ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

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ABSTRACT

BACKGROUND

Cabozantinib is an oral, small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) as well as MET and AXL, each of which has been implicated in the pathobiology of metastatic renal-cell carcinoma or in the development of resistance to antiangiogenic drugs. This randomized, open-label, phase 3 trial evaluated the efficacy of cabozantinib, as compared with everolimus, in patients with renal-cell carcinoma that had progressed after VEGFR-targeted therapy.

METHODS

We randomly assigned 658 patients to receive cabozantinib at a dose of 60 mg daily or everolimus at a dose of 10 mg daily. The primary end point was progression-free survival. Secondary efficacy end points were overall survival and objective response rate.

RESULTS

Median progression-free survival was 7.4 months with cabozantinib and 3.8 months with everolimus. The rate of progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio, 0.58; 95% confidence interval [CI] 0.45 to 0.75; P<0.001). The objective response rate was 21% with cabozantinib and 5% with everolimus (P<0.001). A planned interim analysis showed that overall survival was longer with cabozantinib than with everolimus (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P=0.005) but did not cross the significance boundary for the interim analysis. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib and in 25% of those who received everolimus. Discontinuation of study treatment owing to adverse events occurred in 9% of the patients who received cabozantinib and in 10% of those who received everolimus.

CONCLUSIONS

Progression-free survival was longer with cabozantinib than with everolimus among patients with renal-cell carcinoma that had progressed after VEGFR-targeted therapy. (Funded by Exelixis; METEOR ClinicalTrials.gov number, NCT01865747.)

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*A complete list of investigators in the Metastatic RCC Phase 3 Study Evaluating Cabozantinib versus Everolimus (METEOR) is provided in the Supplementary Appendix, available at NEJM.org.

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Renal-cell carcinoma is the most common form of kidney cancer, with more than 330,000 cases diagnosed and more than 140,000 deaths attributed to it worldwide every year.[1] Approximately one third of patients present with metastatic disease at diagnosis,[2] and in about one third of treated patients with localized disease, the disease will relapse.[3-5]

Inactivation of the von Hippel–Lindau (VHL) tumor-suppressor protein characterizes clear-cell tumors, the predominant histologic subtype in patients with renal-cell carcinoma, and results in the up-regulation of vascular endothelial growth factor (VEGF) production.[6,7] Antiangiogenic drugs that target VEGF (bevacizumab) and its receptors (sunitinib, sorafenib, pazopanib, and axitinib) are standard treatments, owing to improved progression-free survival in randomized, phase 3 trials as compared with interferon alfa, placebo, or other targeted drugs.[8-12] Sunitinib, pazopanib, and bevacizumab (with interferon alfa) were investigated in the first-line setting, and sorafenib and axitinib were investigated after progression with a first-line treatment.

Resistance develops in nearly all patients treated with one or more of these drugs, as evidenced by disease progression. The median progression-free survival ranges from 8 to 11 months with first-line sunitinib or pazopanib[8-10] and from 3 to 5 months with sorafenib or axitinib after progression with first-line sunitinib treatment.[12,13] In the second-line setting or later, the mammalian target of rapamycin (mTOR) inhibitor everolimus was associated with longer progression-free survival than placebo (median, 4.9 vs. 1.9 months) in a phase 3 trial involving patients with renal-cell carcinoma that had progressed during or after treatment with sunitinib, sorafenib, or both.[14] However, no significant improvement in overall survival was observed.

Cabozantinib is an oral, small-molecule inhibitor of tyrosine kinases, including MET, VEGF receptors (VEGFRs), and AXL, and is currently approved for the treatment of patients with progressive, metastatic medullary thyroid cancer.[15,16] MET and AXL are up-regulated in renal-cell carcinoma as a consequence of VHL inactivation, and high expression of each is associated with poor prognosis.[17,18] In addition, increased expression of MET and AXL has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of several cancers, including renal-cell carcinoma.[19-22] A single-group trial showed objective responses and prolonged disease control with cabozantinib in patients with renal-cell carcinoma with tumors resistant to VEGFR and mTOR inhibitors.[23]

On the basis of these results, we conducted a randomized, open-label, phase 3 trial that compared cabozantinib with everolimus in patients with advanced renal-cell carcinoma that had progressed after VEGFR tyrosine kinase inhibitor therapy. The trial design allowed for appropriate statistical power for both a primary end point of progression-free survival and a secondary end point of overall survival while avoiding overrepresentation of patients with rapidly progressing disease for the primary end point.

Methods

Patients

Eligible patients were 18 years of age or older with advanced or metastatic renal-cell carcinoma with a clear-cell component and measurable disease. Patients must have received prior treatment with at least one VEGFR-targeting tyrosine kinase inhibitor and must have had radiographic progression during treatment or within 6 months after the most recent dose of the VEGFR inhibitor. Patients with known brain metastases that were adequately treated and stable were eligible. There was no limit to the number of previous anticancer therapies, which could include cytokines, chemotherapy, and monoclonal antibodies, including those targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligand PD-L1. Eligible patients also had a Karnofsky performance-status score of at least 70% (on a scale from 0 to 100%, with higher scores indicating better performance status) and adequate organ and marrow function. Key exclusion criteria were previous therapy with an mTOR inhibitor or cabozantinib or a history of uncontrolled, clinically significant illness.

Study Design and Treatment

Patients were randomly assigned in a 1:1 ratio to receive either cabozantinib or everolimus. Randomization was stratified according to the number of previous VEGFR-targeting tyrosine kinase inhibitors (1 or ≥2) and prognostic risk category (favorable, intermediate, or poor) according to the Memorial Sloan Kettering Cancer Center (MSKCC)

criteria[24] (for details on the MSKCC criteria, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Cabozantinib and everolimus were provided by the sponsor (Exelixis). Cabozantinib was administered orally at a dose of 60 mg once daily, and everolimus was administered orally at a dose of 10 mg once daily. Dose reductions for cabozantinib (40 mg, then 20 mg) and everolimus (5 mg, then 2.5 mg) and interruptions of study treatment were specified for management of adverse events. Treatment was continued as long as clinical benefit was observed by the investigator or until the development of unacceptable toxic effects. Crossover between treatment groups was not allowed.

END POINTS AND ASSESSMENTS

The primary end point was duration of progression-free survival, defined as the interval between the dates of randomization and first documentation of disease progression (assessed by an independent radiology review committee) or death from any cause. Secondary efficacy end points were duration of overall survival and objective response rate. Tumor response and progression were assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1,[25] in all patients at screening, every 8 weeks after randomization during the first 12 months, and every 12 weeks thereafter. Routine safety evaluations were performed and adverse-event severity was assessed by the investigator with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[26]

STUDY OVERSIGHT

The protocol was approved by the institutional review board or ethics committee at each center, and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Safety was monitored by an independent data monitoring committee. Data were collected by the sponsor and were analyzed in collaboration with the authors. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. The first draft of the manuscript was written by the first and last authors, with all the authors contributing to subsequent drafts. Medical-writing support, funded by the sponsor, was provided by Bellbird Medical Communications. All the authors made the decision to submit the manuscript for publication. The study protocol and statistical analysis plan are available at NEJM.org.

STATISTICAL ANALYSIS

The trial was designed to provide adequate power for assessment of both the primary end point of progression-free survival and the secondary end point of overall survival. For the primary end point, we estimated that 259 events (disease progression or death) would be required to provide 90% power to detect a hazard ratio of 0.667 (7.5 months with cabozantinib vs. 5 months with everolimus), using the log-rank test and a two-sided significance level of 0.05. For the overall-survival end point, assuming a single interim analysis at the time of the primary end-point analysis and a subsequent final analysis, we estimated that 408 deaths would be required to provide 80% power to detect a hazard ratio of 0.75 (20 months with cabozantinib vs. 15 months with everolimus), using the log-rank test and a two-sided significance level of 0.04.

Efficacy was evaluated in two populations according to the intention-to-treat principle. To evaluate the secondary end point of overall survival, 650 patients were planned (the overall-survival population). However, only 375 patients were required to achieve appropriate statistical power for the primary end point of progression-free survival. Thus, the study was designed to evaluate the primary end point in the first 375 patients who underwent randomization (the progression-free–survival population) to allow longer follow-up of progression-free survival (Fig. 1).

Hypothesis testing for progression-free and overall survival was performed with the use of the stratified log-rank test according to the stratification factors used at randomization. Median duration of progression-free survival and overall survival and associated 95% confidence intervals for each treatment group were estimated with the Kaplan–Meier method. Hazard ratios were estimated with a Cox regression model. A prespecified interim analysis for overall survival was conducted at the time of the primary end-point analysis. The type I error for the interim analysis was controlled by a Lan–DeMets alpha spending function, with O'Brien–Fleming boundaries, to account for the fraction of planned events at the time of the analysis.

RESULTS

PATIENTS

From August 2013 through November 2014, a total of 658 patients from 173 centers in 26 countries were randomly assigned to receive cabozantinib (330 patients) or everolimus (328 patients); these patients together compose the overall-survival population (Fig. S1 in the Supplementary Appendix). The first 375 patients who underwent randomization (187 assigned to cabozantinib and 188 assigned to everolimus) compose the progression-free–survival population for the primary end-point analysis (Fig. S2 in the Supplementary Appendix). The safety population comprises all patients who received study treatment (331 received cabozantinib and 322 received everolimus) (Fig. S1 in the Supplementary Appendix).

As of the data-cutoff date of May 22, 2015, a total of 133 patients assigned to cabozantinib and 67 patients assigned to everolimus were continuing to receive study treatment. Minimum follow-up time was 11 months in the progression-free–survival population and 6 months in the overall-survival population. The most common reason for discontinuing treatment was progression of disease on radiography.

The treatment groups were balanced with respect to baseline demographic and disease characteristics (Table 1). The most common previous therapy was sunitinib, and the majority of patients had received only one prior VEGFR inhibitor.

EFFICACY

The duration of progression-free survival was determined by an independent radiology review committee in the first 375 patients who underwent randomization. The estimated median progression-free survival was 7.4 months (95% confidence interval [CI], 5.6 to 9.1) with cabozantinib and 3.8 months (95% CI, 3.7 to 5.4) with everolimus. The rate of disease progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio for progression or death, 0.58; 95% CI, 0.45 to 0.75; P<0.001) (Fig. 2). The results were similar in a supportive analysis involving investigator assessment of progression-free survival (median, 7.4 months [95% CI, 6.3 to 7.6] with cabozantinib vs. 5.3 months [95% CI, 3.8 to 5.6] with everolimus; hazard ratio for progression or death, 0.60; 95% CI, 0.47 to 0.76; P<0.001) (Fig. S3 in the Supplementary Appendix).

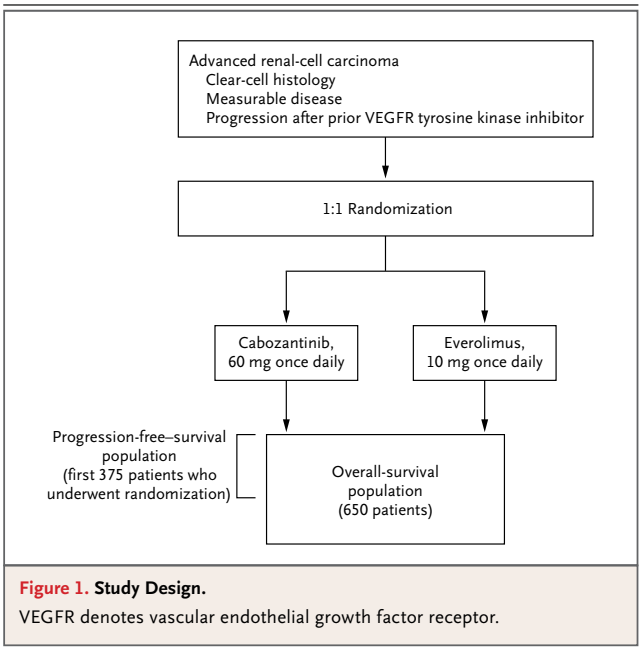

Figure 1. Study Design.
VEGFR denotes vascular endothelial growth factor receptor.

A progression-free survival benefit associated with cabozantinib was consistently observed in prespecified subgroups defined according to the number of prior VEGFR inhibitors and MSKCC prognostic risk category (Fig. S4 in the Supplementary Appendix). In a post hoc analysis of the subgroup of 153 patients who received sunitinib as their only prior VEGFR inhibitor, the estimated median progression-free survival was 9.1 months (95% CI, 5.6 to 11.2) with cabozantinib and 3.7 months (95% CI, 1.9 to 4.2) with everolimus (hazard ratio for progression or death, 0.41).

Among the first 375 patients who underwent randomization, the objective response rate, as assessed by an independent radiology review committee, was significantly higher with cabozantinib than with everolimus (partial responses in 40 of the 187 patients [21%] assigned to cabozantinib vs. 9 of the 188 patients [5%] assigned to everolimus; P<0.001) (Table S2 in the Supplementary Appendix). A best response of stable disease occurred in 116 patients (62%) in each group, and progressive disease occurred in 26 patients (14%) assigned to cabozantinib versus 51 patients (27%) assigned to everolimus. In the subgroup of 153 patients who received sunitinib as their only prior VEGFR inhibitor, objective responses occurred in 17 of the 76 patients assigned

Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	Progression-free–Survival Population		Overall-Survival Population	
	Cabozantinib (N=187)	Everolimus (N=188)	Cabozantinib (N=330)	Everolimus (N=328)
Age — yr				
Median	62	61	63	62
Range	36–83	31–84	32–86	31–84
Sex — no. (%)				
Male	142 (76)	130 (69)	253 (77)	241 (73)
Female	45 (24)	57 (30)	77 (23)	86 (26)
Not reported	0	1 (<1)	0	1 (<1)
Geographic region — no. (%)				
Europe	83 (44)	84 (45)	167 (51)	153 (47)
North America	76 (41)	64 (34)	118 (36)	122 (37)
Asia–Pacific	25 (13)	36 (19)	39 (12)	47 (14)
Latin America	3 (2)	4 (2)	6 (2)	6 (2)
Race — no. (%)†				
White	157 (84)	147 (78)	269 (82)	263 (80)
Asian	12 (6)	20 (11)	21 (6)	26 (8)
Black	4 (2)	2 (1)	6 (2)	3 (<1)
Other	10 (5)	6 (3)	19 (6)	13 (4)
Not reported	4 (2)	12 (6)	15 (5)	22 (7)
Missing data	0	1 (<1)	0	1 (<1)
ECOG performance-status score — no. (%)‡				
0	129 (69)	116 (62)	226 (68)	217 (66)
1	58 (31)	72 (38)	104 (32)	111 (34)
MSKCC prognostic risk category — no. (%)§				
Favorable	80 (43)	83 (44)	150 (45)	150 (46)
Intermediate	80 (43)	75 (40)	139 (42)	135 (41)
Poor	27 (14)	30 (16)	41 (12)	43 (13)
Prior VEGFR tyrosine kinase inhibitors — no. (%)				
1	137 (73)	136 (72)	235 (71)	229 (70)
≥2	50 (27)	52 (28)	95 (29)	99 (30)
Previous systemic therapy — no. (%)				
Sunitinib	114 (61)	113 (60)	210 (64)	205 (62)
Pazopanib	87 (47)	78 (41)	144 (44)	136 (41)
Axitinib	28 (15)	28 (15)	52 (16)	55 (17)
Sorafenib	11 (6)	19 (10)	21 (6)	31 (9)
Bevacizumab	1 (<1)	7 (4)	5 (2)	11 (3)
Interleukin-2	11 (6)	13 (7)	20 (6)	29 (9)
Interferon alfa	6 (3)	13 (7)	19 (6)	24 (7)
Nivolumab	9 (5)	11 (6)	17 (5)	14 (4)
Radiotherapy — no. (%)	56 (30)	61 (32)	110 (33)	108 (33)
Nephrectomy — no. (%)	156 (83)	153 (81)	282 (85)	279 (85)

* Statistical testing of differences in baseline characteristics between groups was not included in the statistical analysis plan. VEGFR denotes vascular endothelial growth factor receptor.
† Race was self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.
§ The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk category[24] was determined by the number of three factors (anemia, hypercalcemia, and poor performance) that were present. Patients with zero factors had a favorable prognosis, patients with one factor had an intermediate prognosis, and patients with two or three factors had a poor prognosis.

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