Original Article

Correlative Analyses of *RET* and RAS Mutations in a Phase 3 Trial of Cabozantinib in Patients With Progressive, Metastatic Medullary Thyroid Cancer

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BACKGROUND: Cabozantinib significantly prolonged progression-free survival (PFS) versus a placebo in patients with progressive, metastatic medullary thyroid cancer (MTC; $P < .001$). An exploratory analysis of phase 3 trial data evaluated the influence of rearranged during transfection (*RET*) and RAS (HRAS, KRAS, and NRAS) mutations on cabozantinib clinical activity. **METHODS:** Patients (n = 330) were randomized to cabozantinib (140 mg/day) or a placebo. The primary endpoint was PFS. Additional outcome measures included PFS, objective response rates (ORRs), and adverse events in *RET* and RAS mutation subgroups. **RESULTS:** Among all study patients, 51.2% were *RET* mutation–positive (38.2% with *RET* M918T), 34.8% were *RET* mutation–unknown, and 13.9% were *RET* mutation–negative. Sixteen patients were RAS mutation–positive. Cabozantinib appeared to prolong PFS versus the placebo in the *RET* mutation–positive subgroup (hazard ratio [HR], 0.23; 95% confidence interval [CI], 0.14-0.38; $P < .0001$), the *RET* mutation–unknown subgroup (HR, 0.30; 95% CI, 0.16-0.57; $P = .0001$), and the RAS mutation–positive subgroup (HR, 0.15; 95% CI, 0.02-1.10; $P = .0317$). The *RET* M918T subgroup achieved the greatest observed PFS benefit from cabozantinib versus the placebo (HR, 0.15; 95% CI, 0.08-0.28; $P < .0001$). The ORRs for *RET* mutation–positive, *RET* mutation–negative, and RAS mutation–positive patients were 32%, 22%, and 31%, respectively. No PFS benefit was observed in patients lacking both *RET* and RAS mutations, although the ORR was 21%. The safety profile for all subgroups was similar to that for the overall cabozantinib arm. **CONCLUSIONS:** These data suggest that cabozantinib provides the greatest clinical benefit to patients with MTC who have *RET* M918T or RAS mutations. However, a prospective trial is needed to confirm the relation between genetic variation and the response to cabozantinib. ***Cancer*** **2016;122:3856-64.** *© 2016 American Cancer Society.*

KEYWORDS: cabozantinib, medullary thyroid cancer, RAS, *RET*, tyrosine kinase inhibitor.

INTRODUCTION

Medullary thyroid cancer (MTC) accounts for approximately 2% of all thyroid malignancies and approximately 1000 new cancer diagnoses each year in the United States.[1,2] Overall, the 10-year survival rate in patients with MTC is approximately 75%, but it is lower in patients with stage III disease (71%) or stage IV disease (21%-40%).[3-5]

The development of MTC can occur spontaneously in approximately 75% of cases or as part of an inherited cancer syndrome called multiple endocrine neoplasia type 2.[6] Activating mutations in the rearranged during transfection (*RET*) proto-oncogene have a central role in tumorigenesis, and *RET* genetic alterations are detected in 95% and approximately 65% of patients with hereditary and sporadic MTC, respectively.[6,7] Approximately 50% to 80% of tumors from patients with sporadic MTC harbor a somatic mutation at codon 918 of *RET* (M918T), which has been associated with a poor prognosis and the development of distant metastasis.[8,9] One retrospective analysis reported a 10-year survival rate of 56% for patients with tumors containing M918T mutations but 87% survival for those without M918T mutations.[10]

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Portions of the preliminary data from this exploratory study were presented at the Annual Meeting of the American Society of Clinical Oncology; May 31-June 4, 2013; Chicago, IL (abstract 6000). Portions were also presented at the 83rd Annual Meeting of the American Thyroid Association; October 16-20, 2013; San Juan, Puerto Rico (highlighted oral 4).

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This trial is registered at ClinicalTrials.gov (NCT00704730).

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In sporadic MTC cases, tumors that lack a mutation in *RET* often contain a mutation in RAS family members such as *HRAS* and *KRAS*,[11-13] and this contributes to oncogenesis by increasing tumor cell survival, invasion, and metastasis. Also, the expression of oncogenic factors involved in tumor growth and development, including hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor 2, is increased in MTC.[14,15]

Surgical resection is the main form of treatment and is effective in many patients; however, the prognosis is poor for patients with advanced MTC, and limited treatment options are available.[2] Several multitargeted kinase inhibitors have been approved or are currently under investigation for MTC treatment. Vandetanib is approved for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease.[16] Cabozantinib is approved in the United States for the treatment of progressive, metastatic MTC and in the European Union for the treatment of progressive, unresectable, locally advanced, or metastatic MTC.[17] Other drugs under investigation for the treatment of MTC include kinase inhibitors such as lenvatinib,[18] pazopanib,[19] ponatinib,[20] and sorafenib.[21]

Cabozantinib is an oral inhibitor of tyrosine kinases, including RET, MET, and vascular endothelial growth factor receptor 2.[22] In the phase 3 Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) trial, patients with progressive MTC treated with cabozantinib had significantly improved progression-free survival (PFS) and a significantly improved objective response rate (ORR) in comparison with placebo-treated patients.[23] The median PFS was 11.2 with cabozantinib versus 4.0 months with a placebo (hazard ratio [HR], 0.28; $P < .001$). No patients treated with the placebo achieved an objective tumor response, whereas 28% of cabozantinib-treated patients did ($P < .001$). In this trial, all *RET* mutation subgroups (positive, negative, and unknown) treated with cabozantinib showed varying degrees of improvement in PFS.[23] Here we report more detailed exploratory analyses examining the relation between mutations in the genes encoding RET and RAS proteins and the clinical response to cabozantinib.

MATERIALS AND METHODS

Patients

Patients with histologically confirmed unresectable, locally advanced, or metastatic MTC with documented radiographic disease progression were enrolled as previously described.[23] There were no limits on the number of prior therapies, but patients who had received systemic anticancer treatment within 4 weeks or had significant cardiac, hematopoietic, hepatic, or renal dysfunction were excluded.[23] This study was conducted according to the Declaration of Helsinki and was approved by the local institutional review board for each study site. All patients provided written informed consent. The study is registered at ClinicalTrials.gov (NCT00704730).[24]

Study Design

This was an international, randomized, double-blind, placebo-controlled phase 3 study. Patients were randomized 2:1 in a double-blind fashion to receive either a single oral daily dose of 140 mg (freebase equivalent weight) of cabozantinib or a placebo in 4-week cycles as previously described.[23] Radiographic tumor assessments were performed every 12 weeks with modified Response Evaluation Criteria in Solid Tumors guidelines.[25]

Mutational Assessment

The *RET* mutational status was assessed with a blood sample collected before the dose (cycle 1, day 1) from all patients and with formalin-fixed, paraffin-embedded archival tissue collected from the primary lesion, a metastatic site, or both unless a *RET* mutation could be verified from a previous analysis, as previously reported.[23] Exons 10, 11, and 13 to 16 were chosen for analysis on the basis of the distribution of *RET* mutations found in hereditary and sporadic MTC.[4,6] Patients were considered *RET* mutation–positive if an identified mutation was listed as associated with a hereditary MTC syndrome, as previously described in the 2009 American Thyroid Association medullary thyroid cancer guidelines.[4] For a patient to be considered negative for a *RET* mutation, complete sequence data demonstrating no *RET* alterations in a tumor sample, with the exception of a known single-nucleotide polymorphism (G691S or R982C), were required from *RET* exons 10, 11, and 13 to 16. Samples with sequence differences not previously described in the guidelines[4] or samples that had no detected *RET* gene alterations but had insufficient sequence coverage of *RET* were classified as *RET* mutation–unknown for this subgroup analysis.

Patients were considered *RET* M918T mutation–positive if *RET* codon 918 in the blood or tumor showed the presence of the M918T mutation. Patients were considered *RET* M918T mutation–negative if no evidence of an M918T mutation was found after the sequencing of *RET* exon 16 from a tumor sample, and they were considered *RET* M918T mutation–unknown if sequence data for codon 918 were unavailable.

TABLE 1. Summary of *RET* and RAS Genotyping Results

Mutational Subgroup[a]	Patients, No. (%)		
	Total (n = 330)[b]	Cabozantinib (n = 219)[c]	Placebo (n = 111)[c]
RET mutational status			
RET mutation–positive	169 (51.2)	107 (48.9)	62 (55.9)
RET mutation–negative	46 (13.9)	35 (16.0)	11 (9.9)
RET mutation–unknown	115 (34.8)	77 (35.2)	38 (34.2)
RET mutation of unknown function[d]	21 (6.4)	15 (6.8)	6 (5.4)
RET M918T mutational status			
RET M918T mutation–positive[e]	126 (38.2)	81 (37.0)	45 (40.5)
RET M918T mutation–negative	107 (32.4)	75 (34.2)	32 (28.8)
Non-M918T *RET* mutation–positive[f]	43 (13.0)	26 (11.9)	17 (15.3)
RET M918T mutation–unknown	97 (29.4)	63 (28.8)	34 (30.6)
RAS mutational status			
RAS mutation–positive	16 (4.8)	13 (5.9)	3 (2.7)
RET and RAS mutation–negative	30 (9.1)	22 (10.0)	8 (7.2)

[a] See the Materials and Methods section for definitions of the mutational subgroups.
[b] A total of 330 patients were enrolled; 215 were evaluable for the *RET* mutational status.
[c] Percentages may not add up to 100% because of rounding.
[d] *RET* mutation that is not associated with hereditary forms of medullary thyroid cancer and is of undetermined function (a subset of the *RET* mutation–unknown subgroup).
[e] Four of these samples also contained other *RET* mutations in addition to M918T.
[f] Samples harboring *RET* mutations but lacking *RET* M918T.

Patient samples with a negative or unknown *RET* mutational status (n = 85) were evaluated for DNA sequence alterations in genes encoding RAS proteins. Patient samples known to harbor mutations in *RET* were not included in this analysis because *RET* and RAS family mutations are almost always mutually exclusive according to published research.[11-13,26] Next-generation sequencing with the Ion Torrent platform was used to evaluate the mutational status of codons 12, 13, and 61 in *KRAS, NRAS*, and *HRAS*.

Safety

Safety assessments included monitoring for adverse events, standard laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, and electrocardiograms. The severity of adverse events was assessed with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0), as previously described.[23]

Efficacy Endpoints

As presented in the primary analysis,[23] the primary endpoint was to evaluate PFS. Secondary endpoints included an assessment of the potential relation between *RET* DNA sequence alterations and the efficacy of cabozantinib; this included the evaluation of PFS and ORR in patient subgroups defined by the *RET* and RAS mutational status and adverse events by the *RET* mutational status.

Statistical Analysis

The Kaplan-Meier method was used to estimate the duration of PFS in the various subgroups as well as the median and associated 95% confidence interval (CI) for each treatment arm. Hypothesis testing for the duration of PFS between the 2 treatment arms for the subgroups was performed with the log-rank test with a 2-sided level of significance of .05. The HR was estimated with a Cox regression model, with the treatment groups used as the main effect. For the ORR and patient incidence of adverse events, the percentages and frequencies are presented.

RESULTS

Patients

Among 330 total patients (Table 1), 215 (65%) were assigned a *RET* mutational status on the basis of sequencing data or previous *RET* testing. In the total population, 51.2% of the patients were positive for a *RET* mutation in blood and/or tumor samples, 13.9% were considered *RET* mutation–negative, and 34.8% were classified as having an unknown *RET* mutational status. A summary of the identified *RET* mutations can be found in the online supporting information. Among patients with a known *RET* mutational status (n = 215), 78.6% were classified as *RET* mutation–positive, and 21.4% were classified as *RET* mutation–negative. The *RET* M918T mutation was observed in 38.2% of the total study population and in 74.6% of the patients found to have *RET* mutations (126 of 169). Mutations in extracellular cysteine

TABLE 2. Progression-Free Survival and Hazard Ratios of Mutational Subgroups

	No.	Median Progression-Free Survival, wk		Hazard Ratio (95% Confidence Interval)	*P*
		Placebo	Cabozantinib		
All cabozantinib patients[a]	330	17	49	0.28 (0.19-0.40)	<.0001
Mutational subgroups					
RET mutational status					
RET mutation–positive	169	20	60	0.23 (0.14-0.38)	<.0001
RET mutation–negative[b]	46	23	25	0.53 (0.19-1.50)	.2142
RET mutation–unknown	115	13	48	0.30 (0.16-0.57)	.0001
RET mutations of unknown function	21	13	24	0.47 (0.14-1.60)	.3280
RET M918T mutational status					
RET M918T mutation–positive	126	17	61	0.15 (0.08-0.28)	<.0001
RET M918T mutation–negative	107	24	25	0.67 (0.37-1.23)	.1875
Non-M918T *RET* mutation–positive	43	24	36	0.70 (0.26-1.87)	.4729
RET M918T mutation–unknown	97	12	49	0.27 (0.13-0.56)	.0002
RAS mutational status					
RAS mutation–positive	16	8	47	0.15 (0.02-1.10)	.0317
RET and RAS mutation–negative[b]	30	23	24	0.88 (0.24-3.22)	.8330

[a] The hazard ratio for the entire study population was calculated with stratification factors.
[b] The hazards are not proportional.

residues (ranging from C611 to C634) were found in 33 patients. Only a small subset of patients (n = 21) had *RET* mutations of unidentified significance (largely small in-frame deletions of the extracellular domain), and they were classified with the unknown *RET* status group for analysis. Three uncommon germline *RET* alterations were identified (*RET* I852M, *RET* M1064T, and *RET* C478Y), and *RET* I852M and *RET* M1064T were accompanied by somatic *RET* M918T mutations in tumor samples.

A subset of the *RET* mutation–negative or mutation–unknown patients had a RAS gene mutation. A total of 16 patients with RAS gene mutations were identified, 13 of whom were from the *RET* mutation–negative population (see Supporting Table 1 in the online supporting information). Overall, 30 patients had neither *RET* nor RAS mutations in analyzed tumor samples. The mutation rate for genes in the RAS family was approximately 7% (16 of 244 patients with a known *RET* and/or RAS status; a mutually exclusive distribution of *RET* and RAS mutations was assumed).

Efficacy Assessment

Cabozantinib appeared to improve PFS versus the placebo in the *RET* mutation–positive, *RET* mutation–unknown, and RAS gene mutation–positive subgroups (Table 2 and Fig. 1). The median PFS for the *RET* mutation–positive population was 60 weeks with cabozantinib and 20 weeks with the placebo (HR, 0.23; 95% CI, 0.14-0.38; $P < .0001$; Table 2). Patients in the *RET* mutation–negative population had a median PFS of 25 weeks with cabozantinib and 23 weeks with the placebo (HR, 0.53; 95% CI, 0.19-1.50; $P = .2142$; Table 2); however, because of the small size and unequal distribution of the *RET* mutation–negative population (35 in the cabozantinib arm and 11 in the placebo arm), no conclusions can be drawn regarding the activity of cabozantinib in this subpopulation. The median PFS for the *RET* mutation–unknown population was 48 weeks with cabozantinib and 13 weeks with the placebo (HR, 0.30; 95% CI, 0.16-0.57; $P = .0001$). The PFS benefit appeared to be greatest in the *RET* M918T subgroup, which had median PFS values of 61 weeks with cabozantinib and 17 weeks with the placebo (HR, 0.15; 95% CI, 0.08-0.28; $P < .0001$; Fig. 1), whereas no difference in the median PFS was observed for patients without *RET* M918T mutations (25 weeks for cabozantinib vs 24 weeks for the placebo; Table 2).

In the RAS mutation–positive population (Fig. 2A), the median PFS was 47 weeks with cabozantinib and 8 weeks with the placebo (HR, 0.15; 95% CI, 0.02-1.10; $P = .0317$; Table 2). However, the subgroup of patients with RAS mutations was small (n = 16), with only 3 patients randomized to the placebo arm. No difference in the median PFS was observed in the *RET*/RAS gene mutation–negative population between patients treated with cabozantinib and patients treated with the placebo (Fig. 2B and Table 2).

The ORR with cabozantinib was highest among patients with *RET* or RAS gene mutations (Table 3). For *RET* mutation–positive patients treated with

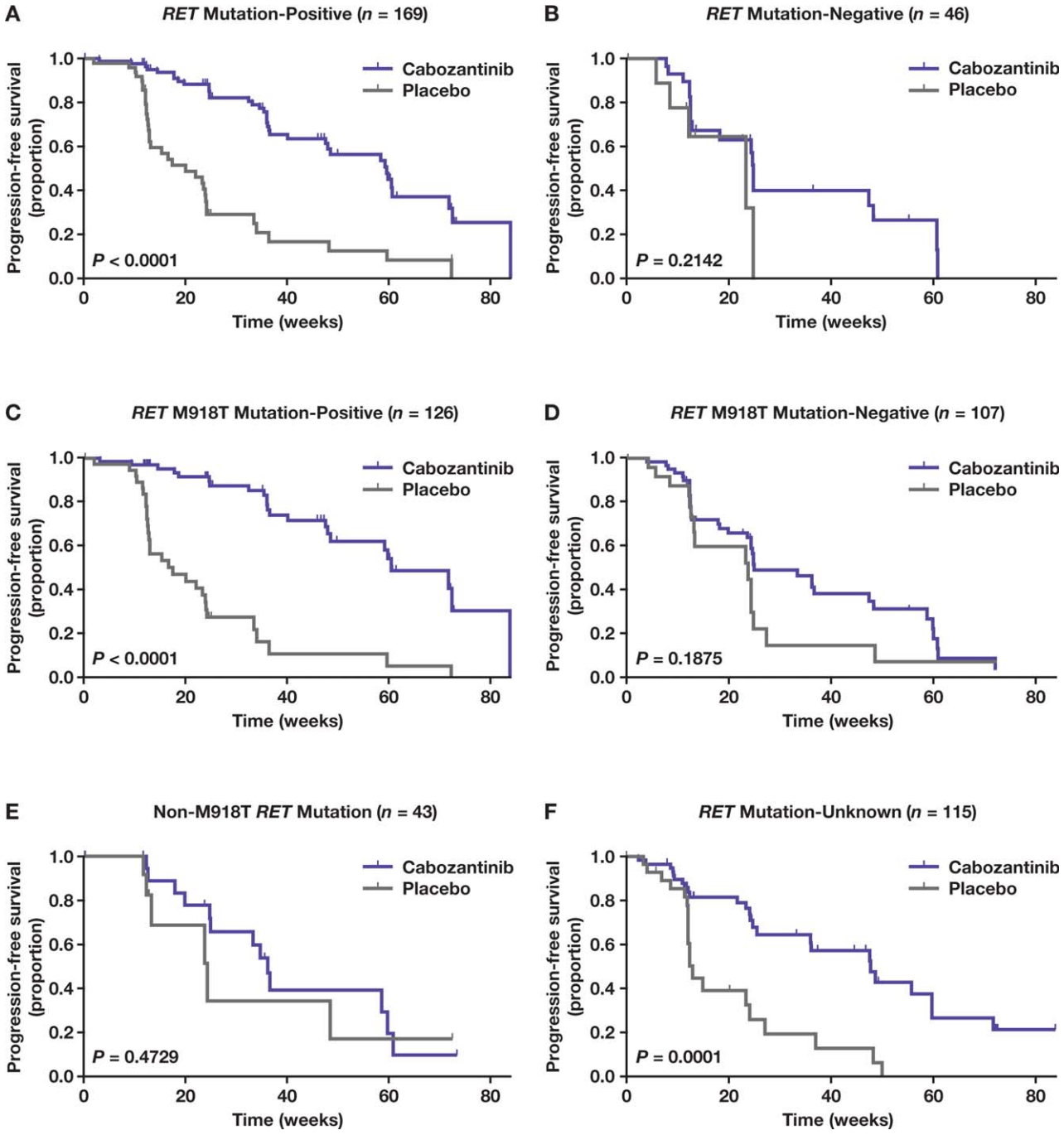

Figure 1. Kaplan-Meier estimates of progression-free survival by the *RET* mutational status: (A) *RET* mutation–positive, (B) *RET* mutation–negative, (C) *RET* M918T mutation–positive, (D) *RET* M918T mutation–negative, (E) non-M918T *RET* mutation, and (F) *RET* mutation–unknown.

cabozantinib, the ORR was 32%, whereas 22% was observed for *RET* mutation–negative patients, and 25% was observed for the *RET* mutation–unknown patients. Similarly, the ORR with cabozantinib was higher for RAS mutation–positive patients versus *RET*/RAS mutation–negative patients (31% vs 21%, respectively).

Safety Evaluation

The safety profile of cabozantinib was similar among the *RET* mutation subgroups and was generally similar to that reported for the overall cabozantinib treatment arm. The most frequent adverse events in the cabozantinib-treated population were diarrhea, palmar-plantar erythrodysesthesia

syndrome, decreased weight, decreased appetite, and nausea (see Supporting Table 2 in the online supporting information). The reported serious adverse events with cabozantinib were similar for the cabozantinib-treated *RET* mutation–positive (50 of 106 or 47.2%) and *RET* mutation–negative patient subpopulations (13 of 35 or 37.1%).

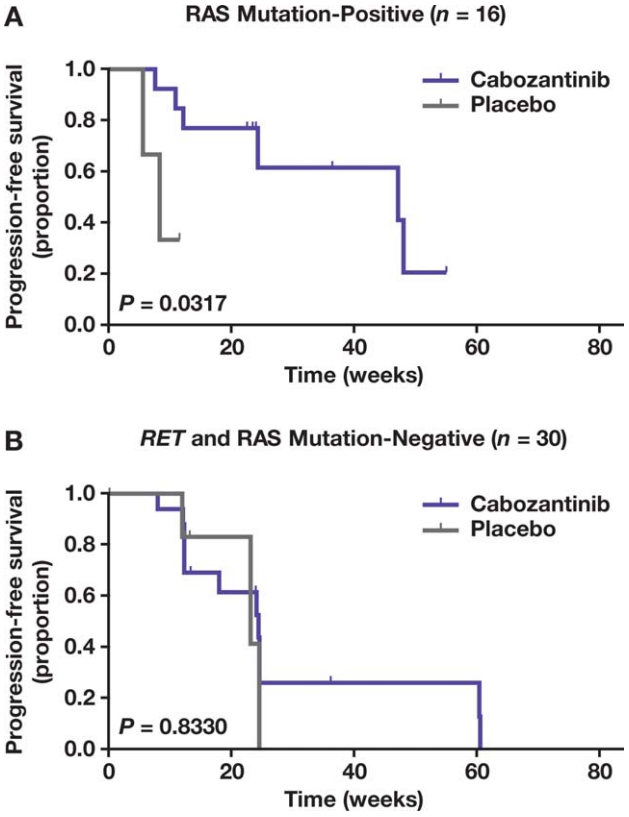

Figure 2. Kaplan-Meier estimates of progression-free survival by the RAS and *RET* mutational status: (A) RAS mutation–positive and (B) *RET* and RAS mutation–negative.

DISCUSSION

Patients with progressive, metastatic MTC have few treatment options, and therapies are needed that can extend the time to disease progression and increase survival. *RET* mutations are associated with a poor prognosis, the development of distant metastasis, and a worse outcome for patients with sporadic MTC.[8] Patients with inherited forms of MTC have a better prognosis, potentially because of the younger age at presentation or the earlier detection of disease.[27]

Among the 215 patients examined for their *RET* mutational status in the current exploratory analysis, we observed *RET* mutations in 169 patients (78.6%), and 46 patients (21.4%) were *RET* mutation–negative. Although cabozantinib significantly improved PFS and ORR in comparison with a placebo in the overall population of the EXAM trial,[23] the current analysis showed an observed PFS benefit with cabozantinib versus the placebo in *RET* mutation–positive and *RET* mutation–unknown patients. The shape of the PFS curve for the *RET* mutation–negative population suggests that a subset of this population, which includes patients with RAS gene mutations, may be experiencing a clinical benefit with cabozantinib. The cabozantinib safety profiles were similar for the *RET* mutation–positive and *RET* mutation–negative subgroups, and this suggests that the adverse event incidence was independent of the mutational state

TABLE 3. Objective Response Rates in Mutational Subgroups

	Patients With Measurable Disease (Cabozantinib Arm), No.[a]	Tumor Responses, No.	Objective Response Rate, %
All cabozantinib patients	208	58	28
Mutational subgroups			
RET mutational status			
RET mutation–positive	101	32	32
RET mutation–negative	32	7	22
RET mutation–unknown	75	19	25
RET mutations of unknown function	13	1	8
RET M918T mutational status			
RET M918T mutation–positive	77	26	34
RET M918T mutation–negative	69	14	20
Non-M918T *RET* mutation–positive	25	6	24
RET M918T mutation–unknown	63	18	29
RAS mutational status			
RAS mutation–positive	13	4	31
RET and RAS mutation–negative	19	4	21

[a] No tumor responses were observed in the placebo arm.

of the tumor. A detailed examination of the safety profile of cabozantinib in the overall EXAM trial population has been previously reported.[23]

More than half of the *RET* mutation–positive population had tumors harboring the *RET* M918T mutation (126 of 215 or 58.6%), and this is consistent with the rates observed in other small studies that investigated genetic alterations in patients with sporadic MTC.[8,9] In general, the prognosis for patients with sporadic MTC harboring *RET* M918T mutations is considered poor.[8] In this study, the median PFS in the placebo arm for patients with *RET* M918T was 17 weeks, whereas it was 24 weeks for patients with any other *RET* mutation; this suggests a more rapid course of the disease. However, this high-risk population appeared to experience the greatest PFS benefit with cabozantinib treatment versus a placebo (an improvement of 44 weeks; HR, 0.15), whereas the patients without *RET* M918T appeared to have a reduced benefit.

Mutations in *HRAS* and *KRAS* have been observed in sporadic MTC and are generally mutually exclusive to *RET* mutations.[11-13,26] In the current study, assuming a mutually exclusive distribution of *RET* and RAS mutations, we found that the mutation rate for genes in the RAS family was 6.6% (16 of 244) in this population of patients with progressive MTC, and this is consistent with other reports.[11,13,26] Although the subgroup in this analysis was small, there was an apparent PFS benefit for patients with tumors harboring a RAS gene mutation. In contrast, the *RET*/RAS mutation–negative subgroup did not appear to experience a PFS benefit with cabozantinib, although some tumor responses were observed in this patient population.

Tumor responses confirm that cabozantinib is clinically active in all MTC subgroups, regardless of the genotype, with ORRs varying from 34% (*RET* M918T mutation–positive population) to 20% (*RET* M918T mutation–negative population); in contrast, no objective responses were observed in patients who received the placebo. RAS mutation–positive patients achieved an ORR similar to that observed in *RET* mutation–positive patients (31%).

The specific mechanisms through which cabozantinib demonstrates clinical activity in MTC patients have not been definitively determined. Cabozantinib inhibits several receptor tyrosine kinases known to be involved in tumor cell proliferation, invasiveness, metastasis, and tumor angiogenesis.[22] Inhibition of tumor angiogenesis, through the dual inhibition of MET and vascular endothelial growth factor receptor signaling, may provide an antitumor effect through reduced tumor growth and metastasis that may be largely independent of the tumor genotype.[28] Through its targeting of RET, cabozantinib may also inhibit the signaling pathways required for tumor cell proliferation and survival (ie, targeting oncogene addiction) in a fashion similar to that observed with other kinase inhibitors that target driver oncogenes in specific tumors.[29] Furthermore, RET M918T has demonstrated constitutive kinase activation through autophosphorylation and increased activation of downstream phosphatidyl-inositol-3-kinase and mitogen-activated protein kinase signaling pathways in comparison with other common RET mutants.[30,31] These differences in downstream signaling could in turn affect the sensitivity to RET inhibition in tumors with different *RET* mutations.

The underlying mechanisms that contribute to the activity observed with cabozantinib in patients with RAS mutations are unclear. Activation of RET in turn activates the RAS/mitogen-activated protein kinase signaling cascade, and thus a significant proportion of MTC tumors are likely dependent on RAS pathway signaling through either RAS gene mutation or activation by RET.[32] One potential mechanism for sensitivity to cabozantinib may involve RAS-mediated activation or upregulation of kinases targeted by cabozantinib. For example, with in vitro models, anchorage-independent growth promoted by activated KRAS was found to be dependent on the activity of the MET kinase.[33] Clearly defining the mechanisms underlying the activity of cabozantinib in tumors containing RAS gene mutations will require further study.

Determining the *RET* and RAS gene mutational status continues to provide challenges in the clinical setting because of technical limitations of sequencing, the age of archival tumor samples, and access to metastatic tumor sites for fresh tumor samples. In addition, tumor heterogeneity makes it difficult to capture the full genetic landscape at all metastatic sites. Circulating tumor DNA sampling and high-throughput mutational analysis methods are being developed to improve diagnostic stratification in oncology, and these may help to guide personalized therapeutic approaches for treating MTC in the future.[34] Further investigation with a prospective clinical trial is required to fully understand the connection between genetic variation and cabozantinib treatment response in patients with MTC; however, the rare nature of this disease makes these studies challenging.

Cabozantinib represents an important therapeutic option for patients with progressive, metastatic MTC, and it is a viable option regardless of the mutational status. This exploratory analysis suggests that the *RET* and RAS gene mutational status may potentially help to predict the

extent of cabozantinib benefit. However, a prospective biomarker study would be necessary to definitively determine whether the tumor genotype could be used to guide cabozantinib treatment in MTC.

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CONFLICT OF INTEREST DISCLOSURES

Steven I. Sherman reports personal fees from Bayer, Eisai, Exelixis, Veracyte, Rosetta Genomics, Novo Nordisk, and Onyx Pharmaceuticals and grants and personal fees from Genzyme. Douglas O. Clary is an employee and shareholder of Exelixis. Rossella Elisei is a consultant for AstraZeneca, Bayer, Swedish Orphan Biovitrum, Eisai, Genzyme, and Exelixis. Martin J. Schlumberger reports research funding and honoraria from AstraZeneca, Bayer, Eisai, Genzyme, and Exelixis–Swedish Orphan Biovitrum. Ezra E. W. Cohen is a consultant for Eisai, Bayer, Merck, Pfizer, and AstraZeneca, is part of the speaker program for Eisai, and reports personal fees from Merck, Pfizer, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, and Human Longevity, Inc. Patrick Schöffski reports institutional financial support for translational research and institutional honoraria for advisory functions and educational activities from Exelixis, institutional honoraria for advisory and educational activities from Swedish Orphan Biovitrum, institutional honoraria for educational and advisory functions from AstraZeneca, and institutional honoraria from Ipsen for an advisory function. Lori J. Wirth reports personal fees from Eisai, Loxo, and Ashion. Milan Mangeshkar is an employee and shareholder of Exelixis. Dana T. Aftab is an employee and shareholder of Exelixis. Marcia S. Brose is a consultant for Eisai, Bayer, and Exelixis and reports research funding from Eisai, Bayer, Exelixis, Genentech, AstraZeneca, and Novartis.

AUTHOR CONTRIBUTIONS

Steven I. Sherman: Conception and design; acquisition of data; and writing, review, and/or revision of the manuscript. **Douglas O. Clary**: Conception and design; development of methodology; analysis and interpretation of data; and writing, review, and/or revision of the manuscript. **Rossella Elisei**: Acquisition of data and writing, review, and/or revision of the manuscript. **Martin J. Schlumberger**: Acquisition of data and writing, review, and/or revision of the manuscript. **Ezra E. W. Cohen**: Acquisition of data and writing, review, and/or revision of the manuscript. **Patrick Schöffski**: Acquisition of data and writing, review, and/or revision of the manuscript. **Lori J. Wirth**: Acquisition of data and writing, review, and/or revision of the manuscript. **Milan Mangeshkar**: Development of methodology; analysis and interpretation of data; and writing, review, and/or revision of the manuscript. **Dana T. Aftab**: Conception and design; development of methodology; and writing, review, and/or revision of the manuscript. **Marcia S. Brose**: Acquisition of data and writing, review, and/or revision of the manuscript.

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