2	1.7	5.9	0	32.9	2.6	8.8	0	28.0	0	0	0
Palmar-plantar erythrodysesthesia syndrome	31.0	3.4	1.0	0	29.0	2.6	1.3	0	26.0	2.0	0	0
Headache	28.7	2.3	5.9	0	25.8	3.2	6.3	0	16.0	0	0	0
Dysphonia	25.9	1.1	3.0	0	23.9	1.3	5.0	0	26.0	0	0	0
Asthenia	23.6	3.4	9.9	1.0	20.6	4.5	10.0	1.3	14.0	2.0	4.3	0
Arthralgia	20.1	0	0	0	14.2	0	1.3	0	10.0	0	0	0
Dysgeusia	16.7	0	2.0	0	18.1	0	1.3	0	20.0	0	0	0

TEAE, treatment-emergent adverse event.

of the criteria used to define the parameters of the radioiodine refractoriness. Likewise, patients in all three groups were similarly tolerant of the treatment, with little variation in the safety outcomes between the three RR-DTC groups. It is important to note that there was a large number of patients who satisfied the criteria for more than one RR-DTC group, including nearly 30% of patients who fulfilled both the “no RAI uptake” and “disease progression despite RAI avidity” criteria, which likely influenced the comparable efficacy and safety profiles between RR-DTC criteria groups. In addition, all patients in SELECT had disease progression, and this is a major confounding factor in this analysis.

The three RR-DTC criteria used in this study have been used in a number of other studies (11,14,18). However, the criteria have been considered unsatisfactory by some researchers, as the RAI activity given per treatment has often been undefined in studies, leading to uncertainty as to whether the activity was truly in the therapeutic range or if, in fact, radioiodine-refractory properties were defined based on lack of response to sub-therapeutic RAI activity (19). The maximum cumulative RAI activity (600 mCi or 22 GBq) is somewhat arbitrary and is based on studies that showed that cumulative activity >600 mCi increased the risk of secondary cancers but was unlikely to be associated with complete responses (4,14,19). It is possible that a patient classified with RR-DTC using these criteria may in fact not be refractory to RAI at all, and some authors have argued that the total cumulative RAI activity should be based on toxicity and efficacy in individual patients rather than on broad guidelines (20).

Disease progression, despite RAI treatment, has been identified as an important indication for starting a patient on a TKI, as differentiated thyroid cancer follows a generally indolent path (5). Initiation of treatment with a TKI should be done in order to achieve a specific patient-related outcome, such as tumor response or symptom control, and with due consideration of toxicity risks (5). Notably, lenvatinib also demonstrated activity in patients who had already progressed after receiving a different TKI, possibly because of lenvatinib inhibiting a unique set of kinase receptors, including FGFRs (10). The present analysis suggests that lenvatinib may also be effective, irrespective of the RR-DTC criteria used to identify radioiodine-refractory patients who showed disease progression within the previous 13 months. This disease progression requirement for inclusion in the study may also contribute to similarities in PFS among patients treated with lenvatinib presented here.

In conclusion, this analysis demonstrates that lenvatinib-treated patients experience comparable efficacy and safety profiles regardless of RR-DTC criteria used. These results may indicate that differing definitions for RR-DTC are equally valid for selection for lenvatinib therapy.

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