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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 has been implicated in metastatic renal cell carcinoma (RCC) pathobiology or development of resistance to antiangiogenic drugs. This randomized open-label phase 3 trial evaluated the efficacy of cabozantinib compared to everolimus in RCC patients who progressed after VEGFR-targeted therapy.

Methods—The trial randomized 658 patients to receive cabozantinib at a dose of 60 mg daily, or everolimus at a dose of 10 mg daily. The primary endpoint was progression-free survival. Secondary efficacy endpoints 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 risk of progression or death was 42% lower with cabozantinib compared to everolimus (hazard ratio, 0.58; 95% confidence interval [CI] 0.45 to 0.75; $P < 0.001$). Objective response rates were 21% with cabozantinib and 5% with everolimus ($P < 0.001$). A planned interim analysis showed that overall survival was improved with cabozantinib (hazard ratio, 0.67; 95% CI, 0.51 to 0.89; $P = 0.005$) but did not cross the significance boundary. Adverse events (grade 3 or 4, regardless of causality) were reported in 74% of cabozantinib patients and 65% of

everolimus patients. Discontinuation of study treatment for adverse events occurred in 9.1% of cabozantinib patients and 10% of everolimus patients.

Conclusions—Cabozantinib improved progression-free survival compared to everolimus in RCC patients who progressed after VEGFR-targeted therapy.

INTRODUCTION

Renal cell carcinoma (RCC) is the most common form of kidney cancer, with over 330,000 patients diagnosed and over 140,000 deaths worldwide annually.[1] Approximately one-third of patients present with metastatic disease at diagnosis[2] and about one-third of treated patients with localized disease will relapse.[3–5]

Inactivation of the von Hippel-Lindau (VHL) tumor suppressor protein characterizes clear cell tumors, the predominant histology in RCC, and results in the upregulation 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 based on improved progression-free survival in randomized phase 3 trials compared to interferon-alpha, placebo, or other targeted drugs.[7] Sunitinib, pazopanib, and bevacizumab (plus interferon-alpha) were investigated in the first-line setting, and sorafenib and axitinib were investigated following progression with a first-line treatment.

Nearly all patients treated with one or more of these drugs ultimately develop resistance as evidenced by disease progression. The median progression-free survival time ranges from 8 through 11 months for first-line sunitinib or pazopanib,[8–10] and from 3 through 5 months with sorafenib or axitinib following progression with first-line sunitinib treatment.[11,12] In the second- or later-line setting, the mammalian target of rapamycin (mTOR) inhibitor everolimus demonstrated improved progression-free survival compared to placebo in a phase 3 trial in RCC patients who previously progressed on sunitinib and/or sorafenib.[13] However, the benefit was modest, with most patients progressing within 5 months of treatment, and 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.[14] MET and AXL are upregulated in RCC as a consequence of VHL inactivation,[14,15] and high expression of each is associated with poor prognosis in RCC.[15,16] Also, increased MET expression has been implicated in the development of resistance to VEGFR inhibitors in preclinical models of several cancers including RCC.[17–20] A single-arm trial demonstrated objective responses and prolonged disease control with cabozantinib in RCC patients with tumors resistant to VEGFR and mTOR inhibitors.[21] On the basis of these results we conducted a randomized open-label phase 3 trial, called METEOR, which compared cabozantinib versus everolimus in patients with advanced RCC that progressed after prior VEGFR tyrosine kinase inhibitor therapy. METEOR employed a novel trial design to allow for appropriate statistical power for both a primary endpoint of progression-free survival and a secondary endpoint of overall survival while avoiding over-representation of rapidly-progressing patients for the primary endpoint.

METHODS

PATIENTS

Eligible patients were 18 years of age and older with advanced or metastatic RCC with a clear-cell component and measurable disease. Patients must have received prior treatment with at least one VEGFR-targeting tyrosine kinase inhibitor and experienced radiographic progression during treatment or within 6 months of the last 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 prior anti-cancer therapies, which could include cytokines, chemotherapy, and monoclonal antibodies, including those targeting VEGF, the programmed death (PD) 1 receptor, or its ligand PD-L1. Eligible patients also had a Karnofsky performance status score of ≥ 70% and adequate organ and marrow function. Key exclusion criteria were previous therapy with an mTOR inhibitor or cabozantinib, or a history of uncontrolled significant illness.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned 1:1 to either cabozantinib or everolimus. Randomization was stratified by the number of prior VEGFR-targeting tyrosine kinase inhibitor therapies (1, 2 or more) and risk category per Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria (favorable, intermediate, poor)[22] (Fig. 1).

Cabozantinib and everolimus were provided by the sponsor (Exelixis, Inc.), and administered orally daily at 60 mg and 10 mg, respectively. 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.[23] Treatment was continued as long as clinical benefit was observed per investigator, or until development of unacceptable toxicity. Cross over between treatment arms was not allowed.

ENDPOINTS AND ASSESSMENTS

The primary endpoint 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 endpoints were duration of overall survival and objective response rate. Tumor response and progression were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[24] on 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 grades were assessed by the investigator using the Common Terminology Criteria for Adverse Events version 4.0.[23]

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 the fidelity of

the study to the protocol. The first draft of the manuscript was written by the first and last authors, with all authors contributing to subsequent drafts. Medical writing support funded by the sponsor was provided by Bellbird Medical Communications. All authors agreed 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 endpoint of progression-free survival and the secondary endpoint of overall survival. For the primary endpoint, 259 events (disease progression or death) are 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 5%. For the overall survival endpoint, assuming a single interim analysis at the 33% information fraction at the time of the primary endpoint analysis and a subsequent final analysis, 408 deaths are 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 4%.

Efficacy was evaluated using two populations, each following the intention-to-treat principle. To evaluate the secondary endpoint 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 endpoint of progression-free survival. Thus, the study was designed to evaluate the primary endpoint in the first 375 randomized patients (the progression-free survival population) to allow longer and more robust follow-up of progression-free survival (Fig. 1).

Hypothesis testing for progression-free and overall survival was performed using 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 (CI) for each treatment arm were estimated using 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 endpoint analysis. The type I error for the interim analysis was controlled by a Lan-DeMets O'Brien-Fleming alpha spending function to account for the actual information fraction at the time of the analysis.

RESULTS

PATIENTS

From August 2013 to November 2014, 658 patients from 173 centers in 26 countries were randomly assigned to receive cabozantinib (n=330) or everolimus (n=328) and comprise the overall survival population (Fig. S1). The first 375 randomized patients comprise the progression-free survival population (cabozantinib, n=187; everolimus, n=188) for the primary endpoint analysis (Fig. S2). The safety population comprises all patients who received study treatment (cabozantinib, n=331; everolimus, n=322) (Fig. S1).

As of the data cutoff date of May 22, 2015, 133 cabozantinib patients and 66 everolimus patients 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 radiographic disease progression.

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

EFFICACY

The duration of progression-free survival as determined by an independent radiology review committee in the first 375 randomized patients was improved with cabozantinib, which reduced the risk of disease progression or death by 42% compared to everolimus (hazard ratio for progression or death, 0.58; 95% CI, 0.45 to 0.75; P<0.001) (Fig. 2). The estimated median progression-free survival was 7.4 months (95% CI, 5.6 to 9.1) with cabozantinib and 3.8 months (95% CI, 3.7 to 5.4) with everolimus. The results were similar in a supportive analysis using investigator-assessment of progression-free survival (hazard ratio for progression or death, 0.60; 95% CI, 0.45 to 0.76; P<0.001; 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) (Fig. S3).

A progression-free survival benefit associated with cabozantinib was consistently observed in prespecified subgroups defined by the number of prior VEGFR inhibitor therapies and by MSKCC risk categories (Fig. S4). In a post-hoc analysis of a subgroup of patients who received sunitinib as their only prior VEGFR inhibitor (N=153), the estimated median progression-free survival was 9.1 months with cabozantinib and 3.7 months with everolimus (hazard ratio, 0.41).

Cabozantinib was associated with a significant improvement in objective response rate, as assessed by independent review, in the first 375 randomized patients (partial responses in 21% [n=40] of patients with cabozantinib vs. 5% [n=9] with everolimus; P<0.001) (Table S1). Best response of stable disease occurred in 116 patients (62%) in each group, and progressive disease occurred in 26 patients (14%) with cabozantinib vs. 51 patients (27%) with everolimus. In the subgroup who received sunitinib as their only prior VEGFR inhibitor (N=153), objective responses occurred in 17 of 76 patients with cabozantinib (22%) and 2 of 77 patients with everolimus (3%).

At the prespecified interim analysis of overall survival, 202 deaths had occurred in the overall survival population. A trend for increased overall survival with cabozantinib was observed (hazard ratio 0.67, unadjusted 95% CI, 0.51 to 0.89; P=0.005) (Fig. 3). The P-value of ≤0.0019 required to achieve statistical significance at the time of the interim analysis was not reached, and survival follow-up is continuing to the planned final analysis after 408 deaths occur. The trend for improved survival with cabozantinib occurred despite more frequent subsequent anticancer therapies in the everolimus group (47%; n=154) than in the cabozantinib group (38%; n=125) (Table S2). The most common subsequent anticancer

therapies in the everolimus and cabozantinib groups were axitinib (40%; n=132) and everolimus (23%; n=75), respectively.

SAFETY

The median duration of treatment was 7.6 months among patients who received cabozantinib and 4.0 months among patients who received everolimus. Dose reductions occurred in 199 patients (60%) treated with cabozantinib, and in 82 patients (26%) treated with everolimus. The rate of treatment discontinuation due to adverse events not related to RCC was 9.1% (n=30) and 10% (n=33) in the cabozantinib and everolimus groups, respectively.

The incidence of adverse events (any grade) regardless of causality was 100% with cabozantinib and 99% with everolimus, and the incidence of adverse events of grade 3 or 4 was 74% with cabozantinib and 65% with everolimus (Table 2). The most common grade 3 or 4 adverse events with cabozantinib were hypertension (15%), diarrhea (11%), and fatigue (9%), and with everolimus were anemia (15%), fatigue (7%), and hyperglycemia (5%). Grade 5 adverse events occurred in 15 patients (4.5%) in the cabozantinib group and in 23 patients (7.1%) in the everolimus group, and were primarily related to disease progression. Treatment-related grade 5 events occurred in one patient in each treatment group: death not otherwise specified with cabozantinib and aspergillus infection with everolimus.

DISCUSSION

Cabozantinib improved progression-free survival compared to everolimus in this randomized phase 3 trial in patients with RCC who had previously progressed on at least one VEGFR-targeted therapy. The efficacy with cabozantinib was robust, with an estimated median progression-free survival of 7.4 months compared to 3.8 months with everolimus, and a hazard ratio of 0.58, corresponding to a 42% reduction in the risk of disease progression or death. Objective tumor responses were observed in 21% of patients with cabozantinib compared to 5% in the everolimus group.

Data pertaining to overall survival, a secondary endpoint in this trial, were immature at the prespecified interim analysis. Nonetheless, a 33% decrease in the risk of death with cabozantinib was observed, indicating a strong trend for improved survival. The interim boundary for significance was not reached, and follow-up for survival is continuing to the planned final analysis.

The safety profile of cabozantinib in this trial was similar to prior experience in this patient population.[21] Common adverse events with cabozantinib included diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, and hypertension, which are also observed with other VEGFR tyrosine kinase inhibitors in patients with RCC.[8,11] Adverse events observed with everolimus at higher rates and severity than with cabozantinib included pneumonitis, peripheral edema, anemia, and hyperglycemia. Discontinuation of study treatment due to adverse events not related to RCC occurred in 9.1% of cabozantinib patients and 10% of everolimus patients, indicating that overall tolerability of the two agents was similar.

This study employed a novel “trial within a trial” design because the optimal sample size to evaluate the primary endpoint of progression-free survival is too small to adequately assess the important secondary endpoint of overall survival. An event-driven analysis of progression-free survival in the larger sample required for overall survival could have been over-weighted with patients who experience early progression, and patients with longer progression times might not have been sufficiently represented. Therefore, to provide the longer follow-up required for a robust event-driven analysis of progression-free survival, the primary analysis of this endpoint was prespecified to occur in the first 375 randomized patients.

Everolimus was used as the comparator because it is a standard treatment for patients who previously progressed with a VEGFR-targeted therapy. Due to the absence of comparative phase 3 data, an area of controversy has been the relative benefit of a VEGFR inhibitor compared to everolimus as a second-line treatment in RCC.[25] METEOR is the first phase 3 trial to compare a tyrosine kinase inhibitor with everolimus in this setting. Over 70% of the METEOR study population is comprised of patients pretreated with only one prior VEGFR inhibitor, primarily sunitinib. Consistent with the overall results, benefit was observed with cabozantinib in the subgroup of patients who received one prior VEGFR-targeted therapy.

Axitinib is also an option as second-line treatment for patients with RCC based on the results of the phase 3 AXIS trial, which showed a benefit in progression-free survival compared to sorafenib as a second-line therapy.[11] AXIS trial eligibility allowed varied first-line therapies, and the two largest populations were patients pretreated with sunitinib (54%) or cytokines (35%). The estimated median progression-free survival in the overall population was 6.7 months with axitinib compared to 4.7 months with sorafenib, and the benefit was strongest in cytokine-pretreated patients. The subgroup of patients who received sunitinib as their front-line therapy showed an estimated median progression-free survival of 4.8 months and an objective response rate of 11% with axitinib.[11,26] Thus, the estimated median progression-free survival of 9.1 months and objective response rate of 22% with cabozantinib in a similar population of patients are noteworthy, potentially reflecting cabozantinib’s novel mechanism of action, beyond targeting VEGFR, with the addition of MET and AXL inhibition.

In conclusion, cabozantinib is a novel multi-targeted MET, VEGFR, and AXL tyrosine kinase inhibitor that improved progression-free survival compared to everolimus in patients with RCC who progressed after prior VEGFR inhibitor therapy. A strong trend for improved overall survival with cabozantinib was demonstrated in an interim analysis, and the adverse events were manageable. These results support a new treatment paradigm, whereby cabozantinib may become the standard of care for patients with RCC who progress on one or more prior VEGFR-targeted therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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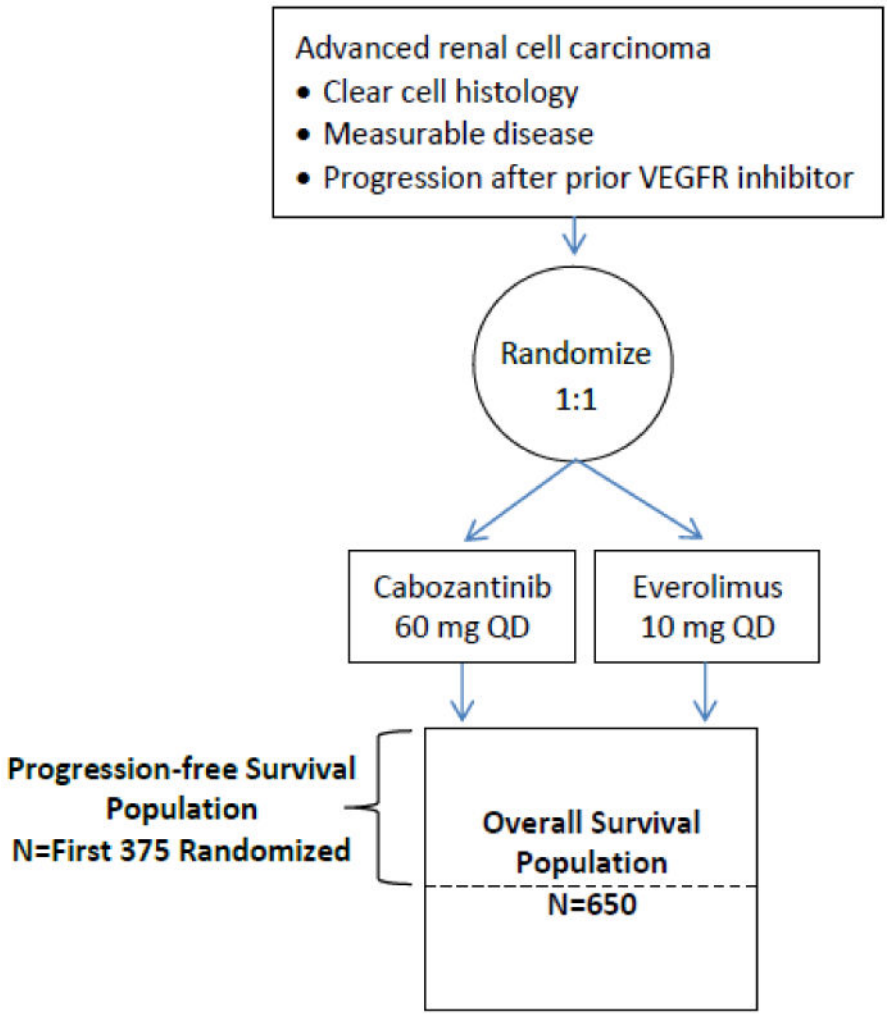


Figure 1.
METEOR Study Design

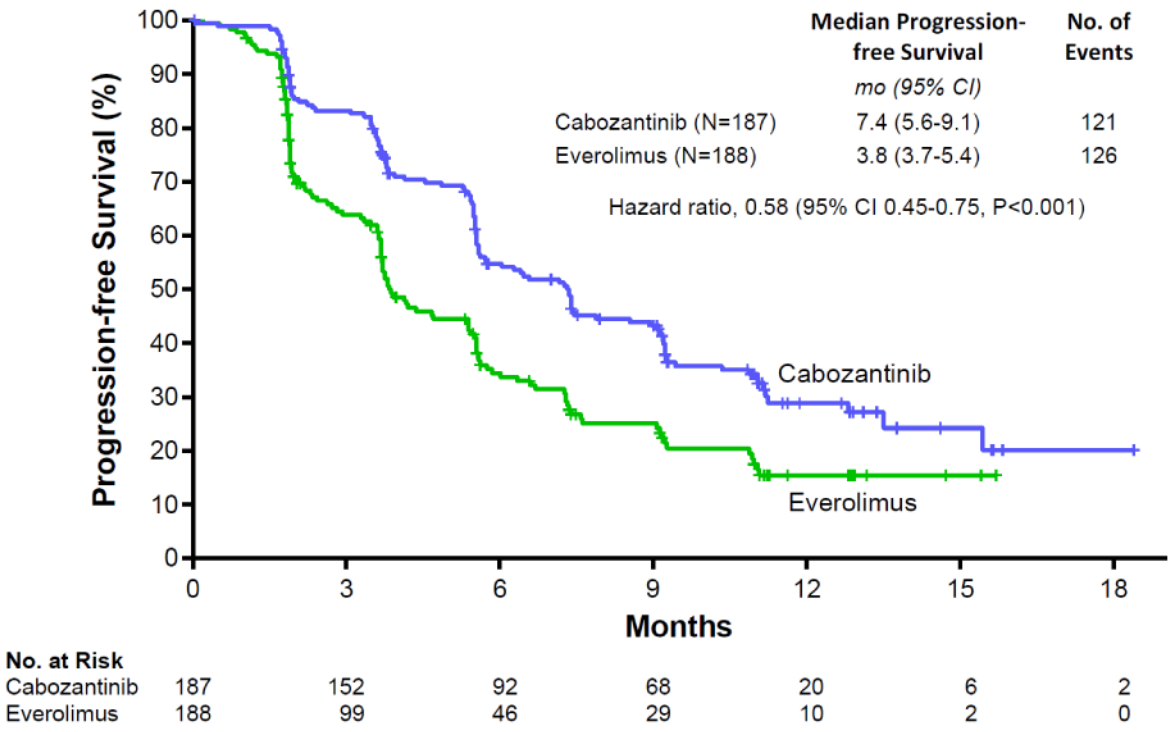
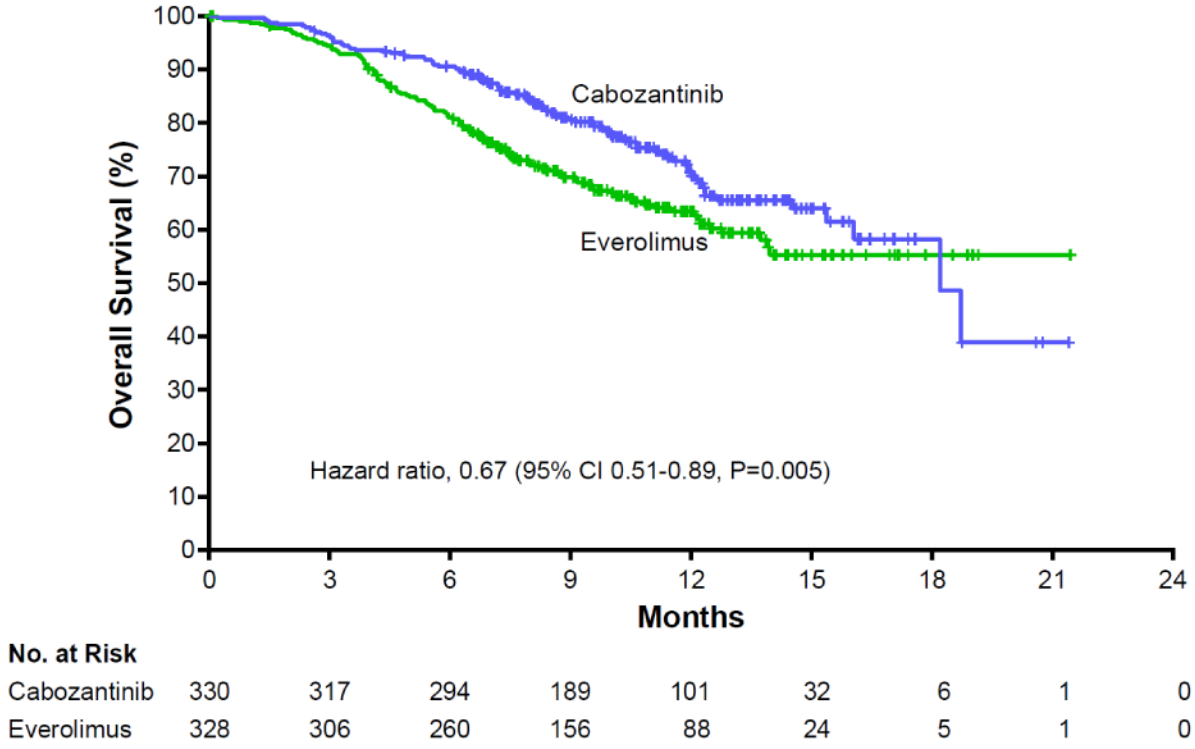


Figure 2.

Kaplan-Meier Estimates of Progression-free Survival (Independent Radiology Review Committee)



No. at Risk									
Cabozantinib	330	317	294	189	101	32	6	1	0
Everolimus	328	306	260	156	88	24	5	1	0

Figure 3.
Kaplan-Meier Estimates of Overall Survival

Table 1

Baseline Demographics and Clinical Characteristics.

	PFS Population		OS Population	
Characteristic	**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)
Ethnic origin – no. (%)				
White	157 (84)	147 (78)	269 (82)	263 (80)
Asian	12 (6)	20 (11)	21 (6)	26 (8)
Black or African-American	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	0	1 (<1)	0	1 (<1)
ECOG performance status – no. (%)				
0	129 (69)	116 (62)	226 (69)	217 (66)
1	58 (31)	72 (38)	104 (32)	111 (34)
MSKCC risk group[22] – no. (%)				
Favorable	80 (43)	83 (44)	150 (45)	150 (46)
Intermediate	78 (42)	75 (40)	137 (42)	135 (41)
Poor	29 (16)	30 (16)	43 (13)	43 (13)
Prior VEGFR TKIs – no. (%)				
1	137 (73)	136 (72)	235 (71)	229 (70)
≥ 2	50 (27)	52 (28)	95 (29)	99 (30)
Previous systemic therapy – no. (%)				
Sunitinib	122 (65)	121 (64)	226 (69)	224 (68)
Pazopanib	89 (48)	80 (43)	149 (45)	138 (42)
Axitinib	28 (15)	27 (14)	52 (16)	56 (17)
Sorafenib	11 (6)	19 (10)	21 (6)	33 (10)
Bevacizumab	1 (<1)	7 (4)	5 (2)	10 (3)

	PFS Population		OS Population	
Characteristic	**Cabozantinib (N=187)**	**Everolimus (N=188)**	**Cabozantinib (N=330)**	**Everolimus (N=328)**
Interleukin 2	11 (6)	13 (7)	20 (6)	31 (10)
Interferon-α	6 (3)	12 (6)	21 (6)	23 (7)
Nivolumab	9 (5)	11 (6)	17 (5)	14 (4)
Radiotherapy – no. (%)	55 (29)	59 (31)	109 (33)	107 (32)
Nephrectomy – no. (%)	156 (83)	154 (82)	284 (86)	280 (85)

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, Progression-free Survival; OS, Overall Survival; VEGFR TKI, Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor.

Table 2

Adverse Events *

Event	Cabozantinib (N=331)		Everolimus (N=322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any adverse event	331 (100)	245 (74)	320 (99)	208 (65)
Diarrhea	244 (74)	38 (11)	88 (27)	7 (2)
Fatigue	186 (56)	30 (9)	146 (45)	22 (7)
Nausea	164 (50)	12 (4)	88 (27)	1 (<1)
Decreased appetite	152 (46)	8 (2)	105 (33)	3 (<1)
Palmar-plantar erythrodysesthesia syndrome	138 (42)	28 (9)	18 (6)	3 (<1)
Hypertension	122 (37)	49 (15)	23 (7)	10 (3)
Vomiting	104 (31)	7 (2)	45 (14)	3 (<1)
Weight decreased	102 (31)	6 (2)	39 (12)	0
Constipation	82 (25)	1 (<1)	57 (18)	1 (<1)
Dysgeusia	78 (24)	0	30 (9)	0
Stomatitis	73 (22)	8 (2)	77 (24)	7 (2.2)
Hypothyroidism	67 (20)	0	1 (<1)	0
Dysphonia	64 (19)	2 (<1)	10 (3)	0
Asthenia	62 (19)	14 (4)	50 (16)	6 (2)
Mucosal inflammation	62 (19)	3 (<1)	72 (22)	11 (3)
Cough	60 (18)	1 (<1)	107 (33)	3 (<1)
Dyspnea	60 (18)	10 (3)	90 (28)	12 (4)
Back pain	56 (17)	7 (2)	46 (14)	7 (2)
Abdominal pain	53 (16)	12 (4)	31 (9.6)	4 (1)
Rash	49 (15)	2 (<1)	89 (28)	2 (<1)
Pain in extremity	47 (14)	3 (<1)	26 (8)	1 (<1)
Muscle spasms	41 (12)	0	15 (5)	0
Dyspepsia	38 (11)	1 (<1)	15 (5)	0
Headache	37 (11)	1 (<1)	38 (12)	1 (<1)
Arthralgia	36 (11)	1 (<1)	44 14)	4 (1)
Dizziness	36 (11)	0	21 (7)	0
Dry skin	36 (11)	0	32 (10)	0
Edema peripheral	31 (9.4)	0	71 (22)	5 (2)
Pyrexia	26 (7.9)	2 (<1)	51 (16)	1 (<1)
Pruritus	25 (7.6)	0	47 (15)	1 (<1)
Pneumonitis	0	0	33 (10)	6 (2)
Laboratory abnormalities				
Aspartate aminotransferase increased	58 (18)	5 (2)	18 (6)	1 (<1)

Event	Cabozantinib (N=331)		Everolimus (N=322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Anemia	54 (16)	17 (5)	120 (37)	49 (15)
Alanine aminotransferase increased	53 (16)	8 (2)	19 (6)	1 (<1)
Hypomagnesemia	52 (16)	16 (5)	5 (2)	0
Proteinuria	41 (12)	8 (2)	29 (9)	1 (<1)
Hypokalemia	38 (11)	15 (5)	21 (7)	7 (2)
Hypophosphatemia	33 (10)	12 (4)	18 (6)	7 (2)
Hyperglycemia	15 (5)	2 (<1)	61 (19)	16 (5)
Hypertryglyceridemia	20 (6)	5 (2)	40 (12)	9 (3)
Blood creatinine increased	15 (5)	2 (<1)	34 (11)	0

*The most common treatment-emergent adverse events regardless of causality are reported. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[23] The adverse events and laboratory abnormalities listed here were reported in at least 10% of the patients in each study group.