A Phase II Trial of the Multitargeted Tyrosine Kinase Inhibitor Lenvatinib (E7080) in Advanced Medullary Thyroid Cancer

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Abstract

Purpose: Positive results of phase I studies evaluating lenvatinib in solid tumors, including thyroid cancer, prompted a phase II trial in advanced medullary thyroid carcinoma (MTC).

Experimental Design: Fifty-nine patients with unresectable progressive MTC per Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 within the prior 12 months received lenvatinib (24-mg daily, 28-day cycles) until disease progression, unmanageable toxicity, withdrawal, or death. Prior anti-VEGFR therapy was permitted. The primary endpoint was objective response rate (ORR) by RECIST v1.0 and independent imaging review.

Results: Lenvatinib ORR was 36% [95% confidence interval (CI), 24%–49%]; all partial responses. ORR was comparable between patients with (35%) or without (36%) prior anti-VEGFR therapy. Disease control rate (DCR) was 80% (95% CI, 67%–89%); 44% had stable disease. Among responders, median time to response (TTR) was 3.5 months (95% CI, 1.9–3.7). Median progression-free survival (PFS) was 9.0 months (95% CI, 7.0–not evaluable). Common toxicity criteria grade 3/4 treatment-emergent adverse events included diarrhea (14%), hypertension (7%), decreased appetite (7%), fatigue, dysphagia, and increased alanine aminotransferase levels (5% each). Ret proto-oncogene status did not correlate with outcomes. Low baseline levels of angiotensin-2, hepatocyte growth factor, and IL8 were associated with tumor reduction and prolonged PFS. High baseline levels of VEGF, soluble VEGFR3, and platelet-derived growth factor BB, and low baseline levels of soluble Tie-2, were associated with tumor reduction.

Conclusions: Lenvatinib had a high ORR, high DCR, and a short TTR in patients with documented progressive MTC. Toxicities were managed with dose modifications and medications.

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Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor arising from the parafollicular C cells in the thyroid gland. MTC accounts for about 4% of all thyroid cancers (1), whereas differentiated thyroid cancer (DTC), a crine tumor arising from the parafollicular C cells in the thyroid gland. MTC accounts for about 4% of all thyroid cancers (1). MTC may be familial in 10% of patients, with the MEN2 syndrome (2).

The overall 10-year survival rate of patients with MTC ranges from 96% for patients with intrathyroid disease to 40% for patients with locally advanced disease or with distant metastases (3). Total thyroidectomy and neck lymph node dissection is considered the most effective therapeutic approach (1, 4, 5), although patients with distant metastases may not fully benefit from extensive surgery (3). For these...
Translational Relevance

Lenvatinib, an oral, multitargeted tyrosine kinase inhibitor of the VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT signaling networks, demonstrated antitumor activity in phase I studies against several solid tumors, including in advanced medullary thyroid cancer (MTC). This phase II study demonstrated an objective response rate (ORR) for lenvatinib of 36% in patients with progressive MTC. The ORR was similar between patients with (35%) and without prior anti-VEGF therapy (36%). Treatment with lenvatinib was associated with a well-defined safety profile that was managed with dose modifications and medications. This study also explored potential biomarkers that may be indicative of a response to lenvatinib, with lower baseline levels of angiopoietin-2 associated with greater tumor reduction and prolonged progression-free survival. These findings support the continued investigation of lenvatinib for the management of advanced MTC.

Patients

Patients were ≥18 years of age with unresectable or metastatic histologically or cytologically confirmed MTC with at least one measurable lesion by Response Evaluation Criteria In Solid Tumors version 1.0 (RECIST v1.0; ref. 30) and either computed tomography (CT) or MRI scans. Patients also had documented disease progression within 12 months prior to study entry (as assessed by the investigator with CT or MRI scans per RECIST). Prior chemotherapy and anti-VEGFR treatments were allowed but must have been discontinued at least 30 days prior to study entry. Patients with significant cardiac, hematopoietic, hepatic, or renal dysfunction; metastases to the brain or leptomeningeal metastases; or use of anticoagulants were excluded.

Tumor response

The primary endpoint was objective response rate (ORR), per RECIST v1.0 criteria as assessed by independent imaging review (IRR). Secondary endpoints included PFS, overall survival (OS), disease control rate (DCR; defined as complete response (CR), partial response (PR), or stable disease (SD)), time to response (TTR) based on IRR, duration of response, and safety and tolerability. SD was defined as stable disease lasting ≥7 weeks; durable SD was defined as SD for ≥23 weeks.

Patient monitoring and tumor assessment

Physical examinations and laboratory evaluations were conducted on days 1, 8, 15, and 22 of cycle 1; on day 1 of cycle 2; and then on day 1 of every 28-day cycle. Investigators were permitted to continue lenvatinib treatment until documented disease progression or unacceptable toxicity.

Within 4 weeks prior to initiation of treatment, tumor assessments using CT of the neck/chest/pelvis or MRI of the abdomen were performed and assessed as the baseline tumor burden. Follow-up assessments in accordance with RECIST v1.0 were performed every other cycle or sooner if there was suspicion of progressive disease (PD). Tumor response was evaluated at the site, and if PR or CR was reported, the response was verified at least 4 weeks after first observed. The IRR of tumor response was used for the primary and secondary efficacy assessments. Designation of SD for best overall response (BOR) required at least one post-treatment assessment of SD at a minimum of 7 weeks after the first
dose. At baseline [cycle 1 day 1 (C1D1)] and every 4 cycles, bone scans were performed.

Archival tumor tissues were available and obtained from 24 of 59 patients. Exploratory correlative analyses of tumor genetics, serum levels of 51 circulating cytokine and angiogenic factors (CAF), calcitonin (Ct), and carcinoembryonic antigen (CEA) with tumor responses to lenvatinib treatment were conducted. A total of 32 genes and 443 mutations were assessed using the Sequenom Mass ARRAY iPLEX OncoCarta v1.0 and v3.0 Platform (Sequenom, Inc.). A panel of 51 CAFs was assayed using ELISA and multiplex assays. Sample data acquisition and analysis were performed on either an ELISA plate reader using SoftmaxPro software (Molecular Devices) or the BioRad Bio-Plex System (Bio-Rad Laboratories) using Bio-Plex Manager 4.1 software for multiplex assays. CAFs for which >20% of patients had out-of-range measurements were not included in correlative analyses. Ct and CEA measurements were performed using chemiluminescence immunoassays on Immulite 2000 and Gentaur instruments, respectively.

Statistical analysis
Sample size estimates were calculated on the basis of Simon optimal 2-stage design, assuming an expected ORR of 15% with lenvatinib compared with 2.5% based on historical controls, at 90% power and α of 0.5. In this two-stage design, 16 patients were required in stage 1; if at least 1 confirmed CR or PR was observed by IIR, the study would continue to stage 2 to enroll a total of 52 patients. Otherwise, enrollment would be stopped for futility. However, because of rapid enrollment, all subjects were enrolled before the scheduled interim analysis (when the 16th evaluable patient completed 6 treatment cycles); nevertheless, because more than one confirmed responder was observed among the first 16 patients prior to the enrollment of additional patients, the criterion for moving to the second stage was already met. All patients received at least one lenvatinib dose and had at least one posttreatment safety assessment and were therefore included in both the intent-to-treat (ITT) and safety populations. The ITT population included patients prior to the enrollment of additional patients, the criterion for moving to the second stage was already met. All patients patient choice (3%) received prior anti-VEGFR therapy, 49% had received radiotherapy and 15% had received conventional chemotherapy. The most common sites of metastases were liver (68%), mediastinum (58%), lung (53%), and bone (44%). Sixteen of the 24 analyzed patient tumors (67%) were RET mutant-positive (RET*539E; n = 14; RET*536E; n = 2).

Patient disposition
Thirty (51%) patients discontinued treatment for the following primary reasons: disease progression (25%), AE (22%), and patient choice (3%).

Tumor response
After a minimum 8 months of follow-up, the ORR as assessed by IIR was 36% (95% CI, 24%–49%), with only PRs reported (Table 2). No obvious differences in ORR by age, gender, or prior anti-VEGFR therapy were observed. A BOR of SD was observed in 44% of patients and durable SD in 29% of patients. The DCR was 80% (95% CI, 67%–89%). For patients who responded to treatment, the median TTR was 8.5 months (95% CI, 1.9–37), and the median duration of response based on IIR assessments was not reached because of the high proportion of censored patients. A waterfall plot of the maximum tumor percentage change from baseline to postbaseline nadir is shown in Fig. 1A. The overall median PFS as assessed by IIR was 9.0 months [95% CI, 7.0–not evaluable (NE); Fig. 1B]. The 6-month PFS rate was 67% (95% CI, 52%–78%) and the 12-month PFS rate was 46% (95% CI, 31%–60%). The overall median OS was 16.6 months (95% CI, 16.4–NE; Supplementary Fig. S1).

Tumor response based on prior anti-VEGFR therapy
Tumor responses were similar regardless of prior history of anti-VEGFR therapy. The ORR for patients who did (n = 26) or did not (n = 33) receive prior VEGFR therapy was 35% (95% CI, 17%–56%) and 36% (95% CI, 20%–55%), respectively (all PRs). The median duration of response for patients who had received prior VEGFR treatment and responded to lenvatinib therapy (n = 9) was 5.7 months (95% CI, 4.5–NE) and was not reached for lenvatinib responders without prior VEGFR treatment (n = 12). The median PFS was 7.3 months (95% CI, 4.0–NE) in patients with prior VEGFR therapy and 12.9 months (95% CI, 7.1–NE) for patients without prior VEGFR therapy. The median OS for patients with prior VEGF-targeted therapy was also
Pharmacogenomic and pharmacodynamics analyses

An examination of genetic alterations in 24 archival patient tumor tissues yielded a total of 11 different mutations in 7 genes from 18 patient tumors. Of note, RET tumor mutation status did not show a statistically significant association with tumor shrinkage (P = 0.920), ORR (P = 1.000), or PFS (P = 0.313). An NRAS mutant–positive patient achieved SD and 2 patients with dual PIK3CA and RETM918T mutations had PRs.

After 8 days of treatment with lenvatinib, changes were observed in the levels of VEGF, sVEGFR3, and the homodimer of PDGF-beta polypeptide (PDGF-BB) were associated with greater tumor shrinkage (Fig. 3A). Low baseline levels of angiopoietin-2, HGF, and IL8 were associated with prolonged PFS (Fig. 3B).

Serum Ct and CEA levels decreased upon lenvatinib treatment in almost all patients [Ct decreased by a median 0.49-fold by cycle 2 day 1 (C2D1) in 47 of 52 patients; CEA decreased by a median 0.60-fold by cycle 3 day 1 (C3D1) in 44 of 50 patients]. These changes were significantly correlated with ORR and prolonged PFS, respectively (C2D1 Ct, P = 0.012 and P = 0.001; HR, 1.72; 95% CI, 1.25–2.38; C3D1 CEA, P = 0.032 and P = 0.003, HR, 2.06; 95% CI, 1.28–3.32). When adjusted for multiple comparisons, these associations were no longer significant (C2D1 Ct, FDR P = 0.311 for ORR and FDR P = 0.086 for PFS; C3D1 CEA, FDR P = 0.327 for ORR and FDR P = 0.114 for PFS).

Treatment duration, safety, and tolerability

All patients experienced treatment-emergent AEs (TEAE). The most common TEAEs were diarrhea (75%), proteinuria (59%), fatigue (53%), hypertension (51%), decreased appetite (49%), nausea (48%), decreased weight (42%), headache (41%), vomiting (37%), and cough (36%; Table 3). Most hypertension and proteinuria events were grade 1 or 2 and managed with standard medical interventions. The median duration of treatment was 264 days (range, 13–547 days). At least 8 cycles of lenvatinib treatment were received by 64% of patients, with a mean dose intensity of 19.1 mg/d. Dose reduction, interruption, or treatment withdrawal due to TEAEs was required in 59%, 75%, and 24% of patients, respectively. Dose reductions to 20, 14, 10, and 8 mg/d of lenvatinib occurred in 56%, 39%, 8%, and 2% of patients, respectively. The median time to the first dose reduction was 2.2 months (range, 0.5–16.6). TEAEs that led to lenvatinib withdrawal and occurred in more than one patient were decreased appetite and decreased weight (3% each). Withdrawal from treatment due to hypertension occurred in one patient (2%).

Skin-related TEAEs included palmar–plantar erythrodysesthesia syndrome (24%), rash (22%), dry skin (17%), alopecia and hyperkeratosis (12% each), and skin exfoliation (10%). One patient (2%) experienced grade 1 folliculitis. Two patients (3%) experienced grade 3 palmar–plantar erythrodysesthesia syndrome and one patient (2%) experienced grade 4 exfoliative rash. The grade 4 exfoliative rash lasted for 8 days and was deemed unrelated to study treatment by the investigator; the study dose was therefore not changed, and the patient recovered.

Table 2. Tumor responses based on IIR assessments (ITT population)

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>Overall (N = 59)</th>
</tr>
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<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>21 (36)</td>
</tr>
<tr>
<td>95% CI</td>
<td>24–49</td>
</tr>
<tr>
<td>Best overall tumor response*</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>21 (36)</td>
</tr>
<tr>
<td>SD (≥7 wks)</td>
<td>26 (44)</td>
</tr>
<tr>
<td>PD</td>
<td>17 (29)</td>
</tr>
<tr>
<td>NE</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (5)</td>
</tr>
<tr>
<td>DCR (CR + PR + SD)</td>
<td>47 (80)</td>
</tr>
<tr>
<td>95% CI</td>
<td>67–89</td>
</tr>
<tr>
<td>TTR, mo, median (95% CI)</td>
<td>3.5 (1.9–3.7)</td>
</tr>
<tr>
<td>Duration of response, mo, median (95% CI)</td>
<td>NE (5.7–NE)</td>
</tr>
</tbody>
</table>

*Responses were evaluated on the basis of the modified RECIST criteria.
We evaluated oral lenvatinib (24 mg administered once-daily) for the treatment of unresectable or metastatic MTC and RECIST v1.0–documented disease progression at baseline in 59 patients, of which almost half of all patients had received prior anti-VEGFR treatment or had bone metastases. A confirmed ORR was observed in 36% of patients with only PRs reported. The median PFS was 9 months and the estimated PFS rate at 6 months was 67%. In this study, although there was a numerical difference in median PFS between patients with and without prior VEGF-targeted therapy, tumor response was similar in both groups, confirming the lack of cross-resistance between TKIs previously suggested in a study of cabozaantinib therapy in patients with prior VEGFR-targeted treatment (19).

Although results across different clinical trials are difficult to interpret, the tumor responses observed for lenvatinib in this trial are encouraging in the context of what has been reported for other TKIs. A phase II trial of vandetanib in patients with locally advanced or metastatic hereditary MTC showed a confirmed/unconfirmed PR rate of 30% (31), and the subsequent phase III trial reported a 45% ORR in vandetanib-treated MTC patients, with a 6-month PFS rate of 83% (18). However, PD was not required to be present at study entry in either of these vandetanib trials, and the phase II trial was limited to patients with hereditary disease, both of which could have influenced the observed tumor response. Of note, a median PFS of 19 months was observed for placebo patients in the ZETA trial. In contrast, a phase III study of cabozaantinib in unresectable locally advanced or metastatic MTC did require evidence of disease progression within 14 months of screening (19).

Results showed statistically significant advantages in favor of cabozaantinib over placebo in ORR (28% vs. 0%) and the median PFS was 11.2 months in the cabozaantinib arm and 4 months in the placebo arm. Therefore, despite the approval of both vandetanib and cabozaantinib for the treatment of MTC, there is clearly still a need for effective TKI treatments in patients with progressive MTC.

Lenvatinib at the starting dose of 24 mg once daily has a toxicity profile characterized by predominantly CTC grade ≤ 2 TEAEs, including diarrhea, proteinuria, hypertension, fatigue, decreased appetite, nausea, decreased weight, vomiting, and abdominal pain. Twenty-two percent of patients withdrew from the study due to TEAEs. The AE profile of lenvatinib was generally consistent with anti-VEGFR treatment of advanced MTC (14). Most hypertension and proteinuria events were grade ≤ 2 and most TEAEs were managed with standard medical care and dose interruption.
or reduction when necessary. A high incidence of diarrhea was seen, although diarrhea is often also a complication of MTC. CTC grade 3 or 4 TEAEs, most of which were of grade 3 severity, were experienced by 70% of patients, most commonly diarrhea (12%), hypertension (7%), and decreased appetite (7%). Fifty-one percent of patients had SAEs.

Of interest in this study was the generally low incidence of grade 3 skin toxicities. The incidence of palmar–plantar erythrodysesthesia syndrome (also known as hand–foot syndrome) was 24%; grade 3 palmar–plantar erythrodysesthesia syndrome occurred in 3.4% of patients. The incidence of rash was 22% and one grade 4 exfoliative rash event occurred. In a phase II trial of sorafenib for metastatic MTC, the incidence of palmar–plantar erythrodysesthesia syndrome was 76% with grade ≥ 3 events occurring in 14% of patients (32). In the same trial, the incidence of rash was 67% with no grade 3 rash events. In the ZETA trial, 45% of vandetanib-treated patients experienced rash and 4% experienced grade ≥ 3 rash events (18). In the present study, only one patient experienced grade 1 folliculitis. Folliculitis has been noted as a common AE identified in clinical studies with patients receiving vandetanib as treatment for MTC (33). Therefore, the use of lenvatinib may be associated with fewer skin toxicities, but this would need confirmation in placebo-controlled trials.

In this exploratory biomarker study of a limited number of patients, tumor response did not appear to correlate with RET mutation status. In addition, although RAS mutations are the second most important driver mutation in MTC, only a single NRAS-mutant tumor was identified in this study, possibly due to the limited number of tumors analyzed, as well as the method of genetic testing, which limited the range of mutations that could be identified. The associations found between changes in CAF levels
and clinical outcomes of lenvatinib treatment suggest that anti-angiogenic activity contributed to the observed antitumor activity in this study. This is consistent with results of a phase I clinical trial in metastatic MTC that showed that exposure to cabozantinib resulted in significant changes in the levels of placental growth factor, VEGF-A, and VEGFR2 (34). Correspondingly, the present study detected changes in the levels of sVEGFR2, sVEGFR3, and VEGF-A in patient serum, as well as changes in levels of angiopoietin-2, sTie-2, SDF-1α, and IP-10 after 8 days of lenvatinib treatment.

We also observed that low baseline levels of angiopoietin-2, sTie-2, HGF, and IL8 were associated with greater tumor shrinkage; angiopoietin-2, HGF, and IL8 were additionally associated with prolonged PFS. HGF and IL8 are factors known to be
associated with resistance to anti-VEGF therapy (35, 36). Our results suggest that angiopoietin-2/Tie-2 signaling may also contribute to VEGF or TKI treatment resistance (37); however, most of these markers lose statistical significance after adjustment for multiple analyses. Therefore, further study is needed to validate these proposed angiogenic biomarkers in appropriately powered and controlled clinical trials.

In conclusion, oral lenvatinib, dosed once daily at 24 mg, was associated with an ORR of 36%, short TTR, prolonged duration of response, and a 6-month PFS rate of 67%. The observed toxicity profile was consistent with anti-VEGF treatment but with potentially greater incidence of weight loss and less clinically bothersome dermatological TEAEs. These results suggest that lenvatinib provides clinically meaningful tumor control with toxicities that were managed by symptomatic treatments and dose modifications in this pretreated population of patients.

Table 3. TEAEs, all grades in ≥20% of patients

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>All grades (N = 59)</th>
<th>Grade 3/4 (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>44 (75)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>35 (59)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (53)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (51)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>29 (49)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28 (48)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>25 (42)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (41)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (37)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (36)</td>
<td>0</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>19 (32)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17 (29)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16 (27)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>15 (25)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (25)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>15 (25)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodysesthesia syndrome</td>
<td>14 (24)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>13 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>13 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Blood thyroid-stimulating hormone level increased</td>
<td>12 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>12 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>12 (20)</td>
<td>0</td>
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</tbody>
</table>

Figure 3. (Continued).

Disclosure of Potential Conflicts of Interest
M. Schlumberger is a consultant/advisory board member for AstraZeneca, Bayer, Eisai, and Exelixis. M.E. Cabanillas is a consultant/advisory board member for and reports receiving commercial research grants from Eisai. B. Robinson has ownership interest (including patents) in Mayne Pharma and is a consultant/advisory board member for AstraZeneca, Bayer, and Eisai. D.W. Ball is a consultant/advisory board member for Eisai. K. Newbold reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Astra-Zeneca, Eisai, and Genzyme. M.H. Shah reports receiving commercial research grants from Eisai and Exelixis. R. Elisei is a consultant/advisory board member for AstraZeneca, Bayer, Exelixis, and Genzyme. S.I. Sherman is a consultant/advisory board member for AstraZeneca, Bayer, Eisai, and Exelixis. No potential conflicts of interest were disclosed by the other authors.

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