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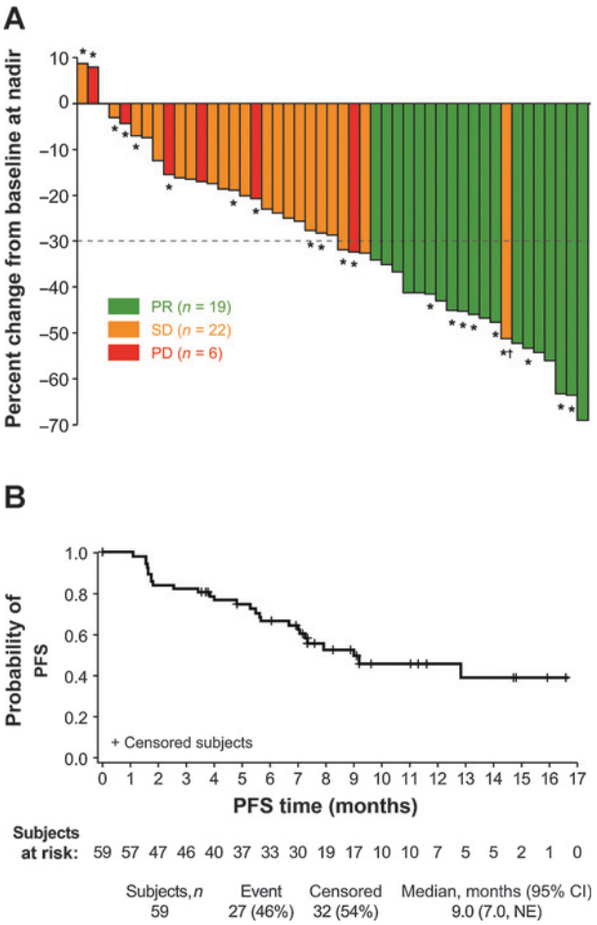

Figure 1.
A, waterfall plot of percent change in summed longest diameter of target lesions from baseline by independent imaging review of the efficacy evaluable subjects per protocol (n=50). No tumor change data were available for 3 patients with "Unknown" as their BOR. B, PFS by independent imaging review of the ITT population. *, patients previously treated with an anti-VEGFR therapy; †, although this patient had tumor shrinkage in the target lesion, the BOR of the patient was considered SD, as a baseline nontarget lesion became nonevaluable at a later assessment.

Common Toxicity Criteria (CTC) grade 3 TEAEs occurred in 36 patients (61%). Grade 3 TEAEs that occurred in at least 5% of patients included diarrhea (14%), hypertension (7%), decreased appetite (7%), fatigue (5%), dysphagia (5%), and increased levels of alanine aminotransferase (5%). There were 5 grade 4 TEAEs that occurred in one patient each: increased levels of amylase, increased levels of lipase, exfoliative rash, accidental narcotic overdose, and pneumonia aspiration.

Serious AEs (SAE) occurred in 51% of patients and those that occurred in at least two patients included decreased appetite (5%), pulmonary embolism, abdominal pain, pneumonia, lung infection, dehydration, and premature menopause (3.4% each). SAEs led to dose interruption in 15.3%, dose reduction in 8.5%, and study drug withdrawal in 8.5% of patients. Four deaths occurred during treatment or within 30 days of the last lenvatinib dose. Of these, one death was due to clinical PD and 3 were due to AEs, including respiratory arrest (not otherwise specified), respiratory failure, and paraneoplastic syndrome—with only the death by respiratory failure deemed treatment-related by the treating physician. An additional death occurred in a patient with tracheal–esophageal fistula that was study treatment–related; this event was recorded as an SAE, but not as a fatal AE.

Discussion

Distant metastases are the main cause of death in patients with advanced MTC with little evidence supporting the use of cytotoxic chemotherapy in these patients (14). Increased understanding of molecular mechanisms implicated in the pathogenesis and progression of MTC has prompted development of TKIs with activity against critical mediators of the relevant signaling pathways involved, including RET and VEGFR (6).

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 cabozantinib 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 cabozantinib 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 cabozantinib over placebo in ORR (28% vs. 0%) and the median PFS was 11.2 months in the cabozantinib arm and 4 months in the placebo arm. Therefore, despite the approval of both vandetanib and cabozantinib 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 $\leq$ 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 $\leq$ 2 and most TEAEs were managed with standard medical care and dose interruption

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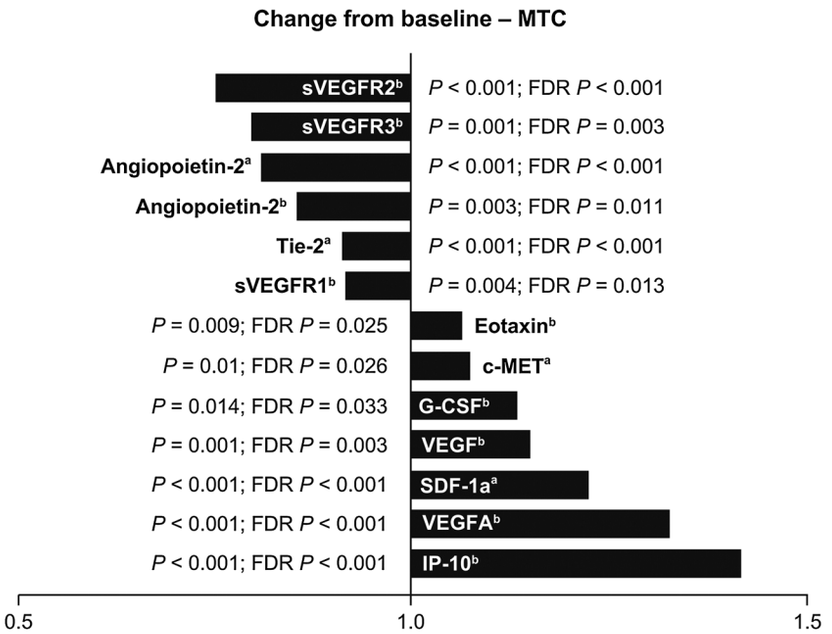

Figure 2.
Change in serum CAF levels during lenvatinib treatment. a, by ELISA; b, by multiplex array.

Serum CAF	Median fold change
sVEGFR2[b]	0.753
sVEGFR3[b]	0.800
Angiopoietin-2[a]	0.810
Angiopoietin-2[b]	0.855
Tie-2[a]	0.916
sVEGFR1[b]	0.918
Eotaxin[b]	1.067
c-MET[a]	1.074
G-CSF[b]	1.134
VEGF[b]	1.151
SDF-1a[a]	1.224
VEGFA[b]	1.329
IP-10[b]	1.418

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 $\geq$3 events occurring in 14% of patients (32). In the same trial, the incidence of rash was 67% with no $\geq$grade 3 rash events. In the ZETA trial, 45% of vandetanib-treated patients experienced rash and 4% experienced grade $\geq$ 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

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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-1a, 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

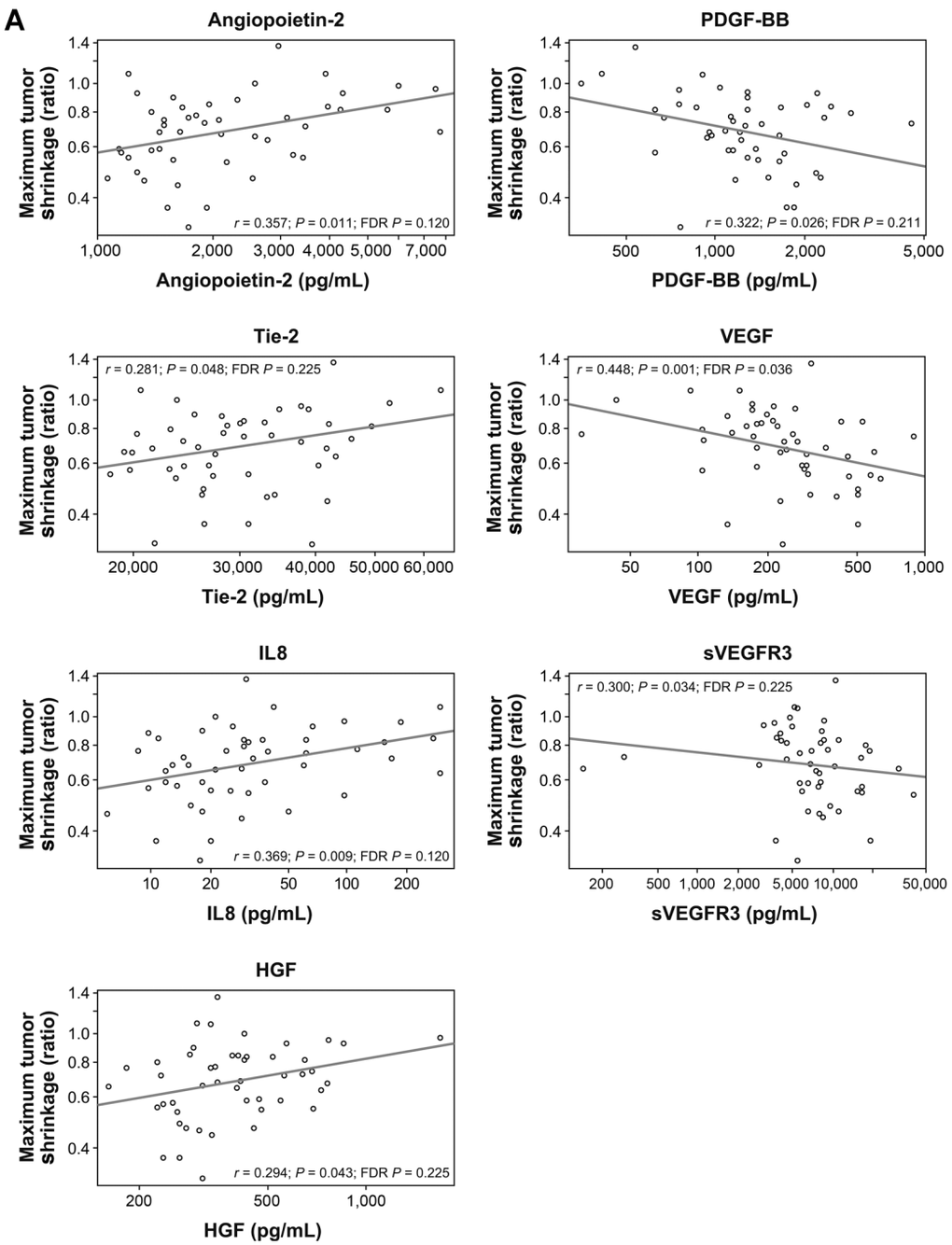

Figure 3.
Correlation of baseline cytokine and angiogenic factor levels with clinical outcome. A, correlation of baseline cytokine and angiogenic factor levels with maximum tumor shrinkage. B, Kaplan–Meier plots of PFS stratified by high and low baseline cytokine and angiogenic factor levels (median cutoff). (*Continued on the following page.*)

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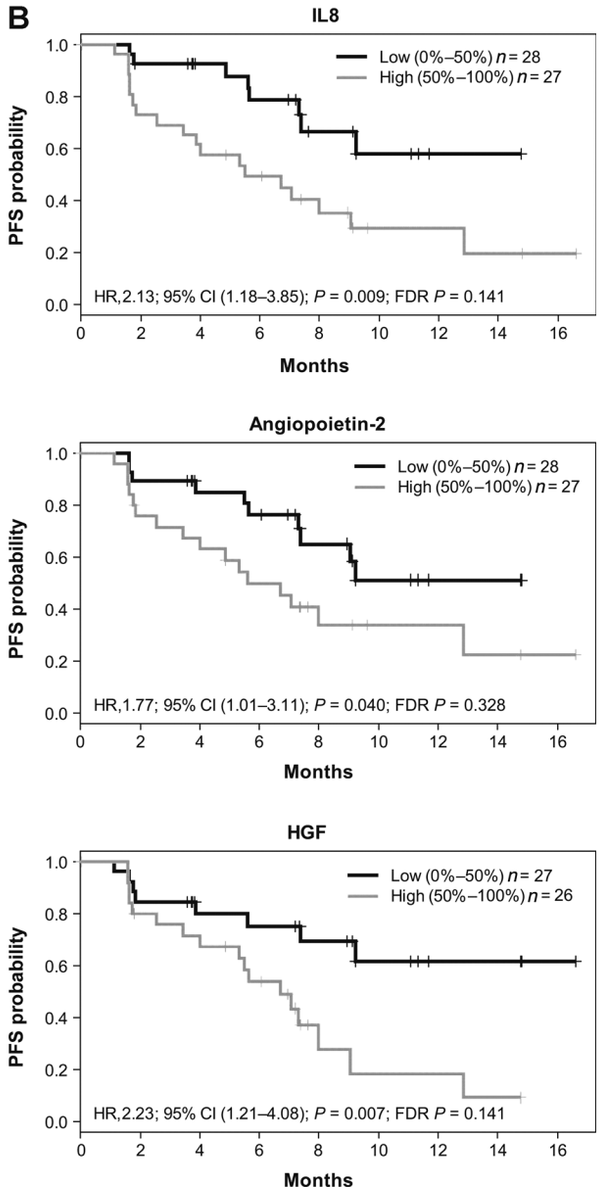

Figure 3.
(*Continued*).

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

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

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 AstraZeneca, 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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Study supervision: M. Schlumberger, L.F. Licitra, R. Elisei, J.P. O'Brien

Other (biomarker research): Y. Funahashi

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