Original Article

A Phase 2 Trial of Lenvatinib (E7080) in Advanced, Progressive, Radioiodine-Refractory, Differentiated Thyroid Cancer: A Clinical Outcomes and Biomarker Assessment

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BACKGROUND: Lenvatinib is an oral, multitargeted tyrosine kinase inhibitor of the vascular endothelial growth factor receptors 1 through 3 (VEGFR1-VEGFR3), fibroblast growth factor receptors 1 through 4 (FGFR1-FGFR4), platelet-derived growth factor receptor α (PDGFRα), ret proto-oncogene (RET), and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) signaling networks implicated in tumor angiogenesis. Positive phase 1 results in solid tumors prompted a phase 2 trial in patients with advanced, radioiodine-refractory, differentiated thyroid cancer (RR-DTC). **METHODS:** Fifty-eight patients with RR-DTC who had disease progression during the previous 12 months received lenvatinib 24 mg once daily in 28-day cycles until disease progression, unmanageable toxicity, withdrawal, or death. Previous VEGFR-targeted therapy was permitted. The primary endpoint was the objective response rate (ORR) based on independent imaging review. Secondary endpoints included progression-free survival (PFS) and safety. Serum levels of 51 circulating cytokines and angiogenic factors also were assessed. **RESULTS:** After ≥14 months of follow-up, patients had an ORR of 50% (95% confidence interval [CI], 37%-63%) with only partial responses reported. The median time to response was 3.6 months, the median response duration was 12.7 months, and the median PFS was 12.6 months (95% CI, 9.9-16.1 months). The ORR for patients who had received previous VEGF therapy (n = 17) was 59% (95% CI, 33%-82%). Lower baseline levels of angiopoietin-2 were suggestive of tumor response and longer PFS. Grade 3 and 4 treatment-emergent adverse events, regardless of their relation to treatment, occurred in 72% of patients and most frequently included weight loss (12%), hypertension (10%), proteinuria (10%), and diarrhea (10%). **CONCLUSIONS:** In patients with and without prior exposure to VEGF therapy, the encouraging response rates, median time to response, and PFS for lenvatinib have prompted further investigation in a phase 3 trial. ***Cancer* 2015;121:2749-56.** © 2015 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: biomarkers, differentiated thyroid cancer, lenvatinib, multikinase inhibitor, radioiodine refractory, phase 2.

INTRODUCTION

Differentiated thyroid cancer (DTC) includes papillary and follicular histologies and accounts for ≥90% of all thyroid cancers,[1] 2% of all cancers (180,000 globally), but <0.5% of all cancer deaths, and 90% of patients survive ≥10 years.[2-4]

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We thank the patients who participated in this trial and their families as well as all the investigators and centers involved. We also thank Phase Five Communications Inc and Oxford PharmaGenesis Inc for medical writing support, which was funded by Eisai Inc. Finally, we thank Anne Gold, Pallavi Sachdev, Tadashi Kadowaki, and Mark Matijevic (all employees of Eisai Inc) for their contributions to this study and its analyses.

Additional Supporting Information may be found in the online version of this article.

DOI: 10.1002/cncr.29395, **Received:** November 26, 2014; **Revised:** March 3, 2015; **Accepted:** March 5, 2015, **Published online** April 24, 2015 in Wiley Online Library (wileyonlinelibrary.com)

However, patients with radioiodine-refractory DTC (RR-DTC) have a 10-year survival rate of only 10% from the detection of distant metastases.[5] Consensus guidelines have recommended clinical trials with systemic therapies targeted to specific molecules, because traditional cytotoxic agents have demonstrated marginal efficacy and significant toxicities.[6-8]

Multiple molecular signaling pathways have been implicated in the pathogenesis of DTC and are potential targets for therapy.[9] Specifically, alterations in several molecular signaling pathways, including B-raf proto-oncogene, serine/threonine kinase (*BRAF*), v-ras oncogene homolog (*RAS*), fibroblast growth factor receptor (FGFR), and ret proto-oncogene (RET), have been implicated in the pathogenesis and proliferation of DTC. Furthermore, tumor angiogenesis, primarily mediated by vascular endothelial growth factor receptor 2 (VEGFR2), has been associated with metastatic disease, increased recurrence, and shorter disease-free survival.[10] Receptor tyrosine kinase inhibitors (TKIs) with activity on these angiogenic pathways have demonstrated efficacy in clinical trials of patients with RR-DTC.[11-13] Recently, 1 such therapy (sorafenib) was approved by the US Food and Drug Administration and by the European Medicines Agency for the treatment of RR-DTC,[13] and another TKI (vandetanib) is currently being investigated in a phase 3 clinical study for the same indication. In addition, components of these signaling pathways—as well as others—have been investigated for their potential to provide information with respect to patient prognosis or response to TKI therapy in thyroid cancer.[14,15]

Lenvatinib (E7080; Eisai Inc, Woodcliff Lake NJ) is an oral, multitargeted TKI of VEGFR1, VEGFR2, and VEGFR3; FGFR1, FGFR2, FGFR3, and FGFR4; platelet-derived growth factor receptor α (PDGFRα); RET; and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT).[16-18] Preliminary evidence of efficacy in phase 1 trials of lenvatinib in a variety of solid tumor types, including the thyroid,[19,20] prompted the initiation of this phase 2 trial to investigate its efficacy and safety in patients with RR-DTC. In addition, this report presents findings from the correlations of lenvatinib treatment outcomes with levels of circulating cytokines and angiogenic factors (CAFs).

MATERIALS AND METHODS

This open-label, single-arm, phase 2 trial (clinicaltrials.gov identifier: NCT00784303) of oral lenvatinib for the treatment of RR-DTC was conducted at 30 sites in 6 countries. Treatment consisted of lenvatinib 24 mg administered once daily for a minimum of eight 28-day cycles; discontinuations occurred because of disease progression, unacceptable toxicity, withdrawal, or death. Two patients received lenvatinib 10 mg twice daily before a protocol amendment that identified the dose as 24 mg once daily. Protocol-directed dose reductions occurred for all grade ≥2 adverse events (AEs), except for hypertension, nausea, and vomiting, which were managed first by optimum medical treatment. Once the dose was reduced, it could not be increased. All patients provided signed informed consent before entry, and the study was approved by the institutional review board at each participating site and was carried out in accordance with the Declaration of Helsinki and in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

PATIENTS

Patients were aged ≥18 years who had histologically confirmed DTC (including papillary, follicular, Hürthle cell, and poorly differentiated) that proved to be radioiodine-refractory (see online supporting information), evidence of measurable and progressive disease (PD) (according to modified Response Evaluation Criteria In Solid Tumors, version 1.0)[21] within the previous 12 months, and an Eastern Cooperative Oncology Group performance status of 0 to 2. The receipt of prior chemotherapy or antiangiogenic therapy was permitted; however, it must have been discontinued at least 30 days before study entry. Patients with anaplastic thyroid cancer; central nervous system metastasis; active hemoptysis; bleeding or thrombotic disorders; receipt of anticoagulants; or significant cardiovascular, hematopoietic, hepatic, or renal dysfunction were excluded.

Patient Monitoring and Tumor Assessment

Pretreatment tumor assessments using computed tomography scans of the neck, chest, abdomen, pelvis, and other areas of known or newly suspected disease were performed within 4 weeks before the first dose and then every 8 weeks, and bone scans were obtained every 4 cycles. Responses (complete response [CR] or partial response [PR]) were confirmed at a repeat tumor evaluation at least 4 weeks after they were first observed. For a designation of stable disease (SD) as the best overall response, at least 1 post-treatment measurement must have met SD criteria a minimum of 7 weeks after the first dose. Patients who achieved SD for ≥6 months or who had a PR but had progression in a single bony metastasis were permitted to receive palliative radiotherapy at the single site followed

by the resumption of lenvatinib treatment. These patients had previously met criteria for PD at the time progression was documented in the single bone metastasis. Patients who discontinued treatment before they developed PD continued to undergo tumor assessment every 3 months from the last assessment until PD was documented or different treatment was initiated. Blood samples for serum protein biomarkers were collected at baseline (cycle 1, day 1), 8 days post-treatment (cycle 1, day 8), and 36 days post-treatment (cycle 2, day 8).

Assessment of Clinical Endpoints

The primary endpoint was the objective response rate (ORR), defined as a CR or a PR based on modified Response Evaluation Criteria In Solid Tumors, version 1.0, by an independent imaging review (IIR). Secondary endpoints included progression-free survival (PFS), overall survival, time to response, response duration, safety, and tolerability. PFS was defined as the time during and after treatment during which the patient was alive and without PD. Prespecified subgroup analyses of the primary endpoint were based on the following criteria: age ($<$65 years, $\geq$65 years), sex, race (white, nonwhite), and previous receipt of VEGFR-targeted therapy.

Biomarker Assessments

A panel of 51 CAFs was assayed using enzyme-linked immunosorbent assays and multiplex assays. Sample data acquisition and analysis were performed on either an enzyme-linked immunosorbent assay plate reader using SoftmaxPro software (Molecular Devices, Sunnyvale, Calif) or the Bio-Rad Bio-Plex System (Bio-Rad Laboratories, Hercules, Calif) using Bio-Plex Manager 4.1 software for multiplex assays (Bio-Rad Laboratories). CAFs for which $>$20% of patients had out-of-range measurements were not used for the correlative analyses.

Statistical Analyses

All patients who had received at least 1 dose of lenvatinib (the intent-to-treat population) were included in the primary efficacy analyses. The safety population included all patients who had received at least 1 dose of study medication and at least 1 post-treatment safety assessment. In this study, the intent-to-treat and safety populations were identical. The ORR was calculated at the end of the treatment phase, when patients had completed $\geq$8 cycles or had discontinued before this, and are presented with 2-sided 95% Clopper and Pearson confidence intervals (CIs). Patient demographic data and safety parameters were summarized using descriptive statistics. Sample size estimates based on the Simon optimal 2-stage design assumed $\alpha = .05$, 90% power, and an expected ORR of 15% with lenvatinib compared with 2.5% based on historic controls. Unexpectedly rapid enrollment resulted in completion of the second stage before the scheduled interim cutoff; consequently, the optimal 2-stage design was not implemented. Median PFS and overall survival are presented with 2-sided 95% CIs and were calculated using the Kaplan-Meier method and plotted over time after therapy. Clinical statistical analyses were performed using Statistical Analysis System software (UNIX version 8.2 and Windows version 9.1; SAS Institute, Cary, NC).

Post-treatment fold changes in serum biomarker levels from baseline (cycle 1, day 1) were analyzed using the Wilcoxon signed-rank test for paired samples. Wilcoxon signed-rank tests also were used to analyze the correlation of baseline serum biomarker levels and objective responses. To test for associations between PFS and baseline serum biomarkers, log-transformed values were used as independent variables in univariate Cox proportional hazard models with Wald-test *P* values. False discovery rate analyses were performed to adjust for multiple testing; however, unadjusted *P* values were considered because of the exploratory nature of the biomarker analyses. Statistical analyses were performed using R version 2.15.0 or later (R Foundation for Statistical Computing, Vienna, Austria) with the survival and doMC (parallel computation) packages.

RESULTS

Between October 2008 and February 2010, 58 patients with DTC were treated (the intent-to-treat population) (Table 1). The median patient age was 63 years, the median weight was 81.1 kg, and most patients were men (59%), white (86%), and had a baseline Eastern Cooperative Oncology Group performance status $\leq$1 (93%). Prior VEGFR-targeted therapy was reported in 29% of patients. The most common sites of distant metastases were lung (93%), hilar-mediastinal lymph nodes (57%), and bone (45%). Thirty-five patients (60%) discontinued treatment primarily for PD (31%) and AEs (24%), in addition to patient choice (3%) and withdrawal of consent (2%); whereas 23 patients (40%) continued on treatment.

Efficacy

After a minimum follow-up of 14 months, the ORR was 50% (Clopper-Pearson 95% CI, 37%-63%) as assessed by IIR, and only PRs were reported (Table 2). No differences in the ORR according to age or sex were observed

(Table 2, Supporting Fig. 1; see online supporting information). In addition, the ORR according to prior VEGFR-targeted therapy was similar (the ORR was 59% [10 of 17 patients] for those who had received prior VEGFR-targeted therapy and 46% [19 of 41 patients] for those who had not received such therapy). Ten of 14 patients who had previously received sorafenib had PRs, for an ORR of 71%. In an analysis of tumor response according to histology, 24 of 43 patients (56%) with papillary thyroid carcinoma and 5 of 15 patients (33%) with follicular thyroid cancer had PRs. A difference in ORR was observed between nonwhites and whites (Supporting Fig. 1; see online supporting information); however, this may have been because of the skewed racial demographic of the study population (Table 1). Overall, 29 patients (50%) patients achieved a PR, 25 patients (43%) attained SD (≥7 weeks), and 16 patients (28%) experienced durable SD (≥23 weeks). A waterfall plot of each efficacy-evaluable patient's maximum percentage tumor change in the sum of the greatest dimensions from baseline to postbaseline nadir is provided in Figure 1a.

The median time to response was 3.6 months (95% CI, 1.8-3.7 months) based on IIR, and the median response duration was 12.7 months (95% CI, 8.8 months to not evaluable [NE]). The median PFS was 12.6 months (95% CI, 9.9-16.1 months) (Fig. 1b) and was similar in patients who received (PFS, 12.2 months; 95% CI, 7.9 months to NE) or did not receive (PFS, 12.6 months; 95% CI, 9.1 months to NE) prior VEGFR-targeted therapy. The 6-month PFS rate was 78% (95% CI, 64%-87%), and the 12-month PFS rate was 55% (95% CI, 40%-67%). In an analysis of PFS in which patients were censored at the time of drug withdrawal (ie, at the last tumor assessment within 30 days of the last study treatment), the median PFS was 15.9 months (95% CI, 10.8 months to NE) (Supporting Fig. 2; see online supporting information). At the time of analysis, the median overall survival could not be reliably estimated based on the Kaplan-Meier analysis presented in Supporting Figure 3 (see online supporting information). Exploratory biomarker analyses are

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	No. of Patients (%)
Total no.	58 (100)
Age: Median [range], y	63 [34-77]
Sex	
Women	24 (41)
Men	34 (59)
Race	
Nonwhite	8 (14)
White	50 (86)
Weight, kg	
Mean ± SD	84.6 ± 22
Median [range]	81.1 [47-158]
ECOG performance status	
0	30 (52)
1	24 (41)
2	4 (7)
NYHA classification	
I	51 (88)
II	6 (10)
III	0 (0)
IV	0 (0)
Missing	1 (2)
Histology subtype	
Papillary	43 (74)
Follicular, including Hürthle cell	15 (26)
Size of baseline target lesions: Mean ± SD, mm	116.7 ± 77.6
Prior treatment	
Prior VEGFR-targeted therapy[a]	17 (29)
Axitinib	1 (2)
Motesanib	1 (2)
Sorafenib	14 (24)
Sunitinib	3 (5)
Prior anthracycline therapy	8 (14)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; SD, standard deviation; VEGFR, vascular endothelial growth factor receptor.
[a] One patient received motesanib and sunitinib, and 1 patient received both sorafenib and sunitinib.

TABLE 2. The Best Overall Tumor Response Determined by Independent Imaging Review

Tumor Response	No. of Patients (%)		
	Overall, n = 58	Prior VEGFR-Targeted Therapy, n = 17	No Prior VEGFR-Targeted Therapy, n = 41
PR	29 (50)	10 (59)	19 (46)
SD ≥7 wk	25 (43)	6 (35)	19 (46)
Durable SD ≥23 wk	16 (28)	5 (29)	11 (27)
Progressive disease	3 (5)	1 (6)	2 (5)
Unevaluable	1 (2)	0 (0)	1 (2)
ORR: CR + PR [95% CI]	29 (50) [37%-63%]	10 (59) [33%-82%]	19 (46) [31%-63%]

Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease; VEGFR, vascular endothelial growth factor receptor.

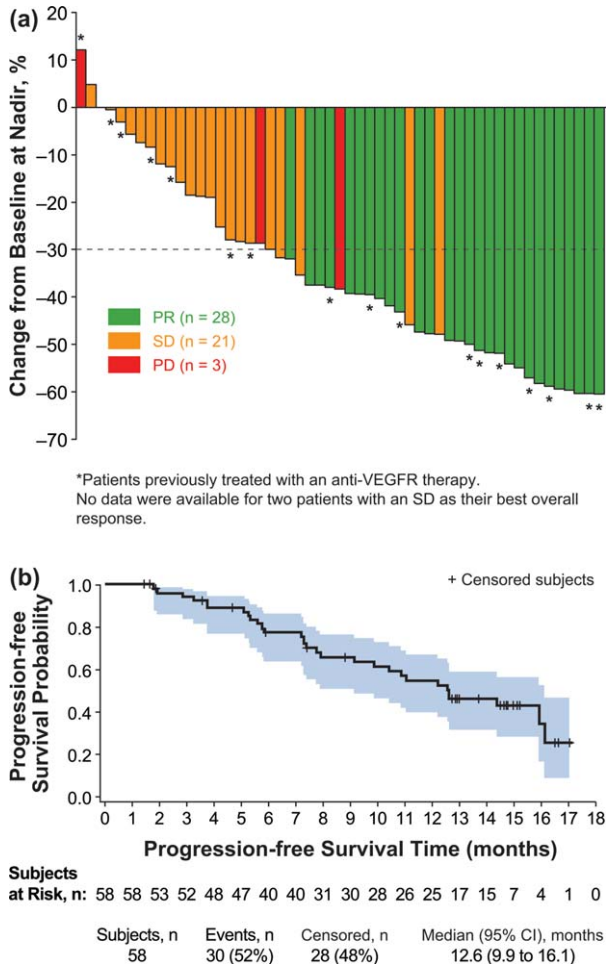

Figure 1. Lenvatinib efficacy results are illustrated. (a) This waterfall graph illustrates the percentage change in the summed greatest dimension of target lesions from baseline to nadir (evaluable population, n = 55). PD indicates progressive disease; PR, partial response; SD, stable disease; VEGFR, vascular endothelial growth factor receptor. (b) This Kaplan-Meier estimate of progression-free survival was based on data from an independent imaging review (intent-to-treat population, n = 58). CI indicates confidence interval.

presented in Supporting Figures 4 and 5 (see online supporting information).

Treatment Duration and AEs

The median treatment duration was 13.5 cycles (range, 1-19 cycles). Treatment-emergent AEs (TEAEs) led to dose interruptions, reductions, or study drug withdrawal in 74%, 66%, and 26% of patients, respectively. All patients experienced TEAEs, which most frequently were hypertension (76%), weight decrease (69%), diarrhea (67%), proteinuria (64%), fatigue (60%), decreased appetite (52%), and nausea (50%) (Table 3). Most hypertension and proteinuria events were grade 1 or 2 and were managed without dose adjustments or withdrawal of treatment.

TABLE 3. The Most Common (≥25%) Treatment-Emergent Adverse Events

TEAE[b]	No. of Events (%)[a]	
	All-Grade TEAEs, n = 58	Grade 3 TEAEs[c]
Hypertension	44 (76)	6 (10)
Weight decreased	40 (69)	7 (12)
Diarrhea	39 (67)	6 (10)
Proteinuria	37 (64)	6 (10)
Fatigue	35 (60)	5 (9)
Decreased appetite	30 (52)	1 (2)
Nausea	29 (50)	0 (0)
Cough	26 (45)	1 (2)
Dysphonia	25 (43)	0 (0)
Headache	25 (43)	1 (2)
Vomiting	22 (38)	0 (0)
Arthralgia	21 (36)	3 (5)
Dry mouth	20 (35)	0 (0)
Back pain	19 (33)	2 (3)
Pain in extremity	19 (33)	0 (0)
Dyspnea	18 (31)	0 (0)
Musculoskeletal pain	18 (31)	1 (2)
Stomatitis	18 (31)	1 (2)
Abdominal pain upper	18 (31)	1 (2)
Abdominal pain	16 (28)	1 (2)
Epistaxis	16 (28)	0 (0)

Abbreviation: TEAEs, treatment-emergent adverse events.
[a] Patients with TEAEs were counted only once even if they had >1 event.
[b] Two patients died from serious adverse events (arterial hemorrhage and cardiac arrest).
[c] No grade 4 TEAEs were reported for the listed events.

Common toxicity criteria grade 3 or 4 TEAEs occurred in 42 patients (72%). Six grade 4 TEAEs were reported and included hypocalcemia, hyperkalemia, abasia, and acute myocardial infarction (1 report each) and 2 reports of pulmonary embolism. However, no grade 4 events occurred in ≥5% of patients. Grade 3 TEAEs that occurred in at least 5% of patients included weight loss (12%); hypertension, proteinuria, and diarrhea (10% each); fatigue (9%); dehydration (9%); and arthralgia (5%). TEAEs that led to lenvatinib withdrawal and occurred in at least 2 patients were proteinuria (5%), pulmonary embolism (3%), and deep vein thrombosis (3%). Skin-related TEAEs included palmar-plantar erythrodysesthesia (PPE) syndrome (22%; including grade 3 PPE in 1 patient [2%]), rash (14%), dry skin (14%), and alopecia (9%).

Nonfatal, serious AEs occurred in 28 patients (48%), and those that occurred in at least 2 patients included dehydration (7%), hypotension (5%), pulmonary embolism, lower abdominal pain, hypertension, and cardiac failure (3% each). Three deaths occurred within 30 days of the last dose of lenvatinib: 1 patient died from

PD, and 2 patients died after serious AEs (1 arterial hemorrhage and 1 cardiac arrest).

DISCUSSION

Historically, there have been limited treatment options for patients with RR-DTC. Multitargeted TKI agents under investigation for the treatment of RR-DTC have demonstrated response rates ranging between 8% and 49% and PFS ranging between 10.8 months and 18.1 months.[13,22-26] In the current study, lenvatinib treatment was associated with an ORR of 50% (all PRs), as determined by IIR, and a durable ($\geq$23 weeks) SD rate of 28%. The median PFS was 12.6 months. Similar tumor responses were observed for patients who did or did not receive prior VEGFR-targeted therapy. This finding may have important clinical implications, because the use of VEGFR-targeted therapy in RR-DTC is likely to increase in the near future given the approval of sorafenib and lenvatinib as well as the investigation of vandetanib in a phase 3 trial for this indication.

All patients who received treatment on this study had PD within the 12 months before enrollment. The mean sum size of target lesions in these patients was 11.7 cm, and nearly half of the patients (45%) had bone metastasis. It is noteworthy that the majority of patients in this study were men (59%), consistent with other clinical trials of DTC.[22,25] Although DTC is more prevalent in women, men typically have a worse prognosis,[27] which may explain their over-representation in clinical studies.

Although comparisons cannot be drawn from different clinical trials, the median PFS for lenvatinib of 12.6 months in our study was similar to that reported in the literature for patients who received other multitargeted TKIs.[13,22-26] Although those trials supported the use of multitargeted TKIs, they had different entry criteria, and some also included medullary and anaplastic thyroid cancers, which behave quite differently.[28] Not all studies required evidence of disease progression for eligibility, which was required in the current study. It is difficult to determine whether the inclusion of patients with SD in the other studies may have influenced observed efficacy.

Lenvatinib had a toxicity profile principally characterized by hypertension, proteinuria, fatigue, and gastrointestinal complaints, which generally were manageable with standard medical care and dose interruption or reduction when necessary. TEAEs resulted in dose interruptions, reductions, or treatment withdrawals in 74%, 66%, and 26% of patients, respectively. Grade 3 or 4 TEAEs were experienced by 72% of patients, and 48% of patients had nonfatal, serious AEs. The most common grade 3 TEAEs were weight decrease (12%); hypertension, proteinuria, and diarrhea (10% each); and fatigue and dehydration (9% each). Hypertension and proteinuria have been commonly reported for other VEGFR-targeted therapies.[22,29] Most patients with hypertension and proteinuria were managed successfully without lenvatinib dose adjustments. It is noteworthy that, in the current trial, skin-related TEAEs—specifically grade 1 or 2 rash—occurred in 8 patients (14%), and grade 3 PPE syndrome occurred in 1 patient (2%). There were 3 treatment-emergent deaths, including 1 patient who died after experiencing an arterial hemorrhage and 1 patient who died after a cardiac arrest. Thromboembolic events are known AEs associated with VEGFR inhibitors.[30] These findings underscore the importance of careful screening to ensure that only patients who have clinically significant disease are included for treatment.

In this hypothesis-generating, exploratory biomarker analysis, changes were observed in the levels of 16 of the 51 CAFs assessed after 8 days of lenvatinib treatment. These included increases in the VEGFR ligands VEGFA and placental growth factor and decreases in angiopoietin-2, soluble TEK tyrosine kinase 2 (TIE2), and soluble VEGFR2. Angiopoietins, including angiopoietin-2, are ligands of TIE2; and together with VEGFA, they form a critical interface of the angiogenic network to promote the initiation and maturation of new blood vessels.[31,32] The angiopoietin-2/angiopoietin-1/TIE2 axis may either promote or inhibit the formation of tumors in different contexts.[32] The exact role of angiopoietin-2 in this signaling pathway is complex, acting as either an antagonist or a partial agonist for TIE2. Nevertheless, anticancer approaches that inhibit angiopoietin-2 to augment VEGF-targeted therapies appeared promising in preclinical and early clinical studies.[33] In addition, angiogenic factors like angiopoietin-2 are potential markers for resistance to therapy, and upregulation of angiopoietin-2 has been implicated in the development of resistance to antiangiogenic TKIs in other cancers.[34,35] These findings warrant further investigation in a larger population.

In summary, our trial of once-daily oral lenvatinib in patients with RR-DTC demonstrated an ORR of 50%, a time to response of 3.6 months, and a median PFS of 12.6 months, supporting further evaluation of lenvatinib in this patient population. Results from an international, multicenter, randomized phase 3 trial recently were published.[36]

FUNDING SUPPORT

This study was supported by Eisai Inc. Medical editorial writing assistance was provided by Phase Five Communications Inc and Oxford PharmaGenesis Inc and was supported by Eisai Inc. Dr. Martins received research support from funding provided for this trial to the University of Washington.

CONFLICT OF INTEREST DISCLOSURES

Dr. Cabanillas reports research funding from Eisai, Exelixis, Roche, and Salient; service on the advisory boards of Eisai, Exelixis, and Bayer; and service as a consultant to AstraZeneca. Dr. Schlumberger reports service as a consultant to AstraZeneca, Bayer, and Eisai; honoraria from AstraZeneca and Bayer; and research funding from AstraZeneca, Bayer, Eisai, and Exelixis. Dr. Jarzab reports grants from Genzyme; grants and personal fees from Novartis and Ipsen; and personal fees from AstraZeneca, Sobi, Exelixis, Bayer, and Oxigene. Dr. Robinson reports service as a consultant to AstraZeneca, Bayer, and Eisai and research funding from the National Health and Medical Research Council. Dr. McCaffrey reports research funding from Eisai. Dr. Shah reports research funding from Bayer, Eisai, and Exelixis. Dr. Topliss reports receipt by his institution of fees from Eisai to conduct clinical trials on lenvatinib. Dr. Funahashi reports stock ownership (self and family member) in Eisai Company, Ltd and is a coinventor of US Patent 7,253,286, which is owned by Eisai R&D Management Company, Ltd. Dr. Elisei reports personal consulting fees from Bayer, Genzyme, Exelixis/Sobi, and Eisai. Dr. Newbold reports research support from the UK National Health Service through the National Institute for Health Research Biomedical Research Centre and service as a consultant in an advisory role to Eisai, AstraZeneca, and Genzyme. Dr. Licitra reports service as a consultant in an advisory role to Bristol-Myers Squibb, Glaxo, Lilly, Merck-Serono, Amgen, Boehringer Ingelheim, Debiopharm, VentiRX, and Sobi; research funding (institutional or self) from Eisai, Exelixis, Lilly, Merck-Serono, Amgen, Boehringer Ingelheim, and Pfizer; and institutional travel support from Merck-Serono and Debiopharm. Dr. Sherman reports grants and personal fees from Pfizer and Genzyme and personal fees from Eisai, Exelixis, Bayer, Onyx, AstraZeneca, Vercyte, NovoNordisk, Eli Lilly and Company, and Roche. Dr. Ball reports service as a consultant in advisory role to Eisai. Drs. O'Brien, Ren, and Funahashi are employees of Eisai Inc.

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