

ORIGINAL ARTICLE

Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors

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ABSTRACT

BACKGROUND

Treatment options for patients with advanced neuroendocrine tumors are limited. The efficacy of cabozantinib in the treatment of previously treated, progressive extrapancreatic or pancreatic neuroendocrine tumors is unclear.

METHODS

We enrolled two independent cohorts of patients — those with extrapancreatic neuroendocrine tumors and those with pancreatic neuroendocrine tumors — who had received peptide receptor radionuclide therapy or targeted therapy or both. Patients were randomly assigned in a 2:1 ratio to receive cabozantinib at a dose of 60 mg daily or placebo. The primary end point was progression-free survival as assessed by blinded independent central review. Key secondary end points included objective response, overall survival, and safety.

RESULTS

In the cohort of 203 patients with extrapancreatic neuroendocrine tumors, the median progression-free survival with cabozantinib was 8.4 months, as compared with 3.9 months with placebo (stratified hazard ratio for progression or death, 0.38; 95% confidence interval [CI], 0.25 to 0.59; $P < 0.001$). In the cohort of 95 patients with pancreatic neuroendocrine tumors, the median progression-free survival with cabozantinib was 13.8 months, as compared with 4.4 months with placebo (stratified hazard ratio, 0.23; 95% CI, 0.12 to 0.42; $P < 0.001$). The incidence of confirmed objective response with cabozantinib was 5% and 19% among patients with extrapancreatic and pancreatic neuroendocrine tumors, respectively, as compared with 0% with placebo. Grade 3 or higher adverse events were noted in 62 to 65% of the patients treated with cabozantinib, as compared with 23 to 27% of the patients who received placebo. Common treatment-related adverse events of grade 3 or higher included hypertension, fatigue, diarrhea, and thromboembolic events.

CONCLUSIONS

Cabozantinib, as compared with placebo, significantly improved progression-free survival in patients with previously treated, progressive advanced extrapancreatic or pancreatic neuroendocrine tumors. Adverse events were consistent with the known safety profile of cabozantinib. (Funded by the National Cancer Institute and others; CABINET ClinicalTrials.gov number, NCT03375320.)

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NEUROENDOCRINE TUMORS ARE A HETEROGENEOUS group of neoplasms that arise most commonly in the gastrointestinal tract, lungs, and pancreas.¹ Treatment of advanced neuroendocrine tumors is guided by features including the primary tumor location, pathological differentiation and grade, presence of symptoms related to hormone secretion or extent of disease, and somatostatin-receptor expression. Depending on these factors, treatment options for extrapancreatic neuroendocrine tumors include somatostatin analogues, lutetium Lu-177 dotatate, or everolimus.²⁻⁶ For pancreatic neuroendocrine tumors, sunitinib or alkylating agent chemotherapy also can be considered.⁷⁻⁹ Most patients eventually have disease progression with available therapies.

Angiogenesis plays a key role in the pathogenesis of neuroendocrine tumors.^{10,11} Antiangiogenic agents targeting vascular endothelial growth factor (VEGF) and its receptors have shown activity in the treatment of neuroendocrine tumors. Cabozantinib is an oral small-molecule inhibitor of multiple tyrosine kinases including VEGF receptors, MET, AXL, and RET.¹² Clinical activity of cabozantinib was shown in a phase 2 trial involving patients with advanced extrapancreatic neuroendocrine tumors or pancreatic neuroendocrine tumors.¹³ On the basis of these results, we conducted the double-blind, randomized, controlled Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET) trial to evaluate the efficacy of cabozantinib in patients with previously treated, progressive extrapancreatic neuroendocrine tumors or pancreatic neuroendocrine tumors.

METHODS

PATIENTS

Patients 18 years of age or older with histologically confirmed, locally advanced or metastatic well- or moderately differentiated neuroendocrine tumors of extrapancreatic or pancreatic origin and World Health Organization tumor grades of 1 to 3 (a three-point scale, with 3 indicating tumors with higher proliferation indexes) were eligible. Patients with poorly differentiated neuroendocrine carcinoma and those with high-grade neuroendocrine carcinoma without specification of differentiation status were not eligible. Patients

were required to have progressive disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), in the 12 months before enrollment and an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a scale of 0 to 5, with higher numbers reflecting greater disability). Disease progression or an unacceptable side-effect profile leading to discontinuation of at least one Food and Drug Administration (FDA)-approved line of therapy, depending on primary tumor site, was required. Because of changes in the treatment landscape and approval of peptide receptor radionuclide therapy with Lu-177 dotatate, a protocol amendment in November 2020 expanded eligibility related to previous therapy to include Lu-177 dotatate or everolimus for patients with extrapancreatic neuroendocrine tumors (excluding lung neuroendocrine tumors), everolimus for lung neuroendocrine tumors, and Lu-177 dotatate, everolimus, or sunitinib for pancreatic neuroendocrine tumors (see the protocol, available with the full text of this article at NEJM.org). Before this amendment, the protocol specified previous therapy with everolimus for all patients. Continuation of treatment with somatostatin analogues was allowed if the dose had been stable for at least 2 months before enrollment.

TRIAL DESIGN AND OVERSIGHT

The CABINET trial was a multicenter, phase 3 trial designed and conducted by the Alliance for Clinical Trials in Oncology (the Alliance), a member of the National Clinical Trials Network sponsored by the National Cancer Institute (NCI). The trial began in July 2018 and enrolled patients with extrapancreatic neuroendocrine tumors or pancreatic neuroendocrine tumors in two independent cohorts. Within each cohort, patients were randomly assigned in a 2:1 ratio to receive cabozantinib or placebo. Randomization was stratified according to concurrent somatostatin analogue use and primary tumor site (midgut gastrointestinal and unknown primary vs. nonmidgut gastrointestinal, lung, or other sites) in the extrapancreatic neuroendocrine tumors cohort and according to concurrent somatostatin analogue use and previous sunitinib therapy in the pancreatic neuroendocrine tumors cohort. Patients received cabozantinib (at a dose of 60 mg) or placebo orally once daily. Interruptions in treatment and dose reductions for

cabozantinib (to 40 mg, then to 20 mg) and placebo were specified for the management of adverse events. Patients continued the blinded trial regimen until the occurrence of disease progression, unacceptable toxic effects, or withdrawal of consent. A protocol amendment activated in November 2020 permitted patients who were receiving placebo to cross over to open-label cabozantinib after real-time central confirmation of progressive disease.

The protocol was approved by the NCI central institutional review board. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. All the patients provided written informed consent before enrollment. The trial was regularly monitored by the Alliance data and safety monitoring board. Data were collected by the Alliance, reviewed by the trial chairperson (the first author), and analyzed by all the authors in collaboration with the Alliance Statistics and Data Management Center (of which some of the authors are members). The authors wrote the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

END POINTS AND ASSESSMENT

Progression-free survival has been recommended to be the primary end point for phase 3 trials evaluating new systemic therapies in neuroendocrine tumors.^{14,15} The primary end point in our trial was defined as the time from randomization to radiographic progressive disease, according to RECIST 1.1, as determined retrospectively by blinded independent central review, or death from any cause. Patients were evaluated every 12 weeks by means of radiographic imaging for tumor response and progression. If investigator assessments of progressive disease were confirmed in real time by central reviewers unaware of trial-group assignments, patients were made aware of their trial-group assignment; if progression was not confirmed, patients continued with their assigned protocol unaware of their assigned group. Key secondary end points included confirmed objective response, overall survival, and safety. A confirmed response was defined as two consecutive scans showing complete

or partial response, according to RECIST 1.1, as assessed by blinded independent central review. Overall survival was defined as the time from randomization to death from any cause. The severity of adverse events and the perceived attribution to cabozantinib or placebo were assessed by investigators using the NCI Common Terminology Criteria for Adverse Events, version 5.0. An optional correlative study assessed health-related quality of life before the start of the treatment period and every 12 weeks thereafter until progression or start of a new cancer treatment, primarily with the use of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and QLQ-GINET21 (see the Supplementary Appendix, available at NEJM.org, for details).^{16,17}

STATISTICAL ANALYSIS

The trial was designed with targeted sample sizes of 210 and 185 patients in the extrapancreatic neuroendocrine tumors and pancreatic neuroendocrine tumors cohorts, respectively, to provide the trial with 90% power to detect a true hazard ratio for disease progression or death of 0.583 in patients who received cabozantinib as compared with 0.568 in patients who received placebo, with the use of stratified one-sided log-rank tests (overall significance level, 0.025, corresponding to a two-sided significance level of 0.05). This statistical design required a total of 164 progression events in the extrapancreatic neuroendocrine tumors cohort and 149 progression events in the pancreatic neuroendocrine tumors cohort. Two interim analyses for futility were included in each cohort after 33% and 66% of the projected numbers of progression events had occurred. Alpha spending of 0.001 for efficacy was included in each interim analysis (corresponding to 0.002 in a two-sided analysis). Although the protocol design and statistical analysis plan were based on one-sided tests for the primary end point, two-sided P values are reported here.

In May 2023, the Alliance independent data and safety monitoring board recommended that the protocol-specified interim analyses of progression-free survival be performed with the use of local assessments owing to a lag in batched assessments of tumors by blinded independent central review and the double-blinded nature of the trial. On the basis of interim analyses that showed superior efficacy with cabozantinib (Ta-

ble S1 in the Supplementary Appendix), the data and safety monitoring board recommended early termination of the trial. Unblinding of trial-group assignments and crossover of patients in the placebo group to receive cabozantinib treatment occurred on August 24, 2023, which was used as the data-cutoff date for the final analyses of the trial end points. A prespecified analysis of overall survival was conducted on the basis of the significance of the primary analysis of progression-free survival, in which hazard ratios for death and corresponding 95% confidence intervals in the trial groups were calculated and reported.

Efficacy analyses were conducted according to the intention-to-treat principle. Hazard ratios were estimated with stratified Cox regression models and stratified log-rank tests calculated with the use of stratification factors at randomization as prespecified. The median progression-free survival and corresponding 95% confidence intervals for each trial group were estimated with the use of Kaplan–Meier methods. Subgroup analyses were performed with the use of Cox models that included trial-group assignment, key demographic factors, and their interaction. Responses were calculated as the number of patients with confirmed response divided by the total number of patients in that group with corresponding 95% exact binomial confidence intervals. Descriptive means and 95% confidence intervals were computed in each group per time point for the health-related quality of life summary score (protocol-specified main correlative end point), which was a combination of function and symptom scores.¹⁸ Full statistical analysis of the data pertaining to health-related quality of life is under way.

RESULTS

PATIENTS

Between October 2018 and August 2023, a total of 203 patients were randomly assigned to the extrapancreatic neuroendocrine tumors cohort and 95 patients were assigned to the pancreatic neuroendocrine tumors cohort at 62 sites in the United States (Table 1 and Table S2A and S2B). The demographic characteristics of the patients are representative and generalizable to patients with neuroendocrine tumors in the United States and elsewhere (Table S3). The intention-to-treat cohorts included 7 patients with pancreatic neuro-

endocrine tumors who were mistakenly assigned to the extrapancreatic neuroendocrine tumors cohort and 3 patients with extrapancreatic neuroendocrine tumors who were mistakenly assigned to the pancreatic neuroendocrine tumors cohort by the registering site. The cabozantinib and placebo groups were balanced with regard to demographic and disease characteristics at baseline in both cohorts, except more patients who were assigned to receive cabozantinib in the extrapancreatic neuroendocrine tumors cohort had tumors of unknown primary site than did patients in that cohort who were assigned to receive placebo. In the extrapancreatic neuroendocrine tumors cohort, patients in both the cabozantinib and the placebo groups had received a median of two previous lines of therapy not including somatostatin analogues; the majority had received Lu-177 dotatate and everolimus. In the pancreatic neuroendocrine tumors cohort, patients in the cabozantinib and placebo groups had a median of three and two previous lines of therapy, respectively; most patients had received Lu-177 dotatate, everolimus, and temozolomide-based therapy.

As of the data-cutoff date, of the patients assigned to receive cabozantinib, 21 (16%) in the extrapancreatic neuroendocrine tumors cohort and 14 (22%) in the pancreatic neuroendocrine tumors cohort were still receiving treatment with cabozantinib. Of the patients assigned to receive placebo, 7 (10%) in the extrapancreatic neuroendocrine tumors cohort and 2 (6%) in the pancreatic neuroendocrine tumors cohort were still receiving placebo as of the data-cutoff date. The most common reason for discontinuing the regimen in both the cabozantinib and placebo groups of the two cohorts was disease progression (Fig. S1A and S1B).

EFFICACY

Extrapancreatic Neuroendocrine Tumors Cohort

Among the 203 patients in the extrapancreatic neuroendocrine tumors cohort, 111 progression events as assessed by blinded independent central review were reported, with a median follow-up of 10.2 months (95% confidence interval [CI], 8.2 to 13.8). At the data-cutoff date, 71 patients (53%) in the cabozantinib group and 40 patients (58%) in the placebo group had disease progression or had died. Cabozantinib was associated with a 62% lower risk of disease progression or

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Extrapancreatic NET Cohort		Pancreatic NET Cohort	
	Cabozantinib (N=134)	Placebo (N=69)	Cabozantinib (N=64)	Placebo (N=31)
Median age (range) — yr	66 (28–86)	66 (30–82)	60 (29–79)	64 (39–79)
Female sex — no. (%)	74 (55)	31 (45)	27 (42)	13 (42)
ECOG performance-status score — no. (%)†				
0	49 (37)	32 (46)	35 (55)	15 (48)
1	84 (63)	36 (52)	28 (44)	16 (52)
Primary tumor site — no. (%)‡				
Gastrointestinal	70 (52)	46 (67)	2 (3)	1 (3)
Lung	27 (20)	12 (17)	NA	NA
Thymus	6 (4)	4 (6)	NA	NA
Pancreas	4 (3)	3 (4)	62 (97)	30 (97)
Other	5 (4)	2 (3)	NA	NA
Unknown	22 (16)	2 (3)	NA	NA
Tumor grade — no. (%)				
Grade 1	37 (28)	15 (22)	14 (22)	7 (22)
Grade 2	86 (64)	48 (70)	39 (61)	19 (61)
Grade 3	8 (6)	5 (7)	8 (12)	3 (10)
Unknown	3 (2)	1 (1)	3 (5)	2 (6)
Hormone syndrome present: functional tumor — no. (%)	41 (31)	25 (36)	11 (17)	5 (16)
Concurrent somatostatin analogue — no. (%)	92 (69)	48 (70)	35 (55)	17 (55)
Median no. (range) of previous systemic therapies not including somatostatin analogue A	2 (1–6)	2 (1–6)	3 (1–9)	2 (1–7)
Previous systemic therapy — no. (%)				
Somatostatin analogue	125 (93)	64 (93)	63 (98)	30 (97)
Lu-177 dotatate	80 (60)	41 (59)	38 (59)	18 (58)
Everolimus	96 (72)	44 (64)	51 (80)	25 (81)
Temozolomide with or without capecitabine	43 (32)	20 (29)	43 (67)	16 (52)
Cisplatin or carboplatin plus etoposide	11 (8)	8 (12)	NA	NA
Sunitinib	NA	NA	18 (28)	7 (22)

* Percentages may not total 100 because of rounding. NA denotes not applicable, and NET neuroendocrine tumors.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

‡ The intention-to-treat population in the extrapancreatic neuroendocrine tumors cohort included seven patients with pancreatic neuroendocrine tumors (four in the cabozantinib group and three in the placebo group) who were misallocated to the extrapancreatic neuroendocrine tumors cohort by the registering site. The intention-to-treat population in the pancreatic neuroendocrine tumors cohort included three patients with extrapancreatic neuroendocrine tumors (two in the cabozantinib group and one in the placebo group) who were misallocated to the pancreatic neuroendocrine tumors cohort by the registering site.

death, on average, than placebo (stratified hazard ratio, 0.38; 95% CI, 0.25 to 0.59; $P<0.001$) (Fig. 1A). The median progression-free survival was 8.4 months (95% CI, 7.6 to 12.7) with cabozantinib and 3.9 months (95% CI, 3.0 to 5.7)

with placebo. Subgroup analyses defined according to stratification factors and key factors — including primary tumor site, grade, and previous treatment — are shown in Figure 1C. Results from sensitivity analyses, including progression-

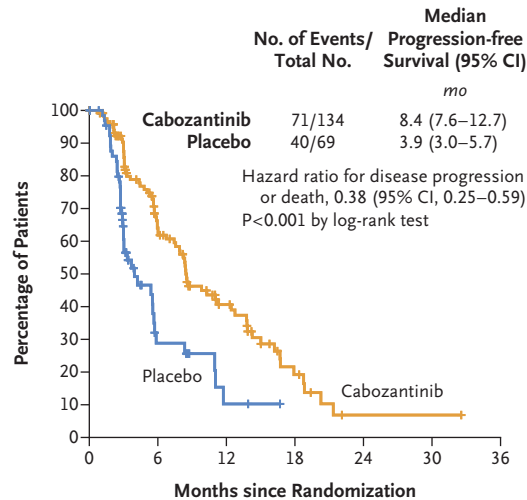
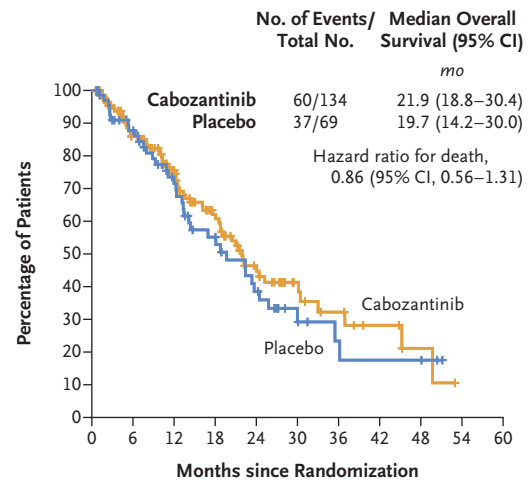
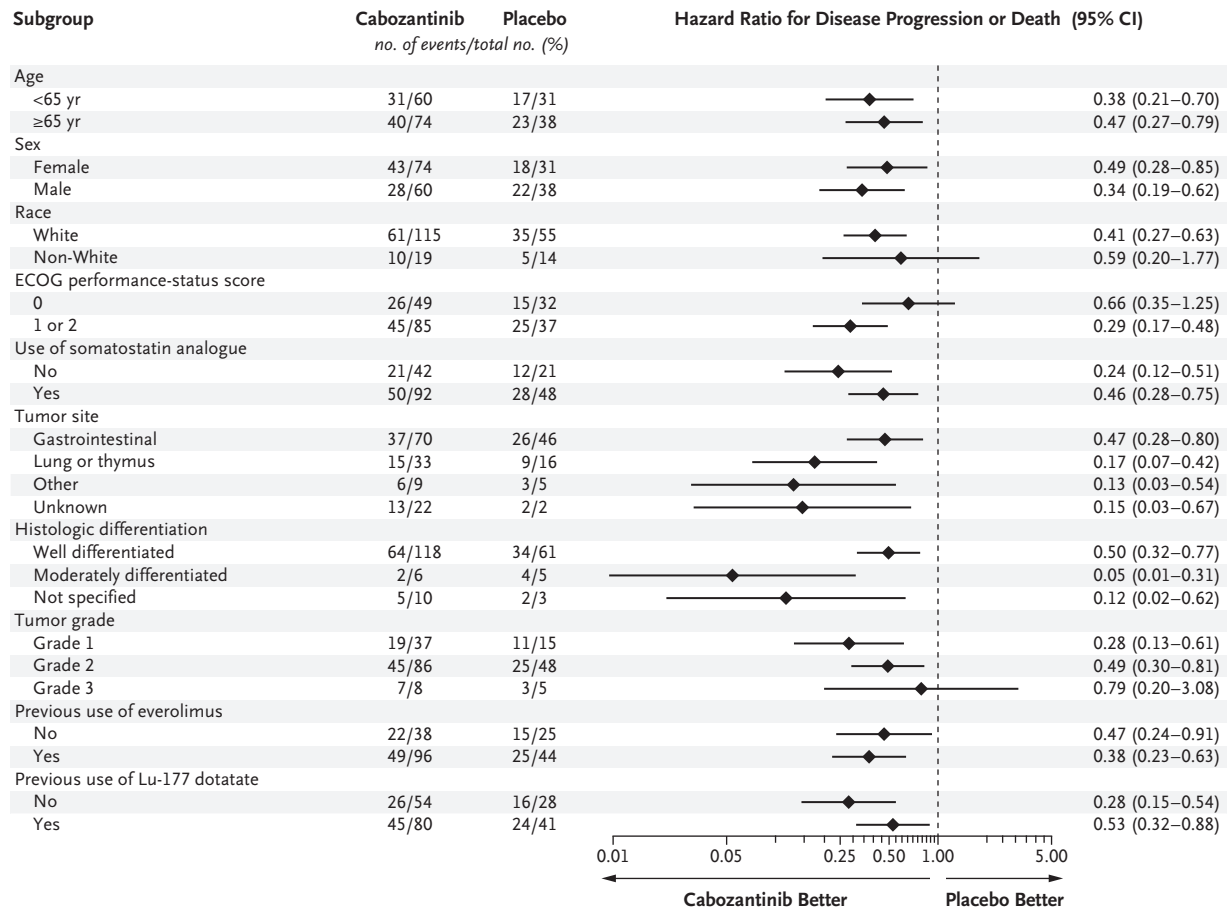
A Progression-free Survival in the Extrapancreatic NET Cohort**B Overall Survival in the Extrapancreatic NET Cohort****C Subgroup Analysis of Progression-free Survival in the Extrapancreatic NET Cohort**

Figure 1 (facing page). Progression-free Survival and Overall Survival in the Extrapancreatic Neuroendocrine Tumors Cohort.

Panel A shows progression-free survival, as assessed retrospectively by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (two-sided stratified log-rank $P < 0.001$ for the comparison between the cabozantinib and placebo groups), among patients in the extrapancreatic neuroendocrine tumors cohort, and Panel B shows overall survival. Panel C shows progression-free survival according to stratification factors and selected clinical subgroups of patients in the extrapancreatic neuroendocrine tumors cohort. For the subgroup analysis of tumor grade, the “unknown” subgroup is not shown, owing to there having been no progression events in either the cabozantinib group or the placebo group. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers reflecting greater disability.

free survival as assessed by investigators and analyses accounting for misallocation of patients into the incorrect disease cohort, were consistent with results from the primary analysis (Figs. S2A and S3A).

Partial responses were observed in 5% of patients in the cabozantinib group (95% CI, 2 to 10), as compared with 0% (95% CI, 0 to 5) in the placebo group ($P = 0.05$). A best response of stable disease occurred in 65% of patients receiving cabozantinib and in 54% of those receiving placebo, and a best response of progressive disease occurred in 11% of patients receiving cabozantinib and in 35% of those receiving placebo (Table 2). Any reduction in target lesions was observed in 67% and 29% of the patients in the

cabozantinib and placebo groups, respectively (Fig. S4A).

The median follow-up time for survival was 24.2 months, with 60 deaths (45%) in the cabozantinib group and 37 deaths (54%) in the placebo group. The median overall survival was 21.9 months with cabozantinib and 19.7 months with placebo (hazard ratio, 0.86; 95% CI, 0.56 to 1.31) (Fig. 1B). Subsequent anticancer therapy was received by 45% of the patients in the cabozantinib group and 67% of the patients in the placebo group, including 20 patients (33%) who crossed over to open-label cabozantinib (Table S4). Overall health-related quality of life remained stable over time and was similar in the two groups among patients who completed questionnaires (Fig. S5A).

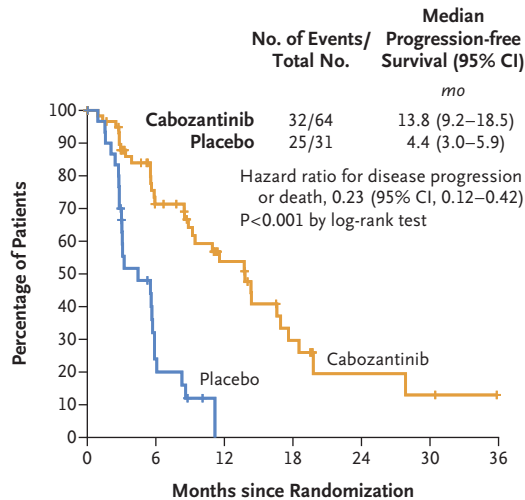
Pancreatic Neuroendocrine Tumors Cohort

Among the 95 patients in the pancreatic neuroendocrine tumors cohort, 57 progression events as assessed by blinded independent central review were reported, with a median follow-up of 13.8 months (95% CI, 10.1 to 19.7). At the data-cutoff date, 32 patients (50%) in the cabozantinib group and 25 patients (81%) in the placebo group had disease progression or had died. Cabozantinib was associated with a 77% lower risk of disease progression or death, on average, than placebo (stratified hazard ratio, 0.23; 95% CI, 0.12 to 0.42; $P < 0.001$) (Fig. 2A). The median progression-free survival was 13.8 months (95% CI, 9.2 to 18.5) with cabozantinib and 4.4 months (95% CI, 3.0 to 5.9) with placebo. Subgroup analyses are shown in Figure 2C. Sensitivity analyses, including progression-free survival as assessed by investigators

Table 2. Objective Tumor Response.*

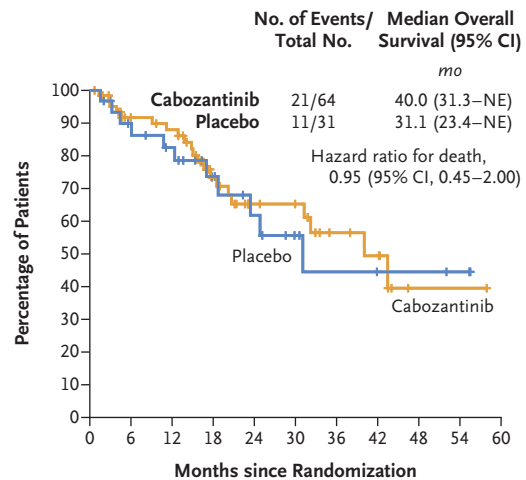
Response	Extrapancreatic NET Cohort		Pancreatic NET Cohort	
	Cabozantinib (N = 134)	Placebo (N = 69)	Cabozantinib (N = 64)	Placebo (N = 31)
Objective response — % (95% CI)	5 (2 to 10)	0 (0 to 5)	19 (10 to 30)	0 (0 to 11)
Best overall response — no. (%)				
Partial response	7 (5)	0	12 (19)	0
Stable disease	87 (65)	37 (54)	39 (61)	17 (55)
Progressive disease	15 (11)	24 (35)	5 (8)	12 (39)
Not evaluable	25 (19)	8 (12)	8 (12)	2 (6)

* Objective response was defined as the percentage of patients who had a confirmed complete or partial response as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors, version 1.1. All responses were partial responses. Percentages may not total 100 because of rounding.

A Progression-free Survival in the Pancreatic NET Cohort

No. at Risk (no. with censored data)

Cabozantinib	64 (0)	33 (16)	18 (24)	8 (27)	3 (30)	2 (30)	0 (32)
Placebo	31 (0)	6 (4)	0 (6)				

B Overall Survival in the Pancreatic NET Cohort

No. at Risk (no. with censored data)

Cabozantinib	64 (0)	47 (10)	18 (29)	9 (36)	1 (42)	0 (43)
Placebo	31 (0)	21 (5)	10 (12)	4 (16)	3 (17)	0 (20)

C Subgroup Analysis for Progression-free Survival in the Pancreatic NET Cohort

Subgroup	Cabozantinib no. of events/total no. (%)	Placebo no. of events/total no. (%)	Hazard Ratio for Disease Progression or Death (95% CI)
Age			
<65 yr	20/40	13/16	0.25 (0.12–0.53)
≥65 yr	12/24	12/15	0.19 (0.08–0.46)
Sex			
Female	15/27	10/13	0.19 (0.08–0.44)
Male	17/37	15/18	0.23 (0.11–0.51)
Race			
White	25/54	19/25	0.19 (0.10–0.37)
Non-White	7/10	6/6	0.59 (0.19–1.86)
ECOG performance-status score			
0	18/35	13/15	0.20 (0.09–0.43)
1 or 2	14/29	12/16	0.27 (0.11–0.61)
Use of somatostatin analogue			
No	13/29	13/14	0.17 (0.07–0.39)
Yes	19/35	12/17	0.28 (0.13–0.62)
Previous use of sunitinib			
No	21/47	17/22	0.20 (0.10–0.41)
Yes	11/17	8/9	0.27 (0.10–0.71)
Tumor grade			
Grade 1	9/14	5/7	0.19 (0.06–0.60)
Grade 2	18/39	16/19	0.21 (0.10–0.45)
Grade 3	4/8	3/3	0.02 (0.00–0.11)
Unknown	1/3	1/2	0.46 (0.03–7.77)
Previous use of everolimus			
No	6/13	5/6	0.52 (0.16–1.74)
Yes	26/51	20/25	0.18 (0.09–0.36)
Previous use of Lu-177 dotatate			
No	12/26	10/13	0.15 (0.06–0.37)
Yes	20/38	15/18	0.29 (0.14–0.60)

0.01 0.05 0.25 0.50 1.00 5.00

Cabozantinib Better Placebo Better

Figure 2 (facing page). Progression-free Survival and Overall Survival in the Pancreatic Neuroendocrine Tumors Cohort.

Panel A shows progression-free survival, as assessed retrospectively by blinded independent central review according to RECIST 1.1 (two-sided stratified log-rank $P < 0.001$ for the comparison between the cabozantinib and placebo groups), among patients in the pancreatic neuroendocrine tumors cohort, and Panel B shows overall survival. Panel C shows progression-free survival according to stratification factors and selected clinical subgroups of patients in the pancreatic neuroendocrine tumors cohort. The subgroup analysis of histologic differentiations is not shown because there were no progression events in either the cabozantinib group or the placebo group in the “moderately differentiated” and the “not specified” subgroups.

and analyses accounting for misallocation of patients into the incorrect disease cohort, were consistent with the primary progression-free survival analysis (Figs. S2B and S3B).

Partial responses were observed in 19% of patients in the cabozantinib group (95% CI, 10 to 30), as compared with 0% (95% CI, 0 to 11) in the placebo group. A best response of stable disease occurred in 61% of patients receiving cabozantinib and in 55% of those receiving placebo, and a best response of progressive disease occurred in 8% of patients receiving cabozantinib and in 39% of those receiving placebo (Table 2). Any reduction in target lesions was observed in 80% and 24% of the patients in the cabozantinib and placebo groups, respectively (Fig. S4B).

The median survival follow-up was 23.1 months, with 21 deaths (33%) reported in the cabozantinib group and 11 deaths (35%) reported in the placebo group. The median overall survival was 40.0 months with cabozantinib and 31.1 months with placebo (hazard ratio for death, 0.95; 95% CI, 0.45 to 2.00) (Fig. 2B). Subsequent anticancer therapy was received by 51% of patients in the cabozantinib group and 62% of patients in the placebo group, including 12 patients (41%) who crossed over to open-label cabozantinib (Table S5). As in the extrapancreatic neuroendocrine tumors cohort, overall health-related quality of life remained stable over time and was similar in the two groups in this cohort (Fig. S5B).

EXPOSURE AND SAFETY

Extrapancreatic Neuroendocrine Tumors Cohort

The safety population in the extrapancreatic neuroendocrine tumors cohort consisted of 132 patients who were treated with cabozantinib and 67 who received placebo; the median duration of treatment with cabozantinib was 5.5 months (range, 0.2 to 32.4) and the median duration of placebo exposure was 2.8 months (range, 0.6 to 21.4). Dose reductions occurred in 66% of patients with cabozantinib and 10% with placebo. The median average daily dose was 38.4 mg of cabozantinib and 59.0 mg of placebo. The percentage of patients who stopped taking cabozantinib or placebo owing to adverse events was 31% (34 patients) in the cabozantinib group and 15% (9 patients) in the placebo group.

The incidence of adverse events (of any grade) attributed to cabozantinib was 98% and to placebo was 82%, with an incidence of grade 3 or higher treatment-related adverse events of 62% with cabozantinib and 27% with placebo (Table 3). The most common treatment-related grade 3 or 4 adverse events with cabozantinib were hypertension (in 21% of the patients), fatigue (in 13%), and diarrhea (in 11%). Grade 5 events, primarily attributed to underlying disease, occurred in nine patients (7%) in the cabozantinib group and four patients (6%) in the placebo group. Four patients in the cabozantinib group had a grade 5 event that was deemed to be at least possibly related to treatment — gastric hemorrhage in one patient, cardiac arrest in one patient, and cause of death not specified in two patients.

Pancreatic Neuroendocrine Tumors Cohort

The safety population in the pancreatic neuroendocrine tumors cohort consisted of 63 patients who were treated with cabozantinib and 31 who received placebo; the median duration of treatment with cabozantinib was 8.3 months (range, 0.5 to 39.6) and the median duration of placebo exposure was 2.9 months (range, 0.5 to 11.2). Dose reductions occurred in 68% of patients with cabozantinib and 19% with placebo. The median average daily dose was 37.9 mg of cabozantinib and 56.9 mg of placebo. The percentage of patients who stopped taking cabozantinib or

Table 3. Treatment-Related Adverse Events.*

Adverse Event	Extrapancreatic NET Cohort				Pancreatic NET Cohort			
	Cabozantinib (N=132)		Placebo (N=67)		Cabozantinib (N=63)		Placebo (N=31)	
	Any Grade	Grades 3–5†	Any Grade	Grades 3–5	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any event at least possibly related to treatment	130 (98)	82 (62)	55 (82)	18 (27)	62 (98)	41 (65)	26 (84)	7 (23)
Common treatment-related event‡								
Fatigue	82 (62)	17 (13)	28 (42)	5 (7)	47 (75)	7 (11)	10 (32)	1 (3)
Diarrhea	74 (56)	14 (11)	20 (30)	3 (4)	37 (59)	4 (6)	4 (13)	0
AST increase	86 (65)	4 (3)	12 (18)	0	40 (63)	1 (2)	9 (29)	0
ALT increase	77 (58)	1 (1)	9 (13)	0	39 (62)	1 (2)	9 (29)	0
Hypertension	70 (53)	28 (21)	13 (19)	2 (3)	36 (57)	14 (22)	7 (23)	3 (10)
Thrombocytopenia	62 (47)	1 (1)	5 (7)	1 (1)	21 (33)	0	3 (10)	0
Nausea	46 (35)	2 (2)	10 (15)	0	24 (38)	5 (8)	7 (23)	1 (3)
Oral mucositis	48 (36)	5 (4)	6 (9)	0	30 (48)	5 (8)	1 (3)	0
Palmar–plantar erythrodysesthesia	48 (36)	4 (3)	5 (7)	0	28 (44)	6 (10)	4 (13)	0
Anorexia	40 (30)	2 (2)	6 (9)	0	13 (21)	1 (2)	3 (10)	0
Dysgeusia	45 (34)	0	1 (1)	0	19 (30)	0	3 (10)	0
Neutropenia	40 (30)	4 (3)	2 (3)	0	17 (27)	1 (2)	2 (6)	0
Alkaline phosphatase increase	—	—	—	—	13 (21)	0	3 (10)	0
Vomiting	—	—	—	—	13 (21)	4 (6)	3 (10)	0
Hypophosphatemia	—	—	—	—	13 (21)	0	2 (6)	0
Thromboembolic event	—	—	—	—	11 (17)	7 (11)	0	0
Leukopenia	46 (35)	4 (3)	2 (3)	0	—	—	—	—
Anemia	28 (21)	2 (2)	8 (12)	0	—	—	—	—
Lymphopenia	31 (23)	5 (4)	6 (9)	0	—	—	—	—
Hypothyroidism	36 (27)	0	1 (1)	0	—	—	—	—
Maculopapular rash	30 (23)	0	2 (3)	0	—	—	—	—
Weight loss	28 (21)	3 (2)	2 (3)	0	—	—	—	—

* The safety population included all patients who underwent randomization and received at least one dose of cabozantinib or placebo. The presence or absence of the following adverse events was solicited for each treatment cycle: neutropenia, thrombocytopenia, alanine or aspartate aminotransferase increase, palmar–plantar erythrodysesthesia syndrome, maculopapular rash, hyperglycemia, hypothyroidism, hypertension, fatigue, diarrhea, and oral mucositis. ALT denotes alanine aminotransferase and AST aspartate aminotransferase.

† Grade 5 events in the cabozantinib group were possibly related to treatment (gastrointestinal hemorrhage in one patient, cardiac arrest in one patient, and death not otherwise specified in two patients).

‡ Shown are all adverse events that were considered by the investigators to be at least possibly related to cabozantinib or placebo that were reported in 20% or more of the patients in the cabozantinib group across all grades, or common grade 3 or higher treatment-related adverse events that were reported in 10% or more of the patients in the cabozantinib group.

placebo owing to adverse events was 20% (10 patients) in the cabozantinib group and 0% in the placebo group.

The incidence of adverse events (any grade) attributed to cabozantinib was 98% and to placebo was 84%, with an incidence of grade 3 or 4 treatment-related adverse events of 65% with cabozantinib and 23% with placebo (Table 3). The most common treatment-related grade 3 or 4 adverse events with cabozantinib were hypertension (in 22% of the patients), fatigue (in 11%), and thromboembolic events (in 11%). No grade 5 events were noted in the pancreatic neuroendocrine tumors cohort.

DISCUSSION

Cabozantinib significantly improved progression-free survival as compared with placebo in patients with previously treated, progressive extrapancreatic neuroendocrine tumors or pancreatic neuroendocrine tumors. No overall survival difference between the trial groups has been observed to date; however, overall survival data were not mature at the time of the analyses and may have been affected by crossover and by the high rate of treatment with subsequent anticancer therapies. Adverse events observed in this trial were consistent with the known safety profile of cabozantinib and consistent with those observed with cabozantinib as a single agent in other diseases.¹⁹⁻²¹ A majority of patients treated with cabozantinib had dose modifications or reductions to manage adverse events.

The treatment landscape in neuroendocrine tumors has evolved over the last 15 years with the addition of molecularly targeted agents, Lu-177 dotatate for patients with gastrointestinal neuroendocrine tumors and pancreatic neuroendocrine tumors, and alkylating agent chemotherapy with temozolomide-based regimens for patients with pancreatic neuroendocrine tumors. The use of these agents in clinical practice can be extended to neuroendocrine tumors arising in other locations. Because disease ultimately will progress during or after treatment with these agents, additional therapies are needed. The CABINET trial was a randomized trial designed to evaluate the efficacy of therapy after treatment with FDA-approved therapies such as Lu-177 dotatate or targeted therapy (or both). The results support the use of cabozantinib as a new treatment op-

tion for patients with advanced extrapancreatic neuroendocrine tumors or pancreatic neuroendocrine tumors whose disease has progressed after at least one other line of therapy, not including somatostatin analogues, or in whom unacceptable side effects have developed after such therapy. The choice of therapy should be individualized and based on the characteristics of the patient and the tumor. Future clinical trials evaluating the appropriate sequencing of therapy are needed.

Although our results show significant efficacy of cabozantinib, our trial has several limitations. The early termination of the trial on the basis of interim analysis results could potentially lead to overestimation of the treatment effect. However, results for both cohorts represent relatively mature analyses of progression-free survival. In the extrapancreatic neuroendocrine tumors cohort, 111 of the planned 164 events had been observed, and in the pancreatic neuroendocrine tumors cohort, 57 of the 95 enrolled patients had a progression event as assessed by blinded independent central review. In addition, placebo rather than an active comparator was used. Notably, placebo was selected because the efficacy of therapy for patients with advanced neuroendocrine tumors whose disease has progressed after treatment with Lu-177 dotatate or targeted agents (or both) has not been well established. Although everolimus, sunitinib, and Lu-177 dotatate are approved agents, the phase 3 trials evaluating these agents primarily involved patients who had not yet received molecularly targeted therapy or peptide receptor radionuclide therapy. Furthermore, placebo was chosen as a control because patients could have received all available therapies before enrollment in the trial.

Antiangiogenic agents and tyrosine kinase inhibitors targeting the VEGF receptor have established efficacy in the treatment of neuroendocrine tumors, and sunitinib is approved for treatment of pancreatic neuroendocrine tumors on the basis of the results of a phase 3 trial.⁷ Other VEGF receptor–targeting tyrosine kinase inhibitors, including axitinib, lenvatinib, pazopanib, and surufatinib, have been evaluated in the treatment of patients with extrapancreatic neuroendocrine tumors and with pancreatic neuroendocrine tumors but are not approved for use in the United States or Europe.²²⁻²⁶ The anti-VEGF monoclonal antibody bevacizumab has also been evaluated in randomized trials involving patients with neuro-

endocrine tumors.^{27,28} The antitumor activity of cabozantinib may be related to its receptor targets, including MET. Previous studies have shown that MET activation can stimulate growth of neuroendocrine tumors and contribute to increased tumor invasion and metastasis that can be overcome by combining anti-VEGF therapy with a MET inhibitor or treatment with cabozantinib.^{12,29,30} Inhibition of MET and AXL also can impede resistance to VEGF inhibition and may contribute to superior efficacy with cabozantinib as compared with sunitinib in patients with renal-cell carcinoma.^{21,31}

In this trial, cabozantinib, as compared with placebo, resulted in longer progression-free survival in patients with extrapancreatic neuroendocrine tumors or pancreatic neuroendocrine tumors that had progressed after previous therapy with Lu-177 dotatate or targeted agents, including everolimus or sunitinib. Adverse events, which were managed with dose reduction in a majority

of the patients, were consistent with the known safety profile of cabozantinib.

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APPENDIX

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