A Phase II study of the safety and efficacy of lenvatinib in patients with advanced thyroid cancer

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Aim: To investigate the safety and efficacy of lenvatinib in advanced thyroid cancer. **Patients/methods:** In this Phase II study, 51 Japanese patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC), medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC) received once-daily lenvatinib 24 mg. The primary end point was safety. **Results:** All patients experienced ≥ 1 adverse event (AE); only one patient experienced an AE leading to discontinuation. The most common any-grade AEs were hypertension, decreased appetite, palmar-plantar erythrodysesthesia, fatigue and proteinuria. Response rates for RR-DTC: 68%; MTC: 22%; ATC: 24%. Median progression-free survival for RR-DTC: 25.8 months; MTC: 9.2 months; ATC: 7.4 months. **Conclusion:** Lenvatinib demonstrated a manageable safety profile, proven antitumor activity in RR-DTC and promising efficacy in MTC and ATC.

Clinical trial registration: clinicaltrials.gov NCT01728623

Lay abstract: Lenvatinib is approved in Japan and elsewhere to treat radioiodine-refractory differentiated thyroid cancer; however, new therapies are also needed for other forms of advanced thyroid cancer (such as medullary thyroid cancer and anaplastic thyroid cancer). Fifty-one patients from Japan with advanced thyroid cancer received lenvatinib in this clinical trial. All patients experienced at least one side effect during treatment but only one patient experienced a side effect that necessitated stopping lenvatinib therapy. In general, patients tolerated lenvatinib treatment because the side effects were manageable. Lenvatinib treatment showed promising antitumor effects for patients across all thyroid cancer subtypes tested.

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Thyroid cancer is clinically diverse, but can be grouped into three main subtypes: differentiated thyroid cancer (DTC; 94.3% of cases), medullary thyroid cancer (MTC; 2.2% of cases) and anaplastic thyroid cancer (ATC; 1.3% of cases) [1]. Initial treatment options for thyroid cancer are dependent on the type and the disease stage at diagnosis. DTC is initially treated with surgery, followed by radioactive iodine ablation therapy to reduce the risk of recurrence and metastatic disease [2]. Some patients (up to 15%) will develop radioiodine-refractory DTC (RR-DTC) [3], which has a 10-year survival rate of 10% from time of detection of metastatic disease [4]. MTC, which usually occurs spontaneously but can be hereditary in up to 25% of cases [5], may be successfully treated with

surgery in the first instance if diagnosed early when the disease is localized; however, once it metastasizes, survival time is generally short [5]. Nearly 50% of patients with ATC present with metastatic disease at initial diagnosis [6]. The current treatment options for ATC are limited, and the mortality rate is estimated at 90% in the first year [7,8]. New, effective, systemic therapies are, therefore, needed to treat all advanced thyroid cancer subtypes that have metastasized beyond a stage that can be treated with localized therapy or resection.

Lenvatinib is an oral multityrosine kinase inhibitor that acts on the VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor- α and RET and KIT proto-oncogenes [9–11]. Lenvatinib was approved for the treatment of RR-DTC based on the pivotal Phase III Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT), a randomized, double-blind placebo-controlled trial in which lenvatinib significantly prolonged progression-free survival (PFS) in patients with RR-DTC compared with placebo (median PFS: 18.3 vs 3.6 months, respectively; $p < 0.001$) [12]. SELECT included an exploratory analysis of potential biomarkers associated with clinical outcomes; however, this analysis was limited to circulating cytokine/angiogenic factors and mutations of the *BRAF*, *NRAS*, *KRAS* and *HRAS* genes [13]. Recently, the role of the neutrophil-to-lymphocyte ratio (NLR) – a measure of inflammation – as a biomarker for survival in several types of cancers has attracted more attention [14–16].

This Phase II study was undertaken primarily to assess the safety of once-daily lenvatinib in predominantly Japanese patients with advanced thyroid cancers (including RR-DTC, MTC, and ATC). An exploratory analysis of the NLR and its association with clinical outcome was also performed.

Patients & methods

Patients

Patients aged 20 years or older were eligible if they had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90 mmHg; adequate renal, bone marrow, liver and blood coagulation functions; and histologically or cytologically confirmed diagnosis of advanced thyroid cancer of any of the specified subtypes (RR-DTC, MTC or ATC).

Patients with RR-DTC must have had disease progression (according to Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1], confirmed by computerized tomography [CT] or MRI within 12 months before informed consent), a measurable lesion, been receiving thyroxine suppression therapy, and been confirmed as radioiodine-refractory or resistant (one or more measurable lesions with no iodine uptake per radioiodine scanning, or one or more measurable lesions that progressed per RECIST criteria within 12 months of radioiodine therapy despite uptake, or cumulative activity of radioiodine of >600 mCi or 22 gigabecquerel, with the last dose administered at least 6 months before study entry).

Patients with MTC were required to have histologically or cytologically confirmed diagnosis of MTC, evidence of disease progression according to RECIST v1.1 (by CT or MRI) within 12 months before informed consent, and/or clinical disease progression, and an evaluable target lesion or nontarget lesion according to RECIST v1.1.

Patients with ATC were required to have had an evaluable target lesion according to RECIST v1.1, agreed to hospitalization in cycle 1, and be expected to survive for 8 weeks or longer after the first dose of the study drug. Key exclusion criteria included concomitant brain metastases (unless previously treated and clinically stable for ≥ 1 month prior to screening), history of cardiovascular impairment, bleeding, or thrombotic disorders, or use of anticoagulants such as warfarin, proteinuria or previous treatment with lenvatinib.

Study design

This was a nonrandomized, open-label, multicenter, Phase II study. The trial was conducted at three study sites in Japan from 3 September 2012 to 9 July 2015. Study enrollment continued until lenvatinib was approved for unresectable thyroid cancer in Japan. After approval, the trial continued as a postmarketing study until lenvatinib was commercially available at each site. The protocol was amended to reflect this, but the end points and analyses were not changed.

Patients received a once-daily oral lenvatinib dose of 24 mg in 28-day continuous cycles. Treatment continued until disease progression according to RECIST v1.1 or development of unacceptable toxicity occurred. For patients with RR-DTC and MTC, tumor assessments were performed every 8 weeks after the first dose based on investigator assessment per RECIST v1.1. For patients with ATC, tumor assessments were performed at 4, 8, 12 and 16 weeks after the first dose, and every 8 weeks thereafter, based on investigator assessment per RECIST v1.1.

The study was designed in accordance with the Guidelines for Clinical Evaluation of Anti-Cancer Drugs in Japan and with the Declaration of Helsinki and local laws. All patients provided written informed consent.

The institutional review boards of each medical institution (National Cancer Center Hospital East, Kashiwa, Japan; the Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; and the Kobe University Hospital, Kobe, Japan) approved the study and protocol. The trial was registered at www.clinicaltrials.gov (NCT01728623). Statistical analyses were performed by Eisai Co., Ltd, and Takumi Information Technology Inc.

Safety & efficacy analyses

The primary objective was to evaluate the safety of lenvatinib in patients with advanced thyroid cancer. Safety measures included recording of adverse events (AEs), clinical laboratory results (including urinalysis, hematology and blood chemistry), vital signs, weight, electrocardiography and physical exam. AEs were graded using Common Terminology Criteria for AEs version 4.0 (CTCAE v4.0).

Efficacy measures were secondary end points. Key efficacy analyses included PFS (defined as time from the date of first dose to first documentation of disease progression as determined by investigator assessment or death from any causes, whichever occurred first), overall survival (OS; defined as time from the date of first dose to the date of death from any cause), objective response rate (defined as the proportion of patients with a complete or partial response [PR] by RECIST v1.1), disease control rate (defined as the proportion of patients with complete or PR, or stable disease) and clinical benefit rate (defined as the proportion of patients with complete or PR, or durable stable disease [defined as ≥ 23 weeks for DTC and MTC; ≥ 11 weeks for ATC]). An exploratory analysis was undertaken to investigate the NLR at baseline and its effect on PFS.

Statistical analysis

Statistical analyses were performed using Statistical Analysis System (version 9.2 or later). The sample size was based on feasibility. A sample size of ≥ 16 was planned, which was estimated to have a probability of >0.8 (or 80%) to detect AEs with a frequency of $\geq 10\%$. No adjustments for covariates and no statistical comparisons were planned. PFS and OS outcomes were summarized using Kaplan–Meier estimates. For the exploratory biomarker analysis, the effects of baseline NLR on PFS were evaluated using a Cox proportional hazard model. Each cancer classification had varied baseline NLR and PFS results, and were therefore also included in the model as a covariate, for adjustment purposes.

Results

Results for the ATC subgroup in this study have been previously reported [17]. Here, we provide the overall results of the study, inclusive of all thyroid cancer subtypes.

Disposition

The disposition of the study patients has been previously published [17]. In brief, between 3 September 2012 and 9 July 2015, 60 patients were screened for the study, and 51 (RR-DTC, $n = 25$; MTC, $n = 9$; ATC, $n = 17$) were enrolled. All 51 patients received at least one dose of the study drug. Twenty-three patients discontinued due to the termination of the study after approval of lenvatinib, and a further 26 discontinued the study drug due to disease progression. One patient discontinued the study-drug treatment due to a treatment-emergent AE (TEAE), and one discontinued the study drug by choice. All 51 patients were included in the efficacy and safety analysis sets.

Baseline demographics & characteristics

Most (59%) patients were women, and all patients were Japanese. Baseline patient demographics and disease characteristics are shown in Table 1. Baseline ECOG scores were either 0 or 1 for most patients, except for two patients from the ATC group who had an ECOG score of 2 [17]. Surgery was the most common previous treatment across all three thyroid cancer types. Other prior treatments received are listed in Table 1. Of note, all patients with RR-DTC in the study had received previous radioiodine therapy, and only three patients (RR-DTC, $n = 2$; MTC, $n = 1$) had received prior treatment with a VEGF-targeted agent for their cancer. As previously reported, chemotherapy had mostly been received by patients with ATC [17].

Exposure to study drug

Overall, the median number of cycles of study drug received was 15.0 (range: 1–37), and the median duration of exposure was 407 days (range: 22–1009), or 13.4 months (range: 0.7–33.1). In patients with RR-DTC, the median duration of exposure was 727 days (range: 22–981) or 23.9 months (range: 0.7–32.2). In patients with

Table 1. Demographic and baseline disease characteristics.

Parameter	RR-DTC (n = 25)	MTC (n = 9)	ATC (n = 17)	Overall (N = 51)
Age, median (range), years	58 (21–74)	58 (41–79)	65 (36–84)	61 (21–84)
Female sex, n (%)	16 (64)	3 (33)	11 (65)	30 (59)
Weight, median (range), kg	57 (44–99)	52 (40–78)	54 (40–85)	56 (40–99)
ECOG performance status, n (%):				
– 0	17 (68)	8 (89)	5 (29)	30 (59)
– 1	8 (32)	1 (11)	10 (59)	19 (37)
– 2	0	0	2 (12)	2 (4)
Baseline lesion diameter, median (range), mm	51 (19–217)	56 (20–202)	52 (15–232)	–
Previous anticancer therapy or therapies, n (%):				
– Surgery	25 (100)	8 (89)	14 (82)	47 (92)
– Chemotherapy	1 (4)	0	7 (41)	8 (16)
– VEGF therapy	2 (8)	1 (11)	0	3 (6)
– Radiotherapy	8 (32)	1 (11)	9 (53)	18 (35)

ATC: Anaplastic thyroid cancer; ECOG: Eastern Cooperative Oncology Group; MTC: Medullary thyroid cancer; RR-DTC: Radioiodine-refractory differentiated thyroid cancer.

Table 2. Summary of treatment-emergent adverse events.

Category	RR-DTC (n = 25) n (%)	MTC (n = 9) n (%)	ATC (n = 17) n (%)	Overall (N = 51) n (%)
TEAEs:	25 (100)	9 (100)	17 (100)	51 (100)
– Treatment-related TEAEs	25 (100)	9 (100)	17 (100)	51 (100)
– CTCAE Grade 3 or 4 TEAEs	18 (72)	9 (100)	15 (88)	42 (82)
SAEs:	8 (32)	6 (67)	13 (77)	27 (53)
– Deaths	0	1 (11)	3 (18)	4 (8) [†]
– Other SAEs:				
– Life threatening	0	0	1 (6)	1 (2)
– Required inpatient hospitalization or prolongation of existing hospitalization	7 (28)	6 (67)	13 (77)	26 (51)
TEAEs leading to study-drug dose adjustment:				
– TEAEs leading to study-drug withdrawal	0	0	1 (6)	1 (2)
– TEAEs leading to study-drug dose reduction	25 (100)	9 (100)	15 (88)	49 (96)
– TEAEs leading to study-drug interruption	17 (68)	6 (67)	11 (65)	34 (67)

[†] Occurring within 30 days of the last dose of study drug.

A patient with two or more TEAEs in that category is counted only once; if TEAEs had different CTCAE grades, then the event with the highest grade was used for that patient. Treatment-related TEAEs were considered by the investigator to be possibly or probably related to study drug.

ATC: Anaplastic thyroid cancer; CTCAE: Common Terminology Criteria for Adverse Event; MTC: Medullary thyroid cancer; RR-DTC: Radioiodine-refractory differentiated thyroid cancer; SAE: Serious adverse event; TEAE: Treatment-emergent adverse event.

MTC, median duration of exposure was 293 days (range: 77–867) or 9.6 months (range: 2.5–28.5); for patients with ATC, 166 days (range: 22–1009) or 5.5 months (range: 0.7–33.1). Overall, the median percentage of received dose versus planned starting dose (24 mg/d) was 47% (range: 21–100%) (Supplemental Table 1).

Safety

Table 2 presents an overview of TEAEs. All 51 (100%) patients experienced at least one TEAE, and all patients also had at least one treatment-related TEAE. Most (n = 42; 82%) patients had at least one CTCAE grade 3 or 4 TEAE. Serious AEs (SAEs) occurred in 27 (53%) patients. Five patients experienced a fatal SAE, four of whom died within 30 days of the last dose of study drug. All fatal SAEs were reported as unrelated to the study drug by the investigator. One death was due to hepatic failure caused by liver metastases associated with disease progression, and the other four deaths were due to disease progression.

A TEAE of suicide attempt led to study-drug withdrawal in one (2%; with ATC) patient. TEAEs leading to study-drug dose reduction occurred in 49 (96%) patients. All TEAEs leading to lenvatinib-dose reduction were

Table 3. Treatment-emergent adverse events occurring in $\geq 10\%$ of patients overall.

Preferred MedDRA Term, n (%)	RR-DTC (n = 25)	MTC (n = 9)	ATC (n = 17)	Overall (N = 51)
Patients with any TEAE	25 (100)	9 (100)	17 (100)	51 (100)
Hypertension	24 (96)	8 (89)	14 (82)	46 (90)
Decreased appetite	17 (68)	9 (100)	14 (82)	40 (78)
Palmar-plantar erythrodysesthesia syndrome	23 (92)	8 (89)	8 (47)	39 (77)
Fatigue	20 (80)	7 (78)	10 (59)	37 (73)
Proteinuria	15 (60)	6 (67)	10 (59)	31 (61)
Stomatitis	17 (68)	4 (44)	8 (47)	29 (57)
Diarrhea	15 (60)	8 (89)	5 (29)	28 (55)
Dysphonia	10 (40)	4 (44)	7 (41)	21 (41)
Nausea	9 (36)	2 (22)	10 (59)	21 (41)
Arthralgia	14 (56)	1 (11)	4 (24)	19 (37)
Weight decreased	5 (20)	4 (44)	7 (41)	16 (31)
Nasopharyngitis	11 (44)	1 (11)	2 (12)	14 (28)
Edema peripheral	5 (20)	4 (44)	5 (29)	14 (28)
Constipation	3 (12)	3 (33)	7 (41)	13 (26)
Headache	5 (20)	3 (33)	5 (29)	13 (26)
Abdominal pain upper	5 (20)	4 (44)	3 (18)	12 (24)
Myalgia	8 (32)	2 (22)	2 (12)	12 (24)
Vomiting	4 (16)	2 (22)	6 (35)	12 (24)
Thrombocytopenia	4 (16)	2 (22)	5 (29)	11 (22)
Alopecia	7 (28)	0	3 (18)	10 (20)
Epistaxis	4 (16)	2 (22)	4 (24)	10 (20)
Rash	6 (24)	2 (22)	2 (12)	10 (20)
Dermatitis acneiform	6 (24)	0	3 (18)	9 (18)
Insomnia	1 (4)	5 (56)	3 (18)	9 (18)
Cough	5 (20)	0	3 (18)	8 (16)
Cancer pain	3 (12)	2 (22)	2 (12)	7 (14)
Hypocalcemia	3 (12)	2 (22)	2 (12)	7 (14)
Hypothyroidism	0	3 (33)	4 (24)	7 (14)
Malaise	1 (4)	3 (33)	3 (18)	7 (14)
Aspartate aminotransferase increased	0	1 (11)	5 (29)	6 (12)
Back pain	4 (16)	1 (11)	1 (6)	6 (12)
Dehydration	2 (8)	0	4 (24)	6 (12)
Hepatic function abnormal	2 (8)	2 (22)	2 (12)	6 (12)
Pneumonia	3 (12)	0	3 (18)	6 (12)
Pyrexia	1 (4)	1 (11)	4 (24)	6 (12)

A patient with two or more TEAEs in that category is counted only once.
 ATC: Anaplastic thyroid cancer; MedDRA: Medical Dictionary for Regulatory Activities; MTC: Medullary thyroid cancer; RR-DTC: Radioiodine-refractory differentiated thyroid cancer; TEAE: Treatment-emergent adverse event.

grade 2 or grade 3, except for two events (grade 4 thrombocytopenia and grade 4 hypocalcemia). TEAEs leading to study-drug interruption occurred in 34 (67%) patients.

Overall, the most frequently reported TEAE was hypertension (n = 46; 90%), followed by decreased appetite, palmar-plantar erythrodysesthesia, fatigue, proteinuria, stomatitis, diarrhea, dysphonia and nausea (Table 3). Of the 40 patients who experienced decreased appetite, 14 also had decreased weight as a TEAE. The most frequently reported treatment-related TEAE was hypertension (90%), followed by palmar-plantar erythrodysesthesia (75%), decreased appetite (73%), fatigue (69%), proteinuria (61%), stomatitis (57%) and diarrhea (53%).

Grade 3 or 4 TEAEs were experienced by 42 (82%) patients. The most frequently reported grade 3 or grade 4 TEAE was hypertension in 22 patients (43%; RR-DTC, n = 15; MTC, n = 2; ATC, n = 5), followed by decreased appetite in six patients (12%; RR-DTC, n = 1; MTC, n = 2; ATC, n = 3). Four patients experienced one or more

Table 4. Summary of tumor response.

Parameter	RR-DTC (n = 25)	MTC (n = 9)	ATC (n = 17)	Overall (N = 51)
Best overall response:				
– CR, n	0	0	0	0
– PR, n (%)	17 (68)	2 (22)	4 (24)	23 (45)
– SD [†] , n (%)	8 (32)	7 (78)	12 (71)	27 (53)
– PD, n (%)	0	0	1 (6)	1 (2)
– NE, n	0	0	0	0
ORR (CR+PR), n (%)	17 (68)	2 (22)	4 (24)	23 (45)
DCR (CR+PR+SD), n (%)	25 (100)	9 (100)	16 (94)	50 (98)
CBR (CR+PR+dSD [‡]), n (%)	21 (84)	7 (78)	12 (71)	40 (78)

The tumor assessment was evaluated based on RECIST v1.1 criteria by the investigator.

[†]SD is defined as SD lasting ≥ 7 weeks for DTC and MTC, and ≥ 3 weeks for ATC.

[‡]dSD is defined as SD lasting ≥ 23 weeks for DTC and MTC, and ≥ 11 weeks for ATC.

ATC: Anaplastic thyroid cancer; CBR: Clinical benefit rate; CR: Complete response; DCR: Disease control rate; dSD: Durable stable disease; MTC: Medullary thyroid cancer; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; RR-DTC: Radioiodine-refractory differentiated thyroid cancer; SD: Stable disease.

grade 4 TEAEs (hypocalcemia, hyponatremia, laryngeal stenosis, suicide attempt and thrombocytopenia). The grade 4 hypocalcemia and thrombocytopenia events were reported as treatment related by the investigator. The grade 4 TEAEs were resolved with treatment or study-drug dose reduction, with the exception of hypocalcemia, laryngeal stenosis and suicide attempt.

Efficacy

The median PFS in patients with RR-DTC was 25.8 months (95% CI: 18.4–not reached [NR]); in patients with MTC, 9.2 months (95% CI: 1.8–NR); and in patients with ATC, 7.4 months (95% CI: 1.7–12.9). Median OS in patients with RR-DTC was 31.8 months (95% CI: 31.8–NR); in patients with MTC, 12.1 months (95% CI: 3.8–NR); and in patients with ATC, 10.6 months (95% CI: 3.8–19.8).

Responses based on the investigator assessment are summarized in Table 4. The objective response rate was 68% (n = 17) in patients with RR-DTC, 22% (n = 2) in patients with MTC, and 24% (n = 4) in patients with ATC. No subgroup had a complete response. The disease control rate was 100% both in patients with RR-DTC (n = 25) and with MTC (n = 9) and 94% (n = 16) in patients with ATC. The clinical benefit rate was 84% (n = 21) in patients with RR-DTC, 78% (n = 7) in patients with MTC and 71% (n = 12) in patients with ATC. Most patients experienced some degree of tumor shrinkage after beginning study treatment (Figure 1). Of particular note, tumor samples from ten patients with ATC were sent for independent pathological review and all were confirmed as ATC; three of those ten patients achieved PR.

Neutrophil-to-lymphocyte ratio

At baseline, the overall mean NLR was 4.57 (standard deviation [SD]: ± 5.06) and the median was 2.95 (range: 0.95–30.46). For patients with RR-DTC, the mean baseline NLR was 2.82 (SD: ± 1.43), and median was 2.30 (range: 0.95–6.19). In contrast, higher baseline NLRs were observed in patients with MTC (mean: 5.69 [SD: ± 5.05]; median: 3.78 [range: 1.94–14.90]) and ATC (mean: 6.55 [SD: ± 7.37]; median 4.38 [range: 1.41–30.46]).

A multivariable Cox proportional hazard model, with baseline NLR (as a continuous variable) and tumor subtypes (RR-DTC, MTC, ATC) as covariates, was used to estimate the hazard ratio for effect of NLR on PFS (Table 5). After adjustment by tumor subtype, a trend indicating that baseline NLR may affect PFS was seen, although significance was not reached in this exploratory analysis ($p = 0.06$). An additional multivariate analysis with NLR treated as a categorical variable (dichotomized as $\text{NLR} \geq 3$ vs < 3 , because median baseline NLR was 2.95) also showed the same nonsignificant trend (Supplemental Table 2; Supplemental Figure 1).

Discussion

This study demonstrated that lenvatinib had a manageable safety profile in patients with advanced thyroid cancer, irrespective of cancer subtype. The safety profile of lenvatinib in this Phase II study was comparable to that observed in other trials of lenvatinib in thyroid cancer [12,18–20]. The most common AEs were those known to be typical class effects of tyrosine kinase inhibitors, including hypertension, decreased appetite, palmar-plantar erythrodysesthesia,

Figure 1. Maximum percentage change from baseline in the sum of diameters of target lesions.

†ATC confirmed by independent pathologic review.

‡Patients with partial response as best overall response.

ATC: Anaplastic thyroid cancer; MTC: Medullary thyroid cancer; RR-DTC: Radioiodine-refractory differentiated thyroid cancer.

Table 5. Multivariate Cox proportional hazard model for progression-free survival with covariates of baseline neutrophil-to-lymphocyte ratio and thyroid cancer subtype.

Parameter	Hazard ratio	95% CI	p-value
Baseline NLR increased by 1	1.07	1.00–1.14	0.06
MTC vs RR-DTC†	2.32	0.83–6.52	0.11
ATC vs RR-DTC†	3.08	1.25–7.58	0.01

† Used as reference level in the model.

ATC: Anaplastic thyroid cancer; RR-DTC: Radioiodine-refractory differentiated thyroid cancer; MTC: Medullary thyroid cancer; NLR: Neutrophil-to-lymphocyte ratio.

fatigue, proteinuria, stomatitis and diarrhea [18,21,22]. Generally, toxicities were managed with dose interruptions and reductions, and only one patient (with ATC) withdrew from the study due to an AE.

Survival and response rates were highest in RR-DTC, followed by MTC and ATC. The efficacy of lenvatinib in RR-DTC has been demonstrated in the large-scale, placebo-controlled, Phase III SELECT in patients with RR-DTC, and held true irrespective of the criteria used to define RR-DTC [12,23]. The RR-DTC response rate in this study was also similar to that observed in SELECT, including in the subanalysis of Japanese patients who participated in that trial [12,18].

In a Phase II study of sorafenib in patients with MTC or ATC in Japan, median PFS was not reached for MTC, but was 2.8 months for ATC, underscoring the difficult-to-treat nature of this disease [24]. The most common sorafenib-related any-grade AE and grade ≥ 3 AE in that study was palmar-plantar erythrodysesthesia. In this current study of lenvatinib in patients with advanced thyroid cancer, hypertension was the most common any-grade and grade ≥ 3 AE. Although limited by indirect comparison and small sample sizes, results of these studies indicate some differences in the safety profiles of these two agents that are both used to treat advanced thyroid cancer in Japan.

NLR levels have been reported to be a prognostic marker for survival outcomes in several cancers [14–16], and higher NLR levels have been observed in more aggressive papillary thyroid carcinoma tumors [25,26]. Studies have also shown that NLR levels may reflect the pathological inflammatory status of patients with thyroid cancer [27,28]. Although not statistically significant, a trend was observed in this study indicating that increased baseline NLR might correlate with shorter PFS, regardless of thyroid cancer subtype.

Compared with historical data reporting a median baseline NLR of 1.57 among 3870 patients with thyroid cancer [29], the baseline NLRs in this study were relatively high in all subtypes. This may indicate that the patients enrolled in our trial were experiencing aggressive disease, and were thus appropriately administered an anticancer therapy (in this case, lenvatinib). As of this writing, the optimal time to initiate lenvatinib treatment is unclear, with some physicians using disease progression within 6 months or thyroglobulin doubling time within 1 year for guidance [30]. Based on the preliminary analysis in this study, we hypothesize that the baseline NLR may be useful in providing an additional indicator for lenvatinib treatment initiation and should be investigated further. We acknowledge these inferences are limited by the nonrandomized trial design of the current study, the lack of a comparator arm, a small patient population and the lack of biomarker evaluation of tumor samples.

In conclusion, this study provides evidence supporting the use of lenvatinib in Japanese patients with advanced thyroid cancer, as lenvatinib demonstrated a manageable toxicity profile and promising antitumor activity across all thyroid cancer subtypes tested. In addition, results from an exploratory analysis suggested that the NLR may potentially be a prognostic marker for PFS and may possibly also be used as an indicator for timely initiation of lenvatinib treatment, pending further study.

Future perspective

In the upcoming years, additional therapies, both molecular-targeted and combination regimens, will likely be developed for the treatment of advanced thyroid cancer. The combination of a tyrosine kinase inhibitor with an immuno-oncology therapy has shown promise in other cancers, and may also be efficacious in patients with advanced thyroid cancer. Thus, with the number of potential therapies on the horizon, it is becoming increasingly important to determine which patients will derive the most benefit from a specific therapy. Future research into the molecular mechanisms of therapies, as well as the identification of biomarkers or predictors of response, will likely aid physicians in the process of selecting the best therapy for their patients.

Summary points

- Lenvatinib had a manageable safety profile in patients with advanced thyroid cancer (N = 51), including radioiodine-refractory differentiated thyroid cancer (RR-DTC), medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC).
- The safety profile of lenvatinib in this study was consistent with that seen in other clinical trials of lenvatinib, and was consistent with known class effects of tyrosine kinase inhibitors.
- Response rates were 68% for patients with RR-DTC, 22% for patients with MTC and 24% for patients with ATC.
- The median progression-free survival for patients with RR-DTC was 25.8 months; for patients with MTC, 9.2 months; and for patients with ATC, 7.4 months.
- The median overall survival for patients with RR-DTC was 31.8 months; for patients with MTC, 12.1 months; and for patients with ATC, 10.6 months.
- In a preliminary analysis, patients in this study were found to have had higher-than-expected neutrophil-to-lymphocyte ratios, which may be indicative of aggressive disease.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://www.futuremedicine.com/doi/suppl/10.2217/fo-2018-0557>

Authors' contributions

S Takahashi performed study design, data collection, data interpretation, writing and reviewing manuscript. N Kiyota participated as a primary investigator, advised on the conducting of the study and enrolling of patients and also participated in the writing and reviewing of this manuscript. T Yamazaki, K Nakano, L Inagaki, K Toda, H Minami, T Sasaki and CE Dutcus performed data collection, data interpretation; and review of the manuscript. N Chayahara, Y Imamura and N Fukuda participated in patient management and review of the manuscript. T Enokida participated in patient management, and read and approved the final manuscript. T Suzuki performed study design, writing and review of the manuscript. H Ikezawa performed data and statistical analyses and review of manuscript drafts. M Tahara performed data collection, data interpretation and review of the manuscript.

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Ethical disclosure

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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