Cancer Science
Japanese Cancer Association JCA
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Subgroup analysis of Japanese patients in a phase 3 study of lenvatinib in radioiodine-refractory differentiated thyroid cancer

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Key words

Japanese patients, lenvatinib, progression-free survival, thyroid cancer, treatment efficacy

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Funding Information

Eisai Inc.

Received July 28, 2015; Revised September 16, 2015; Accepted September 18, 2015

Cancer Sci **106** (2015) 1714–1721

doi: 10.1111/cas.12826

Lenvatinib significantly prolonged progression-free survival (PFS) *versus* placebo in patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC) in the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial. This subanalysis evaluated the efficacy and safety of lenvatinib in Japanese patients who participated in SELECT. Outcomes for Japanese patients (lenvatinib, *n* = 30; placebo, *n* = 10) were assessed in relationship to the SELECT population (lenvatinib, *n* = 261; placebo, *n* = 131). The primary endpoint was PFS; secondary endpoints included overall survival, overall response rate, and safety. Lenvatinib PFS benefit was shown in Japanese patients (median PFS: lenvatinib, 16.5 months; placebo, 3.7 months), although significance was not reached, presumably due to sample size (hazard ratio, 0.39; 95% confidence interval, 0.10–1.57; *P* = 0.067). Overall response rates were 63.3% and 0% for lenvatinib and placebo, respectively. No significant difference was found in overall survival. The lenvatinib safety profile was similar between the Japanese and overall SELECT population, except for higher incidences of hypertension (any grade: Japanese, 87%; overall, 68%; grade ≥3: Japanese, 80%; overall, 42%), palmar–plantar erythrodysesthesia syndrome (any grade: Japanese, 70%; overall, 32%; grade ≥3: Japanese, 3%; overall, 3%), and proteinuria (any grade: Japanese, 63%; overall, 31%; grade ≥3: Japanese, 20%; overall, 10%). Japanese patients had more dose reductions (Japanese, 90%; overall, 67.8%), but fewer discontinuations due to adverse events (Japanese, 3.3%; overall, 14.2%). There was no difference in lenvatinib exposure between the Japanese and overall SELECT populations after adjusting for body weight. In Japanese patients with radioiodine-refractory differentiated thyroid cancer, lenvatinib showed similar clinical outcomes to the overall SELECT population. Some differences in adverse event frequencies and dose modifications were observed. Clinical trial registration no.: NCT01321554.

The majority of patients with DTC can be successfully treated with surgical resection followed by radioiodine ablation.[1] However, approximately 5% of patients with DTC show aggressive metastatic disease that does not respond to radioiodine therapy.[2] Patients with RR-DTC typically have a poor prognosis, with a 10-year survival rate of approximately 10%.[3] Until recently, treatment options for patients with RR-DTC were limited. Newer treatment strategies have focused on molecules that inhibit multiple angiogenic pathways involved in the development and progression of tumors.[4] This strategy may circumvent compensatory mechanisms that upregulate other angiogenic pathways when a single pathway is blocked.[4] Additionally, clinical evidence has shown that tumor growth and maintenance extends beyond angiogenesis.[4,5]

In thyroid cancer, the variable expression of fibroblast growth factor receptors 1–4 has been associated with tumor development and aggressiveness.[6,7] Recently, two targeted multikinase inhibitors have demonstrated efficacy for the treatment of RR-DTC in phase 3 clinical trials. Sorafenib, an inhibitor of vascular endothelial growth factor receptors 1–3, platelet-derived growth factor receptor β, Raf-1, RET, and BRAF, was approved in Canada, the European Union, Japan, and by the FDA for treatment of locally recurrent or metastatic, progressive RR-DTC.[8] More recently, lenvatinib (E7080), an orally active inhibitor of

the VEGF receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT signaling pathways,[9–11] was approved in the USA and European Union for the treatment of RR-DTC and in Japan for the treatment of unresectable thyroid cancer. These approvals are based on results from the randomized, phase 3 SELECT trial.[12] In SELECT, lenvatinib was shown to significantly prolong median PFS by 14.7 months (lenvatinib, 18.3 months; placebo, 3.6 months; HR, 0.21; $P < 0.001$) and improve the ORR (64.8% *vs.* 1.5%) compared with placebo.[12] The phase 3 studies for both sorafenib and lenvatinib included Japanese patients as a subset of particular interest in light of the observed differences in efficacy and safety between the Japanese and overall study populations in studies of other targeted therapies.[13,14] Therefore, the aim of the present study was to evaluate the efficacy and safety of lenvatinib in the subset of Japanese patients that participated in the SELECT trial and to evaluate these results in context with the overall study population.

Materials and Methods

Patients. A total of 40 Japanese patients with RR-DTC from the randomized, phase 3 SELECT trial were included in this analysis (total, 392 patients in SELECT). Eligible patients had measurable, pathologically confirmed DTC, evidence of radioiodine-refractory (RR) disease, and independently reviewed radiologic evidence of disease progression within the previous 13 months.[12] Radioiodine-refractory disease was defined by the presence of at least one of the following: at least one measurable lesion without iodine uptake on any radioiodine scan; at least one measurable lesion that had progressed per Response Evaluation Criteria in Solid Tumors version 1.1 within 12 months of radioiodine therapy, despite radioiodine avidity at time of treatment; or cumulative activity of ^{131}I >600 mCi. Eligible patients were randomized 2:1 to receive oral lenvatinib (24 mg once daily) or placebo in 28-day cycles. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. All patients provided written informed consent, and the protocol was approved by all relevant institutional review bodies. This study was carried out in accordance with the Declaration of Helsinki and local laws. Further details on the SELECT study design have been previously published.[12]

Pharmacokinetic analyses. To investigate lenvatinib pharmacokinetics in SELECT patients from Japan, a model-based population PK analysis was examined. Lenvatinib plasma concentration data from 260 patients in the SELECT study were pooled with data from eight phase 1 studies in healthy subjects, four phase 1 studies in subjects with solid tumors, and two phase 2 studies in subjects with thyroid cancer. One subject from the SELECT study was not included as dates and times of doses associated with PK samples were missing. This analysis was therefore carried out on 10 265 lenvatinib plasma concentrations obtained from a total of 779 subjects. Of these 779 subjects, 91 were Japanese, and 30 were Japanese patients from SELECT. The models were developed using NONMEM version 7.2.0 (ICON Development Solutions, Ellicott City, MD, USA) interfaced with PDxPop 5.0 (ICON Development Solutions). Final PK model-derived individual clearance values were used to calculate lenvatinib exposure AUC as AUC = dose (mg) × 1000 × relative bioavailability / individual clearance. Lenvatinib AUC results for the subjects in SELECT are presented here.

Statistical analysis. The PFS and OS rates were estimated and plotted using the Kaplan–Meier method and compared using the stratified log–rank test for the primary analysis on the intention-to-treat population. The HR (expressed as lenvatinib/placebo) and CIs were estimated using a stratified Cox proportional hazards model. Overall survival was reported as both unadjusted and adjusted for a potential cross-over bias using the rank-preserving structural failure time model. For ORR analysis, the *P*-value and OR were calculated using Cochran–Mantel–Haenszel tests.

Results

Patients. Of 392 patients randomized to treatment in SELECT, 40 evaluable patients were enrolled in Japan (lenvatinib, $n = 30$; placebo, $n = 10$). All randomized patients (2:1, lenvatinib: placebo) enrolled in SELECT received at least one dose of treatment; therefore, all were included in both the efficacy

Table 1. Demographics and baseline characteristics of the intention-to-treat population of patients with radioiodine-refractory differentiated thyroid cancer treated with lenvatinib

Characteristic	Japan		Overall SELECT[12]	
	Lenvatinib ($n = 30$)	Placebo ($n = 10$)	Lenvatinib ($n = 261$)	Placebo ($n = 131$)
Median age, years (range)	65.5 (33–83)	65.0 (50–77)	64.0 (27–89)	61.0 (21–81)
Women, *n* (%)	19 (63.3)	8 (80.0)	136 (52.1)	56 (42.7)
Median weight, kg (range)	54.3 (32.6–74.6)	54.6 (31.0–87.0)	73.3 (33–155)	74.0 (31–165)
ECOG PS, *n* (%)				
0–1	29 (96.7)	10 (100.0)	248 (95.0)	129 (98.5)
2–3	1 (3.3)	0	13 (5.0)	2 (1.5)
Prior VEGF-targeted therapy, *n* (%)				
0	27 (90.0)	9 (90.0)	195 (74.7)	104 (79.4)
1	3 (10.0)	1 (10.0)	66 (25.3)	27 (20.6)
Histology (investigator-assessed)				
Papillary	22 (73.7)	3 (30.0)	132 (50.6)	68 (51.9)
Poorly differentiated	4 (13.3)	3 (30.0)	28 (10.7)	19 (14.5)
Follicular	4 (13.3)	4 (40.0)	101 (38.7)	44 (33.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; SELECT, Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid; VEGF, vascular endothelial growth factor.

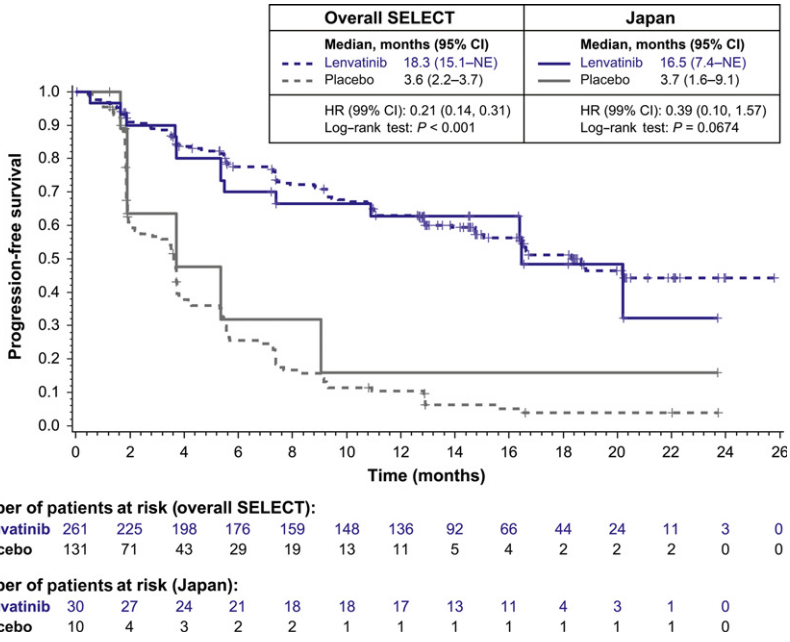

Fig. 1. Progression-free survival rates of overall patients with radioiodine-refractory differentiated thyroid cancer and the Japanese subgroup who participated in the Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial. Kaplan–Meier estimate of progression-free survival in patients treated with lenvatinib (Japanese, $n = 30$; overall, $n = 261$) or placebo (Japanese, $n = 10$; overall, $n = 131$). CI, confidence interval; HR, hazard ratio; NE, not estimable.

Table 2. Summary of efficacy measures of the intention-to-treat population of Japanese patients with radioiodine-refractory differentiated thyroid cancer treated with lenvatinib

Outcome	Lenvatinib ($n = 30$)	Placebo ($n = 10$)	Statistic
PFS			HR (99% CI)
Months, median (95% CI)	16.5 (7.4–NE)	3.7 (1.6–9.1)	0.39 (0.10–1.57)*
Rates, % (95% CI)			
6 months	70.0 (50.3–83.1)	31.7 (4.9–64.7)	
12 months	62.8 (42.9–77.4)	15.9 (0.8–49.6)	
18 months	48.5 (25.5–68.1)	15.9 (0.8–49.6)	
24 months	NE (NE–NE)	NE (NE–NE)	
OS (RPSFT adjusted)			HR (95% CI)
Months, median (95% CI)	20.4 (14.2–NE)	NE (4.9–NE)	1.03 (0.20 to >99.9)**
Rates, % (95% CI)			
6 months	93.3 (75.9–98.3)	90.0 (47.3–98.5)	
12 months	73.3 (53.7–85.7)	77.1 (34.5–93.9)	
18 months	60.1 (39.0–76.0)	77.1 (34.5–93.9)	
24 months	48.1 (21.7–70.4)	NE (NE–NE)	
			OR (95% CI)
ORR,† *n* (%)	19 (63.3)	0 (0.0)	11.64 (1.68–80.82)***
CR, *n* (%)	0 (0.0)	0 (0.0)	
PR, *n* (%)	19 (63.3)	0 (0.0)	
SD, *n* (%)	8 (26.7)	6 (60.0)	
Durable SD ≥23 weeks, *n* (%)	6 (20.0)	3 (30.0)	
PD, *n* (%)	3 (10.0)	3 (30.0)	
NE + unknown, *n* (%)	0 (0.0)	1 (10.0)	
			OR (95% CI)
DCR,‡ *n* (%)	27 (90.0)	6 (60.0)	6.24 (0.92–42.48)****
CBR,§ *n* (%)	25 (83.3)	3 (30.0)	5.68 (0.90–35.92)*****
Time to objective response, months, median (95% CI)	1.9 (1.7–5.6)	–	–
Duration of objective response, months, median (95% CI)	16.6 (14.6–NE)	–	–

†Tumor response was measured according to RECIST by independent centralized radiologic review. ‡Disease control rate (DCR) = complete response (CR) + partial response (PR) + stable disease (SD). §Clinical benefit rate (CBR) = CR + PR + durable SD. –, not applicable; CI, confidence interval; HR, hazard ratio; NE, not estimable (not reached); OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; RPSFT, rank-preserving structural failure time. *$P = 0.067$; **$P = 0.971$; ***$P = 0.0004$; ****$P = 0.029$; *****$P = 0.002$.

(intention-to-treat population) and safety analyses. One patient was excluded from the PK analysis due to missing data. The demographic and baseline characteristics of patients from Japan and the overall study population are summarized in Table 1. Japanese patients were similar to the overall SELECT population in terms of age and baseline Eastern Cooperative

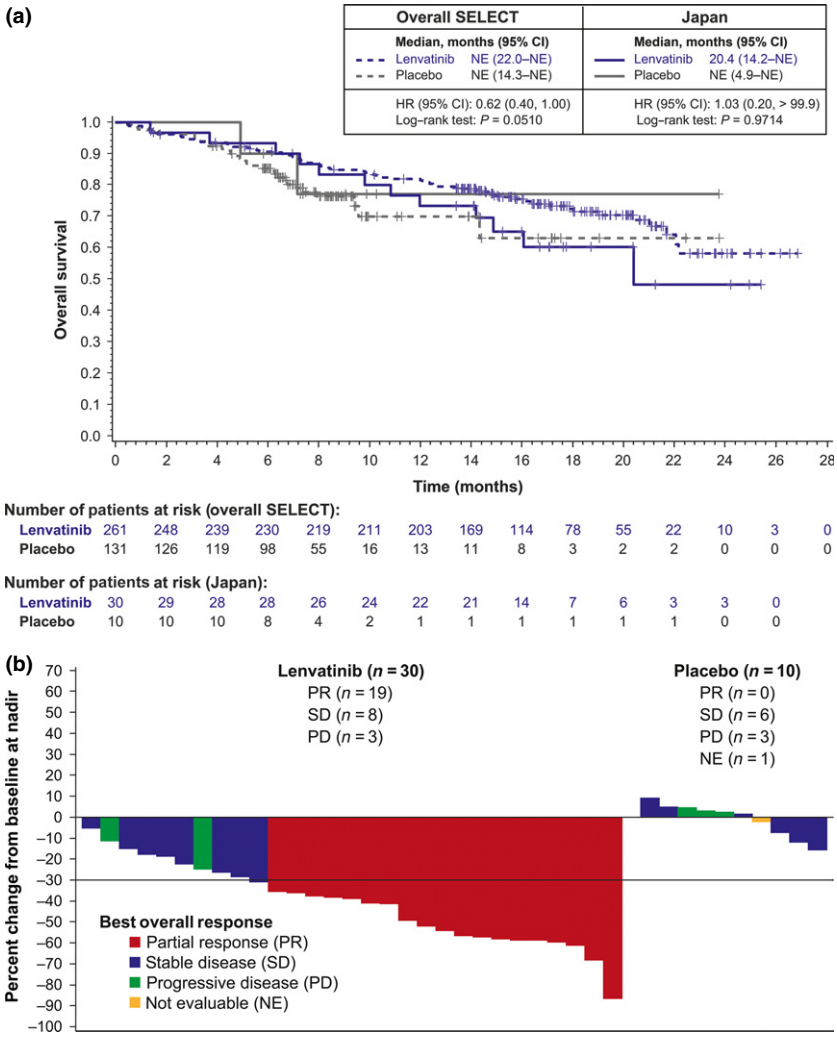

Fig. 2. Overall response and overall survival rates of overall patients with radioiodine-refractory differentiated thyroid cancer and the Japanese subgroup who participated in the Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial. (a) Kaplan–Meier plot of overall survival adjusted with the rank-preserving structural failure time model in patients treated with lenvatinib (Japanese, $n = 30$; overall, $n = 261$) or placebo (Japanese, $n = 10$; overall, $n = 131$). (b) Waterfall graph of maximum percentage change in summed longest diameter of target lesions from baseline to nadir in Japanese patients treated with lenvatinib ($n = 30$) or placebo ($n = 10$). Best overall responses in patients were categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not estimable (NE). CI, confidence interval.

Oncology Group performance status. However, the Japanese subset had a higher proportion of females (Japanese, 67.5%; overall, 49.0%) and lower median body weight (for lenvatinib and placebo arms, respectively: Japanese, 54.3 kg and 54.6 kg; overall, 73.3 kg and 74.0 kg) than those of the overall study population, and a higher proportion of patients in Japan (for lenvatinib and placebo arms, respectively: Japanese, 90% and 90%; overall, 75% and 79%) were naïve to VEGF-targeted therapy. With regard to histology, a higher proportion of Japanese patients randomized to lenvatinib had well-differentiated papillary tumors (73.7%) compared with the placebo group (30.0%) or the overall study population (lenvatinib, 50.6%; placebo, 51.9%).

Efficacy. At the time of data cut-off for the primary analysis (15 November 2013), 14 (46.7%) lenvatinib-treated and 6 (60.0%) placebo-treated patients from Japan had experienced disease progression. Progression-free survival was substantially prolonged with lenvatinib *versus* placebo (HR, 0.39; 95% CI, 0.10–1.57); however, this effect was not statistically significant ($P = 0.067$; Fig. 1, Table 2). Median PFS was 16.5 months (95% CI, 7.4–not estimable) in the lenvatinib arm and 3.7 months (95% CI, 1.6–9.1) in the placebo arm. The 6-month PFS rates were 70.0% and 31.7% for the lenvatinib and placebo arms, respectively (Table 2). These outcomes were consistent with those observed in the overall study population (Fig. 1).

At the time of data cut-off, 12 (40%) lenvatinib-treated and 3 (30%) placebo-treated patients from Japan had died. The difference in OS between treatment arms was not statistically significant in either the unadjusted OS analysis (HR, 2.25; 95% CI, 0.50–10.09; $P = 0.277$; data not shown) or in the analysis adjusting for a potential bias from the cross-over study design (rank-preserving structural failure time-adjusted HR, 1.03; 95% CI, 0.20 to >99.9; $P = 0.971$; Fig. 2a, Table 2). These results are consistent with the estimated OS in SELECT, especially considering the small number of events in the subset of Japanese patients (Fig. 2a).

Lenvatinib showed statistically significant and clinically meaningful improvements in ORR, disease control rate, and clinical benefit rate compared with placebo in the subset of Japanese patients (Table 2). Best overall response is shown in Figure 2(b). The ORR was 63.3% with lenvatinib (all partial responses) compared with 0% for placebo (OR, 11.64; 95% CI, 1.68–80.82; $P = 0.0004$). Patients treated with lenvatinib had a clinical benefit rate of 83.3% compared with 30.0% for placebo (OR, 5.68; 95% CI, 0.90–35.92, $P = 0.002$). Median time to objective response with lenvatinib was 1.9 months (95% CI, 1.7–5.6; Table 2), and median duration of objective response was 16.6 months (95% CI, 14.6–not estimable).

Safety and tolerability. Treatment-emergent adverse events were reported by 100% of lenvatinib-treated and 90% of placebo-treated patients from Japan (Table 3). All 30 lenvatinib-treated patients reported at least one treatment-related TEAE, and 13 (43%) reported a serious AE, of which 7 (23%) were

Table 3. Summary of adverse events in Japanese patients (safety population) with radioiodine-refractory differentiated thyroid cancer treated with lenvatinib

Adverse events, n (%)	Japan		Overall SELECT[12]	
	Lenvatinib (*n* = 30)	Placebo (*n* = 10)	Lenvatinib (*n* = 261)	Placebo (*n* = 131)
Any TEAE	30 (100.0)	9 (90.0)	260 (99.6)	118 (90.1)
Any TRAE	30 (100.0)	6 (60.0)	254 (97.3)	78 (59.5)
Grade ≥3 TRAE	28 (93.3)	1 (10.0)	223 (85.4)	39 (29.8)
Serious AE	13 (43.0)	0 (0.0)	133 (51.0)	31 (23.7)
Treatment-related	7 (23.3)	0 (0.0)	81 (31.0)	8 (6.1)
Fatal TEAE	1 (3.0)	0 (0.0)	20 (7.7)	6 (4.6)
Treatment-related	0 (0.0)	0 (0.0)	6 (2.3)	0 (0.0)
Patient events, *n* (%)				
Dose reduction due to TEAE	27 (90.0)	3 (30.0)	177 (67.8)	6 (4.6)
Dose interruption due to TEAE	24 (80.0)	3 (30.0)	215 (82.4)	24 (18.3)
TEAE-related treatment discontinuation	1 (3.3)	0 (0.0)	37 (14.2)	3 (2.3)
TRAEs (≥20% all grades), %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Hypertension	86.7	80.0	0.0	0.0	67.8	41.8	9.2	2.3
Palmar–plantar erythrodysesthesia syndrome	70.0	3.3	0.0	0.0	31.8	3.4	0.8	0.0
Proteinuria	63.3	20.0	0.0	0.0	31.0	10.0	1.5	0.0
Fatigue/asthenia	60.0	13.3	20.0	0.0	59.0	9.2	27.5	2.3
Diarrhea	60.0	0.0	10.0	0.0	59.4	8.0	8.4	0.0
Decreased appetite	56.7	13.3	10.0	0.0	50.2	5.4	11.5	0.0
Stomatitis	50.0	0.0	0.0	0.0	35.6	4.2	3.8	0.0
Thrombocytopenia	46.7	6.7	20.0	0.0	8.8	1.5	1.5	0.0
Nausea	43.3	0.0	10.0	0.0	41.0	2.3	13.7	0.8
Peripheral edema	40.0	0.0	0.0	0.0	11.1	0.4	0.0	0.0
Vomiting	36.7	0.0	10.0	0.0	28.4	1.9	6.1	0.0
Decreased weight	33.3	3.3	20.0	0.0	46.4	9.6	9.2	0.0
Increased blood-thyroid-stimulating hormone level	30.0	0.0	0.0	0.0	5.7	0.0	0.0	0.0
Dysphonia	26.7	0.0	0.0	0.0	24.1	1.1	3.1	0.0
Arthralgia	26.7	0.0	0.0	0.0	18.0	0.0	0.8	0.0
Constipation	23.3	0.0	30.0	0.0	14.6	0.4	8.4	0.0
Hypoalbuminemia	20.0	3.3	0.0	0.0	5.4	0.4	0.0	0.0
Back pain	20.0	0.0	10.0	0.0	7.3	0.0	3.1	0.0
Dysgeusia	20.0	0.0	0.0	0.0	16.9	0.0	1.5	0.0
Epistaxis	20.0	0.0	0.0	0.0	8.8	0.0	0.8	0.0
Headache	13.3	0.0	0.0	0.0	27.6	2.7	6.1	0.0

AE, adverse event; SELECT, Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

considered treatment-related by the investigator. One lenvatinib-treated patient from Japan experienced a fatal TEAE (hepatic failure due to disease progression) that was considered not related to lenvatinib treatment by the investigator. The five most common treatment-related TEAEs (any grade) in Japanese patients from SELECT were hypertension (86.7%), PPES (70.0%), proteinuria (63.3%), fatigue/asthenia (60.0%), and diarrhea (60.0%; Table 3). In non-Japanese patients from SELECT, these were hypertension (65.4%), PPES (26.8%), proteinuria (26.8%), fatigue/asthenia (58.9%), and diarrhea (59.3%). Grade 3 PPES was reported in 3.3% of lenvatinib-treated patients. The most common treatment-related grade ≥3 TEAEs in the lenvatinib arm were hypertension (80.0%; all grade 3), proteinuria (20.0%), fatigue/asthenia (13.3%), decreased appetite (13.3%), and thrombocytopenia (6.7%). No patient in the placebo group reported a treatment-related grade ≥3 TEAE.

The lenvatinib dose was reduced or interrupted due to AEs in 90.0% and 80.0% of patients, respectively (Table 3). In the placebo arm, dose reduction or interruption due to AEs occurred in 30.0% and 30.0% of patients, respectively. Adverse events that resulted in dose modifications in the placebo arm included increased amylase, parotitis, pneumonia, upper respiratory tract inflammation, prolonged electrocardiogram QT, thrombocytopenia, constipation, fatigue, and herpes zoster (all one case each).The median time to first dose reduction in the lenvatinib arm was 0.9 months (95% CI, 0.5–1.5). Lenvatinib treatment was discontinued due to AEs in one (3.3%) patient (Table 3). The median duration of treatment was 14.3 months (range, 0.5–25.4 months) with lenvatinib and 3.4 months (range, 1.6–23.8 months) with placebo.

Pharmacokinetic assessments. Lenvatinib exposure appeared to be higher in Japanese patients compared with non-Japanese patients from the overall study population (Fig. 3a, left). An analysis of lenvatinib clearance and exposure in relation to body weight, however, indicated that patients with lower body weight tended to have lower lenvatinib clearance and higher lenvatinib exposure (Fig. 3b). Correspondingly, there was no

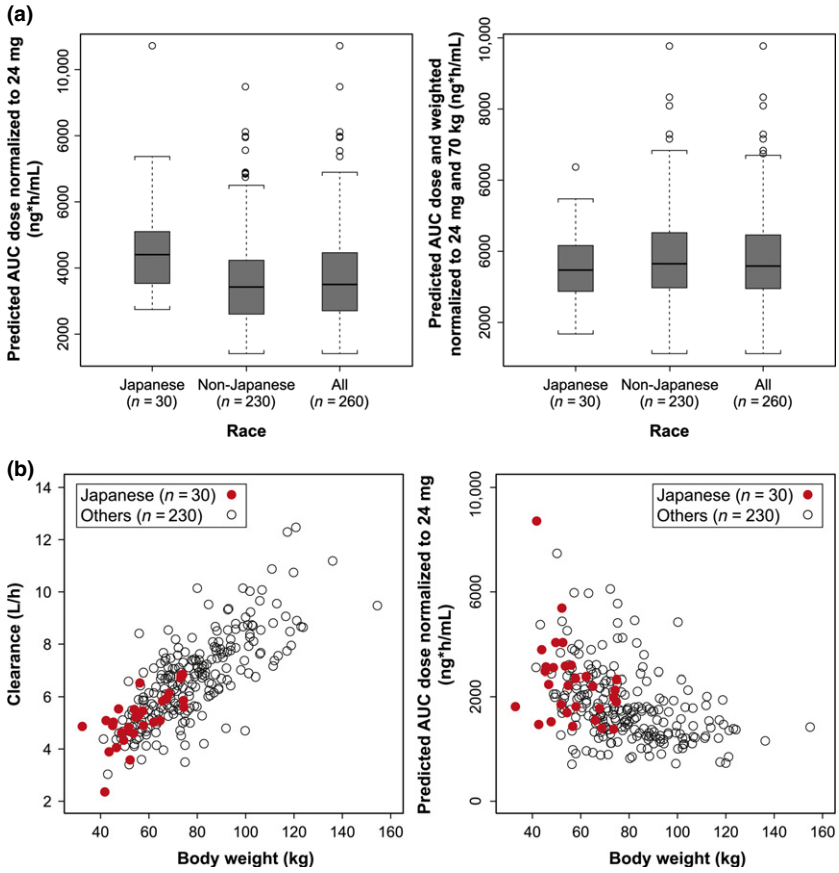

Fig. 3. Pharmacokinetic assessments evaluating lenvatinib exposure in Japanese patients *versus* the overall study population with radioiodine-refractory differentiated thyroid cancer who participated in the Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial. (a) Scatterplot of model-predicted lenvatinib clearance and exposure *versus* body weight in Japanese patients (n = 30) *versus* the remainder of the overall study population (n = 230). (b) Relationship between model-predicted lenvatinib exposure and Japanese race. Lenvatinib exposure was evaluated in Japanese patients (n = 30) *versus* the remainder of the overall study population (non-Japanese patients [n = 230]). AUC, area under the curve.

difference in lenvatinib exposure in Japanese patients compared with non-Japanese patients after adjustment for body weight (Fig. 3a, right).

Discussion

This is the first analysis of Japanese patients with RR-DTC treated with lenvatinib in the phase 3 SELECT trial, and the first SELECT subgroup analysis based on race. Lenvatinib efficacy outcomes in patients from Japan were generally similar to those observed in the overall study population. Japanese patients treated with lenvatinib had prolonged PFS compared with placebo (median, 16.5 *vs*. 3.7 months); however, the PFS results in this subgroup analysis did not reach statistical significance, due to the reduced statistical power associated with the small sample size. Lenvatinib did show a statistically significant and clinically meaningful improvement in ORR within the Japanese subgroup (63.3% compared with 0% for placebo), which was consistent with results in the overall study population (lenvatinib ORR, 64.8%).[12] Median time to response in the lenvatinib arm was also similar for the Japanese subgroup (1.9 months) and the overall study population (2.0 months), which was the time of the first tumor assessment.

Although the small subgroup size limits definite conclusions, a few general observations can be made. The baseline characteristics of patients from Japan were generally similar to that of the overall study population, with a few important exceptions. Lenvatinib-treated patients from Japan tended to have lower body weight (median, 54 kg) than that of the overall study population (median, ~73 kg), and a higher proportion of Japanese patients were naïve to VEGF-targeted therapy. Additionally, there was a higher proportion of papillary thyroid cancer in the Japanese subgroup. Regardless, the efficacy of lenvatinib was remarkably similar in the Japanese subgroup.

The safety profile of lenvatinib among patients from Japan was also similar to that observed in the overall SELECT study population, with a few notable differences in the incidences of several AEs. With respect to the overall study population, Japanese patients treated with lenvatinib had a higher incidence of treatment-related hypertension (any grade: Japanese, 87%; overall, 68%; grade ≥3: Japanese, 80%; overall, 42%), PPES (any grade: Japanese, 70%; overall, 32%; grade ≥3: Japanese, 3%; overall, 3%) and proteinuria (any grade: Japanese, 63%; overall, 31%; grade ≥3: Japanese, 20%; overall, 10%).[12] When compared with non-Japanese patients from SELECT (hypertension, any grade: 65%; grade ≥3: 4%; PPES, any grade: 27%; grade ≥3: 4%; proteinuria, any grade: 27%; grade ≥3: 9%), the higher incidences of these AEs among Japanese patients is still evident. In studies of sunitinib and axitinib, an increased incidence of hypertension, stomatitis, PPES, and grade ≥3 hematological AEs has been observed in Asian patients.[15–17] The frequency and severity of diarrhea (any grade, 43% *vs*. 34%; grade ≥3, 2% *vs*. 1%) and PPES (any grade, 30% *vs*. 55%; grade 3, 6% *vs*. 9%) amongst Caucasian *versus* Japanese patients also differed in studies of patients with renal cell carcioma treated with sorafenib.[18,19] Hypertension and proteinuria are known class-effects of VEGF-targeted therapies,[20–22] whereas PPES was the most frequent AE associated with sorafenib treatment in patients with RR-DTC.[23] Pharmacokinetic assessments showed no clear differences in exposure to lenvatinib among Japanese patients and non-Japanese patients or the overall study popula-

tion after normalizing for dose and body weight. This is consistent with findings reported for other multikinase inhibitors.[17,24] We investigated whether the difference in body weight between Japanese patients and the overall SELECT study population resulted in differences in exposure to lenvatinib, and therefore could possibly explain the observed differences in safety profile. In this study, Japanese patients had increased exposure which was confounded by lower body weight; this could partially contribute to the observed higher incidences of certain AEs in Japanese patients, including hypertension and PPES. However, increased exposure and body weight alone are unlikely to fully explain the observed differences in the incidence of certain AEs between the two populations. Further investigation of interindividual variation in lenvatinib PKs is therefore warranted, and is underway.

Differences in AE management, specifically treatment dose modifications, were also observed in the Japanese subgroup. Patients from Japan had higher rates of dose reductions in both treatment arms than the overall study population (lenvatinib arm: Japanese, 90.0%; overall SELECT, 67.8%; placebo arm: Japanese, 30.0%; overall SELECT, 5%).[12] Lenvatinib dose reductions also occurred earlier during the course of treatment in the Japanese subgroup (median, 0.9 months to the first dose reduction, and 3.0 months in the overall population). However, treatment discontinuations due to AEs occurred less frequently in Japanese lenvatinib-treated patients (3.3% *vs*. 14.2%),[12] indicating that toxicities were managed effectively in this subgroup. Additionally, the median duration of treatment was similar between Japanese patients and the overall study population (14.3 and 13.8 months, respectively),[12] with corresponding clinical efficacy. Therefore, these results suggest that the starting dose of 24 mg lenvatinib was feasible in Japanese patients as well as in the overall study population, when AEs are appropriately managed.

In summary, this analysis indicated a generally similar efficacy and safety profile for lenvatinib in Japanese patients from the overall SELECT study population, although the small number of patients from Japan limited the statistical power needed to make more robust conclusions. The data also suggest that possible regional differences in AE frequencies and dose modifications exist.

Acknowledgments

The authors thank all the patients and their families, as well as all the investigators and their teams who participated in this study. This study was funded by Eisai Inc. Editorial assistance was provided by Oxford PharmaGenesis Inc. and was funded by Eisai Inc.

Disclosure Statement

Naomi Kiyota, Lori Wirth, Bruce Robinson, and Makoto Tahara received research funding and speaker honoraria, Martin Schlumberger and Shunji Takahashi received grants and personal fees, Yuichi Ando and Steven Sherman received speaker honoraria, all from Eisai Inc. Takuya Suzuki, Katsuki Fujino, Anubha Gupta, and Seiichi Hayato are employees of Eisai Inc. Kei Muro and Yasukazu Kawai have no conflicts of interest.

Abbreviations

AE	adverse event
AUC	area under the curve
CI	confidence interval
DTC	differentiated thyroid cancer
HR	hazard ratio
OR	odds ratio
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PPES	palmar–plantar erythrodysesthesia syndrome
RR-DTC	radioiodine-refractory differentiated thyroid cancer
SELECT	Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid
TEAEs	treatment-emergent adverse events
VEGF	vascular endothelial growth factor

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