JOURNAL OF CLINICAL ONCOLOGY

Cabozantinib in Chemotherapy-Pretreated Metastatic Castration-Resistant Prostate Cancer: Results of a Phase II Nonrandomized Expansion Study

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See accompanying article on page 3436; listen to the podcast by Drs Suzman and Antonarakis at www.jco.org/podcasts

ABSTRACT

Purpose
Cabozantinib (XL184), an oral inhibitor of multiple receptor tyrosine kinases such as MET and VEGFR2, was evaluated in a phase II nonrandomized expansion study in castration-resistant prostate cancer (CRPC).

Patients and Methods
Patients received open-label cabozantinib at daily starting doses of 100 mg or 40 mg until disease progression or unacceptable toxicity. The primary end point was bone scan response, defined as ≥ 30% reduction in bone scan lesion area. Other efficacy end points included overall survival, pain, analgesic use, and biomarkers.

Results
One hundred forty-four patients sequentially enrolled in either a 100-mg (n = 93) or 40-mg (n = 51) study cohort. Ninety-one patients (63%) had a bone scan response, often by week 6. Treatment resulted in clinically meaningful pain relief (57% of patients) and reduction or discontinuation of narcotic analgesics (55% of patients), as well as improvements in measurable soft tissue disease, circulating tumor cells, and bone biomarkers. Improvements in each of these outcomes were observed in both cohorts: bone scan response in 73% and 45%, respectively; reductions in measurable soft tissue disease in 80% and 79%, respectively. Median overall survival was 10.8 months for the entire population. Most common grade 3 or 4 adverse events were fatigue (22%) and hypertension (14%). Fewer dose reductions because of toxicity were required in the 40-mg group.

Conclusion
The evidence suggests that cabozantinib has clinically meaningful activity in CRPC. Cabozantinib resulted in improvements in bone scans, pain, analgesic use, measurable soft tissue disease, circulating tumor cells, and bone biomarkers. Taken together, these phase II observations warrant further development of cabozantinib in prostate cancer.

J Clin Oncol 32:3391-3399. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Cabozantinib (XL184) is an oral inhibitor of multiple receptor tyrosine kinases, including MET and vascular endothelial growth factor receptor 2 (VEGFR2). Treatment in multiple tumor xenograft models, including prostate cancer, results in rapid induction of both endothelial and tumor cell apoptosis.[1] Cabozantinib also has potent effects on the bone microenvironment, including osteoclast and osteoblast differentiation in vitro and, at higher concentrations, inhibition of osteoblast activity.[2] Con-

sistent with these effects, cabozantinib inhibits progression of both osteoblastic and osteolytic lesions in xenograft models of metastatic castration-resistant prostate cancer (CRPC).[3,4]

A randomized discontinuation trial (RDT) of cabozantinib suggested a clinically important role for dual MET/VEGFR inhibition in prostate cancer.[5] In men with metastatic CRPC (n = 171), cabozantinib (100 mg daily) treatment markedly increased progression-free survival compared with placebo (hazard ratio, 0.12; P < .001). Cabozantinib was associated with pain improvement and decreased narcotic

requirements, soft tissue disease, and biomarkers of osteoclast and osteoblast activity. In posthoc analyses of patients with bone metastases, cabozantinib resulted in a high rate of rapid and dramatic improvements in bone scan by visual assessment. Notably, more than 60% of patients required dose reductions because of adverse effects, similar to what has been observed with other tyrosine kinase inhibitors that target VEGFR. A subsequent single-institution dose-ranging study of men with metastatic CRPC reported bone scan improvements in most patients treated with cabozantinib at a lower starting dose of 40 mg daily,[6] with more modest effects at the lowest dose tested (20 mg daily). Importantly, fewer dose reductions and treatment interruptions were required at lower starting doses.

Whole-body technetium-99 bone scan is a standard imaging modality for detection and monitoring of bone metastases. Regions of uptake are an indirect measure of metastatic activity reflecting areas of newly deposited hydroxyapatite matrix. In contrast to other radiologic imaging modalities, no accepted standards exist to define a favorable outcome in bone metastases. Brown et al[7] analytically validated a quantitative biomarker of osseous disease on a technetium-99 bone scan, bone scan lesion area (BSLA), measured with a fully automated computer-aided detection system. The software was cleared by the US Food and Drug Administration and enables reproducible assessments of changes in individual lesions and total disease burden over time.

We conducted a nonrandomized expansion study of men with CRPC, bone metastases, and disease progression despite prior treatment with docetaxel (ClinicalTrials.gov trial No. NCT00940225). We enrolled two cohorts at starting doses of 100 mg and 40 mg daily. These dose levels were chosen to confirm encouraging but mostly posthoc observations from the phase II RDT and promising results of a single-institution dose-finding study. The prespecified primary end point was bone scan response, defined as at least a 30% improvement in BSLA. Our article describes the results of these two cohorts.

PATIENTS AND METHODS

Patients

Eligible patients had CRPC and bone metastases on bone scan, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic and end-organ function. All patients had received at least one previous docetaxel-containing regimen (with cumulative docetaxel exposure $\geq$ 225 mg/m^2) and had disease progression (radiographic disease progression in either soft tissue or bone or radiation treatment of bone lesion) during or within 6 months of their most recent standard treatment with a taxane or abiraterone-containing regimen. Patients with more than three previous chemotherapy regimens, brain metastases, or clinically significant intercurrent illnesses were excluded. Our study was conducted in compliance with the Declaration of Helsinki. Institutional review boards of participating institutions reviewed and approved study protocol and informed-consent documents. Informed consent was obtained before any study-specified procedures.

Study Design

Our study sequentially enrolled patients in two cohorts: at a 100-mg starting dose and then at a 39.4-mg (denoted as 40-mg) starting dose. The prespecified primary end point was bone scan response, defined as an at least 30% reduction in BSLA from baseline as assessed by independent radiology review. Additional end points included overall survival (OS), pain, use of analgesic medications, effects on soft tissue, and changes in biomarkers. All patients received study treatment until disease progression or unacceptable toxicity.

Study Drug Administration

Patients received an initial daily starting dose of cabozantinib at 100 mg (first cohort) or 40 mg (second cohort). Treatment was interrupted for intolerable grade 2 toxicity, grade $\geq$ 3 toxicity of significant clinical risk despite optimal management, urine protein/creatinine ratio of more than 1, or any grade 4 hematologic toxicity; therapy was restarted if toxicity resolved to grade $\leq$ 1 or baseline levels within 6 weeks. If the adverse event was unrelated to study therapy, treatment was resumed with no dose change. If the adverse event was related to study treatment, patients in the 100-mg cohort resumed at a reduced dose of 60 mg/day, with subsequent dose reductions to 40 mg/day and 20 mg/day; patients in 40-mg cohort resumed at a dose of 20 mg/day. Dose interruption for more than 6 weeks required discontinuation of study treatment.

Study Assessments

Our study followed Prostate Cancer Working Group 2 guidelines, including description of results by individual disease manifestations.[8]

Bone scans. We acquired whole-body PA and AP bone scans using a Digital Imaging and Communications in Medicine standardized protocol. When possible, we used the same camera, technetium isotope dose, and delay from injection to scanning for baseline and follow-up scans. We analyzed bone scans using a 510(k)-cleared automated computer-aided detection system (IBIS, MedQIA, Los Angeles, CA) to objectively identify and quantify bone metastases.[7] After image normalization, the software automatically identified and marked all candidate lesions. Using a locked sequential reading paradigm, two experienced readers independently reviewed CAD segmentation output. Readers could accept, modify, remove, or add lesions. Readers also classified post-treatment bone scans as complete resolution (complete disappearance of all lesions consistent with bone metastases), partial resolution (clear evidence of improvement), stable disease (unchanged), or progressive disease (evidence of two or more new lesions) relative to baseline scans. All readers were blinded to patients' clinical and biochemical status.

Bone scan lesion area. For each time point, the system calculated BSLA and percentage change in BSLA between each time point and baseline scan. We defined bone scan outcomes based on change from baseline as follows: response was $\geq$ 30% reduction in lesion area; progressive disease was $\geq$ 30% increase in lesion area (or two new lesions); stable disease was any change not categorized as response or progressive disease.[7]

Overall survival. OS was defined as time from first dose until date of death as a result of any cause or censoring at last date known alive at time of data analysis cutoff.

PSA, CTCs, hemoglobin and reticulocytes, and bone turnover markers. Additional outcomes included serum prostate-specific antigen (PSA), circulating tumor cells (CTCs), hemoglobin, reticulocyte count, and bone biomarkers (serum N-terminal cross-linked telopeptides of type I collagen [NTx], C-terminal cross-linked telopeptides of type I collagen [CTx], and bone-specific alkaline phosphatase [BSAP]).

Pain assessments. Patients reported daily their worst pain (via Interactive Voice Response System) and analgesic medication usage (via diary) during 7-day intervals (at least four of seven days) at screening, week 3, week 6, and every 6 weeks thereafter.

Clinical assessments. Clinical assessments included medical and cancer history, physical examination, vital signs, body weight, electrocardiography, Eastern Cooperative Oncology Group performance status, laboratory analyses (serum chemistry, hematology [including reticulocyte counts], coagulation, urinalysis, testosterone), concomitant medications, adverse events, and information on subsequent anticancer treatment.

Sample analyses. Blood samples for CTC analysis were collected in CellSave tubes, and enumeration was performed using CellSearch assay[9] at Veridex (Huntingdon Valley, PA and Beerse, Belgium) or Memorial Sloan-Kettering Cancer Center Clinical Chemistry Laboratory (New York, NY). Bone biomarkers were assessed at Covance Central Laboratories (NTx: Osteomark NTx serum competitive inhibition ELISA kit, Wampole Laboratories, Princeton, NJ; CTx: Crosslaps ELISA, Immunodiagnostic Systems AC-02F1 Immunodiagnostic Systems, Scottsdale, AZ; BSAP: Ostase assay, Beckman Coulter, Brea, CA). For patients with measurable CTx/NTx at baseline whose

postbaseline values dropped below the lower limit of quantitation, the lower limit of quantitation was used in calculations of postbaseline effects.

Statistical Methods and Considerations

The study was designed to enroll a sufficient number of patients to estimate changes in multiple outcome measures rather than focus on a single outcome measure. A sample size of 150 patients at the 100-mg dose level was originally chosen to permit estimation of changes in each outcome with confidence intervals of no more than 16 percentage points. The protocol was subsequently amended to include a 40-mg dose level using the same total sample size of 150 patients.

Study outcomes including prespecified bone scan response were summarized for overall population and each cohort. Time-to-event outcomes were analyzed using Kaplan-Meier plots and summaries.

RESULTS

Patients and Treatment

From February 2011 to April 2012, 144 CRPC patients with bone metastases in the United States and United Kingdom were sequentially enrolled into 100-mg (n = 93) and 40-mg cohorts (n = 51). Baseline demographic and clinical characteristics are listed in Table 1. All but one patient had radiographic progression within 6 months of their last taxane dose. For the overall study population, 44% and 24% had received prior abiraterone and cabazitaxel, respectively. Zoledronic acid or denosumab treatment at baseline was reported in 63% of patients. Compared with the 100-mg cohort, patients in the 40-mg cohort had higher rates of prior abiraterone treatment (65% v 32%) and disease progression within 1 month of last taxane dose (49% v 29%).

Figure 1 summarizes patient disposition as of data cutoff. Median time on treatment was 4.4 months (range, 0.8 to 16.4) for the 100-mg cohort and 4.2 months (range, 0.3 to 9.1) for the 40-mg cohort. Progressive disease or clinical deterioration was the most common reason for treatment discontinuation in both cohorts. The median average daily dose received by patients in 100-mg and 40-mg cohorts was 55 mg and 36 mg, respectively.

Bone Scan Outcomes by Independent Radiology Review

Ninety-one patients (63%) had a prespecified bone scan response ($\geq$ 30% reduction in BSLA), 27 patients (19%) had stable disease, and 14 patients (10%) had progressive disease as best bone scan outcome (Table 2). Figure 2A illustrates percentage change in BSLA in patients evaluable for BSLA changes. Median bone scan response duration was 5.2 months (range, $\geq$ 0.03 to $\geq$ 13.9 months; Table 2). Bone scan response rate was higher in the 100-mg cohort than the 40-mg cohort (73% v 45%). Improvements in bone scans were rapid, with most patients categorized as responders at week 6 (first time point). Reader-determined visual responses and CAD-calculated changes in BSLA were concordant (overall Kappa = 0.8).

Measurable Disease Outcomes

Among 54 patients with measurable soft tissue disease at baseline and at least one adequate postbaseline assessment, 43 patients (80%) had reduction in measurable disease at one or more assessments (Fig 2B). Rates of improvement in measurable disease were similar for the 100-mg and 40-mg cohorts (80% v 79%).

Table 1. Baseline Demographic and Clinical Characteristics of Patients

Characteristic	100-mg Cabozantinib Cohort (n = 93)	40-mg Cabozantinib Cohort (n = 51)	Total (N = 144)
Age, years			
Median	66	65	65
Range	46-85	43-83	43-85
ECOG status, %			
0	34	35	35
1	65	65	65
2	1	0	1
Sites of disease, %			
Bone*	100	100	100
Visceral	31	33	32
Measurable disease, %	41	41	41
Pain score $\geq$ 4, %	44	53	47
Pain score $\geq$ 4 and narcotics, %	42	45	43
Fatigue any grade, %	54	57	55
$\geq$ Two prior regimens for mCRPC, %	73	73	73
Prior therapies, %			
Docetaxel	100	100	100
Abiraterone	32	65	44
Cabazitaxel	24	25	24
Enzalutamide	4	4	4
Radionuclide†	5	6	6
Bone agents, %‡	62	63	63
Time to progression from last taxane dose, %§			
< 1 month	29	49	36
1-6 month	71	49	63
PSA, ng/mL			
Median	194	146	188
Range	0.2-2,990	9-2,428	0.2-2,990
CTC count per 7.5 mL blood			
Median	49	25	37
Range	0-1,659	0-3,959	0-3,959
Hemoglobin, g/dL¶			
Median	11.8	11.5	11.6
Range	8.5-17.1	8.5-14.5	8.5-17.1
Reticulocyte counts, %¶			
Median	1.8	2.1	1.9
Range	0.8-4.5	0.9-3.9	0.8-4.5
LDH, %			
> ULN	56	59	57
$\leq$ ULN	44	39	42

NOTE. Percentages may not add up to 100% because of rounding.
Abbreviations: CAD, computer-aided detection; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; ULN, upper limit of normal.
*Baseline bone scans for 49 of 51 patients (40-mg dose cohort) and 92 of 93 patients (100-mg dose cohort) reported to have bone metastases by the investigator were evaluable by CAD.
†Includes one patient in the 100-mg dose cohort who had prior alpharadin.
‡Zoledronic acid or denosumab at baseline (includes two patients who discontinued zoledronic acid within 60 days before first dose of cabozantinib).
§Not applicable for one patient in the 40-mg dose cohort.
¶Restricted to patients who did not require transfusion or erythropoietin treatment while on study (as analyzed in Table 2).

Bone Pain and Narcotic Use

At baseline, 68 men (47%) reported moderate to severe pain (defined as an average worst pain score $\geq$ 4 on the 11-point (0-10) brief pain inventory scale; Table 1). Among these men, 65 had at least
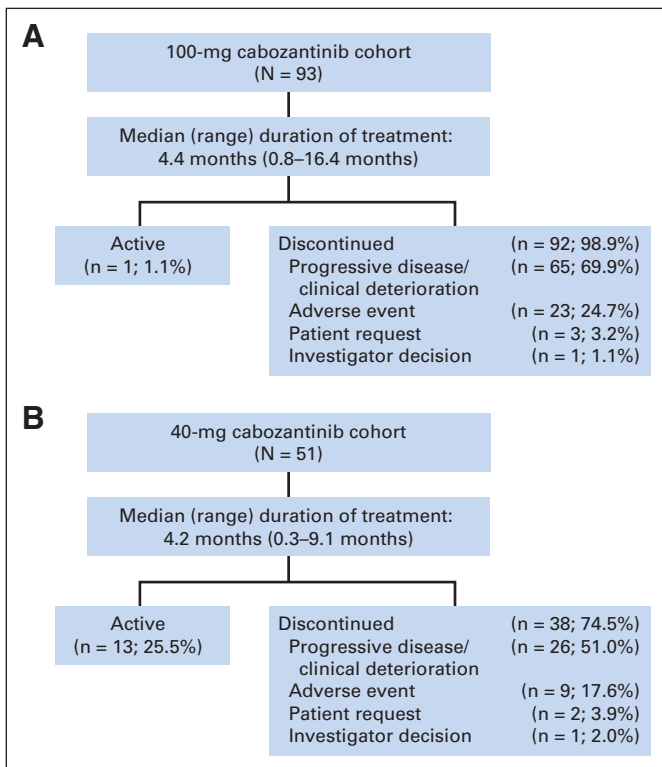
Fig 1. Patient disposition as of data cutoff point for this report.

one adequate postbaseline pain assessment and were evaluated for pain responses (Table 2). Forty-four (68%) of the 65 men reported a pain decrease of at least 30% as their best change (Fig 2C); 37 men (57%) had clinically meaningful pain relief at two consecutive assessments (≥ 30% reduction from baseline; Table 2),[10] with the majority at least 6 weeks apart. Similar effects on pain were observed in both cohorts (Table 2; Fig 2C). Reductions in narcotics occurred in 55% of patients, including discontinuation of narcotics in 13 patients (Table 2). Pain palliation occurred as early as first pain assessment at week 3 (data not shown); detailed analyses on pain and narcotics use in these patients are described elsewhere (Basch et al[11]).

Biomarkers

Circulating tumor cells. Post-treatment changes in CTC counts were assessed in 103 patients with baseline unfavorable CTC counts (≥ 5 per 7.5 mL blood) and at least one follow-up assessment at week 6 or 12 (Table 2). At week 6, 30% of patients converted from unfavorable to favorable CTC counts (< 5 per 7.5 mL blood). Eighty-two percent of patients had a decrease of at least 30% in CTCs at week 6 and/or 12. Changes were similar for both cohorts. Best change in CTCs at week 6 and/or 12 for patients with baseline CTCs ≥ 5 is illustrated for each cohort in Figure 3A. CTC outcomes were not related to prior cancer therapy (data not shown).

Prostate-specific antigen. Among 131 patients with baseline and at least one postbaseline PSA assessment, 14 patients (11%) had a decrease of at least 50% in PSA from baseline as best change (Table 2).

Hemoglobin and reticulocyte counts. RBC transfusions or erythropoietin-based growth factor therapy were required in 27 of 144 patients. Effects on hemoglobin and reticulocyte counts were evalu-

ated in patients who did not require these interventions; median maximum increases in hemoglobin levels and reticulocyte count were 1.4 g/dL (range, −1.3 to 3.7 g/dL) and 0.2% (range, −1.7% to 2.6%), respectively. The largest increases in both hemoglobin and reticulocytes were observed in patients with baseline hemoglobin levels below median value (Table 2).

Bone biomarkers. We analyzed biomarkers of bone metabolism (NTx, CTx, BSAP) in serially collected serum samples. Among patients with at least one follow-up assessment, median changes in CTx from baseline to week 12 were 37% and 31% decreases for the 100- and 40-mg cohorts, respectively (Fig 3B and Table 2). We observed similar changes for NTx (data not shown). Modulations of BSAP were also evident, with 72% and 50% of patients showing a decrease at week 12 or later for the 100- and 40-mg cohorts, respectively (Fig 3C and Table 2). We observed changes in bone biomarkers regardless of prior bisphosphonate or denosumab therapy (data not shown).

Overall Survival

Median OS in the overall study population was 10.8 months (95% CI, 9.1 to 13.0). Median OS was 12.1 months (95% CI, 9.4 to 14.3) and 9.1 months (95% CI, 8.0 to 12.9) in the 100-mg and 40-mg cohorts, respectively.

Safety

The most frequent adverse events reported regardless of attribution are listed in Table 3. All patients experienced at least one adverse event and most patients experienced more than one event. The most common grade ≥ 3 events in all patients, regardless of causality, were fatigue (22%), hypertension (14%), anemia (13%), and pulmonary embolism (11%). Rate of grade ≥ 3 pulmonary embolism was 8% in the 100-mg cohort and 18% in 40-mg cohort. One patient in the 100-mg cohort who had extensive liver involvement experienced a related grade 3 portal vein thrombosis with grade 5 liver failure.

In the 100-mg cohort, 84% of patients had at least one dose reduction and 25% discontinued treatment because of an adverse event. Median time to first dose reduction for the 100-mg cohort was 32 days (range, 5 to 170 days). In the 40-mg cohort, 31% of patients had at least one dose reduction because of an adverse event and 18% of patients discontinued treatment because of an adverse event. These different rates of dose reduction resulted in a lower dose intensity (administered dose/intended dose) for the 100-mg cohort (55%) compared with the 40-mg cohort (90%). Median average daily doses received in the 100-mg and 40-mg cohorts was 55 mg/day and 36 mg/day, respectively.

DISCUSSION

In this multicenter, phase II, nonrandomized expansion study of men with CRPC, bone metastases, and disease progression despite docetaxel treatment, cabozantinib was associated with improvements in bone scans, patient-reported pain and analgesic use, measurable disease, CTCs, and bone biomarkers. Taken together, these observations suggest that cabozantinib (at doses as low as 40 mg daily) is biologically active in metastatic CRPC and support its further development in prostate cancer.

Results of this study extend observations from the previously reported RDT that cabozantinib improves a variety of disease-related outcomes in patients with metastatic CRPC.[5] In contrast to the RDT,

	100-mg Cabozantinib Cohort (n = 93)		40-mg Cabozantinib Cohort (n = 51)		Total (N = 144)	
Table 2. Responses to Treatment						
End Point	No. of Patients	%	No. of Patients	%	No. of Patients	%
Bone scan						
Response rate, primary end point*	68	73	23	45	91	63
Partial response		69		43		60
Complete response		4		2		3
Stable disease		12		31		19
Progressive disease†		8		14		10
Duration of response in months‡						
Median	5.2		NR		5.2	
Range	≥ 0.03-≥ 13.9		1.4-≥ 6.9		≥ 0.03-≥ 13.9	
Pain and narcotics use in patients with baseline pain score ≥ 4						
No. of evaluable patients	39		26		65	
Median best change, % reduction		46		49		46
Pain response§	22	56	15	58	37	57
Decreased narcotics use at any time point¶	22	56	14	54	36	55
CTCs in patients with baseline ≥ 5 per 7.5 mL blood						
No. of patients evaluable for changes at week 6 and/or 12	64		39		103	
Median CTC count, n	80		36		66	
Converted to < 5 per 7.5 mL blood at week 6		34		23		30
At least 30% reduction at week 6 and/or 12		91		67		82
Median change from baseline, % decrease		86		70		84
CTCs in patients with baseline < 5 per 7.5 mL blood						
No. of patients evaluable for changes at week 6 and/or 12	17		10		27	
Converted to ≥ 5 per 7.5 mL blood at week 6 and/or 12		18		10		15
PSA						
No. of patient evaluable	86		45		131	
≥ 50% reduction, best change from baseline		13		7		11
Hemoglobin changes independent of transfusion or erythropoietin						
Median maximal increase in evaluable patients, g/dL	1.4		1.2		1.4	
Median maximal increase in patients with baseline hemoglobin ≤ median	1.7		1.5		1.5	
Reticulocyte changes independent of transfusion or erythropoietin						
Median maximal increase in evaluable patients	0.2		0.1		0.2	
Median maximal increase in patients with baseline hemoglobin ≤ median	0.3		0.3		0.3	
Bone turnover markers						
No. of patients evaluable for CTx changes at week 12	50		16		66	
Median change at week 12, % reduction		37		31		34
No. of patients evaluable for BSAP changes at week 12 or later	74		38		112	
Percentage of patients with a decrease at week 12 or later		72		50		64

NOTE. Percentages may not total 100% because of rounding.
Abbreviations: BSAP, bone-specific alkaline phosphatase; CAD, computer-aided detection; CTC, circulating tumor cell; CTx, C-terminal cross-linked telopeptides of type I collagen; NR, not reached as of data cutoff point; PSA, prostate-specific antigen.
*Complete responders plus partial responders. Complete response is defined as 100% reduction of bone scan lesion area; partial response is defined as ≥ 30% reduction of bone scan lesion area. Of the 144 men enrolled onto the study, 132 (100-mg cohort, 86 patients; 40-mg cohort, 46 patients) had bone metastases on baseline bone scan and at least one evaluable post-baseline scan for bone scan response per CAD.
†Two or more new areas of uptake or unequivocal increase of uptake at metastatic sites.
‡In the 100-mg cohort, 68 patients were evaluated and, in the 40-mg cohort, 23 were evaluated for a total of 91 patients.
§At least a 30% reduction from baseline in average worst pain score measured at two consecutive assessments, which includes eight patients whose consecutive assessments were at weeks 3 and 6. For the remaining patients, the two consecutive assessments were at least 6 weeks apart.
¶Includes patients who discontinued narcotics at any time point (40-mg cohort, n = 1; 100-mg cohort, n = 12). Equianalgesia calculations were used to determine changes in narcotics use for patients who modified narcotics types throughout the assessments.

however, patients in our current study had greater disease burden, more pain and narcotic requirements, and more extensive prior therapy. Notably, all patients in our current study had bone metastases and disease progression despite prior docetaxel treatment. Accordingly, patients in our current study had a worse prognosis than patients enrolled onto the RDT and most other contemporary studies of metastatic CRPC. Improvements in a variety of disease-related outcomes in this heavily treated population suggest that cabozantinib does not share mechanism(s) of resistance with other prostate cancer treat-

ments including docetaxel, cabazitaxel, and abiraterone. The apparent nonoverlapping resistance between cabozantinib and other agents may reflect targeting of tumor, stroma, and tumor-stroma interactions by cabozantinib.

Two ongoing randomized controlled trials will further evaluate the efficacy and safety of cabozantinib in mCRPC. COMET-1 (clinicaltrials.gov identifier: NCT01605227) compares cabozantinib with prednisone; the primary end point is OS. COMET-2 (clinicaltrials.gov identifier: NCT01522443) compares cabozantinib with mitoxantrone
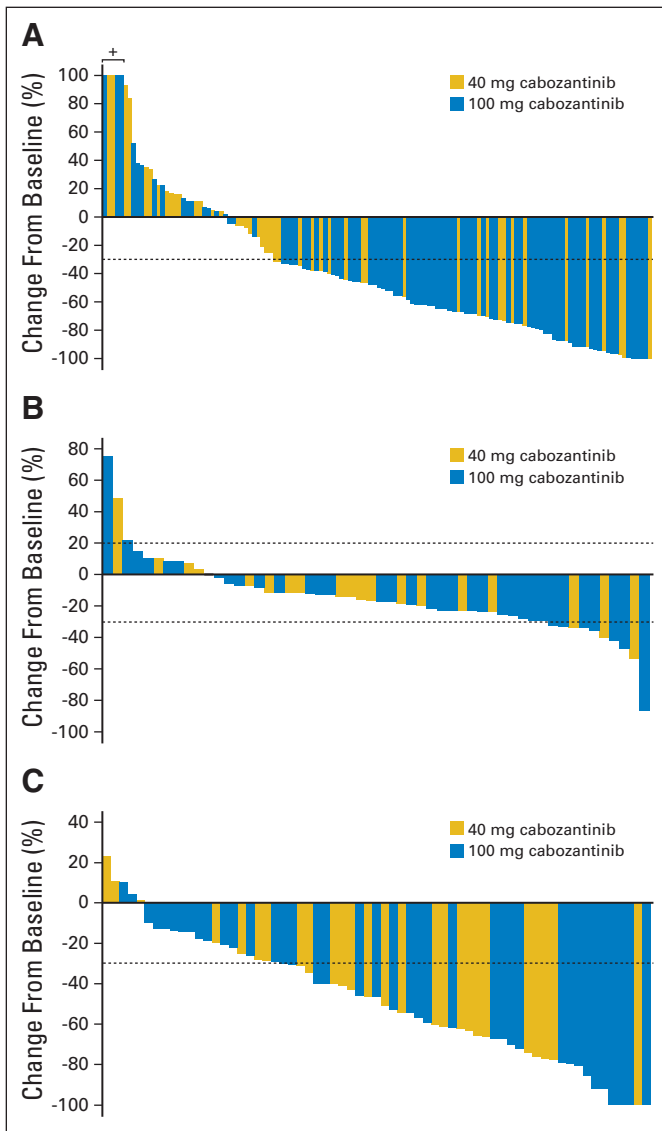
Fig 2. (A) Bone scan lesion area. Best change from baseline in bone scan lesion area in the 132 patients evaluable for the primary end point (100-mg cohort, n = 86; 40-mg cohort, n = 46), bone scan response (Table 2). Median change in bone scan lesion area was a 49% reduction. The dashed line denotes a 30% reduction defined as bone scan response by computer-aided detection (CAD; Table 2). Values higher than 100% are represented as 100% because of y axis truncation at 100%; (+), increases greater than 100%. (B) Soft tissue lesions. Best change from baseline in soft tissue lesions in 54 patients (100-mg cohort, n = 35; 40-mg cohort, n = 19) with measurable disease at baseline and ≥ 1 postbaseline assessment. Median change in sum of longest diameter was a 17% reduction. Stable disease per Response Evaluation Criteria in Solid Tumors is represented by the space between the dashed lines. (C) Pain. Best change from baseline in average worst pain in patients with baseline score ≥ 4 (100-mg cohort, n = 39; 40-mg cohort, n = 26) and at least one adequate postbaseline assessment. The dashed line denotes 30% improvement in average worst pain score.

Fig 3. (A) Circulating tumor cells (CTCs). Best change from baseline in CTCs in patients with at least five baseline CTCs and week 6 and/or week 12 assessment (100-mg cohort, n = 64; 40-mg cohort, n = 39). (B) C-terminal cross-linked telopeptides of type I collagen (CTx). Percentage change from baseline for serum CTx at week 12 (100-mg cohort, n = 50; 40-mg cohort, n = 16). (C) Bone-specific alkaline phosphatase (BSAP). Best change from baseline for serum BSAP at week 12 or later (100-mg cohort, n = 74; 40-mg cohort, n = 38). Values higher than 100% are represented as 100% because of y axis truncation at 100%; (+), denotes increases greater than 100%.

plus prednisone in patients with symptomatic disease; the primary end point is pain response. Both studies include patients with bone metastases and disease progression after docetaxel and either abiraterone or enzalutamide.

Ours is the first multicenter study to use prespecified bone scan response as the primary study outcome. The results demonstrate the potential for CAD-based quantitative bone scan as a dynamic assessment of bone metastases. Notably, the COMET-1 and COMET-2

phase III studies include CAD-based quantitative bone scan outcomes as secondary end points, which will provide the opportunity to critically evaluate relationships between bone scan outcomes and clinical outcomes including pain response and OS.

Outcomes for the 100-mg and 40-mg cohorts are not directly comparable because the study was not randomized and there were important differences in baseline characteristics between sequentially enrolled cohorts. Furthermore, the median average daily dose in the 100-mg cohort was 55 mg/day, further minimizing the true difference in actual dose administered between cohorts. These observations support using 60-mg daily as the starting dose in COMET-1 and COMET-2.

Adverse Event*	All Grades				Grade $\geq$ 3			
	100-mg Cabozantinib Cohort (n = 93)		40-mg Cabozantinib Cohort (n = 51)		100-mg Cabozantinib Cohort (n = 93)†		40-mg Cabozantinib Cohort (n = 51)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Fatigue	77	83	32	63	25	27	7	14
Decreased appetite	70	75	23	45	7	8	4	8
Nausea	67	72	29	57	11	12	0	0
Diarrhea	66	71	22	43	11	12	1	2
Decrease in weight	42	45	19	37	6	6	0	0
Vomiting	38	41	18	35	4	4	0	0
Dysgeusia	35	38	14	27	0	0	0	0
Dysphonia	34	37	9	18	0	0	1	2
Constipation	33	35	16	31	4	4	2	4
Dyspnea	30	32	13	25	6	6	1	2
Hypothyroidism	30	32	4	8	0	0	0	0
Arthralgia	29	31	6	12	4	4	2	4
Back pain	29	31	15	29	10	11	5	10
Anemia	28	30	7	14	16	17	3	6
Pain in extremity	28	30	12	24	4	4	1	2
Palmar-plantar erythrodysesthesia syndrome	24	26	7	14	5	5	0	0
Hypertension	23	25	10	20	14	15	6	12
Dehydration	22	24	5	10	7	8	1	2
Musculoskeletal pain	21	23	7	14	3	3	1	2
Rash	19	20	6	12	0	0	0	0

Table 3. Most Frequently Reported Adverse Events Regardless of Causality

NOTE. Adverse events were $\geq$ 20% for all grades in the 100-mg cohort.
*MedDRA (Medical Dictionary for Regulatory Activities) version 15.1 preferred terms, based on Common Terminology Criteria for Adverse Events version 3.0.
†One patient in the 100-mg cohort who had extensive liver disease experienced a related grade 3 portal vein thrombosis with grade 5 liver failure.

No new or unexpected adverse events were observed in our study. The rate for pulmonary embolus was somewhat higher than previously described in patients with metastatic CRPC.[5] Notably, there are no reliable historical references for the expected rate of thromboembolic events in this patient population. The frequent imaging schedule (every 6 weeks) might have identified some asymptomatic pulmonary emboli and could have contributed to a higher than expected event rate. Importantly, the ongoing phase III studies will characterize the rates of treatment-related adverse events. Compared with patients treated at a starting dose of 100 mg, those who received 40 mg in our current study had lower rates of dose reduction or drug discontinuation because of an adverse event. These observations are consistent with reported tolerability from a single-institution dose-ranging study of cabozantinib in patients with metastatic CRPC.[6]

In summary, the totality of the evidence suggests that cabozantinib is biologically active in metastatic CRPC. In men with CRPC, bone metastases, and disease progression despite prior docetaxel treatment, cabozantinib was associated with improvements in a variety of disease-related outcomes including bone scans, pain and analgesic use, measurable disease, CTCs, and bone biomarkers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Yakes FM, Chen J, Tan J, et al: Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 10:2298-2308, 2011

2. Schimmoller F, Zayzafoon M, Chung LWK, et al: Cabozantinib (XL184), a dual MET-VEGFR2 inhibitor, blocks osteoblastic and osteolytic progression of human prostate cancer xenografts in mouse bone. Mol Cancer Ther 10:233, 2011 (suppl 1; abstr A233)

3. Nguyen HM, Ruppender N, Zhang X, et al: Cabozantinib inhibits growth of androgen-sensitive and castration-resistant prostate cancer and affects bone remodeling. PLoS One 8:e78881, 2013

4. Graham TJ, Box G, Tunariu N, et al: Preclinical evaluation of imaging biomarkers for prostate cancer bone metastasis and response to cabozantinib. J Natl Cancer Inst 106:dju033, 2014

5. Smith DC, Smith MR, Sweeney C, et al: Cabozantinib in patients with advanced prostate cancer: Results of a phase II randomized discontinuation trial. J Clin Oncol 31:412-419, 2013

6. Lee RJ, Saylor PJ, Michaelson MD, et al: A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. Clin Cancer Res 19:3088-3094, 2013

7. Brown MS, Chu GH, Kim HJ, et al: Computer-aided quantitative bone scan assessment of prostate cancer treatment response. Nucl Med Commun 33:384-394, 2012

8. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008

9. Danila DC, Fleisher M, Scher HI: Circulating tumor cells as biomarkers in prostate cancer. Clin Cancer Res 17:3903-3912, 2011

10. Farrar JT, Young JP Jr, LaMoreaux L, et al: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94:149-158, 2001

11. Basch EM, Autio KA, Smith MR, et al: Effects of cabozantinib on pain and narcotic use in patients with castration-resistance prostate cancer: Results from a phase 2 nonrandomized expansion cohort. Eur Urol [epub ahead of print on February 20, 2014]

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GLOSSARY TERMS

apoptosis: also called programmed cell death. Apoptosis is a signaling pathway that leads to cellular suicide in an organized manner. Several factors and receptors are specific to the apoptotic pathway. The net result is that cells shrink and develop blebs on their surface, and their DNA undergoes fragmentation.

circulating tumor cells: demonstration of isolated tumor cell circulation/dissemination in the peripheral blood.

MET: the receptor for hepatocyte growth factor. MET is a transmembrane receptor tyrosine kinase. The primary single chain precursor protein is post-translationally cleaved to produce the alpha and beta subunits; the mature receptor is composed of these subunits linked via disulfide bonds. Various mutations in the *MET* gene have been associated with papillary renal carcinoma.

osteoclast: a cell that breaks down bone and is responsible for bone resorption. Osteoclasts are large multinucleate cells that differentiate from macrophages.

receptor tyrosine kinase: transmembrane protein with intrinsic ability to transfer phosphate groups to tyrosine residues contained in cellular substrates. See tyrosine kinase receptors.

VEGFR (vascular endothelial growth factor receptor): transmembrane tyrosine kinase receptors to which the VEGF ligand binds. VEGFR-1 (also called FLT1) and VEGFR-2 (also called KDR/FLK1[murine homologue]) are expressed on endothelial cells, whereas VEGFR-3 (also called FLT4) is expressed on cells of the lymphatic and vascular endothelium. VEGFR-2 is thought to be principally responsible for angiogenesis and for the proliferation of endothelial cells. Typically, most VEGFRs have seven extracellular immunoglobulin-like domains, responsible for VEGF binding, and an intracellular tyrosine kinase domain.

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