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A Randomized, Double-Blind Noninferiority Study to Evaluate the Efficacy of the Cabozantinib Tablet at 60 mg Per Day Compared with the Cabozantinib Capsule at 140 mg Per Day in Patients with Progressive, Metastatic Medullary Thyroid Cancer

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Background: Cabozantinib inhibits pathways involved in medullary thyroid cancer (MTC). Cabozantinib is approved as 140 mg/day in capsules for MTC and 60 mg/day in tablets for other solid tumors. This study compared the two doses in progressive metastatic MTC.

Methods: In this Phase 4, randomized, double-blind noninferiority (NI) trial (NCT01896479), patients with progressive metastatic MTC were randomized 1:1 to cabozantinib 60 mg/day tablet or 140 mg/day capsules. The primary end point was progression-free survival (PFS) by blinded independent radiology committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. NI would be concluded if the upper 95% confidence interval [CI] for the PFS hazard ratio (HR) was less than the NI margin, 1.58. The secondary end point was objective response rate (ORR) by BIRC per RECIST v1.1; additional end points included safety and pharmacokinetics.

Results: At data cutoff (July 15, 2020), 247 patients were randomized to the 60 mg/day tablet arm ($n = 123$) and the 140 mg/day capsules arm ($n = 124$). NI was not met (median PFS 11.0 months vs. 13.9 months in the 60 and

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140 mg/day arms [HR 1.24; CI 0.90–1.70; $p = 0.19$]). The ORR was 33% in both arms. Generally, adverse event (AE) incidence was lower in the 60 mg/day arm (Grade 3/4, 63% vs. 72%), as were dose reductions (69% vs. 81%) and treatment discontinuations due to AEs (23% vs. 36%). Initially, cabozantinib plasma concentrations were higher in the 140 mg/day arm but became similar between arms at later time points.
Conclusions: PFS NI of the cabozantinib 60 mg/day tablet vs. 140 mg/day capsules was not met. The 60 mg/day tablet had the same ORR and lower rates of AEs.
Clinical Trial Registry: ClinicalTrials.gov NCT01896479.

Keywords: cabozantinib, capsule, medullary thyroid cancer, noninferiority, tablet, tyrosine kinase inhibitor

Introduction

For patients with advanced medullary thyroid cancer (MTC), *RET* mutations, as well as overexpression of vascular endothelial growth factor (VEGF) and its receptor (VEGFR) supported clinical development of tyrosine kinase inhibitors (TKIs) directed at these targets (1,2). Cabozantinib is an oral TKI that targets multiple receptor tyrosine kinases involved in tumor pathology, including VEGFR2, MET, RET, KIT, AXL, and FLT (3). Cabozantinib is available in capsule and tablet formulations. The capsule is approved at 140 mg/day for progressive metastatic MTC (4,5). The tablet is approved at 60 mg/day as monotherapy for advanced renal cell carcinoma (RCC), hepatocellular carcinoma after prior sorafenib, and radioiodine-refractory differentiated thyroid cancer after prior VEGFR TKI and at 40 mg/day in combination with nivolumab for advanced RCC (3,6). Plasma exposure is similar between the capsule and tablet on a per-mg basis, but the formulations are not bioequivalent owing to differences in the maximum plasma concentration (7).

Approval of cabozantinib in MTC was based on the Phase 3 EXAM trial, in which patients with unresectable, locally advanced, or metastatic MTC were randomized to cabozantinib 140 mg/day capsules or placebo (8). Cabozantinib significantly improved the primary end point of progression-free survival (PFS) versus placebo, with median PFS of 11.2 months versus 4.0 months (hazard ratio [HR] 0.28, 95% confidence interval [CI 0.19–0.40]; $p < 0.001$). The objective response rate (ORR) was 28% versus 0% ($p < 0.001$), and the median overall survival (OS) was 26.6 months versus 21.1 months (HR 0.85 [CI 0.64–1.12]; $p = 0.24$) (9).

The safety profile of cabozantinib is manageable with dose modification. Owing to interpatient variability in cabozantinib clearance and exposure, dose modifications to manage adverse events (AEs) are common (10). The 140 mg/day dose can be reduced to 100 mg/day and then to 60 mg/day (8). During EXAM, dose reductions occurred in 82% of patients receiving cabozantinib, with 46% having dose reductions to 60 mg (9).

Based on the rate of cabozantinib dose reductions observed during EXAM, it was hypothesized that a lower starting dose might maintain efficacy while improving tolerability. The goal of this noninferiority (NI) study, the EXAMINER trial, was to compare the efficacy of the cabozantinib 60 mg/day tablet with 140 mg/day capsules in patients with progressive metastatic MTC.

Materials and Methods

Study design and patients

The EXAMINER study was a Phase 4, multicenter, randomized, double-blind NI trial in patients with progressive metastatic MTC. Patients were enrolled at 45 clinics in 14 countries. Eligible patients were ≥18 years old, had histologically confirmed progressive metastatic MTC, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and available tumor tissue for determination of *RET* mutational status or documentation with a blood sample. Radiographic evidence of progressive disease per RECIST as assessed by the investigator was required for study entry, comparing images at screening with those obtained within the prior 14 months.

Patients also were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤1 and adequate organ and marrow function. Prior systemic anticancer therapy was allowed. Patients were excluded if they had previously received cabozantinib or a small-molecule kinase inhibitor, hormonal therapy (i.e., growth hormone therapies), systemic antitumor therapy, or radiation within five half-lives of the compound/active metabolites or 28 days of randomization, whichever is shorter. Additional eligibility criteria are listed in the Supplementary Data.

This study was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by appropriate institutional review boards or ethics committees, and all patients provided written informed consent. The trial is registered at ClinicalTrials.gov

Randomization

Patients were randomized 1:1 in a blinded manner to receive cabozantinib 60 mg/day tablet or 140 mg/day capsules. Randomization was stratified based on *RET* M918T status (positive, negative, or unknown). The M918T-unknown stratum could contain a maximum of 19 patients. Patients were randomized by an authorized clinical research organization using an interactive voice recognition/interactive web response system. A permuted block design was employed to ensure the 1:1 ratio of assignment for the overall population and each level of stratification. Patients, investigators, study centers, and the sponsor were blinded to study treatment.

Procedures

Cabozantinib was administered at 60 mg (tablet) and 140 mg (capsules) doses taken once daily, supplied as 60 and 20 mg tablets and 80 and 20 mg capsules, respectively, with matching placebo capsules and tablets to ensure blinded treatment. Dose reductions or interruptions were permitted to manage AEs (Supplementary Table S1). The 60 mg/day tablet dose could be reduced to 40 mg/day and then to 20 mg/day; the 140 mg/day capsules dose could be reduced to 100 mg/day and then to 60 mg/day. Patients continued

treatment until disease progression or intolerable toxicity. Treatment could continue beyond progression if the investigator believed that there was clinical benefit.

Tumor assessment by magnetic resonance imaging/computed tomography was performed at screening and every 12 weeks. Safety was assessed every 2 weeks for the first 9 weeks, then every 4 weeks thereafter, with a post-treatment follow-up visit 30 days after treatment discontinuation. AEs were assessed by the investigator, using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Outcomes

The primary end point was PFS, defined as time from randomization to the earlier of progressive disease by blinded independent radiology committee (BIRC) per RECIST v1.1, or death from any cause. The secondary end point was ORR, defined as the proportion of patients who experienced a confirmed complete or partial response by BIRC per RECIST v1.1. Additional end points included safety, tolerability, and pharmacokinetics (PK). A set of events to monitor (ETMs) was defined to track AEs known to be associated with VEGFR

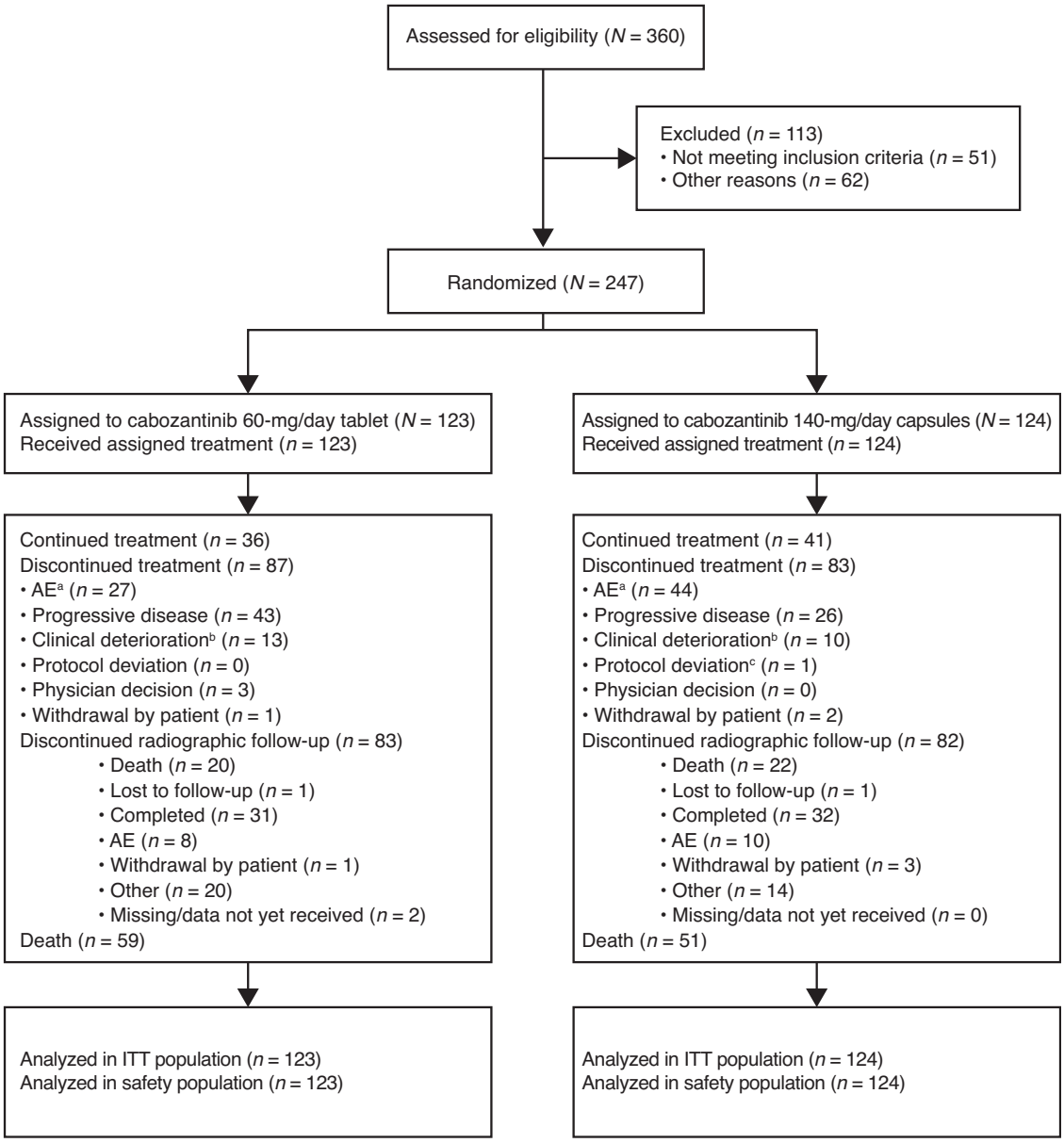

FIG. 1. Patient disposition. [a]Two additional patients (one in each arm) were summarized as having non-PD AEs (regardless of causality) leading to study treatment discontinuation in Supplementary Table S3: one patient in the 60 mg/day arm (decubitus ulcer, Grade 2, treatment not related) and one patient in the 140 mg/day arm (AST increased, Grade 1, treatment related). However, on this flowchart, they were not included because these two patients discontinued study treatment owing to an AE after the data cutoff date for this report. [b]Clinical deterioration comprises AEs or serious AEs related to disease progression. [c]One patient was treated with study drug beyond PD, which was not permitted under Protocol Amendment 3. The subsequent protocol amendment allowed treatment beyond disease progression if patients were eligible. AE, adverse event; AST, aspartate aminotransferase; ITT, intention-to-treat; PD, progressive disease.

TKIs: gastrointestinal perforation, fistula, abscess, hemorrhage (Grade ≥3), arterial thromboembolic events, venous and mixed/unspecified thromboembolic events, wound complications, hypertension, osteonecrosis, palmar–plantar erythrodysesthesia, proteinuria, reversible posterior leukoencephalopathy syndrome, diarrhea, and QT prolongation.

Statistical analyses

Efficacy outcomes were assessed in the intention-to-treat (ITT) population, defined as all randomized patients. Safety was assessed in the safety population, defined as patients who received any amount of study treatment. The PK population consisted of all patients in the safety population with ≥1 plasma PK concentration. PK analyses were performed on concentration records where the sample met stability requirements and was associated with a planned visit; values below a limit of quantification of 0.5 ng/mL were treated as zero.

The primary efficacy analysis evaluated whether PFS by BIRC per RECIST v1.1 in the cabozantinib 60 mg/day tablet arm was noninferior to that of the 140 mg/day capsules arm. The NI margin was chosen using the fraction retention method to preserve 50% of the benefit of cabozantinib 140 mg versus placebo demonstrated in the EXAM study, in which the estimated HR for PFS was 0.28 [CI 0.19–0.40] (8). The NI margin was calculated as follows:

$$\text{NI margin} = \exp[\ln(1/0.40)/2] = 1.58.$$

The primary efficacy analysis was conducted after 150 PFS events were observed. NI would be concluded if the upper CI of the HR was less than the NI margin of 1.58. A sample size of 188 patients was estimated to provide 80% power and could be increased to 250 if review of accumulating PFS events indicated that more patients were required to reach 150 events due to censoring. Prespecified subgroup analyses of PFS included those defined by age, sex, race,

Table 1. Baseline Demographic and Patient Characteristics

	Cabozantinib, 60 mg/day tablet (n = *123*)	*Cabozantinib, 140 mg/day capsules* (n = *124*)	*Total* (N = *247*)
Age (years)			
Median (range)	59.0 (20–81)	61.0 (20–82)	60.0 (20–82)
≥65, *n* (%)	38 (31)	46 (37)	84 (34)
Sex, *n* (%)			
Male	90 (73)	74 (60)	164 (66)
Female	33 (27)	50 (40)	83 (34)
Geographic region, *n* (%)			
Europe[a]	75 (61)	75 (60)	150 (61)
Rest of world[b]	48 (39)	49 (40)	97 (39)
Race, *n* (%)			
White	92 (75)	102 (82)	194 (79)
Non-white	13 (11)	9 (7)	22 (9)
Not reported	18 (15)	13 (10)	31 (13)
RET M918T mutation status per IxRS, *n* (%)			
Positive	66 (54)	65 (52)	131 (53)
Negative	50 (41)	51 (41)	101 (41)
Unknown	7 (6)	8 (6)	15 (6)
ECOG PS, *n* (%)			
0	74 (60)	76 (61)	150 (61)
1	49 (40)	48 (39)	97 (39)
Prior systemic anticancer therapies for MTC, *n* (%)	65 (53)	61 (49)	126 (51)
Number of prior systemic anticancer therapies received for MTC, *n* (%)			
0	58 (47)	63 (51)	121 (49)
1	48 (39)	42 (34)	90 (36)
2	10 (8)	10 (8)	20 (8)
≥3	7 (6)	9 (7)	16 (6)
Prior TKI therapy, *n* (%)	56 (46)	46 (37)	102 (41)
Vandetanib	48 (39)	42 (34)	90 (36)
Sorafenib	8 (6.5)	4 (3.2)	12 (4.9)
Sunitinib	5 (4.1)	3 (2.4)	8 (3.2)
Nintedanib	1 (0.8)	3 (2.4)	4 (1.6)
Lenvatinib	3 (2.4)	0	3 (1.2)
Axitinib	1 (0.8)	1 (0.8)	2 (0.8)
Pazopanib	2 (1.6)	0	2 (0.8)
Dovitinib	1 (0.8)	0	1 (0.4)
Selumetinib	0	1 (0.8)	1 (0.4)

[a]Croatia, France, Hungary, Italy, The Netherlands, Poland, Romania, Spain, Sweden.
[b]Australia, Canada, Israel, Russia, South Korea.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; IxRS, interactive voice/web response system; MTC, medullary thyroid cancer; TKI, tyrosine kinase inhibitor.

ECOG PS, geographic region, prior radiation therapy, M918T mutational status, and number of prior systemic anticancer treatments.

Time-to-event end points were estimated by the Kaplan–Meier method, with *p*-values obtained from a log-rank test. A stratified Cox proportional hazard model was used to estimate HRs. If the null hypothesis for PFS was rejected, the ORR between the two arms would be compared using a two-sided chi-squared test ($\alpha = 0.05$). Analysis of OS was exploratory. Cabozantinib PK was

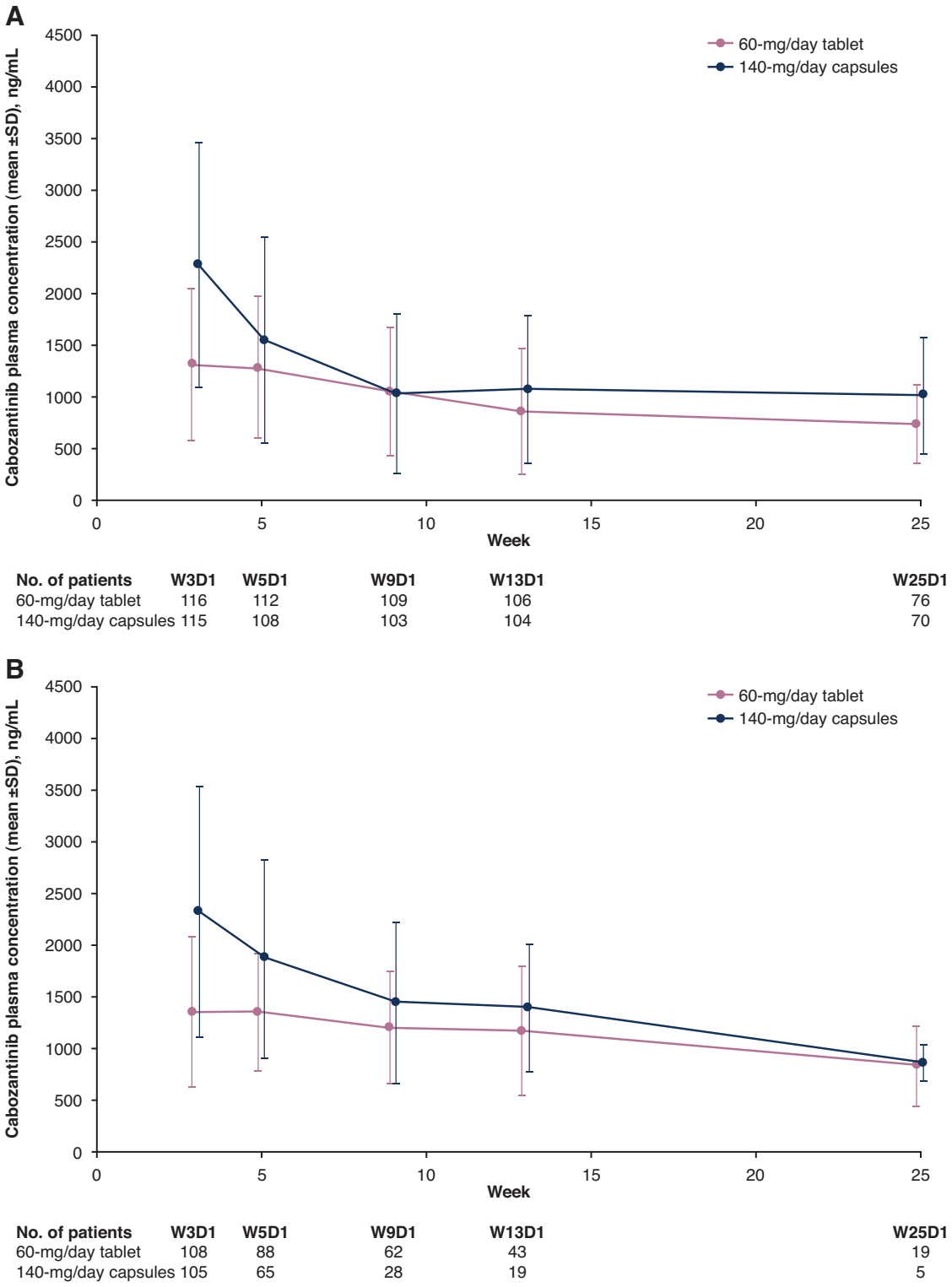

FIG. 2. Cabozantinib plasma pharmacokinetic concentrations by visit for (**A**) patients in the 60 mg/day tablet arm and the 140 mg/day capsules arm and (**B**) censored to select analysis-eligible records before any dose modifications from the initial protocol-assigned cabozantinib dose. SD, standard deviation; W, week; D, day.

summarized with descriptive statistics. Statistical analyses were performed with SAS (Version 9.2, SAS Institute, Inc, Cary, NC).

Results

Patients

From February 25, 2015, through June 2, 2020, 247 patients were randomized 1:1 to cabozantinib 60 mg/day tablet ($n = 123$) or 140 mg/day capsules ($n = 124$) and comprise the ITT population (Fig. 1). All 247 patients received their assigned study treatment and comprise the safety population. The PK population included 121 patients in the 60 mg/day arm and 122 patients in the 140 mg/day arm. Baseline characteristics were generally balanced between treatment arms, except for modest differences in sex and prior TKI therapy (Table 1). Fifty-one percent and 48% of patients in the 60 and 140 mg arms, respectively, were *RET* M918T mutation positive, while 44% and 45% were negative, and 5% and 6% had unknown mutation status.

Data cutoff was July 15, 2020, with a median follow-up of 30 months (range, 1.4–64.7 months). Eighty-seven (71%) patients in the 60 mg/day arm and 83 (67%) patients in the 140 mg/day arm discontinued study treatment (Fig. 1). Primary reasons for discontinuation were AEs (22% and 35% in the 60 and 140 mg/day arms) and progressive disease (35% and 21%).

PK of cabozantinib

Among the 243 patients in the PK population, 242 (121 in each arm) had 1019 eligible records. Interpatient variability in cabozantinib concentrations was high in both arms; the coefficient of variability for weeks 3–25 ranged from 49.8% to 69.4% in the 60 mg/day arm and from 51.9% to 74.0% in the 140 mg/day arm. There was a trend for decreased cabozantinib concentrations over time, which was more marked in the 140 mg/day arm (Fig. 2A). At week 3 day 1 (W3D1), the mean cabozantinib plasma concentration was ∼73% higher in the 140 mg/day arm, while at later time points, the difference ranged from −3% to 38%. Analysis of the exposure dataset censored at the time of any dose modification showed similar results (Fig. 2B).

Efficacy

At data cutoff, 155 PFS events had occurred. The median PFS was 11.0 months with the 60 mg/day tablet arm and 13.9 months with the 140 mg/day capsules arm (HR 1.24 [CI 0.90–1.70]; $p = 0.19$). The study did not demonstrate NI of cabozantinib 60 mg/day tablet versus 140 mg/day capsules, as the upper CI [1.70] exceeded the NI margin of 1.58 (Fig. 3). Analyses of PFS as determined by investigator yielded similar results (Supplementary Fig. S1). Findings of prespecified subgroup analyses of PFS were generally consistent with the primary analysis (Supplementary Fig. S2).

As the primary efficacy end point was not met, summaries for ORR per BIRC are descriptive. The ORR was 33% in both the 60 and 140 mg/day arms, with 1 and 2 patients, respectively, having a confirmed complete response (Table 2). Of patients with ≥1 baseline and postbaseline assessment, 103/110 (94%) in the 60 mg/day arm and 107/113 (95%) in the 140 mg/day arm had a reduction in target lesions by BIRC (Supplementary Fig. S3). The median OS was 29.4 months in the 60 mg/day arm versus 33.0 months in the 140 mg/day arm (HR 1.12 [CI 0.77–1.63]; Fig. 4).

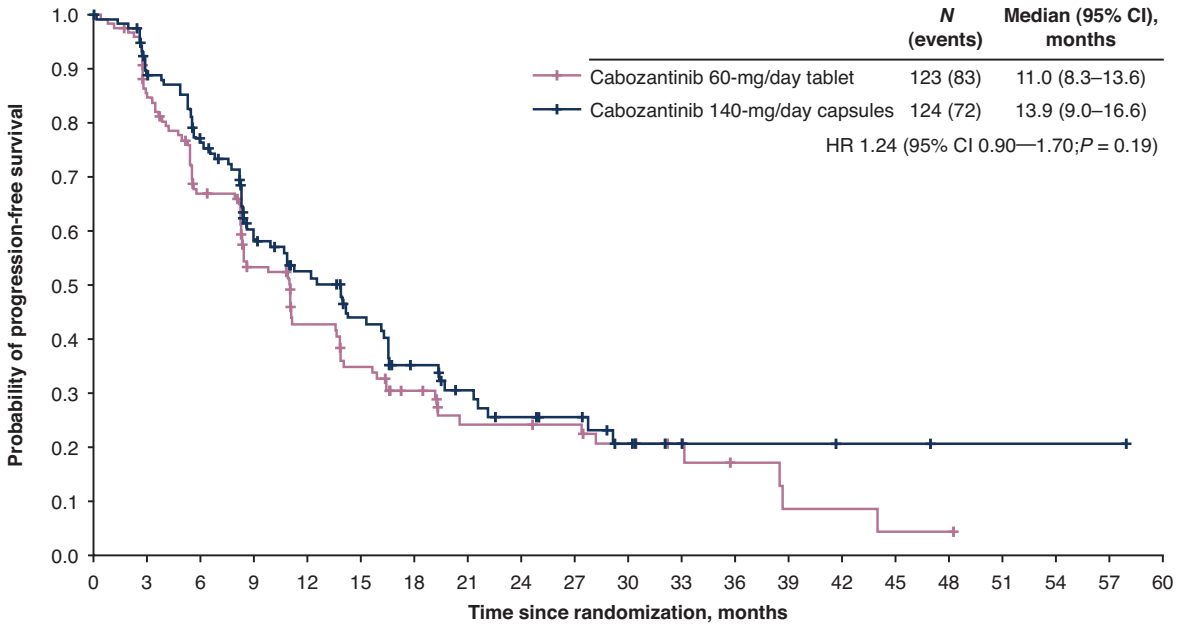

FIG. 3. Kaplan–Meier plot for progression-free survival per BIRC. BIRC, blinded independent radiology committee; CI, 95% confidence interval; HR, hazard ratio.

Table 2. Tumor Response Per Response Evaluation Criteria in Solid Tumors v1.1 by Blinded Independent Radiology Committee

	Cabozantinib, 60 mg/day tablet (n = *123*)	*Cabozantinib, 140 mg/day capsules* (n = *124*)
Objective response rate, % [CI]	33 [25.1–42.4]	33 [24.9–42.1]
Best overall response, *n* (%)		
Confirmed complete response	1 (0.8)	2 (1.6)
Confirmed partial response	40 (33)	39 (31)
Stable disease	58 (47)	64 (52)
Progressive disease	13 (11)	11 (8.9)
Missing	11 (8.9)	7 (5.6)
No measurable disease	0	1 (0.8)
Duration of response, median [CI], months	16.6 [8.4–24.9]	13.8 [13.4–NE]
Time to objective response, median (range), months	2.8 (2.6–13.7)	2.8 (1.7–27.9)

No measurable disease = baseline disease was not detected by BIRC.
BIRC, blinded independent radiology committee; CI, 95% confidence interval; NE, not estimable.

Safety and tolerability

The median duration of exposure was 11.1 months (range, 0.4–60.0 months) for the 60 mg/day arm and 10.1 months (range, 0.2–60.0 months) for the 140 mg/day arm (Table 3), and the median average daily dose of cabozantinib was 38.7 mg/day (range, 7.1–60.0 mg/day) and 73.4 mg/day (range, 25.0–140.0 mg/day), respectively. A lower percentage of patients in the 60 mg/day arm versus the 140 mg/day arm experienced dose holds (75% vs. 91%) and reductions (69% vs. 81%).

There was generally a lower frequency of AEs in the 60 mg/day arm. The most common AEs of any grade and causality with a >5% difference between treatment arms included diarrhea (67% for 60 mg vs. 73% for 140 mg), weight decrease (31% vs. 52%), hypertension (20% vs. 34%), and nausea (20% vs. 32%) (Table 4). Grade 3/4 AEs were experienced by 63% of patients in the 60 mg/day arm and 72% in the 140 mg/day arm (Supplementary Table S2). The most frequent Grade 3/4 AEs with a >5% difference between treatment arms included diarrhea (16% for 60 mg vs. 24% for 140 mg), decreased weight (5.7% vs. 13%), fatigue (12% vs. 6.5%), and increased alanine aminotransferase (1.6% vs. 7.3%). The most frequent AEs leading to dose reductions included diarrhea (20% for 60 mg vs. 26% for 140 mg), palmar–plantar erythrodysesthesia (15% vs. 21%), and decreased appetite (9.8% vs. 8.1%).

The 60 mg/day tablet arm was associated with a lower rate of treatment discontinuations due to AEs versus the 140 mg/day capsules arm (23% vs. 36%). The most frequent AEs leading to treatment discontinuation were diarrhea (2.4% for 60 mg vs. 4.0% for 140 mg), fatigue (1.6% vs. 4.0%), and palmar–plantar erythrodysesthesia (0% vs. 3.2%).

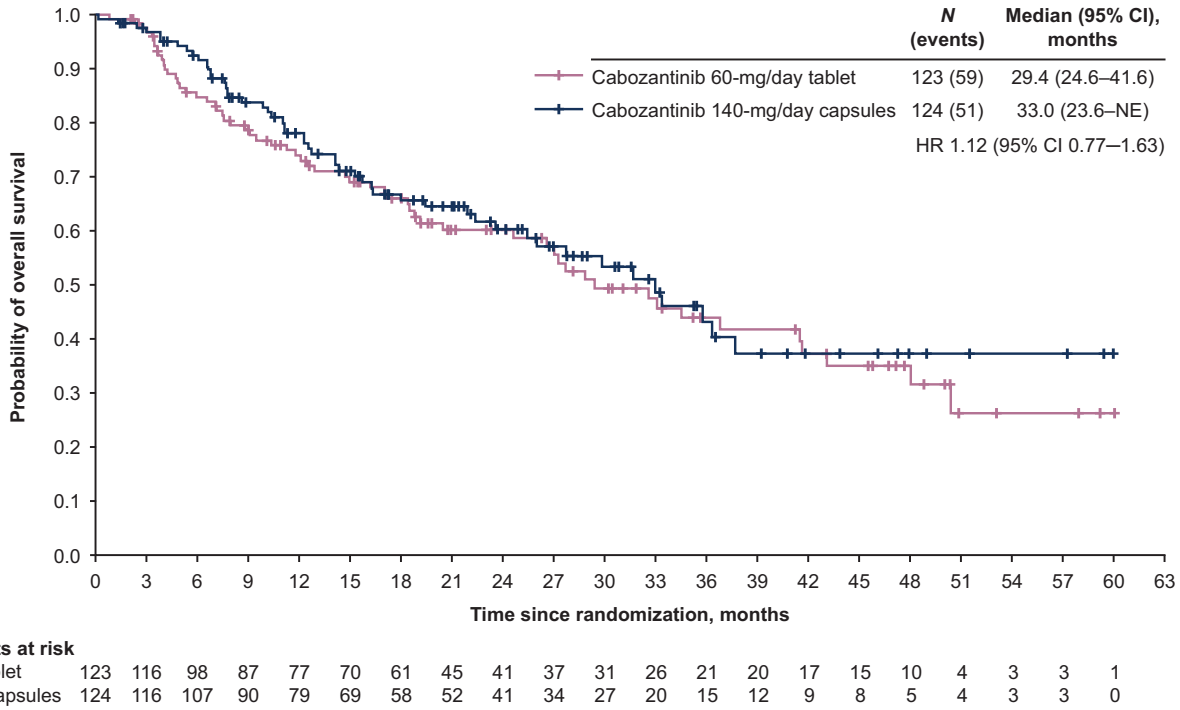

FIG. 4. Kaplan–Meier plot for OS. OS, overall survival; NE, not estimable.

Table 3. Treatment Exposure, and Dose Reduction and Holds Due to Adverse Events

	Cabozantinib, 60 mg/day tablet (n = *123*)	*Cabozantinib, 140 mg/day capsules* (n = *124*)
Exposure		
Duration of exposure (including dose holds), median (range), months	11.07 (0.4–60.0)	10.10 (0.2–60.0)
Percent dose intensity,[a] median (range)	64.52 (11.9–100.0)	52.44 (17.8–100.0)
Average daily dose, median (range), mg	38.71 (7.1–60.0)	73.42 (25.0–140.0)
Dose reductions due to AEs		
Patients with any dose reduction, *n* (%)	85 (69)	101 (81)
First-level dose reduction	82 (67)	91 (73)
Second-level dose reduction	46 (37)	65 (52)
Time to first-level dose (40/100 mg) reduction		
n	82	91
Median (range), days	59.0 (14–1375)	49.0 (13–316)
Time to second-level dose (20/60 mg) reduction		
n	46	65
Median (range), days	131.5 (14–960)	99.0 (28–729)
Dose holds due to AEs		
Patients with any dose hold, *n* (%)	92 (75)	113 (91)
No. of dose holds per patient		
n	92	113
Median (range)	3.00 (1.0–9.0)	3.00 (1.0–78.0)
Duration of total dose holds per patient		
n	92	113
Median (range), days	33.50 (1.0–195.0)	50.00 (1.0–554.0)
Duration of dose holds		
n	281	616
Median (range), days	11.0 (1.0–125.0)	11.0 (1.0–124.0)
Median (range) time to first dose hold, days	54.00 (2.0–1289.0)	29.00 (9.0–832.0)

[a]Percent dose intensity = 100 × average daily dose/starting dose.
AE, adverse event.

Incidence of serious AEs regardless of causality was 45% in the 60 mg/day arm and 50% in the 140 mg/day arm (Supplementary Table S2), with rates of 16% versus 23% for those considered treatment-related. ETMs of Grade ≥3 included hemorrhage (2.4% for 60 mg vs. 4.0% for 140 mg), proteinuria (3.3% vs. 2.4%), and abscess (3.3% vs. 2.4%) (Supplementary Table S3).

Grade 5 AEs were reported in 13 patients (11%) in the 60 mg/day arm and in 12 patients (10%) in the 140 mg/day arm. The most common Grade 5 AE was disease progression

Table 4. Adverse Events (Any Cause) by Preferred Term

	Cabozantinib, 60 mg/day tablet (n = *123*)			*Cabozantinib, 140 mg/day capsules* (n = *124*)		
	Any Grade, n *(%)*	*Grade 3,* n *(%)*	*Grade 4,* n *(%)*	*Any Grade,* n *(%)*	*Grade 3,* n *(%)*	*Grade 4,* n *(%)*
Patients with at least one event	122 (99)	62 (50)	15 (12)	124 (100)	76 (61)	13 (10)
Diarrhea	83 (67)	19 (15)	1 (0.8)	90 (73)	30 (24)	0
PPE	67 (54)	9 (7.3)	0	66 (53)	15 (12)	0
Weight decreased	38 (31)	7 (5.7)	0	65 (52)	16 (13)	0
Fatigue	43 (35)	15 (12)	0	48 (39)	8 (6.5)	0
Decreased appetite	44 (36)	6 (4.9)	0	46 (37)	5 (4.0)	0
Hypertension	25 (20)	9 (7.3)	0	42 (34)	13 (10)	0
Nausea	24 (20)	1 (0.8)	0	40 (32)	3 (2.4)	0
AST increased	35 (28)	1 (0.8)	0	38 (31)	7 (5.6)	0
Mucosal inflammation	24 (20)	3 (2.4)	0	38 (31)	2 (1.6)	0
Hypocalcemia	31 (25)	9 (7.3)	2 (1.6)	37 (30)	8 (6.5)	2 (1.6)
ALT increased	36 (29)	2 (1.6)	0	36 (29)	9 (7.3)	0
Asthenia	33 (27)	6 (4.9)	1 (0.8)	36 (29)	7 (5.6)	0
Vomiting	16 (13)	0	1 (0.8)	36 (29)	5 (4.0)	0
Stomatitis	21 (17)	1 (0.8)	0	31 (25)	7 (5.6)	0

Sorted by descending frequency of any grade in the cabozantinib 140 mg/day arm.
Any attribution, ≥25%.
ALT, alanine aminotransferase increased; AST, aspartate aminotransferase; PPE, palmar–plantar erythrodysesthesia.

in both arms (6 [4.9%] and 3 [2.4%], respectively). There were no treatment-related deaths in the 60 mg/day tablet arm, and 1 in the 140 mg/day capsules arm due to peritonitis, possibly related to gastrointestinal perforation.

Discussion

In the EXAMINER trial, the median PFS was similar between the 60 mg/day tablet arm and the 140 mg/day capsules arm (HR 1.24 [CI 0.90–1.70]), but the primary end point was not met; the upper CI [1.70] for HR exceeded the NI margin of 1.58. The ORR was 33% in both arms, and the median OS was 29.4 months versus 33.0 months (HR 1.12 [CI 0.77–1.63]). The efficacy data from the 140 mg/day capsules are comparable to the results with the cabozantinib 140 mg/day capsules in the EXAM trial. In the cabozantinib arm of EXAM, the median PFS was 11.2 months, the ORR was 28%, and the median OS was 26.6 months (8,9).

In EXAMINER, the mean cabozantinib plasma concentrations in the 60 mg/day tablet arm were generally lower than those in the 140 mg/day capsules arm, which corresponded to a lower median average daily dose (38.71 mg vs. 73.42 mg). There was a trend for cabozantinib plasma concentrations to decrease over time for patients in both treatment arms, which was more marked with the 140 mg/day capsules. The decrease in plasma concentrations were likely related to dose holds and reductions. The analysis of PK-censored data also suggests that patients with higher cabozantinib clearance (lower exposure) were more likely to remain on study at later time points, particularly in the 140 mg/day arm. The lack of NI could be attributed to the initial lower dose and lower average plasma concentration of cabozantinib with 60 mg/day tablet versus 140 mg/day capsules.

Duration of treatment was similar in both arms; however, fewer patients experienced Grade 3/4 AEs with the 60 mg/day tablet arm. These data indicate that the 60 mg/day tablet regimen may be more tolerable. Because of high interpatient variability in clearance, prompt dose modification is an important strategy to manage AEs and improve tolerability with cabozantinib. Exposure–response modeling has shown that patients with low cabozantinib clearance are at increased risk of higher dose exposure, dose modification, and treatment discontinuations due to AEs (11,12).

Although the study did not demonstrate NI between the 60 mg/day tablet and 140 mg/day capsules, the efficacy and safety data support further study of the 60 mg/day tablet as a treatment option in advanced MTC, particularly for patients at high risk of treatment-related AEs.

Conclusions

The primary end point of demonstrating PFS NI of the 60 mg/day tablet was not met in comparison with the 140 mg/day capsules in patients with progressive metastatic MTC. Safety in both arms was consistent with the known profile of cabozantinib, with the 140 mg/day capsules associated with a higher incidence of AEs and dose modifications.

Authors' Contributions

J.C., J.K., and B.J. contributed to the conceptualization of the study, patient accrual, data collection and interpretation, and drafting of the article. A.K., S.L., P.I., C.B., B.R., B.G.M.H., B.K., F.P., R.E., P.G., H.K.G., E.K., and L.L. contributed to patient accrual, data collection and interpretation, and reviewed and edited the article. M.M. conducted statistical analyses and contributed to the drafting of the article. L.F. contributed to the conceptualization of the study, data interpretation, project administration, and drafting of the article. All authors reviewed the article and approved submission.

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Data Sharing Statement

Individual patient data will not be made available.

Author Disclosure Statement

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Supplementary Material

Supplementary Data

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