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Original Research

Impact of dose interruption on the efficacy of lenvatinib in a phase 3 study in patients with radioiodine-refractory differentiated thyroid cancer

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Abstract ***Background:*** In the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT), lenvatinib significantly improved efficacy outcomes versus placebo in patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC). Lenvatinib-treated patients had more adverse events (AEs), which were generally managed with dose modifications, including dose interruption. This exploratory *post hoc* analysis investigated the impact of dose interruption on lenvatinib efficacy.

Methods: Dose modifications were required for grade 3 or intolerable grade 2 AEs in SELECT. Lenvatinib-treated patients were dichotomised based on the duration of dose interruption relative to total treatment duration: shorter dose interruption (<10% of total treatment duration) and longer dose interruption (≥10%).

Results: At the time of primary data cut-off (November 15, 2013; median follow-up, 17.1 months), the median progression-free survival (PFS) for the shorter dose-interruption group had not yet been reached, whereas median PFS for the longer dose-interruption group was 12.8 months (95% confidence interval [CI], 9.3–16.5). Compared with placebo, the hazard

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ratios for PFS in the shorter and longer dose-interruption groups were 0.14 (95% CI, 0.09–0.20) and 0.31 (95% CI, 0.22–0.43), respectively. In a multivariate model, dose interruption was significantly associated with lenvatinib efficacy, even after adjustment for patient characteristics.

Conclusions: Lenvatinib improved efficacy outcomes versus placebo in patients with RR-DTC, regardless of the duration of dose interruption; however, those with shorter dose interruptions had a greater magnitude of benefit versus those with longer interruptions. This analysis highlights the importance of timely management of lenvatinib toxicities to minimise dose interruptions and maximise lenvatinib efficacy in patients with RR-DTC.

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1. Introduction

The incidence of thyroid cancer has been increasing over the past few decades [1]. In 2012, an estimated 298,102 new cases of thyroid cancer were diagnosed worldwide [2]. Three types of thyroid cancer have been defined based on histologic characteristics: differentiated thyroid cancer (DTC), medullary thyroid cancer and anaplastic thyroid cancer [3]. DTC, which includes papillary thyroid and follicular thyroid cancers, accounts for approximately 90% of diagnosed thyroid cancer cases [3]. In terms of treatment, patients with DTC typically receive a combination of surgery, radioiodine ablation and thyroid-stimulating hormone suppression [3]. Approximately 85% of patients with DTC respond to this standard treatment regimen; however, a small percentage of patients with DTC develop metastatic disease that is non-radioactive iodine-avid, which is also termed radioiodine-refractory DTC (RR-DTC) [4]. For these patients with RR-DTC, a different treatment regimen is required.

Lenvatinib is an oral, multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors (VEGFRs) 1, 2 and 3; fibroblast growth factor receptors 1, 2, 3 and 4; platelet-derived growth factor receptor α, RET proto-oncogene, and KIT proto-oncogene receptor tyrosine kinase [5–8]. In the primary analysis of the phase 3 randomised, double-blind, placebo-controlled, multicenter Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT), lenvatinib significantly prolonged progression-free survival (PFS) versus placebo (18.3 versus 3.6 months; hazard ratio [HR], 0.21; 99% confidence interval [CI], 0.14–0.31; $P < 0.001$) in patients with progressive RR-DTC [9]. Based on the results of SELECT, lenvatinib monotherapy was approved for the treatment of RR-DTC in the United States, Europe and Japan [10–12]. Furthermore, in the 2017 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, lenvatinib was distinguished as the 'preferred' treatment for progressive or symptomatic RR-DTC [13].

Despite the efficacy of lenvatinib, patients who received the drug in SELECT had more adverse events (AEs) than those who received placebo; correspondingly, more patients on lenvatinib required a dose interruption versus placebo (82.4% versus 18.3%, respectively) [9]. Toxicities with lenvatinib were generally manageable with dose modifications, and most AEs in SELECT resolved to grade 1 or baseline several days after drug interruption. However, for some patients, certain AEs (e.g. proteinuria) did not resolve, even after several weeks of drug interruption, and it remained unclear whether a long period of dose interruption impacted the efficacy of lenvatinib.

One concern is that during a dose interruption, patients are at risk of tumour regrowth, leading to the hypothesis that longer interruption may correlate with disease progression or with reduced efficacy. The design of SELECT did not allow patients to remain on study drug upon disease progression, which was assessed by Response Evaluation Criteria in Solid Tumors (RECIST). Therefore, for those patients who developed disease progression, treatment had to be discontinued, regardless of dose interruption. Here, we report a *post hoc* analysis of the impact of dose interruption on the efficacy of lenvatinib in patients from SELECT.

2. Materials and methods

2.1. Patients and study design

The full details of the design of SELECT and patient selection have been previously published [9]. Briefly, this phase 3, randomised, double-blind, placebo-controlled, global trial enrolled patients aged ≥18 years who had measurable, histologically or cytologically confirmed DTC; evidence of radioiodine-refractory disease and independently reviewed radiologic evidence of progression within the previous 13 months. In addition, eligible patients had received 0 or 1 prior VEGF/VEGFR-targeted therapy. Patients were randomised in the ratio of 2:1 to receive 24 mg/day of oral lenvatinib or placebo

in 28-day cycles. SELECT was conducted according to the Declaration of Helsinki and local laws, and the study protocol was approved by all relevant institutional review bodies. All participants provided informed consent.

2.2. Study treatment and assessments

In SELECT, study drugs were administered until disease progression, as assessed by independent imaging review, development of unacceptable toxicity or withdrawal of consent [9]. Dose modifications were required for grade 3 AEs or intolerable grade 2 AEs—the study drug was to be interrupted until the AE had resolved to grade 0–1 or baseline, then to be resumed at a lower dose. Specific management plans, which are detailed elsewhere, were also implemented for the management of hypertension and proteinuria [14,15]. Tumour assessments were performed by independent imaging review and used the RECIST, version 1.1.

2.3. Statistical analysis

This exploratory post hoc analysis included only patients randomised to receive lenvatinib in SELECT. Dose interruption included interruption of study therapy for any reason. The overall median duration of dose interruption in SELECT was about 9% of total treatment duration (median total treatment duration: 13.8 months); therefore, for this analysis, patients assigned to lenvatinib in SELECT were dichotomised into the following 2 groups based on the duration of dose interruption (rounded to 10%) relative to the total treatment duration: (1) those with duration of dose interruption <10% of total treatment duration and (2) those with duration of dose interruption ≥10% of total treatment duration. The analysis was repeated using cut-offs based on an absolute measure of duration of dose interruption: the maximum duration of interruption per episode of interruption. These cut-offs included (1) patients with dose interruption of 0–14 days, (2) patients with dose interruption of 15–28 days and (3) patients with dose interruption of ≥29 days. These cut-offs were chosen because each treatment cycle was 28 days and study visits were scheduled on day 1 and day 15 of each treatment cycle.

In this study, PFS was defined as the time from the date of randomisation to the date of the first documentation of disease progression or death, whichever occurred first. The HR of lenvatinib versus placebo for PFS and the 99% and 95% CIs were estimated using the Cox proportional hazards model. The median and quartiles for PFS and the rates of PFS were calculated using the Kaplan–Meier product-limit estimates for each treatment arm and presented with 2-sided 95% CIs. The rates of response, clinical benefit and disease control were compared with the use of Cochran–Mantel–Haenszel tests at a 2-sided significance level of 0.05. The influence of various baseline characteristics on PFS was analysed using a multivariate analysis based on a Cox proportional hazards model with a 2-sided significance level of 0.05. The demographic characteristics included were dose-interruption group, age group, gender, region, race, body mass index (BMI) group and Eastern Cooperative Oncology Group performance status (ECOG PS) scores. The type of histology, thyroid-stimulating hormone group and bone and lung metastases sites were not included in the multivariate analysis because these variables were deemed to be comparable between the dose-interruption groups. All statistical analyses were performed using SAS®, version 9.3 (SAS Institute Inc, Cary, NC, USA).

3. Results

3.1. Patient characteristics

Of the 261 patients randomised to the lenvatinib group in SELECT, all patients experienced a dose interruption. A total of 134 patients experienced a dose interruption of duration <10% of the total treatment duration (shorter dose interruption; median accumulated duration of dose interruption, 19 days), and 127 had a dose interruption of ≥10% (longer dose interruption; median accumulated duration of dose interruption, 61 days). Baseline patient characteristics by dose-interruption duration group are summarised in Table 1; 36 of 134 patients in the shorter dose-interruption group and 30 of 127 patients in the longer dose-interruption group had received 1 prior VEGF-targeted treatment. As expected, there were a few differences in baseline characteristics between the groups, including in age, ECOG PS, sex, region, race and BMI category.

3.2. Duration of treatment interruption and correlation with efficacy

PFS was the primary end-point of SELECT [9]. Therefore, to determine if the duration of treatment interruption affected lenvatinib efficacy, the PFS for each group was examined (Fig. 1). At the time of data cut-off for the primary analysis (November 15, 2013), the median duration of follow-up for the shorter (<10%) lenvatinib dose-interruption group was 16.9 months (95% CI, 15.5–18.1); for the longer (≥10%) group, it was 17.1 months (95% CI, 15.7–17.8). The median duration of follow-up for the placebo group was 17.4 months (95% CI, 15.9–19.0) [9]. The median PFS for the shorter lenvatinib dose-interruption group was not yet reached at the time of data cut-off. However, in comparison with placebo, the HR for this group was 0.14 (95% CI, 0.09–0.20). In contrast, the median PFS for the longer (≥10%) lenvatinib dose-interruption group was 12.8 months (95% CI, 9.3–16.5), and the

Table 1
Baseline characteristics and study drug exposure of patients randomised to lenvatinib in SELECT, grouped by duration of dose interruption (as percentage of total treatment duration).

Characteristics	Lenvatinib (n = 261)	
	Duration of dose interruption <10% (n = 134)	Duration of dose interruption ≥10% (n = 127)
Median age, year (range)	61.5 (27–83)	65.0 (39–89)
Age group (years), n (%)		
≤65	90 (67.2)	65 (51.2)
>65	44 (32.8)	62 (48.8)
Sex, n (%)		
Male	68 (50.7)	57 (44.9)
Female	66 (49.3)	70 (55.1)
Region, n (%)		
Europe	74 (55.2)	57 (44.9)
North America	39 (29.1)	38 (29.9)
Other	21 (15.7)	32 (25.2)
Race, n (%)		
White	115 (85.8)	93 (73.2)
Black/African American	3 (2.2)	1 (0.8)
Asian	14 (10.4)	32 (25.2)
Japanese	9 (6.7)	21 (16.5)
Other Asian	5 (3.7)	11 (8.7)
Native Hawaiian/ Pacific Islander	0	1 (0.8)
Other	2 (1.5)	0
TSH group at baseline (uIU/mL), n (%)		
≤0.5	116 (86.6)	110 (86.6)
>0.5–2.0	12 (9.0)	13 (10.2)
>2.0–5.5	6 (4.5)	4 (3.1)
Mean BMI, kg/m^2 (SD)	27.7 (5.6)	26.8 (6.7)
Minimum, maximum	17.4, 47.6	15.3, 58.8
BMI group, n (%)		
<25 kg/m^2	48 (35.8)	58 (45.7)
25–<30 kg/m^2	43 (32.1)	36 (28.3)
≥30 kg/m^2	43 (32.1)	33 (26.0)
Median weight, kg (range)	75 (42–155)	69 (33–136)
Height (cm), n	131	124
Median height (range)	168 (146–193)	164 (138–191)
ECOG PS score, n (%)		
0	86 (64.2)	58 (45.7)
1	45 (33.6)	59 (46.5)
2	3 (2.2)	9 (7.1)
3	0	1 (0.8)
Number of previous VEGF-targeted therapies, n (%)		
0	98 (73.1)	97 (76.4)
1	36 (26.9)	30 (23.6)
Histology, n (%)		
Papillary	60 (44.8)	72 (56.7)
Poorly differentiated	13 (9.7)	15 (11.8)
Follicular, non-Hürthle cell	31 (23.1)	22 (17.3)
Hürthle cell	30 (22.4)	18 (14.2)
Metastasis site, n (%)		
Bone	52 (39)	52 (41)
Lung	119 (89)	107 (84)
Median dose intensity, mg/day/patient (range)	20.1 (6–25)	14.6 (6–24)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; SELECT, Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid; TSH, thyroid-stimulating hormone; VEGF, vascular endothelial growth factor.
Percentages are based on the total number of randomised patients in the dose-interruption group.

HR for this group compared with placebo was 0.31 (95% CI, 0.22–0.43). To examine if the differences in baseline characteristics observed between the two dose-interruption groups influenced these PFS outcomes, a multivariate analysis was performed (Table 2). Out of the variables tested (dose interruption, age, sex, region, race, BMI and ECOG PS score), only ECOG PS score and dose-interruption group impacted PFS in a statistically significantly manner. The relationship between PFS and lenvatinib dose interruption was also examined by stratifying patients according to their maximum duration of dose interruption per episode of interruption (Supplemental Figure 1 and 2, Supplemental Table S1).

Other efficacy outcomes, including best overall response, disease control rate and clinical benefit rate, were also compared between the dose-interruption groups and are summarised in Table 3. Patients in the shorter dose-interruption group had a better objective response rate (ORR; 76.1%) than those in the longer dose-interruption group (52.8%). This difference was mostly driven by the gain in partial responses in the shorter dose-interruption group, which was achieved by 73.1% of patients (versus 52.8% of patients in the longer dose-interruption group).

3.3. Safety

Study drug administration and extent of exposure by dose-interruption group are shown in Table 4. The shorter dose-interruption group had a median lenvatinib dose intensity of 20.1 mg/day/patient or a median 83.8% of the planned dose. In contrast, the longer dose-interruption group had a median lenvatinib dose intensity of 14.6 mg/day/patient or 60.9% of the planned dose.

Common treatment-emergent adverse events (TEAEs) by dose-interruption group are shown in Table 5. Although almost all patients in both groups experienced at least 1 TEAE, patients in the longer dose-interruption group had lower incidences of diarrhoea and decreased weight but higher incidences of decreased appetite, fatigue, palmar-plantar erythrodysaesthesia, proteinuria and constipation than patients in the shorter dose-interruption group. Common TEAEs leading to dose reduction or interruption are shown in Supplemental Table S2. As expected, more patients in the longer dose-interruption group experienced TEAEs that led to dose reduction or interruption versus the shorter dose-interruption group (95.3% versus 83.6%).

4. Discussion

In SELECT, lenvatinib treatment significantly improved PFS and other efficacy outcomes in patients with RR-DTC compared with placebo [9]. However, almost all patients on lenvatinib experienced TEAEs [9], which

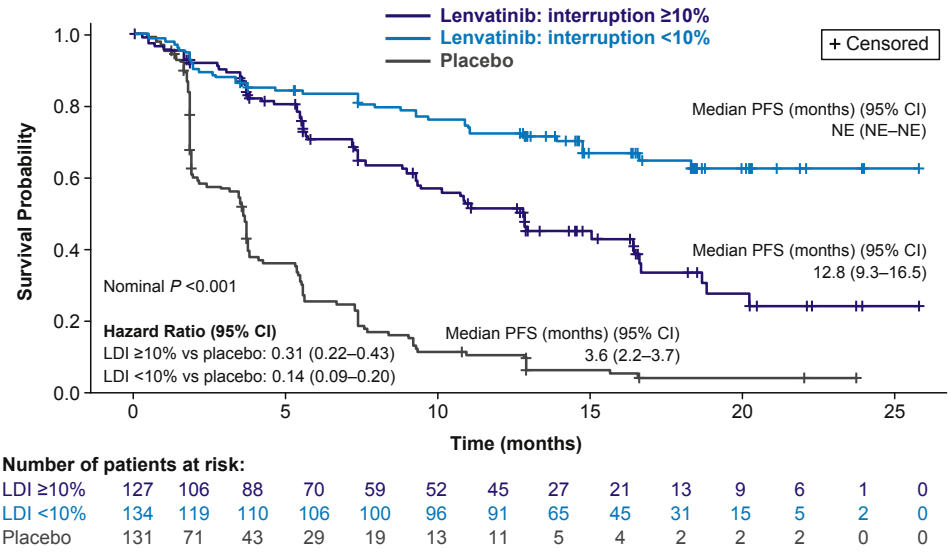

Fig. 1. Kaplan–Meier estimates of progression-free survival. CI, confidence interval; LDI, lenvatinib dose interruption (as percentage of total treatment duration); NE, not evaluable; PFS, progression-free survival.

Table 2
Multivariate analysis of patients randomised to lenvatinib in SELECT.

Parameter	Category	PFS HR	95% CI	Nominal *P* value
Dose interruption	<10% versus ≥10%[a]	0.467	0.307–0.712	0.0004
Age group (years)	≤65 versus >65	0.895	0.606–1.323	0.5781
Sex	Female versus male	0.780	0.529–1.150	0.2095
Region	Europe versus North America	1.381	0.868–2.197	0.3453
	Other versus North America	0.931	0.366–2.370	
Race	Nonwhite versus white	1.081	0.430–2.717	0.8684
BMI category (kg/m^2)	<25 versus ≥ 30	1.321	0.809–2.156	0.5054
	25–<30 versus ≥ 30	1.084	0.637–1.844	
ECOG PS score	0 versus ≥ 1	0.552	0.371–0.821	0.0034

BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival.
[a] Of total treatment duration.

often occurred early in the course of treatment [14]. Consequently, the majority (82.4%) of patients who received lenvatinib had a dose interruption that contributed to a mean lenvatinib dose of 17.2 mg/day (instead of the planned 24 mg/day) [9].

In this report, we performed an exploratory post hoc analysis of the SELECT data to investigate the possible impact of dose interruption on lenvatinib efficacy. Results from our analysis indicated that a longer duration of dose interruption may negatively impact the potential benefit conferred by lenvatinib. Patients with shorter lenvatinib dose interruption (defined as those patients whose duration of dose interruption was <10% of their total treatment duration) derived more PFS benefit from lenvatinib over placebo compared with patients with longer lenvatinib dose interruption (defined as those whose duration of dose interruption was ≥10% of their total treatment duration). Patients with shorter dose interruption also had further improved ORR and clinical benefit rate compared with patients with longer dose interruption. It is important to note, however, that lenvatinib demonstrated improved PFS and ORR compared with placebo, regardless of the duration of lenvatinib dose interruption. The results of our analysis therefore underscore the importance of careful monitoring for AEs, early detection and prompt management of lenvatinib toxicities to minimise lengthy dose interruptions and corresponding reduced dose intensity and exposure, and therefore derive the maximal potential benefit from lenvatinib therapy.

This analysis had several limitations. Notably, it is a post hoc analysis based on post-randomisation events. Consequently, there were several differences in patient characteristics between the non-randomised dose-interruption groups, thus limiting the strength of our conclusions. However, in a multivariate analysis, the duration of dose interruption (<10% or ≥10% of treatment duration) and ECOG PS remained significantly associated with lenvatinib PFS, even after adjusting for patient background characteristics. There was also a technical limitation in the ability to analyse the possible relationship between dose interruption

Table 3
Summary of tumour response.

Parameter	Lenvatinib (n = 261)	
	Duration of dose interruption <10%[a] (n = 134)	Duration of dose interruption ≥10%[a] (n = 127)
Best overall response, n (%)		
CR	4 (3.0)	0
PR	98 (73.1)	67 (52.8)
SD	16 (11.9)	44 (34.6)
Durable SD	12 (9.0)	28 (22.0)
Progressive disease	10 (7.5)	8 (6.3)
Not evaluable	1 (0.7)	0
Unknown	5 (3.7)	8 (6.3)
Objective response rate, n (%)	102 (76.1)	67 (52.8)
95% CI	68.9–83.3	44.1–61.4
Disease control rate, n (%)	118 (88.1)	111 (87.4)
95% CI	82.6–93.5	81.6–93.2
Clinical benefit rate, n (%)	114 (85.1)	95 (74.8)
95% CI	79.0–91.1	67.3–82.4

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.
SD must last ≥7 weeks after randomisation.
Durable SD is a subset of SD with a duration of ≥23 weeks after randomisation.
Objective response = CR + PR; disease control response = CR + PR + SD; clinical benefit response = CR + PR + durable SD.
Percentages are based on the total number of randomised subjects in the relevant treatment group.
[a] Duration of dose interruption as a percentage of total lenvatinib treatment duration.

Table 4
Study drug administration and extent of exposure by dose-interruption group.

Parameter	Lenvatinib (n = 261)	
	Duration of dose interruption <10%[a] (n = 134)	Duration of dose interruption ≥10%[a] (n = 127)
Dose intensity (mg/day/patient)		
Mean (SD)	19.1 (4.25)	15.2 (5.07)
Median (range)	20.1 (6–25)	14.6 (6–24)
Q1, Q3	16.0, 23.1	11.0, 18.2
Received dose as percentage of planned starting dose, %		
Mean (SD)	79.5 (17.69)	63.2 (21.12)
Median (range)	83.8 (27–106)	60.9 (24–100)
Q1, Q3	66.5, 96.3	46.0, 75.7
≤60	19 (14.2)	61 (48.0)
60–70	27 (20.1)	26 (20.5)
70–80	17 (12.7)	11 (8.7)
80–90	21 (15.7)	10 (7.9)
90–100	49 (36.6)	19 (15.0)
>100	1 (0.7)	0

Q, quarter; SD, standard deviation.
Percentages are based on the total number of patients in the safety analysis set within the relevant treatment group.
[a] Duration of dose interruption as a percentage of total lenvatinib treatment duration.

Table 5
Treatment-emergent adverse events occurring in ≥15% of patients in either dose-interruption group.

Preferred term	Lenvatinib (n = 261)	
	Duration of dose interruption <10%[a] (n = 134)	Duration of dose interruption ≥10%[a] (n = 127)
Number of patients with any TEAE	134 (100.0)	126 (99.2)
Hypertension	93 (69.4)	88 (69.3)
Diarrhoea	99 (73.9)	74 (58.3)
Decreased appetite	60 (44.8)	79 (62.2)
Decreased weight	76 (56.7)	56 (44.1)
Nausea	59 (44.0)	62 (48.8)
Fatigue	50 (37.3)	60 (47.2)
Headache	52 (38.8)	48 (37.8)
Stomatitis	45 (33.6)	48 (37.8)
Vomiting	49 (36.6)	43 (33.9)
Palmar-plantar erythrodysaesthesia syndrome	36 (26.9)	48 (37.8)
Proteinuria	31 (23.1)	53 (41.7)
Dysphonia	41 (30.6)	41 (32.3)
Constipation	31 (23.1)	43 (33.9)
Arthralgia	36 (26.9)	30 (23.6)
Asthenia	31 (23.1)	34 (26.8)
Cough	37 (27.6)	21 (16.5)
Myalgia	21 (15.7)	28 (22.0)
Peripheral oedema	22 (16.4)	27 (21.3)
Rash	21 (15.7)	27 (21.3)
Dysgeusia	23 (17.2)	23 (18.1)
Back pain	23 (17.2)	22 (17.3)
Dry mouth	18 (13.4)	26 (20.5)
Abdominal pain	26 (19.4)	16 (12.6)
Musculoskeletal pain	17 (12.7)	25 (19.7)
Upper abdominal pain	23 (17.2)	17 (13.4)
Pain in extremity	25 (18.7)	15 (11.8)
Dizziness	16 (11.9)	23 (18.1)
Dyspnoea	15 (11.2)	24 (18.9)
Oropharyngeal pain	17 (12.7)	19 (15.0)
Pyrexia	15 (11.2)	20 (15.7)
Hypocalcaemia	11 (8.2)	23 (18.1)
Insomnia	8 (6.0)	21 (16.5)

TEAE, treatment-emergent adverse event.
Events ordered by descending frequency in the overall study population.
[a] Duration of dose interruption as a percentage of total lenvatinib treatment duration.

and disease progression—by study design, tumour assessments were conducted every 8 weeks, whereas dose interruption could be implemented by the trial investigator at any point during the study. This analysis also excluded overall survival, so we are unable to conclude if dose interruption had an impact on overall survival. However, this decision was made to focus on the effects of lenvatinib, without the potential confounders of post-study anticancer treatments. An additional limitation is that this analysis was restricted to dose interruptions only and that dose reductions were excluded to avoid analysing two related post-randomisation events. However, the

question of lenvatinib dose intensity is being examined in an ongoing clinical trial comparing lenvatinib starting doses of 18 mg versus 24 mg in patients with RR-DTC [16].

During dose interruption, some patients may develop disease progression. It is important to note that this particular type of progression is likely unrelated to resistance to lenvatinib. Although SELECT did not allow study treatment beyond disease progression, it is possible that some patients with disease progression during a dose interruption could benefit from resuming lenvatinib therapy after AE resolution, as has been observed in a recent study of patients with metastatic renal cell carcinoma [17].

5. Conclusions

In conclusion, our *post hoc* analysis of SELECT indicated that although longer interruption of lenvatinib treatment may impact its efficacy in patients with RR-DTC, lenvatinib treatment nevertheless resulted in significantly improved efficacy outcomes compared with placebo. Appropriate, proactive and thorough management of lenvatinib toxicities to minimise dose interruptions are emphasised to maximise potential lenvatinib efficacy in patients with RR-DTC.

Conflicts of interest statement

Makoto Tahara has received honoraria from Bayer, Bristol-Myers Squibb, Eisai, Merck Serono and Takeda; has had a consulting or advisory role with Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, MSD, Ono Pharmaceutical and Pfizer and has received research funding from AstraZeneca, Bayer, Boehringer-Ingelheim, Eisai, Merck Sharp & Dohme, NanoCarrier, Novartis, Ono Pharmaceutical and Pfizer. Marcia Brose has received honoraria from Bayer; has had a consulting or advisory role with AstraZeneca, Bayer, Blueprint Medicines, Bristol-Myers Squibb, Eisai, Genzyme, Loxo and Novartis and has received research funding from Bayer, Blueprint Medicines, Eisai, Exelixis, Loxo, Novartis and Roche/Genentech. Lori Wirth has had a consulting or advisory role with Amgen, Blueprint Medicines, Eisai, Loxo, Merck and Novartis. Andrew Gianoukakis has had a consulting or advisory role with Eisai and has received research funding from AstraZeneca, Eisai and Roche. Takuya Suzuki, Hideaki Miyagishi and Katsuki Fujino are employees of Eisai Co., Ltd., Japan. Corina Dutcus is an employee of Eisai, Inc., USA.

Previous publication

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Appendix A. Supplementary data

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