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ORIGINAL ARTICLE

Cabozantinib for previously treated radioiodine-refractory differentiated thyroid cancer: Updated results from the phase 3 COSMIC-311 trial

Marcia S. Brose MD, PhD[1,2] | Bruce G. Robinson MD[3] | Steven I. Sherman MD[4] | Barbara Jarzab MD, PhD[5] | Chia-Chi Lin MD, PhD[6] | Fernanda Vaisman MD, PhD[7] | Ana O. Hoff MD[8] | Erika Hitre MD, PhD[9] | Daniel W. Bowles MD[10] | Suvajit Sen PhD[11] | Jennifer W. Oliver MD[11] | Kamalika Banerjee MSc[11] | Bhumsuk Keam MD[12] | Jaume Capdevila MD, PhD[13]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Now at Sidney Kimmel Cancer Center, Jefferson Health, Philadelphia, PA, USA

[3]Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

[4]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

[5]Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska Curie National Research Institute of Oncology, Gliwice, Poland

[6]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

[7]Endocrinology Service, Instituto Nacional de Câncer, Rio de Janeiro, Brazil

[8]Department of Endocrinology, Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil

[9]Department of Medical Oncology and Clinical Pharmacology "B", Országos Onkológiai Intézet, Budapest, Hungary

[10]Division of Medical Oncology, Department of Medicine, Anschutz Medical Campus, University of Colorado, Aurora, Colorado, USA

[11]Exelixis, Inc., Alameda, California, USA

[12]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

[13]Medical Oncology Department Gastrointestinal and Endocrine Tumor Unit, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Spain

Correspondence
Marcia S. Brose, Sidney Kimmel Cancer Center, Jefferson Health Northeast, 10800 Knights Rd, 3rd Floor, Philadelphia, PA 19411, USA.
Email: marcia.brose@jefferson.edu

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Abstract

Background: At an interim analysis (median follow-up, 6.2 months; $n = 187$), the phase 3 COSMIC-311 trial met the primary end point of progression-free survival (PFS): cabozantinib improved PFS versus a placebo (median, not reached vs. 1.9 months; $p < .0001$) in patients with previously treated radioiodine-refractory differentiated thyroid cancer (RAIR-DTC). The results from an exploratory analysis using an extended datacut are presented.

Methods: Patients 16 years old or older with RAIR-DTC who progressed on prior lenvatinib and/or sorafenib were randomized 2:1 to oral cabozantinib tablets (60 mg/day) or a placebo. Placebo patients could cross over to open-label

This trial has been registered at ClinicalTrials.gov (NCT03690388).

cabozantinib upon radiographic disease progression. The objective response rate (ORR) in the first 100 randomized patients and the PFS in the intent-to-treat population, both according to Response Evaluation Criteria in Solid Tumors version 1.1 by blinded, independent review, were the primary end points.

Results: At the data cutoff (February 8, 2021), 258 patients had been randomized (cabozantinib, $n = 170$; placebo, $n = 88$); the median follow-up was 10.1 months. The median PFS was 11.0 months (96% confidence interval [CI], 7.4–13.8 months) for cabozantinib and 1.9 months (96% CI, 1.9–3.7 months) for the placebo (hazard ratio, 0.22; 96% CI, 0.15–0.32; $p < .0001$). The ORR was 11.0% (95% CI, 6.9%–16.9%) versus 0% (95% CI, 0.0%–4.1%) ($p = .0003$) with one complete response with cabozantinib. Forty placebo patients crossed over to open-label cabozantinib. Grade 3/4 treatment-emergent adverse events occurred in 62% and 28% of the cabozantinib- and placebo-treated patients, respectively; the most common were hypertension (12% vs. 2%), palmar–plantar erythrodysesthesia (10% vs. 0%), and fatigue (9% vs. 0%). There were no grade 5 treatment-related events.

Conclusions: At extended follow-up, cabozantinib maintained superior efficacy over a placebo in patients with previously treated RAIR-DTC with no new safety signals.

KEYWORDS
cabozantinib, COSMIC-311, differentiated thyroid cancer, phase 3, placebo, tyrosine kinase inhibitor

INTRODUCTION

Radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) is associated with a poor prognosis.[1] Disease control is often achieved with the vascular endothelial growth factor receptor (VEGFR) inhibitors sorafenib and lenvatinib, but most patients develop treatment resistance and experience disease progression.[2,3] Until recently, there has been no standard of care for patients who progress on VEGFR-targeted therapy.[1]

Cabozantinib is a tyrosine kinase inhibitor (TKI) that inhibits multiple receptor tyrosine kinases involved in DTC pathology, including VEGFR, AXL, MET, and RET.[4–7] Recently, the double-blind, phase 3 COSMIC-311 study evaluated cabozantinib versus a placebo in patients with RAI-refractory DTC who previously had been treated with VEGFR-targeted therapy, including sorafenib and/or lenvatinib.[8] The study was designed with the multiple primary end points of the objective response rate (ORR) in the first 100 randomized patients and progression-free survival (PFS) in all randomized patients (intent-to-treat [ITT] population) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as assessed by a blinded independent radiology committee. The study would be considered positive if either of the primary end points were met. The primary ORR analysis was conducted 6 months after the randomization of the 100th patient, and a contemporaneous preplanned interim analysis of PFS was performed in the ITT population ($n = 187$) with a median follow-up of 6.2 months. At the time of the primary ORR analysis, the ORR was 15% for cabozantinib and 0% for the placebo ($p = .028$), but the difference did not meet the predefined level of significance ($\alpha = .01$). However, the primary end point of PFS was met at the interim analysis (hazard ratio [HR], 0.22; 96% confidence interval [CI], 0.13–0.36; $p < .0001$). Because of the positive results, the study was stopped, and all patients were unblinded. Data from the study led to US Food and Drug Administration approval of cabozantinib for the treatment of adult and pediatric patients aged 12 years or older with locally advanced or metastatic DTC that has progressed after prior VEGFR-targeted therapy and is RAI-refractory or ineligible.[9] Cabozantinib has also been approved by the European Medicines Agency for the treatment of adult patients with locally advanced or metastatic DTC that is refractory to or not eligible for RAI and has progressed during or after prior systemic therapy.[10]

Presented here are updated results for the COSMIC-311 study from an exploratory analysis after extended follow-up (median follow-up of 10.1 months vs. 6.2 months at the interim analysis) and in a larger ITT population (258 patients vs. 187 patients at the interim analysis).

MATERIALS AND METHODS

Study design and participants

COSMIC-311 was a global, randomized, double-blind, phase 3 trial of cabozantinib versus a placebo in patients with RAI-refractory DTC. Patients 16 years old or older were eligible for enrollment if they had a confirmed diagnosis of DTC (papillary, follicular, or one of their

variants), had measurable disease per RECIST v1.1, and were refractory to or deemed ineligible for treatment with iodine-131. Patients were required to have received prior lenvatinib and/or sorafenib and were allowed up to two previous VEGFR TKIs with radiographic progression per RECIST v1.1 during or after treatment. Patients must have had an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ and marrow function and must have been receiving thyroxine replacement therapy with serum thyroid-stimulating hormone concentrations < 0.50 mIU/L. Patients were excluded if they previously had been treated with selective BRAF inhibitors, were being treated with oral anticoagulants or platelet inhibitors, or had untreated brain metastases. Details of the study design have been previously published.[8]

The study protocol was approved by the institutional review board or ethics committee at each center. The trial was performed in compliance with Good Clinical Practice, including the International Conference on Harmonization and the Declaration of Helsinki. All patients provided written informed consent. This trial is registered with ClinicalTrials.gov (NCT03690388).

Treatment and assessments

Patients were randomized 2:1 to receive cabozantinib or a placebo and were stratified by prior lenvatinib usage (yes or no) and age (≤65 or >65 years). Patients self-administered cabozantinib tablets (60 mg) or a matching placebo orally once daily. All patients received best supportive care, and adverse events (AEs) were managed with dose modification (dose reductions or interruptions) and supportive care. Dose modification was recommended for intolerable treatment-related grade 2 AEs and grade 3 or 4 AEs. Dose interruptions were allowed for up to 8 weeks or longer with sponsor approval; doses were reduced from 60 to 40 mg daily and then to 20 mg daily. Patients were treated until disease progression per RECIST v1.1 or unacceptable toxicity; patients could continue treatment beyond disease progression as long as they experienced a clinical benefit according to the investigator.

After radiographic progression was confirmed by a blinded independent radiology committee, patients randomized to the placebo could cross over to open-label cabozantinib, and patients randomized to cabozantinib could transition to open-label cabozantinib if there was a clinical benefit as determined by the investigator. Tumor response and progression were assessed at the baseline with magnetic resonance imaging or computed tomography every 8 weeks for 12 months and every 12 weeks thereafter. Safety, including laboratory tests, was assessed every 2 weeks through Week 9, every 4 weeks thereafter, and 30 days after discontinuation of the study treatment. AEs were assessed by investigators using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0). Serious AEs were defined as AEs that resulted in death, were life-threatening, required hospitalization, disrupted normal life functions, led to a congenital anomaly or birth defect, or were events considered medically important.

End points

Details of the multiple primary end points of ORR and PFS, which were evaluated per RECIST v1.1 by a blinded independent radiology committee, have been reported previously.[8] Updated results for ORR and PFS are presented here. Other efficacy end points included overall survival (OS; the time from randomization to death from any cause) and duration of response (the time from the first documentation of a confirmed objective response to the earliest date of disease progression or death from any cause). The disease stabilization rate was defined as the proportion of patients achieving a confirmed complete or partial response or stable disease with a duration of at least 16 weeks. Safety was assessed in all patients who received at least one dose of their trial regimen.

Statistical analysis

Details of the statistical plan for the primary analysis of ORR and the interim analysis of PFS have been reported previously.[8] The primary end point of PFS used the 96% CI for inferential purposes because the 1% α was spent in the analysis of ORR and could not be reallocated to PFS. Because the primary end point of PFS was met at the interim analysis, this was also the final α-controlled analysis of PFS. For the extended follow-up analysis, efficacy end points were assessed in all randomized patients (the ITT population) per the data cutoff of February 8, 2021. All extended analyses were descriptive and supportive to show that significance was maintained at the same α level per the interim analysis. All *p* values were retained to support the overarching quality of the results from this extended analysis and their consistency with the primary analysis; *p* values were estimated by a stratified log-rank test for PFS and by an unstratified Fisher exact test for ORR. The Kaplan–Meier method was used to estimate medians and associated CIs for time-to-event end points, and HRs were estimated with a Cox proportional hazards model (stratified for PFS and OS in the ITT population). PFS was also analyzed in prespecified subgroups defined by prior therapy (sorafenib, lenvatinib, or both), age (≤65 or >65 years), sex, race, geographic region, Eastern Cooperative Oncology Group performance status, number of prior VEGFR TKIs for DTC (1 or ≥2), receipt of prior RAI, histology (papillary or follicular), and site of metastasis. Categorical and continuous data were summarized with descriptive statistics. All analyses were performed with SAS version 9.4. Safety and efficacy were monitored by an independent data monitoring committee.

RESULTS

Patients

Patients were enrolled into the trial from February 27, 2019, to February 2, 2021. At the data cutoff for the updated analysis (February 8, 2021), 258 patients were randomized to cabozantinib

TABLE 1 Baseline demographics and clinical characteristics

	Cabozantinib (n = 170)	Placebo (n = 88)
Age, median (range), years	65 (31–85)	66 (37–83)
Sex, No. (%)		
Female	87 (51)	49 (56)
Male	83 (49)	39 (44)
Race, No. (%)		
White	121 (71)	59 (67)
Asian	29 (17)	20 (23)
Black	2 (1)	2 (2)
Other	6 (4)	3 (3)
Unknown	12 (7)	4 (5)
Geographic region, No. (%)		
Europe	82 (48)	39 (44)
Asia	24 (14)	19 (22)
United States/Canada	15 (9)	12 (14)
Rest of the world	49 (29)	18 (20)
ECOG performance status, No. (%)		
0	74 (44)	43 (49)
1	95 (56)	45 (51)
Histologic subtype, No. (%)[a]		
Papillary	96 (56)	54 (61)
Follicular	78 (46)	35 (40)
Prior sorafenib or lenvatinib, No. (%)		
Sorafenib	101 (59)	54 (61)
Lenvatinib	108 (64)	55 (63)
Sorafenib and lenvatinib	39 (23)	21 (24)
No. of prior VEGFR TKIs, No. (%)		
1	126 (74)	65 (74)
2	43 (25)	23 (26)
Metastatic lesions, No. (%)[b]		
Bone	51 (30)	21 (24)
Liver	25 (15)	9 (10)
Lung	121 (71)	61 (69)
Other	127 (75)	70 (80)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; No., number; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

[a]Five patients in the intent-to-treat population were noted as having both papillary and follicular histologies.

[b]Per investigator.

(n = 170) or the placebo (n = 88). Baseline demographics and clinical characteristics are described in Table 1. In the overall population, the median age was 65 years (range, 31–85 years). Seventy-four percent of all patients (191 of 258) had received one prior VEGFR TKI, and 26% (66 of 258) had received two prior VEGFR TKIs. Sixty-three percent of all patients (163 of 258) had received prior lenvatinib for DTC, 60% (155 of 258) had received prior sorafenib, and 23% (60 of 258) had received both. Fifty-eight percent (150 of 258) had papillary histology, and 44% (113 of 258) had follicular histology.

At the data cutoff, the median follow-up was 10.1 months (range, 0.2–23.4 months). Forty-five percent of the patients had discontinued blinded cabozantinib, and 69% had discontinued the blinded placebo (Figure 1). The most common reason for discontinuation was disease progression for cabozantinib (21%) and for the placebo (57%). Eleven patients in the cabozantinib arm and 40 patients in the placebo arm transitioned to open-label cabozantinib.

Efficacy

At the data cutoff, 131 PFS events had occurred (62 in the cabozantinib arm and 69 in the placebo arm). The median PFS was 11.0 months (96% CI, 7.4–13.8 months) for cabozantinib and 1.9 months (96% CI, 1.9–3.7 months) for the placebo (HR, 0.22; 96% CI, 0.15–0.32; $p < .0001$; Figure 2). The PFS benefit was maintained across all prespecified subgroups with adequate sample sizes (Figure 3), including those previously treated with lenvatinib (HR, 0.27; 95% CI, 0.18–0.42), sorafenib (HR, 0.19; 95% CI, 0.12–0.30), or both (HR, 0.28; 95% CI, 0.14–0.56).

Eighty percent of the evaluable patients in the cabozantinib arm had a reduction in target lesions versus 24% in the placebo arm (Figure S1). The ORR was 11% (95% CI, 6.9%–16.9%) for cabozantinib and 0% (95% CI, 0.0%–4.1%) for the placebo ($p = .0003$, Table 2). There were 18 confirmed partial responses and one confirmed complete response in the cabozantinib arm. Disease stabilization was achieved in 53% of the patients in the cabozantinib arm and in 19% of the patients in the placebo arm.

There were 37 deaths from any cause (22%) among the 170 patients assigned to the cabozantinib arm and 21 (24%) among the 88 patients assigned to the placebo. Subsequent therapy (not including those who crossed over to open-label cabozantinib) was received by 11% of the patients in both treatment arms (Table S1). Despite 40 patients crossing over from the placebo to cabozantinib, there was a trend for improved survival in the cabozantinib arm with an HR of 0.76 (95% CI, 0.45–1.31).

Safety

The median duration of exposure was 6.0 months (range, 0.2–18.8 months) with cabozantinib and 2.6 months (range, 0.2–15.2 months) with the placebo. Dose reductions due to AEs were required in 67% and 3% of the patients in the cabozantinib and placebo arms, respectively; the median average daily dose was 39.5 mg (range, 9.5–60.0 mg) for cabozantinib and 59.9 mg (range, 18.4–68.3 mg) for the placebo (Table S2). Treatment discontinuation due to treatment-emergent adverse events (TEAEs) unrelated to DTC occurred in 9%

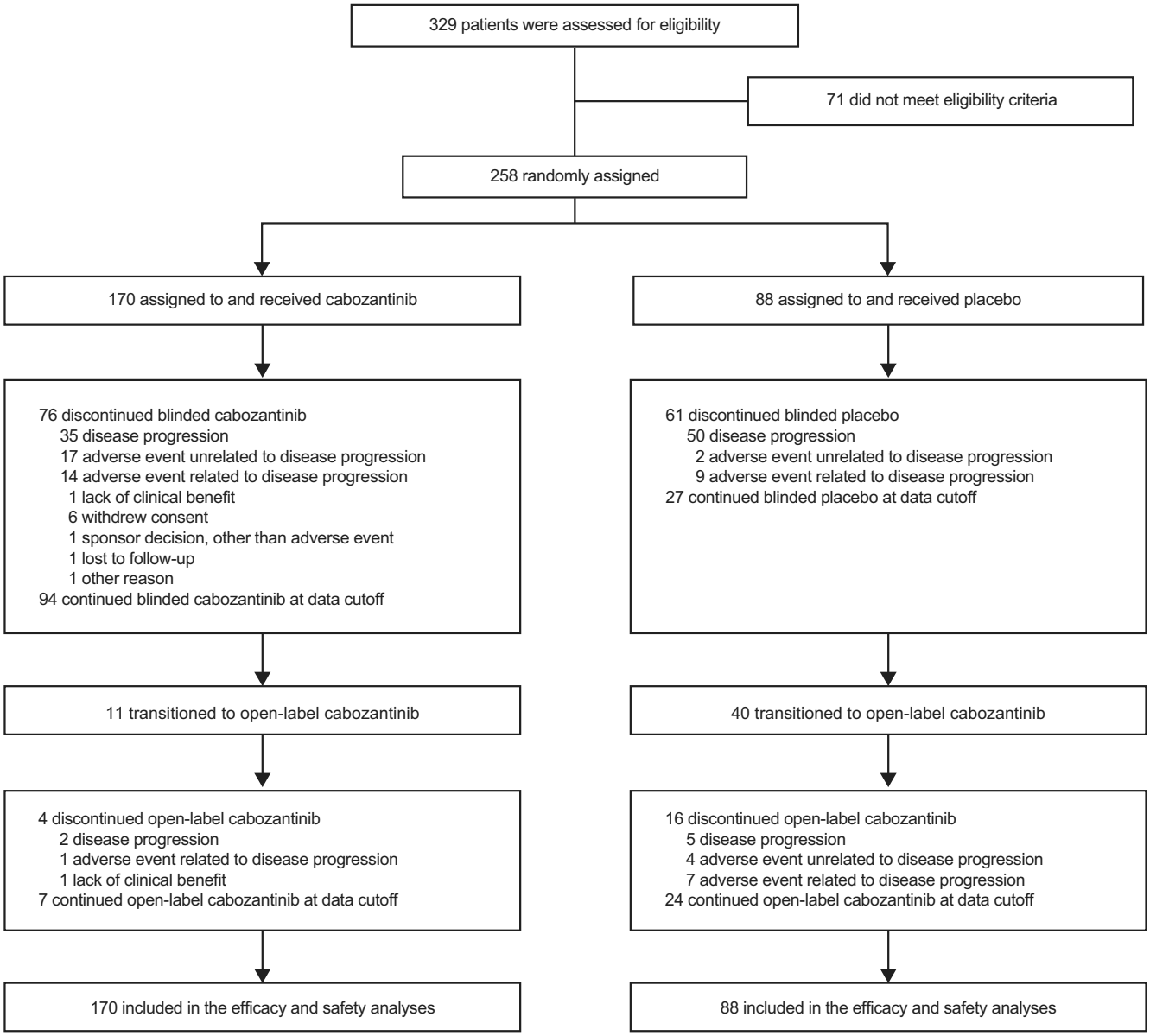

FIGURE 1 Patient disposition

of the patients with cabozantinib and in 0% of the patients with the placebo.

Most patients experienced a TEAE: 98% with cabozantinib and 85% with the placebo. The most common TEAEs of any grade were diarrhea (62% for cabozantinib vs. 3% for the placebo), palmar–plantar erythrodysesthesia (47% vs. 1%), and hypertension (32% vs. 3%). Grade 3/4 TEAEs occurred in 62% of the cabozantinib-treated patients and in 28% of the patients receiving the placebo. The most common grade 3/4 TEAEs were hypertension (12% vs. 2%), palmar–plantar erythrodysesthesia (10% vs. 0%), and fatigue (9% vs. 0%). Grade 4 TEAEs were uncommon and occurred in 6% of the cabozantinib-treated patients and in 2% of the placebo-treated patients (Table 3). Serious AEs occurred in 66 (39%) with cabozantinib and in 24 (27%) with the placebo; the most common were diarrhea (3% vs. 0%), pleural effusion (3% vs. 3%), pneumonia (2% vs. 1%), and pulmonary embolism (2% vs. 0%). There were no grade 5 AEs related to the study treatment. Grade 5 TEAEs not related to DTC that occurred ≤30 days after the last dose of the study treatment occurred in four of the 170 patients (2%) receiving cabozantinib and in one of the 88 patients (1%) receiving the placebo; these included one patient with an unknown cause, one patient with cardiorespiratory arrest, one patient with a pulmonary embolism, and one patient with stress cardiomyopathy in the cabozantinib arm and one patient with a cerebrovascular accident in the placebo arm.

DISCUSSION

After extended follow-up in a larger ITT population, the PFS benefit of cabozantinib was confirmed in this exploratory analysis, with a median PFS of 11.0 months in the cabozantinib arm versus

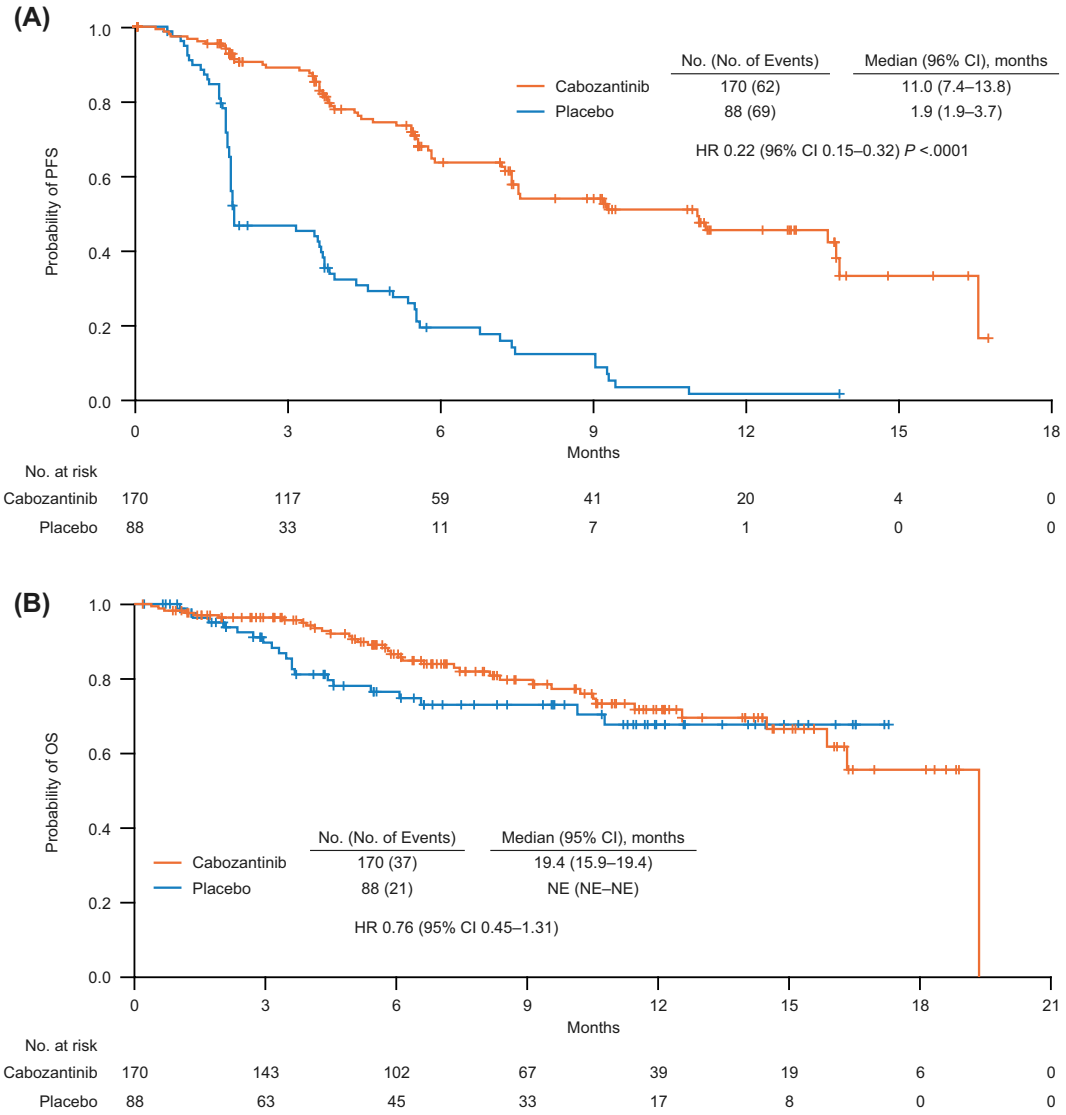

FIGURE 2 Kaplan–Meier estimates of (A) PFS per RECIST v1.1 by a blinded independent radiology committee and (B) OS. CI indicates confidence interval; HR, hazard ratio; NE, not estimable; No., number; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

1.9 months in the placebo arm. Notably, the HR of 0.22 for PFS reported after the extended follow-up matched the HR at the interim analysis.[8] At the interim analysis, the PFS benefit associated with a short follow-up time indicated that cabozantinib imparted disease stabilization in a patient population that otherwise would have had rapid disease progression, as evidenced by the short duration of PFS in the placebo arm, which was approximately the time of the first radiographic assessment. The PFS benefit was observed across all prespecified subgroups of adequate size, including those defined by the type or number of lines of prior therapy, age, sites of metastasis, and DTC histology. An increase in the ORR was also observed with cabozantinib; however, this analysis is descriptive only because significance was not achieved at the primary analysis of ORR.[8] Cabozantinib was associated with a higher rate of reductions in target lesions and a higher disease stabilization rate. In agreement with the previous analysis, OS favored cabozantinib, but interpretation is limited by the crossover of patients from the placebo to open-label cabozantinib. The study was unblinded on April 16, 2021, to enable the potential crossover of patients assigned to the placebo to receive cabozantinib treatment, and this will confound future analyses of OS.

The safety profile of cabozantinib in the extended analysis was consistent with that reported at the interim analysis and the known safety profile of cabozantinib. There were no new safety signals identified. There were few grade 4 AEs, and there were no grade 5 treatment-related events. The rates of AEs were similar to those observed at the first interim analysis: 80% of the patients in the cabozantinib arm had any dose modification due to an AE, 71% had a dose hold, 67% had a dose reduction, and 9% discontinued

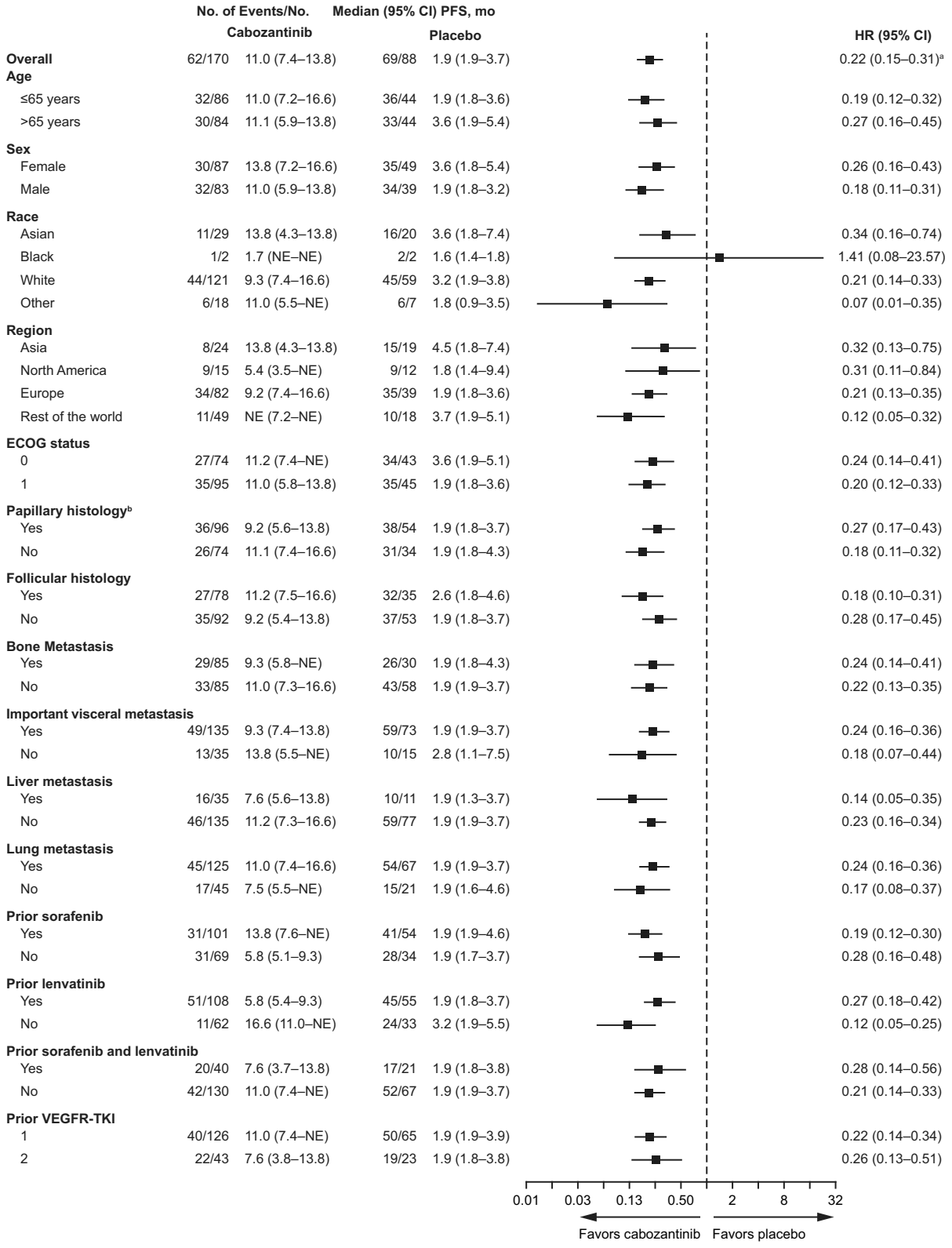

FIGURE 3 PFS in prespecified subgroups. [a]Stratified hazard ratio. [b]Thirty-two patients with papillary differentiated thyroid cancer had a follicular variant. CI indicates confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NE, not estimable; No., number; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

TABLE 2 Tumor responses per RECIST v1.1 by a blinded independent radiology committee

	Cabozantinib (n = 170)	Placebo (n = 88)
Objective response rate, % (95% CI)	11 (6.9–16.9)	0 (0.0–4.1)
p value[a]	.0003	
Best overall response, No. (%)		
Confirmed complete response	1 (1)	0
Confirmed partial response	18 (11)	0
Stable disease	117 (69)	34 (39)
≥16 weeks	71 (42)	17 (19)
Progressive disease	11 (6)	42 (48)
No disease	1 (1)	0
Unable to evaluate	3 (2)	1 (1)
Missing	19 (11)	11 (13)
Disease stabilization rate, No. (%)[b]	90 (53)	17 (19)
Duration of response, median (95% CI), months	10.2 (9.3 to NE)	NA
Time to objective response, median (range), months	3.6 (1.7–7.5)	NA

Note: Tumor responses were assessed with RECIST v1.1 by a blinded independent radiology committee. *No disease* indicates that baseline disease was not detected by the blinded independent radiology committee; all patients had measurable disease per the investigator according to the eligibility criteria. *Missing* indicates a missing baseline or postbaseline assessment or stable disease not meeting the minimum criteria for the interval from randomization. *NE* indicates that the best overall response could not be evaluated with the available assessments (e.g., because of image quality or lesion characteristics).

Abbreviations: CI, confidence interval; NA, not applicable; NE, not estimable; No., number; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

[a]Unstratified Fisher exact test.

[b]Prespecified supportive analysis: complete or partial response or stable disease for ≥16 weeks.

cabozantinib because of a TEAE. Taken together, these data indicate that AEs associated with cabozantinib were well managed with supportive care and dose modification.

RAI-refractory DTC is a disease that has been associated with a poor prognosis. For patients who progress on VEGFR-targeted therapy, there has been no standard of care, with limited clinical studies informing salvage treatments.[11–13] In the phase 3 study of lenvatinib in RAI-refractory DTC, 76% of the patients were previously untreated, and 24% had received one prior TKI, primarily sorafenib; the PFS benefit observed with lenvatinib versus a placebo in the ITT population was maintained in the TKI-naive and prior TKI subgroups.[3] Although sorafenib remains an important first-line treatment option for RAI-refractory DTC, lenvatinib has become more widely used in recent years.[14] Therefore, clinical studies are needed for subsequent therapy in patients who have received prior lenvatinib. Clinical data suggest that lenvatinib resistance may result in more aggressive disease. The median PFS in the placebo arm of the lenvatinib study was 3.6 months for both the TKI-naive and prior TKI subgroups.[3] In the current study, the median PFS in the placebo arm was 1.9 months for the prior lenvatinib subgroup and 3.2 months for the subgroup of patients who had not received prior lenvatinib, and this was consistent with the development of more aggressive disease.

To our knowledge, COSMIC-311 is the first randomized, phase 3 trial to evaluate a VEGFR-targeting TKI in patients with RAI-refractory DTC previously treated with lenvatinib or both sorafenib and lenvatinib. This is also the first study to demonstrate a clinical benefit with subsequent therapy in patients previously treated with lenvatinib. The study population comprised patients who had received one prior VEGFR TKI (74%) and patients who had received two (26%); 60% of the patients had received sorafenib, 63% had received prior lenvatinib, and 23% had received both. The PFS results reported here are consistent with those previously reported in a phase 2 study and an observational study of cabozantinib as a subsequent therapy in patients with RAI-refractory DTC after prior treatment with a VEGFR TKI, including lenvatinib.[15,16] On the basis of positive results from the first preplanned interim analysis of COSMIC-311 and the maintenance of efficacy and safety with extended follow-up, cabozantinib recently has been approved by the US Food and Drug Administration for patients aged 12 years or older with locally advanced or metastatic RAI-refractory DTC that has progressed after prior VEGFR therapy. Cabozantinib also has been approved by the European Medicines Agency for the treatment of adult patients with locally advanced or metastatic DTC refractory to or not eligible for RAI that has progressed during or after prior systemic therapy.[10] The addition of cabozantinib as a subsequent

TABLE 3 Treatment-emergent adverse events

	Cabozantinib (n = 170), No. (%)				Placebo (n = 88), No. (%)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Any event	46 (27)	95 (56)	11 (6)	14 (8)	49 (56)	23 (26)	2 (2)	1 (1)
Diarrhea	92 (54)	13 (8)	0	0	3 (3)	0	0	0
PPE	63 (37)	17 (10)	0	0	1 (1)	0	0	0
Hypertension	34 (20)	19 (11)	1 (1)	0	1 (1)	2 (2)	0	0
Decreased appetite	48 (28)	5 (3)	0	0	11 (13)	0	0	0
Fatigue	34 (20)	15 (9)	0	0	7 (8)	0	0	0
Nausea	44 (26)	4 (2)	0	0	2 (2)	0	0	0
ALT increased	42 (25)	1 (1)	0	0	1 (1)	1 (1)	0	0
AST increased	42 (25)	0	0	0	2 (2)	0	0	0
Hypocalcemia	29 (17)	8 (5)	5 (3)	0	1 (1)	2 (2)	0	0
Weight decreased	33 (19)	4 (2)	0	0	2 (2)	0	0	0
Vomiting	28 (16)	3 (2)	0	0	7 (8)	0	0	0
Stomatitis	24 (14)	6 (4)	0	0	2 (2)	0	0	0
Asthenia	25 (15)	4 (2)	0	0	12 (14)	0	0	0
Mucosal inflammation	26 (15)	3 (2)	0	0	0	0	0	0
Hypomagnesemia	25 (15)	2 (1)	0	0	3 (3)	0	0	0
Proteinuria	23 (14)	4 (2)	0	0	2 (2)	0	0	0
Dyspnea	20 (12)	3 (2)	0	0	13 (15)	2 (2)	1 (1)	0
Cough	16 (9)	0	0	0	17 (19)	0	0	0

Note: This table lists treatment-emergent adverse events of any cause occurring in ≥15% of the patients in either treatment arm.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; No., number; PPE, palmar–plantar erythrodysesthesia.

therapy option should help clinicians to plan and implement sequential treatment with VEGFR TKIs.

AUTHOR CONTRIBUTIONS

Marcia S. Brose: Conception and design and provision of study materials or patients. **Bruce G. Robinson:** Conception and design and provision of study materials or patients. **Steven I. Sherman:** Conception and design and provision of study materials or patients. **Barbara Jarzab:** Provision of study materials or patients. **Chia-Chi Lin:** Provision of study materials or patients. **Fernanda Vaisman:** Provision of study materials or patients. **Ana O. Hoff:** Provision of study materials or patients. **Erika Hitre:** Provision of study materials or patients. **Daniel W. Bowles:** Provision of study materials or patients. **Suvajit Sen:** Administrative support. **Jennifer W. Oliver:** Administrative support. **Bhumsuk Keam:** Provision of study materials or patients. **Jaume Capdevila:** Provision of study materials or patients. All authors participated in the collection and assembly of data, in the data analysis and interpretation, and in the writing of the manuscript; gave final approval of the manuscript; and are accountable for all aspects of the work.

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CONFLICT OF INTEREST

Marcia S. Brose has received honoraria from Bayer, Eisai, and Lilly; has a consulting or advisory role with Bayer, Blueprint Medicines, Eisai, Exelixis, Lilly, and Loxo; and has received institutional research funding from Bayer, Blueprint Medicines, Eisai, Exelixis, Lilly, and Loxo. Bruce G. Robinson has leadership roles with Cochlear and Mayne Pharma; has stock and other ownership interests in Cochlear and Mayne Pharma; has a consulting or advisory role with Eisai and Loxo; has participated in speakers' bureaus with Eisai; and has received travel support, accommodations, or other expenses from Eisai. Steven I. Sherman has received honoraria from Eisai; has a consulting or advisory role with Exelixis, Lilly, and Loxo; and has received institutional research funding from Exelixis. Barbara Jarzab

has received honoraria from Sanofi; has a consulting or advisory role with AstraZeneca, Ewopharma, and Ipsen; has participated in speakers' bureaus with Exelixis; has acted as an independent contractor for Amgen, Eisai, Pfizer, Lilly, Sobi, and Oxigene; and has received travel support, accommodations, or other expenses from Edomed, Ipsen, Novartis, Bayer, Sobi, and Sanofi. Chia-Chi Lin has received honoraria from Daiichi Sankyo, Lilly, Novartis, and Roche; has a consulting or advisory role with Blueprint Medicines, Boehringer Ingelheim, Daiichi Sankyo, and Novartis; has acted as an independent contractor for Bristol-Myers Squibb, EMD Serono, BeiGene, and AbbVie; and has received travel support, accommodations, or other expenses from BeiGene, Daiichi Sankyo, Lilly, and Novartis. Fernanda Vaisman has a consulting or advisory role with Bayer HealthCare and Merck. Ana O. Hoff has received honoraria from Bayer (continuing medical education), Genzyme (continuing medical education), and United (continuing medical education); has a consulting or advisory role with Exelixis, Lilly, and Bayer; and has received institutional research funding from Exelixis and Lilly. Daniel W. Bowles has a consulting or advisory role with Exelixis. Suvajit Sen is an employee of Exelixis and has stock and other ownership interests with Exelixis. Jennifer W. Oliver is an employee of Exelixis and has stock and other ownership interests with Exelixis. Kamalika Mukherjee is an employee of Exelixis and has stock and other ownership interests with Exelixis. Bhumsuk Keam has received honoraria from AstraZeneca, Merck, and MSD Oncology; has a consulting or advisory role with ABL Bio, AstraZeneca, CbsBioscience, Cellid, Genexine, Handok, and MSD Oncology; and has received research funding from AstraZeneca, MSD Oncology, and Ono Pharmaceutical. Jaume Capdevila has a consulting or advisory role with Advanced Accelerator Applications, Bayer, Eisai, Exelixis, Ipsen, Lilly, Merck Serono, Novartis, Pfizer, Sanofi, and Vall Hebron; has participated in speakers' bureaus with Bayer, Eisai, Ipsen, Lilly, Merck Serono, Novartis, Pfizer, and Sanofi; and has received institutional research funding from Advanced Accelerator Applications, AstraZeneca, Bayer, Eisai, Ipsen, Lilly, Novartis, and Pfizer. The other authors made no disclosures.

DATA AVAILABILITY STATEMENT

Individual participant data will not be made available.

ORCID

Bhumsuk Keam https://orcid.org/0000-0001-8196-4247

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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