Cabozantinib, a New Standard of Care for Patients With Advanced Renal Cell Carcinoma and Bone Metastases? Subgroup Analysis of the METEOR Trial

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ABSTRACT

Purpose

Cabozantinib, an inhibitor of tyrosine kinases including MET, vascular endothelial growth factor receptors, and AXL, increased progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) in patients with advanced renal cell carcinoma (RCC) after previous vascular endothelial growth factor receptor–targeted therapy in the phase III METEOR trial. Because bone metastases are associated with increased morbidity in patients with RCC, bone-related outcomes were analyzed in METEOR.

Patients and Methods

Six hundred fifty-eight patients were randomly assigned 1:1 to receive 60 mg cabozantinib or 10 mg everolimus. Prespecified subgroup analyses of PFS, OS, and ORR were conducted in patients grouped by baseline bone metastases status per independent radiology committee (IRC). Additional end points included bone scan response per IRC, skeletal-related events, and changes in bone biomarkers.

Results

For patients with bone metastases at baseline (cabozantinib [n = 77]; everolimus [n = 65]), median PFS was 7.4 months for cabozantinib versus 2.7 months for everolimus (hazard ratio, 0.33 [95% CI, 0.21 to 0.51]). Median OS was also longer with cabozantinib (20.1 months v 12.1 months; hazard ratio, 0.54 [95% CI, 0.34 to 0.84]), and ORR per IRC was higher (17% v 0%). The rate of skeletal-related events was 23% with cabozantinib and 29% with everolimus, and bone scan response per IRC was 20% versus 10%, respectively. PFS, OS, and ORR were also improved with cabozantinib in patients without bone metastases. Changes in bone biomarkers were greater with cabozantinib than with everolimus. The overall safety profiles of cabozantinib and everolimus in patients with bone metastases were consistent with those observed in patients without bone metastases.

Conclusion

Cabozantinib treatment was associated with improved PFS, OS, and ORR when compared with everolimus treatment in patients with advanced RCC and bone metastases and represents a good treatment option for these patients.

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INTRODUCTION

Bone is a common site of metastasis in advanced renal cell carcinoma (RCC), occurring in approximately 30% of patients.¹ Bone metastases are associated with significant morbidity including pain, hypercalcemia, and skeletal-related events (SREs) such as fracture, spinal cord compression, and lesions requiring surgery or radiotherapy. Although the rate of SREs has decreased in recent

years,² up to 85% of patients with RCC and bone metastases may experience an SRE.³ In several studies, bone metastases have been shown to be a negative prognostic factor for patients with metastatic RCC treated with targeted agents.⁴⁻⁷ Using International Metastatic Renal Cell Carcinoma Database Consortium data, the median survival from the start of targeted therapy was 14.9 months for patients with bone metastases and 25.1 months for patients without bone metastases.⁵

ASSOCIATED CONTENT

Appendix

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Data Supplement

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Cabozantinib is an orally bioavailable inhibitor of pro-oncogenic tyrosine kinases including MET, vascular endothelial growth factor receptors (VEGFRs), and AXL.⁸ In preclinical studies, cabozantinib treatment inhibited the growth of prostate tumor xenografts in bone and resulted in changes to the bone microenvironment, including a biphasic effect on osteoblast activity, inhibition of osteoclast production, and changes in bone remodeling.⁹⁻¹³ In clinical studies in prostate cancer, cabozantinib treatment was associated with an increase in bone scan response (BSR), a reduced incidence of SREs, and decreases in biomarkers for bone turnover.¹⁴⁻¹⁶ Cabozantinib was approved recently for the treatment of patients with advanced RCC after previous antiangiogenic therapy on the basis of significant improvements in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) when compared with everolimus in a phase III trial (Metastatic Renal Cell Carcinoma Phase III Study Evaluating Cabozantinib Vs Everolimus [METEOR]).^{17,18} In the current analysis, clinical outcomes, including SREs, were evaluated for patients with bone involvement in the METEOR trial. Data on several serum bone biomarkers are also presented.

PATIENTS AND METHODS

Patients and Treatment

METEOR is a randomized, open-label, international phase III study with patients enrolled at 173 centers in 26 countries. As described previously,^{17,18} eligible patients were 18 years of age or older and had advanced or metastatic RCC with a clear cell component and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).¹⁹ Patients were required to have received at least one previous VEGFR tyrosine kinase inhibitor (TKI) and to have progressed during or within 6 months of their most recent VEGFR TKI and within 6 months of random assignment. A Karnofsky performance status of at least 70% and adequate organ function were also required.

Patients were randomly assigned 1:1 to receive cabozantinib (60 mg once daily) or everolimus (10 mg once daily) and were stratified by the Memorial Sloan Kettering Cancer Center risk group and by the number of previous VEGFR TKIs (one v two or more). The dose could be reduced to 40 mg and 20 mg for cabozantinib and 5 mg and 2.5 mg for everolimus for the management of adverse events. The study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the institutional review board or ethics committee at each center, and written informed consent was obtained from all patients.

Assessments

Assessments have been described previously.^{17,18} Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis were performed at screening, every 8 weeks for the first 12 months, and every 12 weeks thereafter. All patients had baseline technetium bone scans, and scans were performed every 16 weeks for the first 12 months and every 24 weeks thereafter for patients with bone lesions at baseline. Safety, including adverse events, was evaluated every 2 weeks for the first 8 weeks and every 4 weeks thereafter until treatment discontinuation. A follow-up visit occurred 30 days after treatment discontinuation. Adverse events were graded according to Common Terminology Criteria for Adverse Events (version 4.0).²⁰ SREs consisted of pathologic fractures, spinal cord compression, surgery to bone, and external-beam radiation therapy to bone. Blood samples for serum bone biomarker analysis were collected at day 1 before the first dose, at week 5, and at week 9 to analyze bone-specific alkaline phosphatase (BSAP), N-terminal propeptide of type I collagen (PINP), and C-terminal cross-linked telopeptides of type I collagen (CTX).

Statistical Analyses

The primary and secondary end points and safety have been reported previously.^{17,18} The primary end point of PFS was analyzed in the first 375 randomly assigned patients, and the secondary end points of OS and ORR were analyzed in all 658 randomly assigned patients using the intent-to-treat principle. All subgroup analyses of PFS, ORR, and OS used all randomly assigned patients and were prespecified. Safety was assessed in patients who received at least one dose of study treatment. Tumor scans were evaluated according to RECIST (version 1.1).¹⁹ All PFS analyses presented herein are per independent radiology committee (IRC). For subgroup analyses, no adjustments for multiplicity were made, CIs are considered descriptive, and hazard ratios (HRs) are unstratified. The subgroup of patients with bone metastases was defined by the presence of bone metastases at baseline by CT or MRI per IRC. BSR, incidence of SREs, and changes in bone biomarkers were exploratory end points of the study. BSR, defined as a $\geq 30\%$ decrease from baseline in bone scan lesion area, was evaluated for patients who had bone lesions detected by technetium bone scans at baseline by the IRC. An IRC was used to quantitate bone scan tumor burden using computer-assisted detection to measure lesions; confirmation was not required for response.²¹ Two sample *t* tests were conducted to evaluate whether changes in biomarker levels from baseline to week 5 and week 9 differed between treatment groups; *P* values are considered descriptive. The data cutoff was May 22, 2015, for PFS, ORR, BSR, and bone biomarker analyses and December 31, 2015, for OS and safety analyses.

RESULTS

Patients

A total of 658 patients were randomly assigned 1:1 to receive cabozantinib or everolimus from August 8, 2013, to November 24, 2014. A total of 142 patients (22%) had bone metastases at baseline by CT or MRI per IRC (77 in the cabozantinib group and 65 in the everolimus group). Of these, 112 patients (79%) also had visceral metastases (60 in the cabozantinib group and 52 in the everolimus group). Overall, baseline characteristics were similar in patients with or without bone metastases and between treatment groups (Table 1). The use of bone-targeted therapies (bisphosphonates and denosumab) at baseline for patients with bone metastases was 30% (23 of 77) in the cabozantinib group and 20% (13 of 65) in the everolimus group. As of the December 31, 2015 cutoff for OS, 21 of 77 patients (27%) in the cabozantinib group and 3 of 65 patients (5%) in the everolimus group with bone metastases were continuing to receive study treatment (Fig 1).

Efficacy

HRs and CIs for PFS and OS have been reported previously for patients with and without bone metastases by CT or MRI at baseline.¹⁸ As of the May 22, 2015 cutoff, the median PFS for patients with bone metastases was 7.4 months (95% CI, 5.5 to 10.4 months) in the cabozantinib group and 2.7 months (95% CI, 1.9 to 3.8 months) in the everolimus group (HR, 0.33 [95% CI, 0.21 to 0.51]; Fig 2). Patients with bone metastases who also had visceral metastases had a median PFS of 5.6 months (95% CI, 4.5 to 9.4 months) with cabozantinib and 1.9 months (95% CI, 1.8 to 2.9 months) with everolimus (HR, 0.26 [95% CI, 0.16 to 0.43]). For patients without bone metastases, the median PFS was 7.4 months (95% CI, 6.5 to 9.2 months) with cabozantinib and 4.2 months (95% CI, 3.8 to 5.5 months) with everolimus (HR, 0.57 [95% CI, 0.45 to 0.71]).

Table 1. Baseline Characteristics

Characteristic	Patients With Bone Metastases		Patients Without Bone Metastases	
	Cabozantinib (n = 77)	Everolimus (n = 65)	Cabozantinib (n = 253)	Everolimus (n = 263)
Age, years, median (range)	61.0 (32-84)	64.0 (34-84)	63.0 (35-86)	61.0 (31-81)
Sex				
Male	64 (83)	53 (82)	189 (75)	188 (71)
Female	13 (17)	12 (18)	64 (25)	74 (28)
Geographic region				
Europe	36 (47)	34 (52)	131 (52)	119 (45)
North America	32 (42)	23 (35)	86 (34)	99 (38)
Asian Pacific	8 (10)	7 (11)	31 (12)	40 (15)
Latin America	1 (1)	1 (2)	5 (2)	5 (2)
ECOG performance status				
0	64 (83)	60 (92)	237 (94)	246 (94)
1	13 (17)	5 (8)	16 (6)	17 (6)
MSKCC risk group				
Favorable	28 (36)	29 (45)	122 (48)	121 (46)
Intermediate	35 (45)	27 (42)	104 (41)	108 (41)
Poor	14 (18)	9 (14)	27 (11)	34 (13)
IMDC risk group				
Favorable	11 (14)	9 (14)	55 (22)	53 (20)
Intermediate	52 (68)	46 (71)	158 (62)	168 (64)
Poor	14 (18)	10 (15)	40 (16)	42 (16)
Metastatic site per IRC				
Visceral (lung or liver)	60 (78)	52 (80)	181 (72)	193 (73)
Lung	52 (68)	47 (72)	152 (60)	165 (63)
Liver	27 (35)	25 (38)	61 (24)	78 (30)
Bone	77 (100)	65 (100)	0	0
Lymph node	49 (64)	43 (66)	157 (62)	156 (59)
Target lesion diameters per IRC, mm, sum (range)	77 (0-291)	91 (16-229)	62 (0-286)	64 (0-258)
No. of VEGFR TKIs				
1	50 (65)	43 (66)	185 (73)	186 (71)
≥ 2	27 (35)	22 (34)	68 (27)	77 (29)
Previous systemic therapy				
Sunitinib	47 (61)	38 (59)	163 (64)	167 (64)
Pazopanib	35 (46)	31 (48)	109 (43)	105 (40)
Axitinib	17 (22)	15 (23)	35 (14)	40 (15)
Sorafenib	5 (7)	7 (11)	16 (6)	24 (9)
Interleukin-2	6 (8)	3 (5)	14 (6)	26 (10)
Interferon alpha	5 (6)	6 (9)	14 (6)	17 (6)
Nivolumab	4 (5)	4 (6)	13 (5)	10 (4)
Bevacizumab	2 (3)	4 (6)	3 (1)	7 (3)
External-beam radiation therapy	41 (53)	39 (60)	65 (26)	66 (25)
Nephrectomy	67 (87)	47 (72)	216 (85)	232 (88)
Bone-targeted therapy at baseline	23 (30)	13 (20)	18 (7)	23 (9)
Bisphosphonate	14 (18)	7 (11)	14 (6)	16 (6)
Denosumab	9 (12)	6 (9)	4 (2)	8 (3)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IRC, independent radiology committee; MSKCC, Memorial Sloan Kettering Cancer Center; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

ORR was improved with cabozantinib compared with everolimus for patients with bone metastases (Table 2 and Appendix Table A1, online only). Objective responses per IRC with cabozantinib were observed in 13 of 77 patients with bone metastases (17% [95% CI, 9% to 27%]) and in 12 of 60 patients with bone and visceral metastases (20% [95% CI, 11% to 32%]). Per investigator assessment, objective responses with cabozantinib were observed in 21 of 77 patients with bone metastases (27% [95% CI, 18% to 39%]) and in 18 of 60 patients with bone and visceral metastases (30% [95% CI, 19% to 43%]). No responses were observed with everolimus in patients with bone metastases, by either IRC or investigator assessment. In patients without bone metastases, 44 of 253 patients (17% [95% CI, 13% to 23%]) in the cabozantinib

group and 11 of 263 patients (4% [95% CI, 2% to 7%]) in the everolimus group had a response per IRC.

As of the December 31, 2015 cutoff, median OS for patients with bone metastases was 20.1 months (95% CI, 14.9 months to not estimable [NE]) in the cabozantinib group and 12.1 months (95% CI, 9.6 to 16.4 months) in the everolimus group (HR, 0.54 [95% CI, 0.34 to 0.84]; Fig 3). Patients with bone and visceral metastases had a median OS of 20.1 months (95% CI, 12.4 to NE) with cabozantinib and 10.7 months (95% CI, 7.5 to 12.5 months) with everolimus (HR 0.45 [95% CI, 0.28 to 0.72]). For patients without bone metastases, median OS was NE (95% CI, 18.4 months to NE) with cabozantinib and 17.5 months (95% CI, 15.7 to 19.6 months) with everolimus (HR, 0.71 [95% CI, 0.55 to

Fig 1. Patient disposition as of December 31, 2015. Disposition for the overall population has been published.¹⁸ (*) One patient assigned to everolimus received cabozantinib. ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

0.91]). The proportion of patients with bone metastases who received subsequent systemic anticancer therapy was 47% in the cabozantinib group and 58% in the everolimus group, with subsequent radiotherapy received by 17% and 29% of patients, respectively. The use of subsequent therapy was similar for patients without bone metastases (Appendix Table A2, online only).

BSR per IRC was analyzed for patients with baseline bone scans showing bone lesions (95 patients [29%] in the cabozantinib group and 67 patients [20%] in the everolimus group). BSR was 20% (95% CI, 12% to 29%) in the cabozantinib group and 10% (95% CI, 4% to 20%) in the everolimus group (Appendix Table A3, online only).

Fig 2. Kaplan-Meier plots of progression-free survival (PFS). Disease progression was assessed by an independent radiology committee. Data are through May 22, 2015.

Table 2. Tumor Response per Independent Radiology Committee

Response	Patients With Bone Metastases		Patients With Bone and Visceral Metastases*		Patients Without Bone Metastases	
	Cabozantinib (n = 77)	Everolimus (n = 65)	Cabozantinib (n = 60)	Everolimus (n = 52)	Cabozantinib (n = 253)	Everolimus (n = 263)
Objective response rate, † % (95% CI)	17 (9 to 27)	0	20 (11 to 32)	0	17 (13 to 23)	4 (2 to 7)
Best overall response, No. (%)						
Confirmed partial response	13 (17)	0 (0)	12 (20)	0 (0)	44 (17)	11 (4)
Stable disease	54 (70)	35 (54)	39 (65)	23 (44)	162 (64)	168 (64)
Progressive disease	10 (13)	24 (37)	9 (15)	23 (44)	31 (12)	64 (24)
Not evaluable or missing	0 (0)	6 (9)	0 (0)	6 (12)	16 (6)	20 (8)

NOTE. Data are as of May 22, 2015.

*Visceral metastases were defined as lung or liver metastases.

†All responses were partial responses.

Bone biomarkers showed greater changes in BSAP, P1NP, and CTx with cabozantinib than with everolimus (Fig 4), including decreases in the bone formation marker P1NP and bone resorption marker CTx, which were evaluated with two sample *t* tests (Appendix Table A4, online only). Post-baseline use of bone-targeted therapies in patients with bone metastases was 36% in the cabozantinib group and 34% in the everolimus group (Appendix Table A5, online only).

Safety

The median duration of exposure for patients with bone metastases was 9.8 months (range, 1.0 to 23.2 months) for cabozantinib-treated patients and 3.7 months (range, 0.2 to 21.8 months) for everolimus-treated patients. For patients without bone metastases, the median duration of exposure was 8.3 months (range, 0.3 to 27.9 months) for cabozantinib-treated patients and 4.9 months (range, 0.6 to 24.9 months) for everolimus-treated patients. The safety profiles of cabozantinib and everolimus were similar in patients with and without bone metastases (Appendix Table A6, online only). The incidence of grade 3 or 4 adverse events in patients with bone metastases was 73% in cabozantinib-treated patients and 51% in everolimus-treated patients compared with 71%

and 62%, respectively, in patients without bone metastases. Grade 3 or 4 adverse events that differed by $\geq 5\%$ between patients with bone metastases and those without bone metastases were fatigue (16% *v* 9%, respectively) and hypertension (6% *v* 17%) for cabozantinib-treated patients and lymphocytopenia (6% *v* 0%) for everolimus-treated patients. The incidence of grade 3 or 4 hypercalcemia and osteonecrosis of the jaw was similar between treatment groups and in patients with and without bone metastases.

For patients with bone metastases at baseline, on-study SREs were experienced by 23% of patients in the cabozantinib group and by 29% of patients in the everolimus group (Table 3). For patients who did not have bone metastases at baseline, the incidence of on-study SREs was 12% in the cabozantinib group and 10% in the everolimus group.

DISCUSSION

The randomized phase III METEOR trial compared the efficacy of cabozantinib with that of everolimus in patients with advanced RCC who had progressed during or after previous VEGFR TKI therapy.^{17,18} The study design included prespecified analyses of

Fig 3. Kaplan-Meier analyses of overall survival (OS). Data are through December 31, 2015. NE, not estimable.

Fig 4. Effects on bone biomarkers. The bar shows the 25% to 75% quartiles, and the line shows the median. The range and number of patients (n) are listed below the graph. Baseline measurements were taken before the first dose. All available baseline patient data were included regardless of whether corresponding data were available at week 5 or week 9. BSAP, bone-specific alkaline phosphatase; CTx, C-terminal cross-linked telopeptides of type 1 collagen; P1NP, N-terminal propeptide of type 1 collagen.

PFS, OS, and ORR based on bone metastases status at baseline and several exploratory bone-related end points.

Cabozantinib treatment was associated with improved PFS, OS, and ORR in patients with advanced RCC and bone metastases when compared with everolimus treatment. For patients with bone metastases, median PFS was 7.4 months with cabozantinib versus 2.7 months with everolimus (HR, 0.33), and median OS was

20.1 months with cabozantinib versus 12.1 months with everolimus (HR, 0.54). Objective responses per IRC were observed in 17% of patients with bone metastases in the cabozantinib group, whereas no patients with bone metastases had a confirmed response with everolimus. These apparent improvements with cabozantinib were also observed in patients with both bone and visceral metastases and in patients without bone metastases.

Table 3. On-Study SREs

SRE	Patients With Bone Metastases		Patients Without Bone Metastases	
	Cabozantinib (n = 77)	Everolimus (n = 65)	Cabozantinib (n = 253)	Everolimus (n = 263)
SREs, No. (%)	18 (23)	19 (29)	31 (12)	27 (10)
Pathologic fractures	9 (12)	3 (5)	14 (6)	8 (3)
Spinal cord compression	4 (5)	4 (6)	2 (1)	4 (2)
Surgery to bone	6 (8)	5 (8)	6 (2)	5 (2)
External radiation therapy to bone	9 (12)	16 (25)	23 (9)	20 (8)
Time to first SRE, months, median (range)	3.7 (0.4-14.5)	2.5 (0.3-7.3)	5.6 (0.5-18.4)	4.3 (0.7-13.4)

Abbreviation: SRE, skeletal-related event.

Patients were included in the bone metastases subgroup only after verification of bone metastases by CT or MRI per independent review. Other methods, including technetium bone scans, are less reliable given the mainly osteolytic nature of bone metastases in RCC.^{22,23} The bone metastases subgroup comprised 22% of the study population, consistent with the reported incidence of bone metastases in advanced RCC.¹ Within the bone metastases subgroup, baseline characteristics were relatively balanced between the treatment groups. The use of bone-targeted therapies was low in both treatment groups and was consistent with the reported use of these therapies in advanced RCC, where concerns regarding potential renal toxicity and other adverse events may reduce their use.^{6,23}

Bone metastases are associated with a poor prognosis and a reduced benefit from targeted therapies in patients with RCC.^{4-6,24} Although our study was not powered for statistical testing of the subgroup analyses, the values of the HRs and medians for PFS and OS for patients with bone metastases were notable and favored cabozantinib over everolimus. Subsequent systemic therapy was received by approximately 50% of all patients with bone metastases, with approximately 10% more patients receiving therapy in the everolimus group, suggesting that subsequent therapy did not confound the OS results. Objective responses were also higher with cabozantinib, with no responses observed in the everolimus group. Consistent with a clinical benefit with cabozantinib treatment, the median duration of exposure for patients with bone metastases was more than 2.5 times longer for cabozantinib-treated patients than for everolimus-treated patients. Our results are also consistent with those from the phase II CABOSUN trial in first-line patients with advanced RCC, in which a PFS benefit with cabozantinib was maintained in patients with bone metastases compared with sunitinib.²⁵

A variety of second-line treatment options are available for patients with RCC²⁶; however, limited data are available for patients with bone metastases. In a recently published subgroup analysis of the phase III CheckMate 025 trial, the HR for OS was 0.72 (95% CI, 0.47 to 1.09) for nivolumab versus everolimus (median of 18.5 months *v* 13.8 months) for patients with bone metastases,²⁷ whereas in the METEOR trial, the HR for OS for this subgroup was 0.54 (95% CI, 0.34 to 0.84). Although cross-trial comparisons are difficult, our results support the use of cabozantinib in this patient population.

BSR per independent review was an exploratory end point of this study that showed an approximately 10% higher response for cabozantinib compared with everolimus. Technetium-based imaging relies largely on osteoblastic response, whereas bone metastases in RCC tend to be highly osteolytic, making reliable assessment of BSR challenging in this context.^{22,23} In this study, more patients were categorized as having bone lesions by bone scan when compared with the number who had bone metastases by CT or MRI. This discrepancy may be a result of false-positives identified by bone scan, which can result from tracer uptake caused by inflammation or fracture, and differences in body coverage between the two techniques.

Bone biomarkers showed greater changes in BSAP, P1NP, and CTx with cabozantinib than with everolimus, including decreases in the bone formation marker P1NP and the bone resorption marker CTx. The on-study use of bone-targeted therapies, which have been reported to have effects on bone turnover markers,²⁸ was similar in both treatment groups, suggesting that the observed changes were caused by study treatment. Changes in bone biomarkers with cabozantinib may

be a result of a general pharmacodynamic effect because these changes were observed in both patients with bone metastases and those without bone metastases. Cabozantinib treatment has also been associated with a reduction in the levels of bone biomarkers in patients with prostate cancer and bone metastases,¹⁴ consistent with these results.

Safety in patients with bone metastases was consistent with the previously reported safety profiles in the overall study population for both treatments.^{17,18} Common grade 3 or 4 adverse events in patients with bone metastases included fatigue, diarrhea, and palmar-plantar erythrodysesthesia syndrome with cabozantinib and anemia, hyperglycemia, and lymphocytopenia with everolimus. Grade 3 or 4 adverse events of hypercalcemia were low, irrespective of bone metastases status or treatment group. Although the incidence of some grade 3 or 4 adverse events differed between patients with bone metastases and those without bone metastases, the overall safety profiles of cabozantinib and everolimus were similar in both subgroups. The overall incidence of grade 3 or 4 events with everolimus was approximately 10% higher in patients without bone metastases than in patients with bone metastases. The relatively small size of the bone metastases subgroup and differences in time receiving treatment may have contributed to these observed differences.

The incidence of SREs, an exploratory end point of the study, was approximately 6% lower with cabozantinib than with everolimus for patients with bone metastases at baseline. Patients in the cabozantinib group received treatment for a longer duration than did those in the everolimus group, which may have increased the observed incidence of SREs.

Bone metastases are associated with a poor prognosis in advanced RCC,⁵ and additional treatments for these patients are needed. Cabozantinib is a standard of care for previously treated patients with advanced RCC, with clinical benefits in PFS, OS, and ORR that are observed irrespective of the presence of bone metastases. On the basis of these outcomes, cabozantinib represents a good treatment option for this difficult-to-treat patient population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Table A1. Tumor Response per Investigator

Response	Patients With Bone Metastases		Patients With Bone and Visceral Metastases*		Patients Without Bone Metastases	
	Cabozantinib (n = 77)	Everolimus (n = 65)	Cabozantinib (n = 60)	Everolimus (n = 52)	Cabozantinib (n = 253)	Everolimus (n = 263)
Objective response rate,† % (95% CI)	27 (18 to 39)	0	30 (19 to 43)	0	23 (18 to 28)	5 (3 to 9)
Best overall response, No. (%)						
Confirmed partial response	21 (27)	0 (0)	18 (30)	0 (0)	57 (23)	14 (5)
Stable disease	49 (64)	40 (63)	36 (60)	30 (59)	160 (63)	165 (63)
Progressive disease	7 (9)	18 (28)	6 (10)	15 (29)	22 (9)	69 (26)
Not evaluable or missing	0 (0)	6 (9)	0 (0)	6 (12)	14 (6)	14 (5)

NOTE. Data are as of May 22, 2015.

*Visceral metastases were defined as lung or liver metastases.

†All responses were partial responses.

Table A2. Subsequent Anticancer Therapy

Anticancer Therapy	Patients With Bone Metastases		Patients Without Bone Metastases	
	Cabozantinib (n = 77)	Everolimus (n = 65)	Cabozantinib (n = 253)	Everolimus (n = 263)
Any systemic therapy	36 (47)	38 (58)	129 (51)	143 (54)
VEGFR-TKI therapies	17 (22)	30 (46)	60 (24)	126 (48)
Axitinib	10 (13)	18 (28)	45 (18)	72 (27)
Sunitinib	7 (9)	4 (6)	10 (4)	29 (11)
Pazopanib	1 (1)	5 (8)	4 (2)	17 (6)
Sorafenib	1 (1)	6 (9)	8 (3)	25 (10)
Cabozantinib	0 (0)	2 (3)	0 (0)	6 (2)
Everolimus	22 (29)	3 (5)	73 (29)	11 (4)
Bevacizumab	4 (5)	3 (5)	4 (2)	8 (3)
PD-1/PD-L1 targeting agents	3 (4)	5 (8)	12 (5)	13 (5)
Nivolumab	3 (4)	3 (5)	11 (4)	12 (5)
External-beam radiation therapy	13 (17)	19 (29)	49 (19)	58 (22)

NOTE. Data are presented as No. (%).

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Table A3. Bone Scan Response

Bone Scan Response	Patients With Bone Lesions at Baseline by Bone Scan	
	Cabozantinib (n = 95)	Everolimus (n = 67)
Bone scan response, % (95% CI)	20 (12 to 29)	10 (4 to 20)
Responder, No. (%)	19 (20)	7 (10)
Unevaluable or missing, No. (%)	0 (0)	2 (3)

NOTE. Bone scan response was assessed by an independent radiology committee in patients with bone lesions at baseline. It was defined as a $\geq 30\%$ decrease from baseline in bone scan lesion area; confirmation was not required for response. Data are as of May 22, 2015.

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Table A4. Two Sample *T* Tests of Bone Biomarkers

Biomarker	Patients With Bone Metastases				Patients Without Bone Metastases			
	Week 5		Week 9		Week 5		Week 9	
	Cabozantinib	Everolimus	Cabozantinib	Everolimus	Cabozantinib	Everolimus	Cabozantinib	Everolimus
BSAP								
n	68	55	63	46	218	214	200	206
Change from baseline, $\mu\text{g/L}$	4.90 (0.56)	−0.57 (0.61)	2.17 (0.67)	−0.53 (0.74)	5.02 (0.38)	0.07 (0.24)	1.88 (0.38)	−0.36 (0.28)
<i>P</i>	< .0001		.0085		< .0001		.0013	
P1NP								
n	66	53	63	44	215	216	201	206
Change from baseline, $\mu\text{g/L}$	−22.34 (3.89)	−7.89 (3.59)	−29.99 (4.83)	−7.54 (4.29)	−14.15 (1.98)	−10.26 (1.91)	−25.18 (2.36)	−4.69 (3.11)
<i>P</i>	.0086		.0007		.16		< .0001	
CTx								
n	71	54	69	44	211	214	192	203
Change from baseline, $\mu\text{g/L}$	−0.21 (0.02)	−0.03 (0.03)	−0.17 (0.02)	−0.09 (0.04)	−0.23 (0.01)	−0.02 (0.01)	−0.21 (0.02)	−0.01 (0.02)
<i>P</i>	< .0001		.055		< .0001		< .0001	

NOTE. Change from baseline data are presented as mean (SEM). *P* values are considered to be descriptive.
Abbreviations: BSAP, bone-specific alkaline phosphatase; CTx, C-terminal cross-linked telopeptides of type 1 collagen; P1NP, N-terminal propeptide of type 1 collagen; SEM, standard error in the mean.

Table A5. Concomitant Use of Bone-Targeted Therapies in Patients With Bone Metastases

Bone-Targeted Therapy	Cabozantinib (n = 77)	Everolimus (n = 65)
At baseline	23 (30)	13 (20)
Bisphosphonate	14 (18)	7 (11)
Denosumab	9 (12)	6 (9)
After random assignment*	28 (36)	22 (34)
Bisphosphonate	18 (23)	13 (20)
Denosumab	11 (14)	9 (14)

NOTE. Data are presented as No. (%).

*Includes patients who initiated bone-targeted therapy before random assignment.

Table A6. All-Causality Grade 3 or 4 Adverse Events

Adverse Event	Patients With Bone Metastases		Patients Without Bone Metastases	
	Cabozantinib (n = 77)	Everolimus (n = 65)	Cabozantinib (n = 254)	Everolimus (n = 257)
Any adverse event	56 (73)	33 (51)	179 (71)	160 (62)
Fatigue	12 (16)	4 (6)	24 (9)	20 (8)
Diarrhea	11 (14)	0 (0)	32 (13)	7 (3)
PPES	6 (8)	0 (0)	21 (8)	3 (1)
Asthenia	5 (6)	1 (2)	10 (4)	7 (3)
Hypertension	5 (6)	1 (2)	44 (17)	11 (4)
Nausea	5 (6)	0 (0)	10 (4)	1 (< 1)
Anemia	4 (5)	9 (14)	15 (6)	44 (17)
Hypokalemia	4 (5)	1 (2)	12 (5)	5 (2)
Hypomagnesemia	4 (5)	0 (0)	12 (5)	0 (0)
Hyperglycemia	0 (0)	5 (8)	3 (1)	11 (4)
Lymphocyte count decreased	0 (0)	4 (6)	1 (< 1)	0 (0)
Adverse event of interest				
Hypercalcemia	0 (0)	2 (3)	3 (1)	4 (2)
Osteonecrosis of the jaw	1 (1)	1 (2)	0 (0)	1 (< 1)

NOTE. Data are presented as No. (%). Events that occurred at $\geq 5.0\%$ frequency in either treatment arm for patients with bone metastases or patients without bone metastases are summarized, as well as the incidence of hypercalcemia. Patients are counted once at the highest grade for each preferred term. The severity of adverse events was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Abbreviation: PPES, palmar-plantar erythrodysesthesia syndrome.