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ORIGINAL REPORT

Cabozantinib in Progressive Medullary Thyroid Cancer

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ABSTRACT

Purpose
Cabozantinib, a tyrosine kinase inhibitor (TKI) of hepatocyte growth factor receptor (MET), vascular endothelial growth factor receptor 2, and rearranged during transfection (RET), demonstrated clinical activity in patients with medullary thyroid cancer (MTC) in phase I.

Patients and Methods
We conducted a double-blind, phase III trial comparing cabozantinib with placebo in 330 patients with documented radiographic progression of metastatic MTC. Patients were randomly assigned (2:1) to cabozantinib (140 mg per day) or placebo. The primary end point was progression-free survival (PFS). Additional outcome measures included tumor response rate, overall survival, and safety.

Results
The estimated median PFS was 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40; $P < .001$). Prolonged PFS with cabozantinib was observed across all subgroups including by age, prior TKI treatment, and *RET* mutation status (hereditary or sporadic). Response rate was 28% for cabozantinib and 0% for placebo; responses were seen regardless of *RET* mutation status. Kaplan-Meier estimates of patients alive and progression-free at 1 year are 47.3% for cabozantinib and 7.2% for placebo. Common cabozantinib-associated adverse events included diarrhea, palmar-plantar erythrodysesthesia, decreased weight and appetite, nausea, and fatigue and resulted in dose reductions in 79% and holds in 65% of patients. Adverse events led to treatment discontinuation in 16% of cabozantinib-treated patients and in 8% of placebo-treated patients.

Conclusion
Cabozantinib (140 mg per day) achieved a statistically significant improvement of PFS in patients with progressive metastatic MTC and represents an important new treatment option for patients with this rare disease. This dose of cabozantinib was associated with significant but manageable toxicity.

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INTRODUCTION

Medullary thyroid cancer (MTC) is a rare malignancy originating from calcitonin-producing parafollicular C cells of the thyroid.[1,2] The majority (approximately 75%) of cases occur sporadically, and the remaining arise as part of three inherited autosomal dominant syndromes: multiple endocrine neoplasia 2A (MEN2A), MEN2B, or familial MTC.[3,4] Germline mutations in the gene encoding the tyrosine kinase receptor rearranged during transfection (RET) are present in almost all patients with inherited MTC,[5] and somatic mutations are found in approximately 65% of patients with sporadic MTC.[6-8] The activating point mutation M918T, representing approximately 80% of somatic *RET* mutations[7] and 95% of MEN2B cases,[9] is an indicator for poor prognosis.[7,10] In addition to RET, the hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathways are upregulated in thyroid tumors[11,12] and have been implicated in the pathogenesis of MTC through promotion of proinvasive and proangiogenic phenotypes.[13-15]

Whereas complete surgical resection is curative for some patients with MTC, patients with distant metastases have a short median survival time, although progression rates are variable.[16] Serum levels of calcitonin and carcinoembryonic antigen (CEA) are important indicators of tumor burden

and prognosis.[17-22] Cytotoxic chemotherapy or radiotherapy have limited, transient activity in patients with unresectable or metastatic MTC.[23] Although the tyrosine kinase inhibitor (TKI) vandetanib has been approved for use in patients with locally advanced or metastatic MTC, it has not been extensively examined in patients with documented radiographic disease progression at baseline.[24]

Cabozantinib is a TKI that targets three relevant pathways in MTC: MET, VEGFR2, and RET.[25] In a phase I study, cabozantinib demonstrated promising clinical activity in a cohort of heavily pretreated patients with MTC.[26] We report here the results of an international, double-blind, randomized, placebo-controlled phase III study evaluating cabozantinib in patients with metastatic MTC and documented radiographic disease progression at study entry.[27,28]

PATIENTS AND METHODS

Eligibility Requirements

Eligible patients were adults with histologically confirmed, unresectable, locally advanced, or metastatic MTC. Patients were required to have radiographic disease progression per modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines[29] at screening compared with an image obtained within the prior 14 months. Documentation of progressive disease (PD) to establish eligibility was by independent review in 89.4% of patients, and by investigator assessment in the remaining patients. Exclusion criteria included prior systemic anticancer therapy within 4 weeks or significant cardiac, hematopoietic, hepatic, or renal dysfunction. There was no limit on prior therapy, including exposure to other TKIs. All patients provided written informed consent. The protocol was approved by ethics committees or institutional review boards at each clinical site, nationally, or both.

Randomization and Treatments

Patients were randomly assigned in a 2:1 ratio to receive cabozantinib or placebo in a double-blinded fashion and were stratified by age ($\leq$ 65 years, $>$ 65 years) and prior TKI treatment (yes, no). Patients received 140 mg (freebase equivalent) of cabozantinib or placebo capsules orally once per day until either intolerable toxicity or disease progression per mRECIST occurred. Dose holds and up to two dose-level reductions (to a minimum dose of 60 mg per day) were allowed. The study remained blinded until the primary analysis of progression-free survival (PFS) and the interim analysis of overall survival (OS) were complete. Patients receiving placebo were not permitted to cross over to cabozantinib.

Efficacy

The primary end point was duration of PFS. Key secondary end points included OS and objective response rate (ORR). The database cutoff date for all planned analyses was June 15, 2011, except for the primary PFS analysis, which was April 6, 2011 (when the 138th and 139th independent radiology review committee [IRC] -determined PFS events occurred). Radiographic tumor assessments were performed every 12 weeks ($\pm$ 5 days) from random assignment until PD, using mRECIST. Tumor assessments were performed by a blinded IRC to determine response and/or progression for the primary efficacy analyses. PFS was calculated as the time from random assignment to the earlier of documented PD per mRECIST or death.

Biomarker Measurements

Methods for determining *RET* mutational status and changes in calcitonin and CEA are provided in the Data Supplement. Tumor and blood samples collected at screening were analyzed for *RET* mutation; for a sample to be considered negative for *RET* mutation, the complete sequence for exons 10, 11, and 13 to 16 must have been obtained and been free of mutation.[30]

Safety

Safety assessments included monitoring adverse events (AEs), performing standard laboratory tests (hematology, serum chemistry, and urinalysis) and physical examinations, and recording ECGs. Severity of AEs was assessed by using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Serious AEs (SAEs) were defined in accordance with the International Conference on Harmonisation Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

Statistical Analysis

Efficacy analyses for PFS and OS used the Kaplan-Meier method and the stratified log-rank test for inference testing. The stratified Cox proportional hazards model was used to estimate hazard ratios (HRs). The primary analysis of PFS was event driven, included radiographic progression events per the IRC and deaths, and included all randomly assigned patients (ie, the intention-to-treat population). Patients who received subsequent anticancer treatment were censored. Prespecified subgroup analyses and planned sensitivity analyses of PFS are described in the Data Supplement. Safety analyses included patients who received at least one dose of study treatment. For the primary end point of PFS, the study was designed to have 90% power to detect an HR of 0.571 using the log-rank test and a two-sided significance level of 5%. This corresponds to a 43% reduction in the risk of progression or death or a 75% improvement in median PFS from 8 months to 14 months. In all, 138 progression events were required, and 315 patients were planned for enrollment. As a result, all patients except the first 138 to experience an event were censored in the PFS analysis, contributing time-to-event data until the date of censoring. Statistical considerations for the end point of OS are described in the Data Supplement. Statistical analysis was performed independently by the sponsor.

RESULTS

Patients

From September 2008 through February 2011, 330 patients from 23 countries were randomly assigned 2:1 to receive cabozantinib (219 patients) or placebo (111 patients; Fig 1). Baseline characteristics in the treatment groups were well balanced (Table 1). Forty percent of patients (n = 133) had received prior anticancer therapy, and 21% (n = 68) received prior TKI treatment. Twenty-five percent had two or more systemic therapies (24% cabozantinb; 28% placebo). Most patients (285 [86%]) had sporadic disease. Approximately half the patients (48.2%; n = 159) were *RET* mutation–positive, 12% (n = 41) were *RET* mutation–negative, and 39% (n = 130) had unknown *RET* mutation status due to missing sequence data or to the presence of a mutation of unknown significance. M918T was the predominant *RET* mutation (74%; 118 of 159 patients with documented mutations). The main sites of disease in the majority of patients included lymph nodes, liver, lung, and bone.

Treatment

At the database cutoff date, 45% (98 of 219) of patients in the cabozantinib arm and 14% (15 of 111) of patients in the placebo arm were receiving study treatment. The arithmetic median duration of exposure was 204 days for cabozantinib-treated patients (interquartile range, 99 to 392 days), almost twice that of placebo-treated patients (median 105 days; interquartile range, 83 to 170 days). Because of the large percentage of patients receiving treatment at data cutoff, the median duration of exposure is an underestimate in the cabozantinib treatment group. The median time of follow-up was 13.9 months (range, 3.6 to 32.5 months).

PFS

The study met its primary end point of demonstrating improvement in PFS as determined by the IRC (Fig 2A). Cabozantinib treatment led to a substantial improvement in PFS compared with placebo.

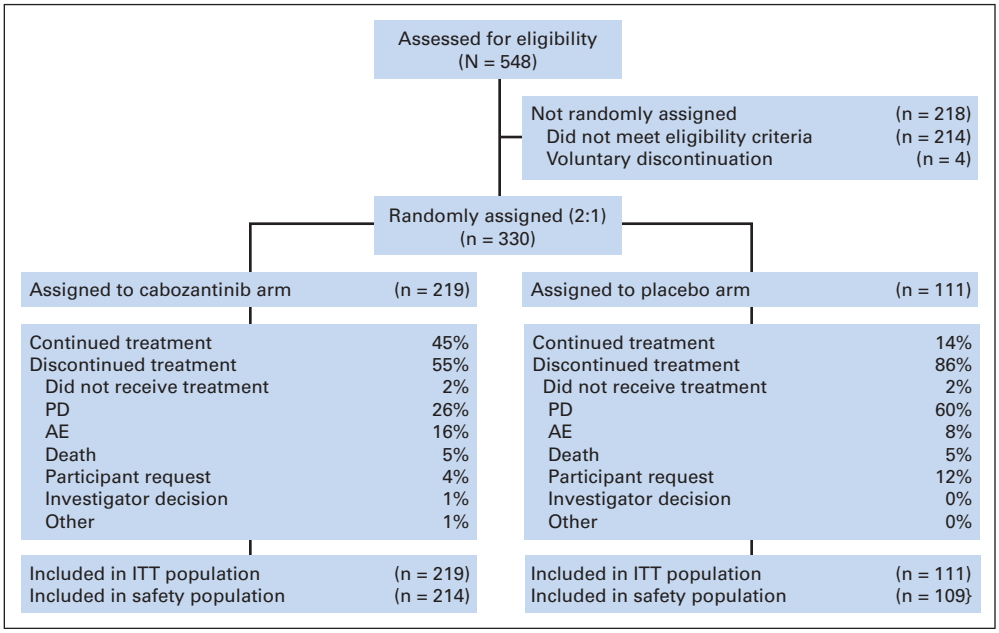

Fig 1. Random assignment and outcomes. Patient disposition as of June 15, 2011. High screen fail rate was largely because of a lack of confirmation of progressive disease (PD) by the independent radiology review committee. AE, adverse event; ITT, intention-to-treat.

Estimated median PFS duration was 11.2 months in the cabozantinib group and 4.0 months in the placebo group. The stratified HR was 0.28 (95% CI, 0.19 to 0.40; $P < .001$). A tabulation of censoring reasons is provided in the Data Supplement. Similar results were obtained in analyses of PFS as determined by investigator (13.8- *v* 3.1-month median PFS; HR, 0.29; 95% CI, 0.21 to 0.42; $P < .001$). HRs obtained in all planned sensitivity analyses of the primary end point were similar to the primary analysis and varied within a narrow range (0.28 to 0.32; Data Supplement). The Kaplan-Meier estimates of the proportions of patients alive and progression-free at 1 year are 47.3% for the cabozantinib arm and 7.2% for the placebo arm.

All prespecified patient subgroups demonstrated prolongation of PFS with cabozantinib treatment (HR < 1), including those with or without prior TKI treatment, bone metastases at baseline, and with hereditary or sporadic forms of MTC (Fig 2B and Data Supplement). All *RET* mutation subgroups showed improved PFS from treatment (*RET* mutation [somatic or germline] status: positive, HR, 0.24; negative, HR, 0.47; unknown, HR, 0.30), although the CI for the *RET* mutation–negative subgroup crosses 1.0.

Key Secondary Efficacy End Points

In total, 312 patients (95%) could be evaluated for tumor response per IRC on the basis of measurable disease at baseline. The ORR (IRC determined) was 28% in the cabozantinib arm (all partial responses) and 0% in the placebo arm ($P < .001$). The median estimated duration of response was 14.6 months (95% CI, 11.1 to 17.5 months). *RET* mutation–positive and -negative subgroups also demonstrated similar ORRs for cabozantinib treatment (32% and 25%, respectively). Ninety-four percent (170 of 180) of cabozantinib-treated patients with measurable disease at baseline and at least one postbaseline assessment had a detectable decrease in target lesion size compared with 27% (24 of 89) of placebo-treated patients (Data Supplement).

A planned interim analysis of OS was conducted, including 96 (44%) of the 217 patient deaths required for the final analysis. In this analysis, no statistically significant difference between treatment arms was observed (HR, 0.98; 95% CI, 0.63 to 1.52). Survival follow-up is planned to continue until at least 217 deaths have been observed.

Calcitonin and CEA

Calcitonin and CEA response at week 12 was evaluable in 140 (64%) and 170 (78%) cabozantinib-treated patients and 61 (55%) and 71 (64%) placebo-treated patients, respectively. The most common reasons patients were not evaluable were the lack of a week-12 assessment or a calcitonin assay change between the baseline and week-12 assessments (details are provided in the Data Supplement). At baseline, the mean value and standard deviation (SD) for calcitonin in the cabozantinib and placebo arms were 6,370 pmol/L (SD, 11,332 pmol/L) and 8,846 pmol/L (SD, 15,722 pmol/L), respectively (Welsh's *t* test $P = .27$). For CEA, the mean values for cabozantinib and placebo arms were 736 μg/L (SD, 3,555 μg/L) and 1,108 μg/L (SD, 5,168 μg/L), respectively (Welsh's *t* test $P = .58$). These baseline values were judged to be not meaningfully different. From baseline to week 12, the cabozantinib arm displayed significant decreases in calcitonin (mean, −45.2% [SD, 60.71%]) compared with increases in the placebo arm (+57.3%; SD, 115.4%; $P < .001$). Changes in CEA levels from baseline to week 12 showed a similar trend (−23.7% [SD, 58.21%] in the cabozantinib arm *v* +88.7% [SD, 182.%] in the placebo arm; $P < .001$. A generally linear relationship was observed when changes in calcitonin and CEA from baseline to week 12 (up to approximately 200% increases) were compared with changes in target lesion size (Fig 3).

Safety and Tolerability

AEs reported in ≥ 10% of cabozantinib-treated patients are summarized in Table 2. Grade 3 or 4 AEs were reported in 69% (148 of 214) and 33% (36 of 109) of patients in the cabozantinib and placebo groups, respectively. In cabozantinib-treated patients, the most frequently reported grade 3 or 4 AEs were diarrhea (15.9%), palmar-plantar erythrodysesthesia (12.6%), and fatigue (9.3%). AEs typically

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Cabozantinib (n = 219) No.	%	Placebo (n = 111) No.	%
Male sex	151	68.9	70	63.1
Age, years				
Median	55.0		55.0	
Range	20-86		21-79	
≤ 65	172	78.5	86	77.5
> 65	47	21.5	25	22.5
ECOG PS				
0	123	56.2	56	50.5
1-2	95	43.4	55	49.5
RET mutation status				
Positive	101	46.1	58	52.3
Negative	31	14.2	10	9.0
Unknown	87	39.7	43	38.7
MTC disease type				
Hereditary	12	5.5	8	7.2
Sporadic	191	87.2	94	84.7
Unknown	16	7.3	9	8.1
RET M918T mutation status				
Positive	75	34.2	43	38.7
Negative	67	30.6	30	27.0
Unknown*	77	35.2	38	34.2
Patients with prior anticancer therapy	85	38.8	48	43.2
Patients with prior systemic therapy for MTC	81	37.0	47	42.3
Patients with two or more prior systemic therapies	52	23.7	31	27.9
Patients with prior thyroidectomy	201	91.8	104	93.7
Prior TKI status				
Yes†	44	20.1	24	21.6
Vandetanib	25	11.4	9	8.1
Sorafenib	11	5.0	8	7.2
Motesanib	7	3.2	2	1.8
Sunitinib	6	2.7	3	2.7
No	171	78.1	86	77.5
Unknown	4	1.8	1	0.9
No. of organs and anatomic locations involved at enrollment				
0-1	28	12.8	15	13.5
≥ 2	191	87.2	96	86.5
Main sites of metastatic disease				
Lymph nodes	175	79.9	86	77.5
Liver	152	69.4	67	60.4
Lung	116	53.0	64	57.7
Bone	112	51.1	56	50.5

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MTC, medullary thyroid cancer; *RET*, rearranged during transfection; TKI, tyrosine kinase inhibitor.

*In the M918T unknown category, five of 77 patients in the cabozantinib group and four of 38 in the placebo group exhibited mutations in other exons and are therefore less likely to harbor an M918T mutation.

†Other prior TKI treatments not shown in the table: axitinib (three patients), pazopanib (three patients), and imatinib (two patients).

associated with vascular endothelial growth factor (VEGF) pathway inhibition,[24,26,31-33] including hypertension, hemorrhage, fistula formation, and GI perforation, occurred more frequently among cabozantinib-treated patients (Table 3).

Laboratory abnormalities with a higher incidence in the cabozantinib arm (between arm difference of ≥ 5% all grades or ≥ 2% grade 3 to 4) consisted of increased AST, increased ALT, increased alkaline phosphatase, hypocalcemia, hypophosphatemia, hyperbilirubinemia, hypomagnesemia, hypokalemia, hyponatremia, lymphopenia, neutropenia, and thrombocytopenia (Data Supplement). There was no drug-induced severe liver injury. Thyroid-stimulating hormone (TSH) level above normal was noted after treatment initiation in 57% of cabozantinib patients compared with 19% of placebo patients.

AEs were generally managed with concomitant medications, dose interruptions, and dose reductions; 79% (169 of 214) of cabozantinib-treated patients and 9% (10 of 109) of placebo patients had dose reductions. Sixty-five percent (140 of 214) of cabozantinib-treated patients and 17% (19 of 109) of placebo patients had dose interruptions due to AEs. AEs were listed as the primary reason for treatment discontinuation in 16% (35 of 214) of cabozantinib-treated patients and in 8% (nine of 109) of placebo-treated patients. In addition, 6% (12 of 214) of the patients in the cabozantinib arm discontinued treatment for reasons other than PD, AE, or death; 11 of these patients had ongoing AEs at the time of treatment discontinuation, although AEs were not reported as the primary reason for treatment discontinuation in these patients.

SAEs were more frequent in cabozantinib- versus placebo-treated patients (42.1% [90 of 214] *v* 22.9% [25 of 109]). SAEs that occurred at a ≥ 2% frequency in cabozantinib- versus placebo-treated patients included mucosal inflammation (2.8% [six of 214] *v* 0% [zero of 109]), hypocalcemia (2.8% [six of 214] *v* 0% [zero of 109]), pulmonary embolism (2.3% [five of 214] *v* 0% [zero of 109]), and hypertension (2.3% [five of 214] *v* 0% [zero of 109]). At the planned interim analysis the overall death rate was balanced between the two treatment arms. Ninety-six deaths were reported: 65 (30%) in the cabozantinib group and 30 (28%) in the placebo group, and one patient who did not receive study drug. Most deaths were attributed to disease progression (77% [50 of 65] in the cabozantinib arm and 80% [24 of 30] in the placebo arm).

Grade 5 AEs occurring within 30 days of last dose were reported in 7.9% of cabozantinib-treated patients and 7.3% of placebo-treated patients. Grade 5 AEs on the cabozantinib arm consisted of fistula (three patients, including one patient with concurrent pneumonia, all related), respiratory failure (two patients, one related), hemorrhage (two patients, one related), multiorgan failure (two patients, none related), and sepsis (not related), sepsis/multiorgan failure (related), sudden death (related), hepatic failure (not related), cardiopulmonary failure (related), pneumonia (not related), general physical health deterioration (not related), and death not otherwise specified (related) in one patient each. Grade 5 AEs on the placebo arm consisted of dysphagia (not related), cardiopulmonary failure (deemed related), shock (likely septic shock, not related), acute respiratory distress syndrome (not related), pneumonia (not related), pneumonia/general physical health deterioration (deemed related), hepatic failure (not related), and asthenia (not related) in one patient each. Some of the grade 5 AEs in both treatment arms were reported in patients whose primary cause of death was reported as PD.

DISCUSSION

Patients with progressive MTC have limited treatment options. Cabozantinib was associated with an improvement in estimated PFS compared with placebo in a patient population with documented

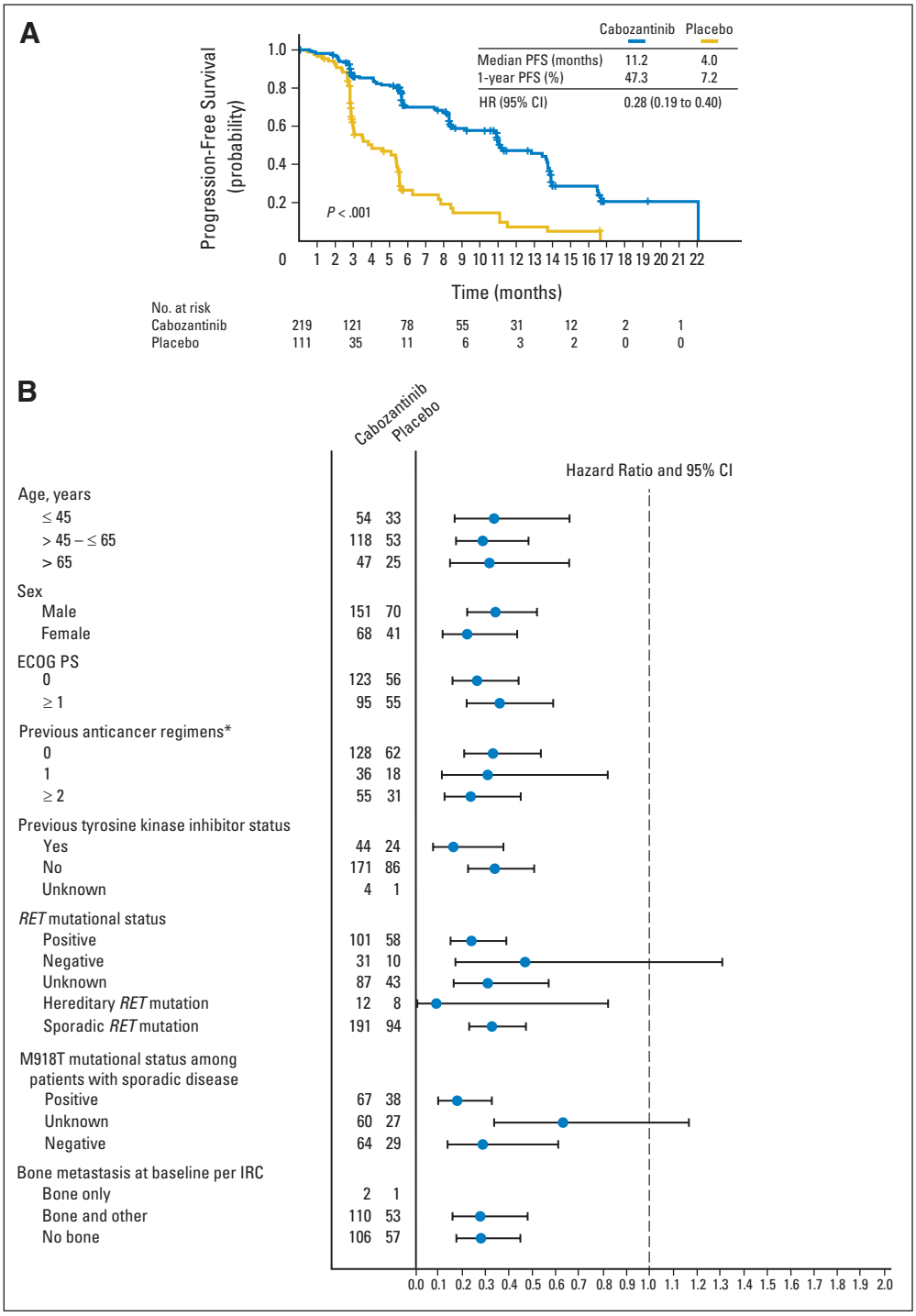

Fig 2. (A) Kaplan-Meier estimates of progression-free survival (PFS) in the intention-to-treat population on the basis of central assessment of radiographic images with analyses stratified according to age and prior tyrosine kinase inhibitor treatment. The estimated median PFS was 7.2 months longer in the cabozantinib group than in the placebo group. (B) Unstratified hazard ratios (HRs) and 95% CIs for subgroup analyses of estimated PFS by prespecified baseline characteristics and by ad hoc *RET* mutational characteristics (sporadic, hereditary, and M918T status). The HRs for the categories of unknown prior tyrosine kinase inhibitor treatment and bone-only metastases at baseline were not quantifiable because of the small numbers of patients in these subgroups. (*) Prior anticancer regimens include local and systemic therapy. ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent radiology review committee.

progressive MTC, with an increase of more than 7 months in estimated median PFS compared with placebo, and a confirmed response rate of 28%. Importantly, benefit from the use of cabozantinib was observed across multiple sensitivity and subgroup analyses, including prior TKI or systemic therapy, the presence of bone metastases, and in all *RET* mutation subgroups analyzed.

This study is one of the largest conducted in patients with MTC. To the best of our knowledge, it is the first randomized phase III trial in a population of patients with MTC rigorously defined with PD per mRECIST within a defined time period (14 months) required at study entry. This population with advanced disease had a short estimated median PFS of 4.0 months and a high rate of morbidity reported as AEs in the placebo arm. The poor prognosis of patients enrolled onto the cabozantinib study is in contrast to the patient population studied in the vandetanib phase III trial, in which PD per mRECIST was not required at study entry, and for which the estimated median PFS in the placebo arm was 19.3 months.[24] This suggests that the patient population studied in the vandetanib trial had relatively indolent disease

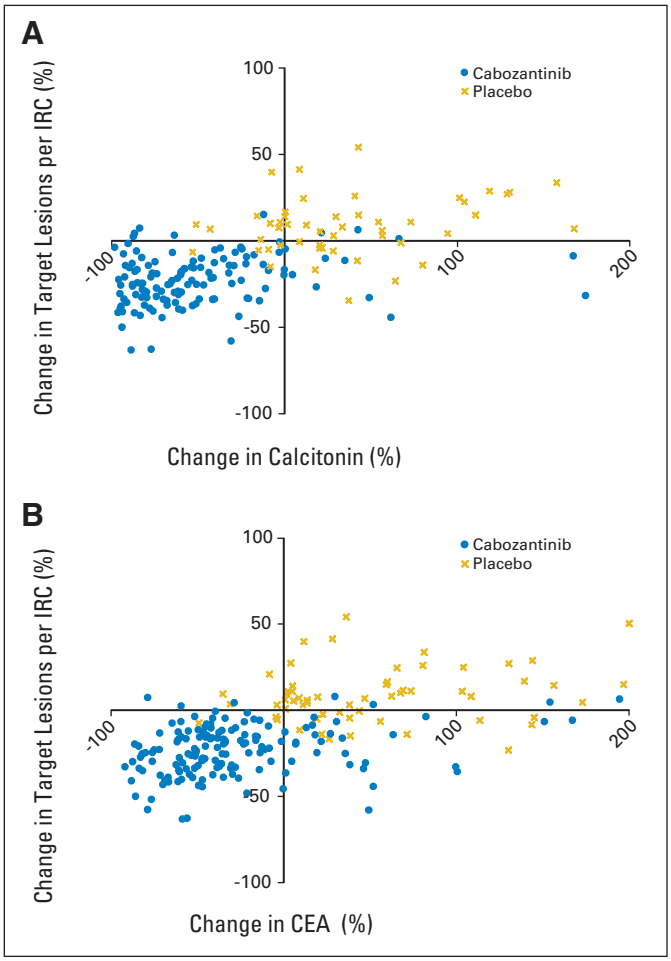

Fig 3. Correlation between changes in calcitonin or carcinoembryonic antigen (CEA) and changes in tumor size. Calcitonin and CEA are shown compared with changes in the sum of tumor diameters from baseline to week 12; a roughly linear relationship is observed between changes in these biomarkers and changes in tumor target lesion size up through approximately 200% increase in each tumor marker. (A) Percent change in calcitonin levels from baseline to week 12. Cabozantinib, n = 131; placebo, n = 54. Linear regression of data through two standard deviations of calcitonin data ($-100 \leq \times \leq 181.5$). For all patients, change in sum of tumor diameters = −9.216 + (0.1896 × change in calcitonin); $r = 0.56$; $P < .001$. For cabozantinib arm only, change in sum of tumor diameters = −17.01 + (0.1084 × change in calcitonin); $r = 0.27$; $P = .0019$. Six points more than 181.5% change in calcitonin (change in sum of tumor diameters ranging from −16.6% to 37.5%) are not included in the analysis. (B) Percent change in CEA levels from baseline to week 12. Cabozantinib, n = 159; placebo, n = 63. Linear regression of data through two standard deviations of CEA data ($-100 \leq \times \leq 243.5$). For all patients, change in sum of tumor diameters = −13.95 + (0.1727 × change in CEA); $r = 0.56$; $P < .001$. For cabozantinib arm only, change in sum of tumor diameters = −20.90 + (0.0908 × change in CEA); $r = 0.23$; $P = .0042$. Four points more than 243.5% change in CEA (change in sum of tumor diameters ranging from −34.5% to 37.5%) are not included in the analysis. IRC, independent radiology review committee.

Table 2. AEs Occurring in ≥ 10% of Cabozantinib-Treated Patients, by Maximum Severity Reported

	Cabozantinib (n = 214)				Placebo (n = 109)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%
Diarrhea	135	63.1	34	15.9	36	33.0	2	1.8
Palmar-plantar erythrodysesthesia*	107	50.0	27	12.6	2	1.8	0	
Decreased weight	102	47.7	10	4.7	11	10.1	0	
Decreased appetite	98	45.8	10	4.7	17	15.6	1	0.9
Nausea	92	43.0	3	1.4	23	21.1	0	
Fatigue	87	40.7	20	9.3	31	28.4	3	2.8
Dysgeusia	73	34.1	1	0.5	6	5.5	0	
Hair color changes	72	33.6	1	0.5	1	0.9	0	
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Stomatitis	62	29.0	4	1.9	3	2.8	0	
Constipation	57	26.6	0		6	5.5	0	
Hemorrhage	54	25.2	7	3.3	17	15.6	1	0.9
Vomiting	52	24.3	5	2.3	2	1.8	1	0.9
Mucosal inflammation	50	23.4	7	3.3	4	3.7	0	
Asthenia	45	21.0	12	5.6	16	14.7	2	1.8
Dysphonia	43	20.1	0		10	9.2	0	
Rash	41	19.2	2	0.9	11	10.1	0	
Dry skin	41	19.2	0		3	2.8	0	
Headache	39	18.2	1	0.5	9	8.3	0	
Oropharyngeal pain	38	17.8	1	0.5	5	4.6	0	
Abdominal pain	36	16.8	6	2.8	7	6.4	1	0.9
Alopecia	35	16.4	0		2	1.8	0	
Pain in extremity	33	15.4	3	1.4	12	11.0	1	0.9
Back pain	32	15.0	5	2.3	12	11.0	1	0.9
Dyspnea	29	13.6	5	2.3	19	17.4	11	10.1
Arthralgia	29	13.6	2	0.9	8	7.3	0	
Dizziness	29	13.6	1	0.5	8	7.3	0	
Oral pain	29	13.6	1	0.5	1	0.9	0	
Dry mouth	28	13.1	0		9	8.3	0	
Dysphagia	27	12.6	9	4.2	7	6.4	1	0.9
Cough	26	12.1	1	0.5	14	12.8	0	
Muscle spasms	26	12.1	1	0.5	5	4.6	0	
Dyspepsia	24	11.2	0		0		0	
Insomnia	23	10.7	0		7	6.4	0	
Erythema	23	10.7	2	0.9	2	1.8	0	
Glossodynia	22	10.3	3	1.4	0		0	

NOTE. Laboratory abnormalities are not included.
Abbreviation: AE, adverse event.
*Hand-foot syndrome.

and confirms that patients who were enrolled onto the cabozantinib study were in significant need of therapy.

At the planned interim analysis for OS, no statistically significant difference between treatment arms was observed. The final analysis of survival will be conducted after 217 events have occurred. This study could offer a unique opportunity to explore a relationship between PFS and OS in MTC.

Recent research has suggested that RET inhibition can lead to early changes in calcitonin levels independent of changes in tumor size,[34] but in this study, correlations were observed between changes in both calcitonin and CEA from baseline to week 12 and changes in target lesion size, suggesting that these serum markers may be predictive of patient benefit.

The most frequent grade 3 or 4 AEs were diarrhea, palmar-plantar erythrodysesthesia, and fatigue, generally consistent with those seen in studies with VEGF pathway inhibitors, with other TKIs, and with prior experience in open-label cabozantinib studies.[24,26,31-33] Gastrointestinal perforations, fistula development, and hemorrhage occurred in the cabozantinib arm of this study. These potentially life-threatening AEs have previously been observed with VEGF pathway inhibition[35] and require caution, especially when treating patients who are at risk for such events. We did not observe clinically relevant QTcF prolongation of more than 500 milliseconds, as was encountered in the vandetanib phase III trial.[24]

Table 3. AEs Associated With VEGF Pathway Inhibition

	Cabozantinib (n = 214)				Placebo (n = 109)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%
Hypertension	70	32.7	18	8.4	5	4.6	1	0.9
Hemorrhage	54	25.2	7	3.3	17	15.6	1	0.9
Venous thrombosis	12	5.6	8	3.7	3	2.8	2	1.8
GI perforation	7	3.3	7	3.3	0		0	
GI fistula	2	0.9	1	0.5	0		0	
Abdominal/pelvic abscess	5	2.3	2	0.9	0		0	
Non-GI fistula	8	3.7	4	1.9	0		0	
Arterial thrombosis	5	2.3	2	0.9	0		0	
Proteinuria	4	1.9	2	0.9	0		0	
Wound complication	4	1.9	2	0.9	1	0.9	0	
Osteonecrosis	3	1.4	1	0.5	0		0	
RPLS	1	0.5	1	0.5	0		0	

Abbreviations: AE, adverse event; RPLS, reversible posterior leukoencephalopathy syndrome; VEGF, vascular endothelial growth factor.

Metabolic changes reported in the cabozantinib arm included increased TSH and hypocalcemia. Increased TSH has been reported during treatment with other TKIs, and is possibly a result of increased type 3 deiodinase activity.[36] Notably, most of the study patients had a prior thyroidectomy and were receiving thyroid hormone and calcium supplementation at baseline.

AEs were managed with supportive care and with dose reductions and holds allowing for patients to remain on treatment for extended periods of time, which is similar to what has been observed with other TKIs.[24,31-33,37] However, the rate of holds and reductions due to AEs was high, and evaluation of a lower starting dose of cabozantinib versus 140 mg in patients with progressive, metastatic MTC is planned.

Cabozantinib treatment substantially improves PFS and response rates and has a manageable AE profile in patients with progressive metastatic MTC, including those previously treated with TKIs. Cabozantinib has been approved by the US Food and Drug Administration for the treatment of patients with progressive, metastatic MTC and represents an important new therapeutic option for patients with this rare malignancy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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