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ORIGINAL REPORT

Cabozantinib in Patients With Advanced Prostate Cancer: Results of a Phase II Randomized Discontinuation Trial

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ABSTRACT

Purpose
Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with activity against MET and vascular endothelial growth factor receptor 2. We evaluated the activity of cabozantinib in patients with castration-resistant prostate cancer (CRPC) in a phase II randomized discontinuation trial with an expansion cohort.

Patients and Methods
Patients received 100 mg of cabozantinib daily. Those with stable disease per RECIST at 12 weeks were randomly assigned to cabozantinib or placebo. Primary end points were objective response rate at 12 weeks and progression-free survival (PFS) after random assignment.

Results
One hundred seventy-one men with CRPC were enrolled. Random assignment was halted early based on the observed activity of cabozantinib. Seventy-two percent of patients had regression in soft tissue lesions, whereas 68% of evaluable patients had improvement on bone scan, including complete resolution in 12%. The objective response rate at 12 weeks was 5%, with stable disease in 75% of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Median PFS was 23.9 weeks (95% CI, 10.7 to 62.4 weeks) with cabozantinib and 5.9 weeks (95% CI, 5.4 to 6.6 weeks) with placebo (hazard ratio, 0.12; $P < .001$). Serum total alkaline phosphatase and plasma cross-linked C-terminal telopeptide of type I collagen were reduced by ≥ 50% in 57% of evaluable patients. On retrospective review, bone pain improved in 67% of evaluable patients, with a decrease in narcotic use in 56%. The most common grade 3 adverse events were fatigue (16%), hypertension (12%), and hand-foot syndrome (8%).

Conclusion
Cabozantinib has clinical activity in men with CRPC, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans, and reductions in bone turnover markers, pain, and narcotic use.

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INTRODUCTION

The receptor tyrosine kinase MET, its ligand hepatocyte growth factor (HGF), and the vascular endothelial growth factor (VEGF) signaling pathway seem to play critical roles in the development and progression of castration-resistant prostate cancer (CPRC). Prominent expression of MET has been observed in primary and metastatic prostate carcinomas,[1,2] with evidence for higher levels of expression in bone metastases compared with lymph node metastases or primary tumors.[3,4] Elevated levels of either HGF or VEGF in plasma or urine are associated with shorter overall survival in men with prostate cancer,[5-7] and expression of MET is higher in tumor samples from patients with CRPC compared with tumor samples from patients who have not yet undergone androgen-deprivation therapy.[8] HGF and MET expression are increased in androgen-sensitive tumor cells after withdrawal of androgen and in castration-resistant xenograft models,[1,9,10] suggesting that upregulation of MET signaling is associated with the emergence of resistance to androgen suppression.

Both HGF and MET are expressed by osteoblasts and osteoclasts in vitro and mediate cellular responses such as proliferation, migration, and differentiation.[11,12] Secretion of HGF by osteoblasts is a key factor in osteoblast/osteoclast coupling[12] and the development of bone metastases by tumor cells

that express MET.[13] Osteoblasts and osteoclasts also express VEGF and its receptors, and VEGF signaling is involved in potential autocrine and/or paracrine feedback mechanisms regulating cellular functions.[14,15] VEGF may also activate the MET pathway in tumor cells by binding to neuropilin-1, which is frequently upregulated in prostate cancer and activates MET in a coreceptor complex.[3]

Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGF receptor 2 (VEGFR2). In vivo, cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial cells and tumor cells, resulting in tumor regression in a variety of xenograft models.[16,17] In a xenograft model of CRPC in bone, cabozantinib blocks the progression of osteolytic and osteoblastic lesions.[18] In phase I clinical studies, treatment with cabozantinib resulted in tumor regression in multiple cancer types.[19] On the basis of the broad activity, a phase II randomized discontinuation trial was conducted in nine selected tumor types including CRPC (ClinicalTrials.gov identifier: NCT00940225).[20] This report describes the results of this trial in the subset of patients with CRPC.

PATIENTS AND METHODS

Patients

Eligible patients had CRPC with measurable disease by RECIST (version 1.0)[21] with progressive disease at screening, Eastern Cooperative Oncology Group performance status of 0 or 1, absolute neutrophil count $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, hemoglobin $\geq$ 9 g/dL, total bilirubin $\leq$ 1.5$\times$ the upper limit of normal (ULN), serum albumin more than 2.8 g/dL, AST and ALT $\leq$ 2.5$\times$ the ULN ($\leq$ 5$\times$ the ULN with liver metastases), and serum creatinine $\leq$ 1.5$\times$ the ULN or calculated creatinine clearance $\geq$ 60 mL/min. Patients had $\leq$ one prior standard chemotherapy regimen completed at least 4 weeks before study entry, and those on combined androgen blockade underwent antiandrogen withdrawal while luteinizing hormone–releasing hormone agonists were maintained. Patients with an increasing prostate-specific antigen (PSA) as their only evidence of progressive disease, brain metastases, radiation therapy within 2 weeks, or clinically significant intercurrent illness were excluded. The study protocol and informed consent documents were reviewed and approved by the institutional review boards of the participating institutions, and informed consent was obtained from all patients before any study-specified procedures.

Study Design

The primary objective of this trial was to evaluate the efficacy of cabozantinib in multiple solid tumors including CRPC. Secondary objectives included assessing the safety and tolerability of the agent and potential pharmacodynamic effects. The study was designed as a randomized discontinuation trial as described by Ratain et al.[22] Key features of this design are the ability to evaluate multiple tumor types simultaneously while minimizing exposure to placebo in tumors with objective regression, yet allowing for randomized evaluation where the activity is to prolong progression without regression. All patients received open-label treatment with cabozantinib during a 12-week lead-in stage (Appendix Fig A1, online only). Patients with stable disease at 12 weeks were randomly assigned to cabozantinib or placebo. Randomly assigned patients were observed until progression, at which point treatment assignment was unblinded. Patients were taken off study if they were receiving cabozantinib or were allowed to restart cabozantinib if on placebo. Patients restarted on cabozantinib after first progression on placebo were observed until subsequent progression.

Study Drug Administration

Patients received an initial daily dose of cabozantinib 100 mg. Dosing was interrupted for intolerable grade 2 toxicity, $\geq$ grade 3 nonhematologic toxicity that was not easily managed, urine protein/creatinine ratio more than 2, persistent hypertension $\geq$ grade 2, or any grade 4 hematologic toxicity. If dosing was interrupted, therapy was restarted if the toxicity had resolved to $\leq$ grade 1 or baseline levels within 3 weeks. If the adverse event was unrelated to study therapy, treatment was resumed with no change in dose. If the adverse event was related to study treatment, dosing resumed at a reduced dose of 60 mg per day, with subsequent reductions to 39.4 mg per day and 19.7 mg per day. Interruption in dosing for more than 3 weeks required discontinuation of the patient from study therapy.

Study Assessments

Patients were evaluated every 3 weeks for safety and every 6 weeks for efficacy. Efficacy assessments included radiographic soft tissue and bone imaging. Progression-defining events for progression-free survival (PFS) analysis were evidence of radiographic tumor progression (RECIST) or death. Response was assessed by the treating investigator. Bone scan changes were independently assessed by a single reader at a radiology facility (MedQIA, Los Angeles, CA) without knowledge of the clinical or biochemical status of the patients. Bone scan effects were categorized as complete resolution, partial resolution, stable disease, or progressive disease (Appendix, online only).

Other clinical assessments included medical and cancer history, physical examination, vital signs and body weight, electrocardiography, Eastern Cooperative Oncology Group performance status, safety laboratories (serum chemistry, hematology, coagulation, and urinalysis), concomitant medications, adverse events, and information on subsequent anticancer treatment. Assessments for analyses of exploratory end points included serum PSA and bone markers (plasma cross-linked C-terminal telopeptide of type I collagen [CTx]

Table 1. Baseline Demographics and Clinical Characteristics of the Patients

Demographic or Clinical Characteristic	No. of Patients	%
Age, years		
Median	68	
Range	47-88	
$\geq$ 75	39	23
ECOG performance status		
0	88	52
1	82	48
Time since diagnosis, years		
Median	6.9	
Range	0.6-22.2	
Measurable disease	170	99
Disease location		
Lymph nodes	136	80
Visceral, lung	42	25
Visceral, liver	25	15
Bone	149	87
$\geq$ 2 disease sites	139	81
Prior treatment		
Chemotherapy	79	46
Docetaxel	74	43
Abiraterone	8	5
Enzalutamide	9	5
Bisphosphonate use*	66	39
Denosumab use*	1	1
Baseline bone pain†	92	54
Narcotics use for bone pain	71	42
Median laboratory values		
Serum prostate-specific antigen, ng/mL	65	
Total alkaline phosphatase, U/L	112	
Hemoglobin, g/dL	12.4	
Lactate dehydrogenase, U/L	232	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Prior or concurrent use of bisphosphonate or denosumab at baseline.
†Investigator survey of patients with bone metastasis at baseline.

and serum total alkaline phosphatase [tALP]). Pain and narcotic analgesic use was retrospectively obtained by survey of medical records.

Statistical Considerations

The study used an adaptive design in which it was assumed that a stable disease rate of at least 35% in a cohort would be of interest and warrant further exploration. Enrollment onto a cohort could be halted by the Study Oversight Committee (SOC) if an insufficient number of patients had disease stabilization as a result of higher than expected rates of either progressive disease or response by RECIST during the lead-in stage. Multiple cohorts were to be closed such that only two cohorts would fully accrue the random assignment stage. Up to 200 patients could be enrolled onto a tumor type cohort to randomly assign 70 patients and achieve 52 events after random assignment. This design had an 80% power to detect a hazard ratio of 0.5 for PFS after random assignment. Random assignment was 1:1 using a permuted-block design with each tumor type cohort without other stratification factors. Each tumor type was analyzed separately, and no adjustments were made for multiple comparisons. The Kaplan-Meier method was used to estimate medians for the analysis of PFS from random assignment, and the log-rank test was used for inference testing. Hazard ratios were estimated using the Cox proportional hazards model. The piecewise estimation method, as described by Ratain et al,[22] was used to analyze overall PFS from the date of first dose, including the lead-in stage. All treated patients contributed to the PFS estimate through the first 12 weeks. After week 12, the PFS was estimated as a weighted average with the weights corresponded to the fraction of patients continuing on open-label treatment and the proportion of patients randomly assigned at week 12 (including placebo).

RESULTS

Patients and Treatment

From October 2009 through February 2011, a total of 171 patients with metastatic CRPC were enrolled in the United States, Belgium, Israel, and Taiwan. Baseline demographics and clinical characteristics are listed in Table 1. Bone metastases were present in 149 patients (87%). Forty-six percent of patients had prior chemotherapy, 94% with docetaxel-based therapy, and 39% of patients had prior and ongoing bisphosphonate treatment. The SOC recommended suspension of random assignment after enrollment of 122 patients because of unexpected changes on bone scan and decrease in pain observed during the lead-in stage. At the time random assignment was suspended, 31 patients had been randomly assigned to either receive cabozantinib or placebo, and 57 patients continued open-label treatment. Numerous potential patients had been approached or consented to the protocol, and an additional 49 eligible patients were enrolled before closure of the cohort. Of these 49 patients, 28 remained on treatment for more than 12 weeks. Overall, treatment was discontinued during the lead-in stage (≤ week 12) in 32% of patients (55 of 171 patients). In 21 patients, this was a result of an adverse event. The median duration of cabozantinib treatment excluding patients randomly assigned to placebo was 4.2 months (range, 0.5 to 17.2 months). Treatment status for all 171 patients is summarized in Figure 1.

Response

Of the 171 men enrolled, 170 had measurable disease at baseline, and 154 were evaluable for response assessment per RECIST with at least one postbaseline radiographic assessment. Nine patients (5%) had a confirmed partial response within the first 12 weeks, 127 (75%) had stable disease, and 18 (11%) had disease progression (Table 2). In addition, four patients with stable disease at week 12 had a confirmed partial response after the lead-in stage. Of 154 patients evaluable for best change in measurable disease,

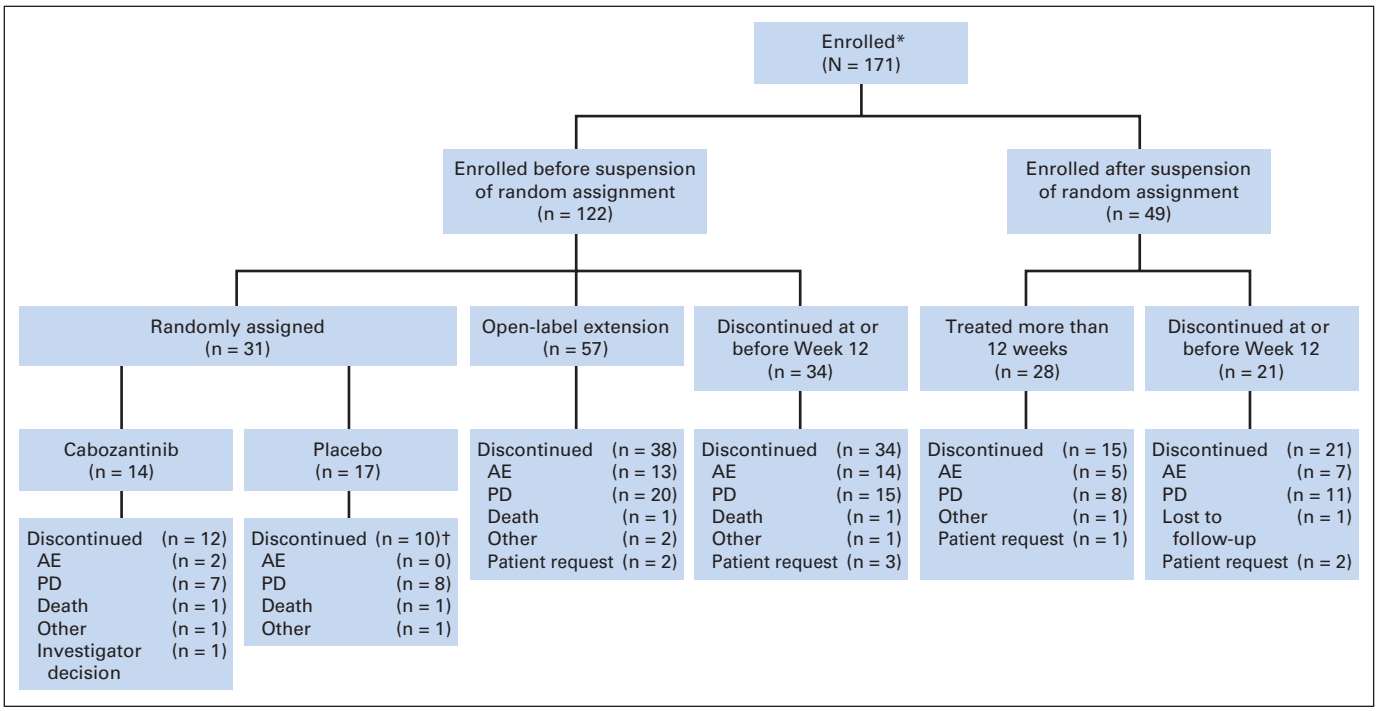

Fig 1. CONSORT diagram, including enrollment, random assignment, and open-label treatment of study patients. (*) Included one patient who did not meet eligibility criteria (no measurable disease). (†) Seven patients who were randomly assigned to placebo and crossed over to open-label cabozantinib treatment after unblinding were still active at the time of data cutoff. AE, adverse event; PD, progressive disease.

Table 2. Response to Treatment

Response	No. of Patients	%
Tumor response*		
No. evaluable	170	
Response		
Confirmed partial response	9	5
Stable disease	127	75
Progressive disease	18	11
Disease control rate at week 12†		66
Bone scan‡		
No. evaluable	116	
Visual read		
Complete resolution		12
Partial resolution		56
Stable disease		28
Progressive disease		3
Pain§		
No. evaluable	83	
Pain improvement at week 6 or week 12		67
Narcotic use‖		
No. evaluable	55	
Decrease or discontinuation		56
Bone turnover markers		
No. evaluable for serum tALP (≥ 2× ULN at baseline)¶	30	
≥ 50% decrease in tALP		57
No. evaluable for plasma CTx#	126	
≥ 50% decrease in CTx		57

NOTE. Percentages may not total 100% because of rounding.
Abbreviations: CTx, cross-linked C-terminal telopeptide of type I collagen; tALP, total alkaline phosphatase; ULN, upper limit of normal.
*Radiographic tumor assessment by investigator using RECIST (version 1.0) during the 12-week lead-in stage. Of 171 enrolled patients, one patient did not have measurable disease at baseline.
†Disease control rate consisting of partial response and stable disease at week 12.
‡Best overall change on bone scan as determined by visual read by an independent radiologist.
§Investigator survey of patients with bone metastases and pain at baseline who had at least one postbaseline assessment.
‖Investigator survey of patients with bone metastases, pain, and narcotic use at baseline who had at least one postbaseline assessment.
¶Patients with bone metastases who had at least reached week 12.
#Patients with bone metastases who had available week 6 and/or week 12 samples analyzed.

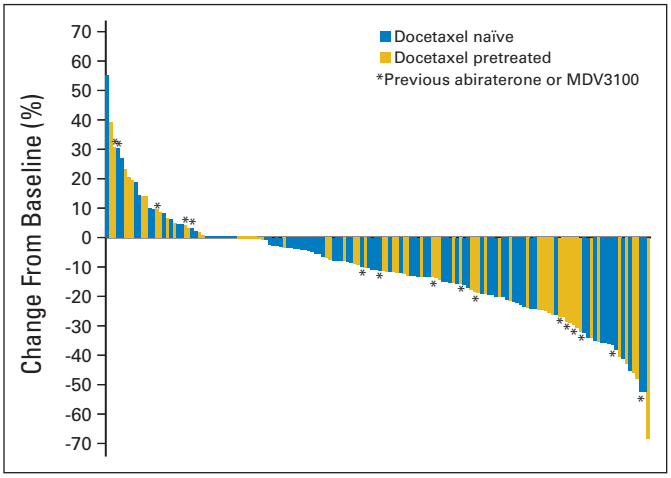

Fig 2. Best changes from baseline in investigator-assessed measurements of tumor lesions in soft tissue using RECIST (version 1.0) in patients with castration-resistant prostate cancer who had measurable disease at baseline and at least one postbaseline radiographic assessment (n = 154). A reduction in the sum of measurable tumor lesions was observed in 72% of patients.

111 (72%) had at least one assessment demonstrating a reduction of soft tissue tumor lesions (Fig 2). Change in measurable disease was independent of prior treatment.

PFS

The primary end point was PFS of patients who had stable disease at week 12 and were randomly assigned to blinded treatment with cabozantinib or placebo. Before suspension of random assignment, 31 patients with CRPC were randomly assigned (14 to cabozantinib and 17 to placebo). A marked increase in PFS (from random assignment) was observed for patients randomly assigned to cabozantinib (median PFS, 23.9 weeks) compared with placebo (median PFS, 5.9 weeks; hazard ratio, 0.12; $P < .001$; Fig 3A).

The median overall PFS for the entire treatment period from the start of the study (week 1, day 1) including all cabozantinib-treated patients (n = 171) was estimated using the piecewise method[22] to be 29.4 weeks. The median PFS was 29.7 weeks for patients who were docetaxel naive (n = 97) and 23.9 weeks for patients who previously received a docetaxel-based therapy (n = 74; Fig 3B).

Exploratory Analyses

Prompted by the observation of bone scan improvement, post hoc analyses of the effects of cabozantinib on bone scan, bone markers, pain and narcotic use, and PSA were performed.

Bone scan. One hundred forty-nine patients had evidence of bone metastases at baseline, and 116 patients (78%) had at least one follow-up bone scan evaluable for response. Bone scans were improved in 79 patients (68%), with complete resolution in 14 patients (12%) and partial resolution in 65 patients (56%); stable disease was observed in 33 patients (28%) and progressive disease in four patients (3%; Table 2). Representative images of patients with bone scan improvement are shown in Figure 4.

Bone markers. Markers of bone formation (serum tALP) and bone resorption (plasma CTx) were analyzed in stored blood specimens from patients with bone metastases. Forty-three patients had baseline levels of tALP at least 2× ULN. Of the 30 patients who reached week 12, 27 had declines in tALP ranging from 9% to 83%, with reductions of 50% or more in 17 (57%) of 30 patients (Table 2; Appendix Fig A2A, online only). Decreases from baseline CTx levels were observed in 108 of 126 patients who had at least one follow-up assessment, with reductions of 50% or more in 72 (57%) of 126 patients (Table 2; Appendix Fig A2B). Changes in both tALP and CTx were independent of prior and/or concurrent bisphosphonate therapy.

Bone pain. Baseline pain was reported by 92 men with bone metastases, with 71 men taking narcotics to control the pain (Table 1). Among patients with at least one available postbaseline assessment of pain or narcotic use, 67% (56 of 83 patients) reported an improvement in pain control with a decrease in or discontinuation of narcotics by 56% (31 of 55 patients; Table 2).

PSA. PSA changes did not correlate with the antitumor effects in bone and soft tissue (Appendix Fig A3, online only), suggesting that

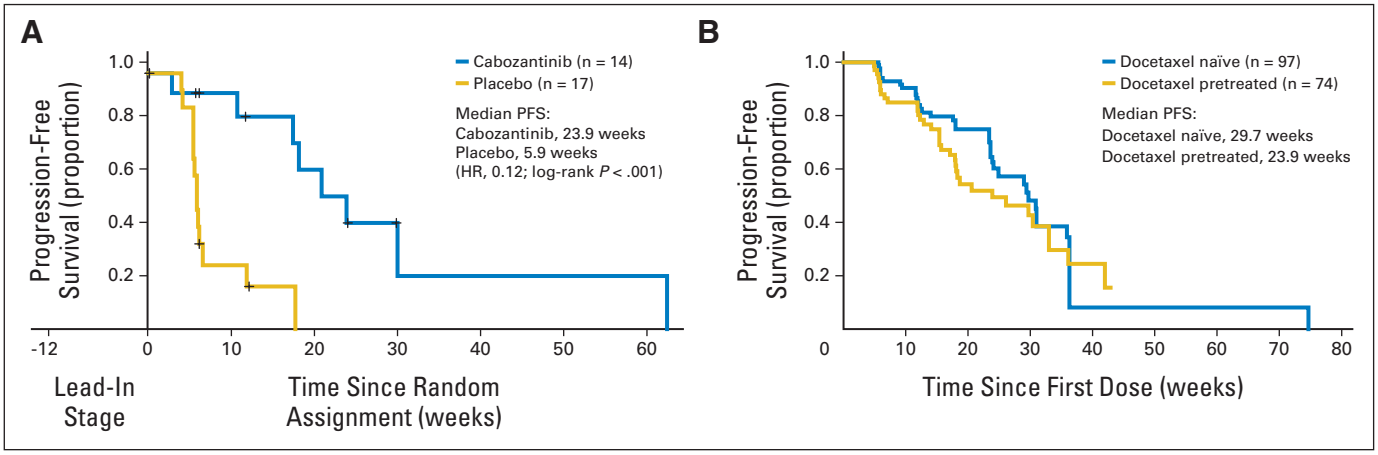

Fig 3. Kaplan-Meier estimates of progression-free survival (PFS) in (A) randomly assigned patients with castration-resistant prostate cancer (CRPC) and (B) patients with CRPC by docetaxel pretreatment status. Panel A shows the probability of PFS from week 12 random assignment for patients with CRPC randomly assigned to continued treatment with cabozantinib (n = 14) or placebo (n = 17). Panel B shows the probability of PFS for all patients with CRPC (n = 171) by docetaxel pretreatment status from first dose of cabozantinib. HR, hazard ratio.

PSA is not a reliable surrogate of clinical outcome in the context of treatment with cabozantinib.

Association of Bone Scan Findings With Other Clinical Parameters

Bone scan improvement was associated with other measures of antitumor effect and clinical benefit (Appendix Fig A4, online only). More patients with complete or partial resolution of bone scans, compared with patients with either stable or progressive bone scans, had regression of measurable soft tissue disease (81% *v* 61%, respectively) and CTx decrease ≥ 50% (62% *v* 48%, respectively); in addition, patients with complete or partial resolution of bone scans demonstrated a higher PFS rate at 6 months (56% *v* 41%, respectively). Moreover, among patients with bone pain and narcotic use at baseline, those with bone scan resolution, compared with those without resolution, were more likely to experience pain relief (93% *v* 35%, respectively) and reduced narcotic use (72% *v* 23%, respectively).

Safety

Adverse events irrespective of causality reported in ≥ 10% of patients during the lead-in stage of the study are listed in Table 3. All patients had at least one adverse event, and the majority of patients experienced more than one. The most common all-grade adverse events were a variable cluster of symptoms consisting of fatigue, decreased appetite, taste alterations, nausea, diarrhea, weight loss, and palmar-plantar erythrodysesthesia (hand-foot syndrome), which resulted in dose reductions in 62% of patients (106 of 171 patients). These events typically responded promptly to drug interruption and dose reduction. The most common grade ≥ 3 adverse events were fatigue (16%), hypertension (12%), palmar-plantar erythrodysesthesia (8%), dehydration (8%), pulmonary embolism (7%), decreased appetite (6%), and nausea (5%). One patient died while on study treatment (unexplained death). The most common serious adverse events were pulmonary embolism (6%) and dehydration and vomiting (each 5%).

DISCUSSION

Bone is the major site of metastatic disease in men with prostate cancer, and bone metastases provide the most significant clinical challenges in the management of patients with CRPC. In this study, cabozantinib demonstrated dramatic and rapid effects on bone scan lesions

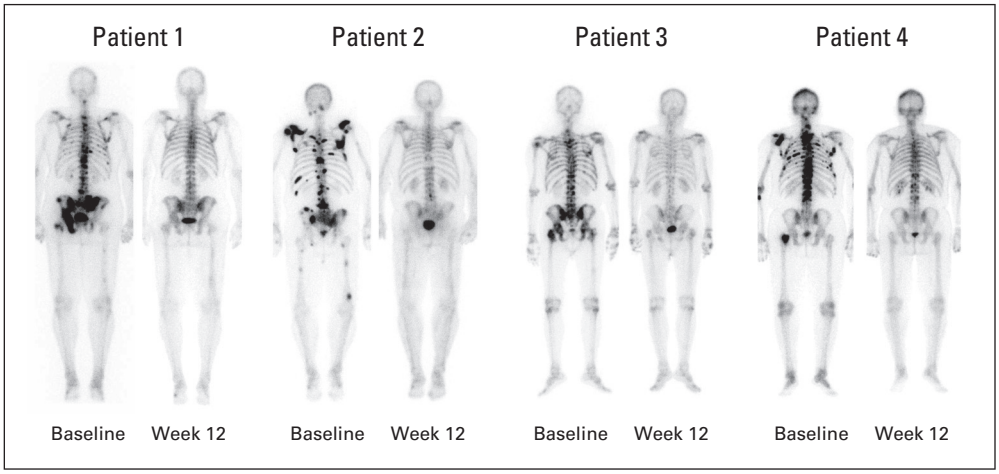

Fig 4. Bone scan effects of cabozantinib treatment on study patients. Sequential whole-body technetium methylene diphosphonate bone scintigraphy is shown of four patients with advanced metastatic prostate cancer. Baseline scans show multiple areas of increased radiotracer uptake indicative of extensive bone metastases. Treatment with cabozantinib resulted in complete or partial resolution of bone scans at week 12. Bone scan resolution correlated with partial response of tumor lesions in soft tissue and pain relief in each patient.

Table 3. Most Frequently Reported Adverse Events During Lead-In Stage Regardless of Causality (N = 171)

Adverse Event	All Grades		Grade ≥3	
	No. of Patients	%	No. of Patients	%
Fatigue	108	63	27	16
Decreased appetite	93	54	10	6
Diarrhea	87	51	5	3
Nausea	83	49	8	5
Weight decreased	58	34		
Constipation	57	33	1	1
PPE syndrome	52	30	13	8
Dysgeusia	50	29		
Dysphonia	50	29		
Vomiting	48	28	6	4
Hypertension	38	22	21	12
Mucosal inflammation	36	21	2	1
Asthenia	34	20	7	4
Dyspnea	28	16	4	2
Hypothyroidism	25	15		
Abdominal pain	24	14	5	3
Rash	23	13	2	1
Cough	22	13	1	1
Dehydration	19	11	13	8
AST increased	19	11	5	3
Dizziness	19	11	1	1
Stomatitis	19	11	1	1
Dyspepsia	18	11	1	1
Dry mouth	18	11		
Oral pain	18	11		
Gastroesophageal reflux disease	17	10		
Insomnia	17	10		

NOTE. For the most frequently reported adverse events (≥ 10%), three grade 4 events were reported (pain, abdominal pain, and AST increased).
Abbreviation: PPE, palmar-plantar erythrodysesthesia.

in a high proportion of patients. The effects seen on bone scan are echoed in other measures of antitumor effect. Although the response rate measured by RECIST is relatively low (5%), four out of five of these men with progressive measurable disease at baseline had at least stable soft tissue disease at the 12-week time point, and more than 70% had a decrease in the measurements of their soft tissue lesions. The objective changes in soft tissue lesions seem to correlate with a decrease in uptake on bone scan in the majority of patients treated, but the effects in bone and soft tissue seem to occur independently of a change in PSA. Cabozantinib-treated patients showed consistent effects on markers of bone formation and resorption, bone pain, and narcotic use, and in the randomly assigned cohort, statistically significant improvement in PFS was seen with cabozantinib compared with the placebo group.

The observed effects on bone scan are unprecedented in the treatment of CRPC. The actual mechanism of the reduction in uptake on bone scan seen in these patients remains unclear. Uptake of radiotracer in bone depends on blood flow and osteoblastic activity, and decreased uptake may be attributable to interruption of blood flow, direct modulation of osteoblastic activity, direct effect on the tumor cells, or a combination of these processes. Only occasional cases of decreased uptake on bone scan in men with CRPC have been reported in clinical trials with other VEGF/VEGFR-targeted therapies, abiraterone, docetaxel, or dasatinib, and no changes in bone lesions were reported in a trial using a selective MET inhibitor.[23-27] These results suggest that selectively targeting VEGFR alone, VEGF alone, MET alone, or the tumor cells and/or osteoclasts individually does not result in the bone scan effects observed in patients with CRPC treated with cabozantinib.[28] The correlations between bone scan and changes in soft tissue, along with the reductions of bone turnover markers and independence of prior bisphosphonate therapy, suggest that cabozantinib has direct effects on tumor cells and the bone microenvironment. Further studies including direct sampling of tissues will be required to define the pathways involved in these effects and to assess the antitumor effects.

The results from this cohort of men with metastatic CRPC raise several additional important questions. On the basis of the unexpected improvement on bone scans coupled with substantial improvements in reported pain and the observation that men randomly assigned to placebo had rapid recurrence of symptoms related to bone disease, the SOC concluded that it was unethical to continue random assignment in this cohort. The result of this decision is a small randomly assigned population. Although the results from the randomized cohorts are suggestive of benefit, PFS is difficult to measure in CRPC, and the impact of therapy on overall survival is unknown. True benefit will only be determined from randomized trials, and phase III studies (Cabozantinib MET Inhibition CRPC Efficacy Trial [COMET] 1 and 2) have been initiated to evaluate the effect of cabozantinib on morbidity and mortality in patients with CRPC with bone metastases. The positive effects on bone and soft tissue lesions were demonstrated in the context of adverse effects, which, while typical of tyrosine kinase inhibitors, resulted in frequent dose reductions. Strategies for the management of these adverse effects and evaluation of alternate dosing regimens will be required. The improvement in bone pain and decrease in narcotic use with cabozantinib treatment were from a retrospective chart review that cannot assess the balance between decreased pain and adverse effects of therapy. The impact of cabozantinib on the quality of life of men with CPRC will require prospective evaluation of patient-reported outcomes using standardized measures.

In conclusion, this study demonstrates that cabozantinib has substantial antitumor activity in patients with advanced CRPC with manageable toxicity consistent with other tyrosine kinase inhibitors targeting multiple pathways. These results indicate a potential cooperative role for c-MET and VEGF signaling in the progression of CRPC and suggest that dual targeting of tumor and microenvironment may lead to an improved outcome for patients with CRPC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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