

Open-Label, Single-Arm, Multicenter, Phase II Trial of Lenvatinib for the Treatment of Patients With Anaplastic Thyroid Cancer

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PURPOSE Anaplastic thyroid cancer (ATC), an aggressive malignancy, is associated with a poor prognosis and an unmet need for effective treatment, especially for patients without *BRAF* mutations or *NTRK* or *RET* fusions. Lenvatinib is US Food and Drug Administration–approved for radioiodine-refractory differentiated thyroid cancer and has previously demonstrated activity in a small study of patients with ATC (n = 17). We aimed to further evaluate lenvatinib in ATC.

METHODS This open-label, multicenter, international, phase II study enrolled patients with ATC, who had ≥ 1 measurable target lesion, to receive lenvatinib 24 mg once daily. The primary end points were objective response rate (ORR) by investigator assessment per RECIST v1.1 and safety. Responses were confirmed ≥ 4 weeks after the initial response. Additional end points included progression-free survival and overall survival (OS).

RESULTS The study was halted for futility as the minimum ORR threshold of 15% was not met upon interim analysis. The interim analysis set included the first 20 patients. The full analysis set includes all 34 enrolled and treated patients. In the full analysis set, one patient achieved a partial response (ORR, 2.9%; 95% CI, 0.1 to 15.3). More than half of the evaluable patients experienced tumor shrinkage; three patients experienced a > 30% tumor reduction. The median progression-free survival was 2.6 months (95% CI, 1.4 to 2.8); the median overall survival was 3.2 months (95% CI, 2.8 to 8.2). The most common treatment-related adverse events (AEs) were hypertension (56%), decreased appetite (29%), fatigue (29%), and stomatitis (29%). No major treatment-related bleeding events or grade 5 treatment-related AEs occurred.

CONCLUSION The safety profile of lenvatinib in ATC was manageable, and many AEs were attributable to the progression of ATC. The results suggest that lenvatinib monotherapy may not be an effective treatment for ATC; further investigation may be warranted.

J Clin Oncol 00. © 2021 by American Society of Clinical Oncology

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INTRODUCTION

Anaplastic thyroid cancer (ATC) is an aggressive follicular cell–derived malignancy associated with a historically poor prognosis and a 5-year survival rate of < 10%.¹ Although ATC is rare and makes up only 2% of all thyroid cancers, it accounts for up to 50% of all thyroid cancer–related deaths.² Until recently, available treatment options had limited efficacy, and the duration of response was generally short (2–5 months).³

Recent advances in the treatment of ATC have in part centered around patients with *BRAF V600E*–mutated tumors, who represent 20%–50% of all patients with ATC.⁴ An open-label, phase II, basket study evaluated the efficacy and safety of dabrafenib plus trametinib in patients with *BRAF V600E*–mutated tumors.⁵ The *BRAF V600E*–mutated ATC cohort (n = 16) demonstrated a confirmed overall response rate of 69% (95%

CI, 41 to 89) and an estimated 12-month progression-free survival (PFS) of 79%.⁵ As a result, dabrafenib in combination with trametinib has been US Food and Drug Administration–approved for the treatment of *BRAF V600E*–mutated ATC.⁶ Additional tumor-agnostic US Food and Drug Administration approvals have recently occurred for *NTRK* fusion–driven and *RET* fusion–driven cancers.^{7–9} However, these genetic rearrangements are not as frequently seen in ATC.¹⁰

There remains an unmet need for effective treatment options for patients with metastatic ATC, especially for those without *BRAF* mutations or *NTRK* or *RET* fusions. A small-scale phase II study conducted in Japan evaluated lenvatinib in 17 patients with ATC, observing a 24% partial response rate.^{3,11} Therefore, in this multicenter, international, phase II study, we aimed to further evaluate the efficacy and safety of lenvatinib

ASSOCIATED CONTENT

Data Sharing Statement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 23, 2021 and published at ascopubs.org/journal/jco on May 7, 2021; DOI <https://doi.org/10.1200/JCO.20.03093>

CONTEXT

Key Objective

To further evaluate the role of lenvatinib in the treatment of anaplastic thyroid cancer (ATC) as there is a lack of effective treatment options for patients with ATC.

Knowledge Generated

In the full analysis set, the objective response rate was low (2.9%; 95% CI, 0.1 to 15.3) with only one patient achieving a confirmed partial response. However, more than half of the evaluable patients ($n = 28$) experienced tumor shrinkage as evaluated by investigator assessment per RECIST v1.1; three of the 28 patients experienced a $> 30\%$ reduction in total target lesion size (sum of diameters) from baseline to postbaseline nadir.

Relevance

Based on these results, lenvatinib monotherapy may not be an effective treatment for ATC. However, further investigation of lenvatinib may be warranted. The authors would recommend future studies evaluating lenvatinib in combination with other anticancer agents.

(a multikinase inhibitor of vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor- α , RET, and KIT¹²⁻¹⁵) in patients with ATC.

METHODS

This open-label, multicenter, international, phase II study enrolled patients with ATC to receive lenvatinib 24 mg once daily. Patients who were unable to swallow the lenvatinib capsule whole could dissolve the capsule in a small glass of liquid. Eligible patients were required to have a histologic diagnosis of ATC by central review of pathology, ≥ 1 measurable target lesion per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 , adequately controlled blood pressure, and adequate liver, kidney, and bone marrow function. Adequate blood coagulation with an International Normalized Ratio ≤ 1 was also required. Patients who had had prior surgery and/or radiation ≥ 2 weeks before the first dose of lenvatinib could be enrolled. Additionally, prior neoadjuvant, adjuvant, or palliative chemotherapy for ATC was allowed except for prior tyrosine kinase inhibitor therapy. Patients with brain metastases who had completed whole brain radiotherapy, stereotactic radiosurgery, or complete surgical resection were eligible if they remained asymptomatic and stable and did not receive steroid treatment within 1 month of enrollment. Patients were excluded if they had radiographic evidence of major blood vessel invasion or if they were candidates for comprehensive multimodality treatment (surgery and/or external beam radiotherapy or chemoradiotherapy).

The primary efficacy end point was confirmed objective response rate (ORR) by investigator assessment per RECIST v1.1. Secondary and exploratory end points included PFS, overall survival (OS), duration of objective response, disease control rate (DCR; complete response + partial response + stable disease [≥ 5 weeks]),

and clinical benefit rate (CBR; complete response + partial response + durable stable disease of ≥ 23 weeks). Tumor assessments were conducted per RECIST v1.1 at screening and every 6 weeks ± 1 week; complete and partial responses were confirmed ≥ 4 weeks after the initial response. A post hoc multivariate analysis was conducted to identify factors that affected OS; factors evaluated included baseline ECOG PS (0 v 1), prior radiotherapy, baseline sum of tumor diameters (mm), and the percent change from baseline to postbaseline nadir in sums of tumor diameters. The hazard ratio (HR) was estimated using a Cox proportional hazard model; all P values and statistical

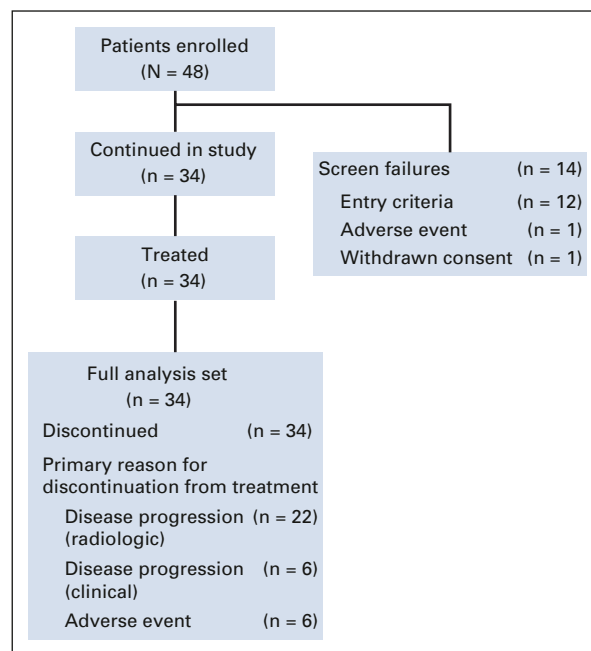


FIG 1. Patient disposition and primary reason for discontinuation from study treatment. The interim analysis set comprised the first 20 evaluable patients who had completed at least two tumor assessments (including the baseline scan and the first on-treatment scan at 6 weeks) or discontinued treatment because of any reason.

significance were nominal. Safety was assessed by monitoring and recording of all adverse events (AEs) per Common Terminology Criteria for Adverse Events version 4.03 and routine laboratory assessments.

The Protocol (online only) specified that a sample size of 57 evaluable patients would be required to have a power of 0.932, using a binomial exact test, to demonstrate a statistical significance of .025 (1-sided alpha), with an assumed ORR of 27% compared with a historic control ORR of 10%. Additionally, the study protocol specified that a descriptive interim analysis would be performed after the first 20 patients had completed at least two tumor assessments (the baseline scan and the first on-treatment scan at 6 weeks) or discontinued treatment for any reason. If the number of responders was ≤ 3 (an ORR $\leq 15\%$) at the interim analysis ($n = 20$), then enrollment would be halted; safety and efficacy would be evaluated to determine whether the study would be terminated. Enrollment continued until the decision to terminate (based on the interim analysis) was made, and the full analysis was to be performed on the full analysis set (FAS), which included all patients enrolled and who received at least one dose of study drug.

This study was performed in full collaboration with the International Thyroid Oncology Group. The protocol was approved by the relevant institutional review boards or ethics committees and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent before study enrollment.

RESULTS

Patients

The interim analysis set included the first 20 patients, and the FAS included the 34 enrolled and treated patients (Fig 1). The total planned population of 57 patients was not reached because enrollment was halted based on the interim analysis. Central pathology review confirmed the diagnosis of ATC in 33 of 34 patients enrolled. Most patients had ≤ 1 prior anticancer therapy regimen for metastatic disease. Additionally, most patients had prior radiation therapy and/or prior surgery (Table 1).

Efficacy

Upon the interim analysis, the confirmed ORR was 0% as there were no patients with a confirmed partial or complete response in the interim analysis set. There was one patient who experienced an unconfirmed partial response for an unconfirmed ORR of 5% (95% CI, 0.1 to 24.9; Table 2). Therefore, the study was halted based on the prespecified criteria for futility, as the minimum ORR threshold of 15% was not met.

In the FAS, one patient achieved a confirmed partial response (ORR, 2.9%; 95% CI, 0.1 to 15.3; Table 2). The

TABLE 1. Patient Demographics and Baseline Characteristics

Parameter	Interim Analysis Set (n = 20)	FAS (n = 34)
Age group, years, No. (%)		
< 65	10 (50)	16 (47)
65-75	5 (25)	12 (35)
> 75	5 (25)	6 (18)
Sex, No. (%)		
Male	7 (35)	13 (38)
Female	13 (65)	21 (62)
Region, No. (%)		
Europe	5 (25)	10 (29)
North America	15 (75)	23 (68)
Australia	0	1 (3)
Race, No. (%)		
White	16 (80)	27 (79)
Black	2 (10)	3 (9)
Others	2 (10)	4 (12) ^a
ECOG PS, No. (%)		
0	10 (50)	16 (47)
1	10 (50)	18 (53)
Location of disease, No. (%)		
Locoregional	0	0
Distant metastatic	6 (30)	12 (35)
Both	14 (70)	22 (65)
No. of prior anticancer regimens, No. (%)		
0	6 (30)	10 (29)
1	6 (30)	13 (38)
2	4 (20)	7 (21)
3	3 (15)	2 (6)
≥ 4	1 (5)	2 (6)
Prior anticancer medication, No. (%)	14 (70)	24 (71)
Previous chemotherapy	11 (55)	21 (62)
Taxanes	6 (30)	12 (35)
Anthracyclines and related substances	6 (30)	10 (29)
Platinum compounds	5 (25)	11 (32)
Monoclonal antibodies	2 (10)	3 (9)
Protein kinase inhibitors	2 (10)	3 (9)
Prior surgery, No. (%)	15 (75)	24 (71)
Prior radiation therapy, No. (%)	15 (75)	22 (65)
Median time from original histologic/cytologic diagnosis to first dose, months	4	5
Median time since last disease progression to first dose ^b , months	1	1

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set.

^aOne patient was classified as other, one patient was Asian, and data were missing for two patients.

^bData on the median time since last disease progression to first dose were available for 15 patients in the interim analysis set and for 25 patients in the FAS.

TABLE 2. Efficacy Summary

Outcome	Interim Analysis Set (n = 20)	FAS (n = 34)
BOR, No. (%)		
Complete response	0	0
Partial response	1 (5.0) ^a	1 (2.9) ^b
Stable disease	9 (45.0)	17 (50.0)
Progressive disease	5 (25.0)	9 (26.5)
Not evaluable or unknown	5 (25.0)	7 (20.6) ^c
ORR, No. (%) (95% CI)	1 (5.0) (0.1 to 24.9) ^{a,d}	1 (2.9) (0.1 to 15.3) ^{b,d}
Median PFS, months (95% CI)	2.6 (1.2 to 2.8)	2.6 (1.4 to 2.8)
Median OS, months (95% CI)	2.9 (2.7 to NE)	3.2 (2.8 to 8.2)
DCR ^e , No. (%) (95% CI)	10 (50.0) (27.2 to 72.8)	18 (52.9) (35.1 to 70.2)
CBR ^f , No. (%) (95% CI)	1 (5.0) (0.1 to 24.9)	3 (8.8) (1.9 to 23.7)

Abbreviations: BOR, best overall response; CBR, clinical benefit rate; DCR, disease control rate; FAS, full analysis set; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

^aUnconfirmed partial response.

^bConfirmed partial response.

^cThree of the seven patients' results were not evaluable because they only had baseline tumor scans available. Two patients had baseline and week 6 scans, but the week 6 scans were not evaluable for target lesion response. One patient was not evaluable because he or she started a new anticancer therapy before week 6. The remaining patient was not included in the BOR above because stable disease was observed < 35 days since study drug initiation.

^dThe patient who experienced an unconfirmed partial response in the interim analysis was the same patient who experienced a confirmed partial response in the FAS.

^eThe DCR was defined as complete response + partial response + stable disease (≥ 5 weeks); the DCR for the interim analysis set included unconfirmed responses.

^fThe CBR was defined as complete response + partial response + durable stable disease of ≥ 23 weeks; the CBR for the interim analysis set included unconfirmed responses.

duration of response for this one patient was 4.1 months. There were two additional patients who also experienced a > 30% reduction in total target lesion size, but their responses could not be confirmed because of disease progression. Of note, more than half of the evaluable patients experienced tumor shrinkage (Fig 2). The median PFS was 2.6 months (95% CI, 1.4 to 2.8) (Fig 3A), and the median OS was 3.2 months (95% CI, 2.8 to 8.2) (Fig 3B). The median follow-up time for OS was 15.3 months (95% CI, 11.6 to 16.9). The DCR and CBR were 52.9% (95% CI, 35.1 to 70.2) and 8.8% (95% CI, 1.9 to 23.7), respectively (Table 2).

A post hoc multivariate analysis of OS demonstrated that the following factors might have had a significant impact on OS: prior radiotherapy (HR, 3.65; 95% CI, 1.15 to 11.52; $P = .0275$), the percent change from baseline to post-baseline nadir in sums of diameters of target lesions (HR, 1.03; 95% CI, 1.01 to 1.04; $P = .0009$), and the baseline sums of tumor diameters (HR, 1.02; 95% CI, 1.01 to 1.04; $P = .0010$). Baseline ECOG PS (0 v 1) did not significantly influence OS (HR, 0.94; 95% CI, 0.38 to 2.32; $P = .8924$).

Study Drug Exposure

In the FAS, the median dose intensity was 21.6 mg/day per patient (range, 11.1-44.0) and the median duration of treatment was 2.3 months (range, 0.3-12.9). Dose reductions were required in 41% of patients (14 patients). The median time to first dose reduction was 4.6 weeks (range, 1.0-16.0).

Safety

All patients in the FAS (n = 34; 100%) experienced treatment-emergent AEs (TEAEs) (Table 3). Treatment-related AEs (TRAEs) occurred in 94% of patients (n = 32). The most common TRAEs were hypertension (56%), decreased appetite (29%), fatigue (29%), and stomatitis (29%). Grade ≥ 3 TRAEs occurred in 62% of patients, and the most common

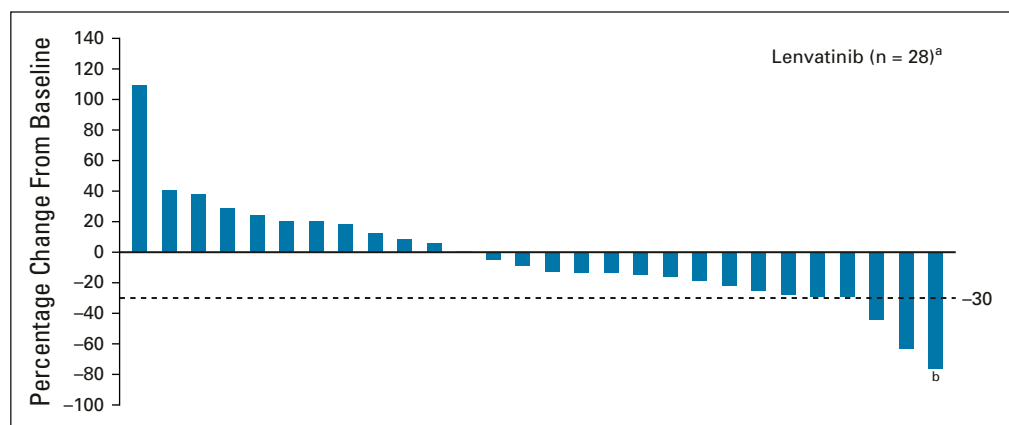


FIG 2. Percentage change in sum of diameters of target lesions from baseline to postbaseline nadir by investigator assessment per RECIST v1.1 (full analysis set). ^aEvaluable patients with both a baseline and at least one postbaseline target lesion assessment. ^bThis bar represents one confirmed responder.

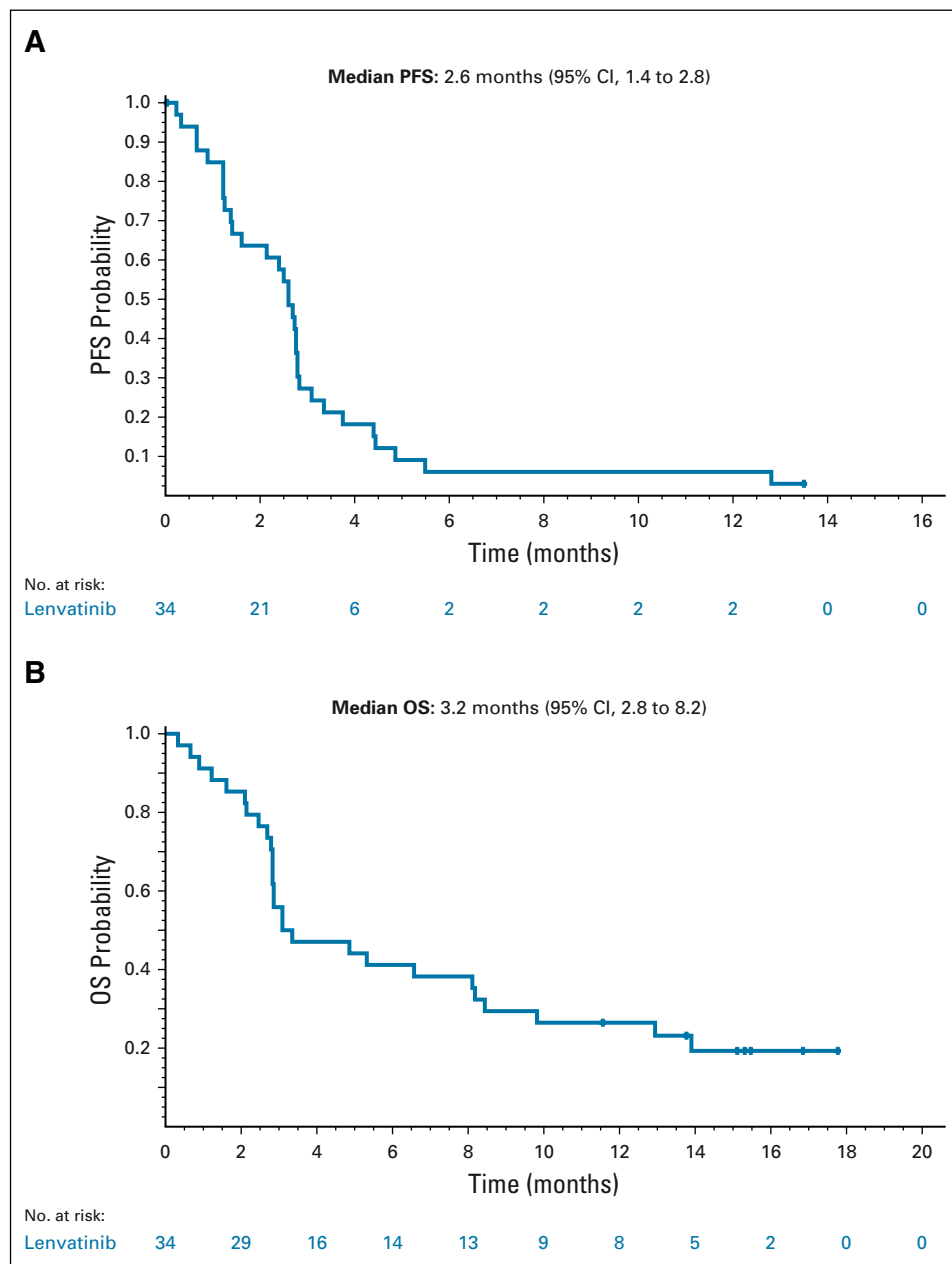


FIG 3. Kaplan-Meier plot of (A) PFS by investigator assessment per RECIST v1.1 (full analysis set) and (B) OS (full analysis set). OS, overall survival; PFS, progression-free survival.

TRAE was hypertension (24%) (Table 4). Of note, there were no major treatment-related bleeding events including those because of fistula formation. Two patients experienced fistula formation; one patient developed a grade 3 tracheal fistula, and the other patient developed a grade 3 anal fistula and a grade 3 perirectal abscess. At the time of data cutoff (October 30, 2018), there had been 27 deaths; 13 of these deaths occurred > 28 days after the last dose of lenvatinib. TEAEs led to 14 deaths that occurred within 28 days of the last dose, but none were considered treatment related. Grade 5 TEAEs included dysphagia (n = 1), septic shock (n = 1), hypoxia (n = 1), and malignant neoplasm progression (n = 10); one

patient was reported with three grade 5 TEAEs comprising cardiopulmonary failure, renal failure, and pulmonary edema.

DISCUSSION

The present study was closed to enrollment following the interim analysis that demonstrated a lack of efficacy per prespecified criteria (ie, ORR < 15%) with lenvatinib treatment in patients with ATC. The response rate was approximately 3%, with half of the 34 patients achieving stable disease (≥ 5 weeks). The median PFS and OS were 2.6 and 3.2 months, respectively. Additionally, the CBR was low (8.8%; 95% CI, 1.9 to 23.7). The safety profile of lenvatinib

TABLE 3. Safety Summary

Category, No. (%)	FAS (n = 34)
TEAEs	34 (100)
CTCAE ^a grade \geq 3	28 (82)
Grade 5	14 ^b (41)
TRAEs	32 (94)
CTCAE ^a grade \geq 3	21 (62)
Grade 5	0 (0)
TRAEs leading to study drug dose ^c	
Adjustment ^d	25 (74)
Withdrawal	2 (6)
Reduction	14 (41)
Interruption	19 (56)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; FAS, full analysis set; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

^aCTCAE version 4.03.

^bGrade 5 TEAEs included dysphagia (n = 1), septic shock (n = 1), hypoxia (n = 1), and malignant neoplasm progression (n = 10). There was one patient who experienced three grade 5 TEAEs (cardiopulmonary failure, renal failure, and pulmonary edema).

^cA single patient could have been counted in multiple categories.

^dAdjustment includes drug withdrawal, dose reduction, or interruption.

in ATC was similar to that observed in other previous lenvatinib studies.¹⁶⁻¹⁸ We did observe two cases of fistula (anal and tracheal), which can be expected with potent antiangiogenic therapy, but there were no severe bleeding events likely because of strict patient selection. Of note, patients with major vessel involvement were excluded from this trial. Additionally, many of the AEs observed in this study were attributable to the progression of ATC; the grade 5 TEAEs that occurred were all likely related to underlying disease progression.

Previously, Tahara et al³ demonstrated that 24% of patients with ATC achieved a partial response with lenvatinib and the median OS was 10.6 months. However, there were several differences between our study and that of Tahara et al, which might have contributed to the poor response observed in our study compared with the activity of lenvatinib in patients with ATC that was observed in the study by Tahara et al. Unlike the previous study, the present study required a central pathology review to confirm a diagnosis of ATC. In the Tahara study, only 10 patients had a confirmed diagnosis of ATC per independent pathologic review. Furthermore, our study enrolled more patients (n = 34; v n = 17 in the study by Tahara et al³), and more patients had received prior chemotherapy (62% v 41%). In the study by Tahara et al,^{3,11} all patients were Japanese and tumor assessments were initially conducted more frequently (every 4 weeks up to week 16 v every 6 weeks). A post hoc analysis of the phase III Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT)

TABLE 4. Grade 3 TRAE^a

Preferred Term, No. (%)	FAS (n = 34)
Hypertension	8 (24)
Asthenia	3 (9)
Proteinuria	2 (6)
Gamma-glutamyl transferase increased	2 (6)
Abdominal pain	1 (3)
Accidental overdose	1 (3)
Anal fistula	1 (3)
Cholecystitis	1 (3)
Confusional state	1 (3)
Cyst	1 (3)
Dehydration	1 (3)
ECG QT prolonged	1 (3)
Hyponatremia	1 (3)
Lymphocyte count decreased	1 (3)
Palmar-plantar erythrodysesthesia syndrome	1 (3)
Pancreatitis	1 (3)
Perirectal abscess	1 (3)
Pleuritic pain	1 (3)
Pneumothorax	1 (3)
Pulmonary embolism	1 (3)
Skin ulcer	1 (3)
Tracheal fistula	1 (3)
Vomiting	1 (3)
Weight decreased	1 (3)

Abbreviations: FAS, full analysis set; TRAE, treatment-related adverse event.

^aThere were three grade 4 TRAEs (agranulocytosis [n = 1], pulmonary embolism [n = 1], and deep vein thrombosis [n = 1]) and no grade 5 TRAEs.

suggested that people of Japanese origin may experience an increased exposure to lenvatinib because a higher rate of several AEs was reported in Japanese patients compared with non-Japanese patients.¹⁹ An increased exposure to lenvatinib because of lower body weight might have also contributed to the greater efficacy observed in the Japanese study. Additionally, our study required confirmation of response. Patients were required to experience stable disease for a longer time period because durable stable disease for the CBR was defined as \geq 23 weeks of duration instead of 11 weeks, and stable disease for best overall response as \geq 5 weeks of duration instead of 3 weeks.^{3,11}

Other multikinase inhibitors of vascular endothelial growth factor receptors and other kinases, namely, sorafenib and pazopanib, have been evaluated as monotherapy in ATC.^{20,21} In a phase II trial assessing sorafenib, two of the 20 patients enrolled experienced a partial response; the median PFS was 1.9 months (95% CI, 1.3 to 3.6), and the median OS was

3.9 months (95% CI, 2.2 to 7.1).²⁰ In a phase II trial assessing pazopanib, no tumor responses were observed among the 15 enrolled patients; the median time to progression was 62 days, and the median OS was 111 days.²¹

Combination therapies involving a multikinase inhibitor have been shown to improve survival outcomes in several tumor types, and therefore, combination therapy is a potential approach to investigate, especially given the aggressive nature of ATC. Specifically, lenvatinib in combination with programmed death (PD)-1 inhibition has demonstrated efficacy and tolerability in other tumor types.^{22,23} Another PD-1 inhibitor, spartalizumab, was evaluated in a phase I/II study that enrolled 42 patients with ATC.²⁴ Spartalizumab demonstrated an ORR of 19% using RECIST v1.1, and although median duration of response was not met by the time of publication, it ranged from 16.7 weeks to 1.6 years. These results, combined with the tumor reduction seen transiently with lenvatinib in this study and in that of Tahara et al,³ suggest that investigation of lenvatinib in combination with an anti-PD-1 antibody for the treatment of ATC is warranted.

Currently (December 2020), there are two ongoing studies evaluating lenvatinib in combination with pembrolizumab for the treatment of ATC^{25,26}. The ATLEP study is a phase II study assessing lenvatinib plus pembrolizumab in patients with ATC and poorly differentiated thyroid cancer,²⁶ and an additional phase II study is planned to evaluate lenvatinib plus pembrolizumab in unresectable locally advanced or metastatic ATC in the United States.²⁵

One limitation to note is that our study did not collect *BRAF* mutation status, and patients with this mutation should be treated with *BRAF*-targeted therapies such as dabrafenib and trametinib. The results from our study, along with those from two previous studies,^{20,21} suggest that monotherapy with the tyrosine kinase inhibitor lenvatinib may not be an effective treatment option for ATC; however, further investigation may be warranted. We hope that data from this study will provide useful information for future studies in patients with ATC, particularly the single-arm studies investigating lenvatinib in combination with other anticancer agents.

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PRIOR PRESENTATION

Presented in part previously as congress abstracts at The Endocrine Society's Annual Meeting; Virtual Format; June 8-22, 2020 (poster no. MON-521).

SUPPORT

Supported by Eisai Inc, Woodcliff Lake, NJ, and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co Inc, Kenilworth, NJ. Medical writing support was provided by Jessica Pannu, PharmD, of Oxford PharmaGenesis Inc, Newtown, PA. This support was funded by Eisai Inc, Woodcliff Lake, NJ, and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ.

CLINICAL TRIAL INFORMATION

NCT02657369

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.20.03093>.

DATA SHARING STATEMENT

The data will not be available for sharing at this time as the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.

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Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

This study and report were conducted and prepared by the authors and funding partners, and performed in collaboration with the International Thyroid Oncology Group.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Open-Label, Single-Arm, Multicenter, Phase II Trial of Lenvatinib for the Treatment of Patients With Anaplastic Thyroid Cancer**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Research Funding: AstraZeneca, Novartis, Roche, MSD, Eisai, Merck Serono, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Exelixis, IRX Therapeutics, Medpace, Pfizer, Debiopharm Group

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No other potential conflicts of interest were reported.