Original Article

Title: A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases.

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Running title: Cabozantinib dose-ranging study in men with metastatic CRPC

Key words: cabozantinib, prostate cancer, MET, VEGFR, bone metastasis

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Translational Relevance.

This study combines a promising targeted therapy, an adaptive trial design, novel imaging analysis, and correlative biomarkers. MET and VEGF pathways play important roles in prostate cancer progression and metastasis. Cabozantinib is an oral MET/VEGFR2 inhibitor with unprecedented improvement in bone scans in men with metastatic castration-resistant prostate cancer (mCRPC) in a phase II study. Because of tolerability concerns at the phase II dose, we evaluated the efficacy and tolerability of cabozantinib at lower starting doses. We used an adaptive scheme to determine the lowest active daily cabozantinib dose among 3 pre-specified dose levels. Our study is the first to use bone scan response at 6 weeks as the prespecified primary study outcome. This study identified a highly active dose of cabozantinib with better tolerability than reported in the phase II trial. These findings have informed the design of trials of cabozantinib in mCRPC, including two phase III studies.
Abstract.

Background

Cabozantinib is an oral MET/VEGFR2 inhibitor. A recent phase II study of cabozantinib (100mg daily) demonstrated improved bone scans in subjects with metastatic castration-resistant prostate cancer (mCRPC), but adverse events (AEs) caused frequent dose reductions. This study was designed to determine the efficacy and tolerability of cabozantinib at lower starting doses.

Patients and Methods

An adaptive design was used to determine the lowest active daily dose among 60mg, 40mg, and 20mg. The primary endpoint was week 6 bone scan response, defined as ≥30% decrease in bone scan lesion area. The secondary endpoint was change in circulating tumor cells (CTCs).

Results

Among 11 evaluable subjects enrolled at 40mg, there were 9 partial responses (PRs), 1 complete response, and 1 stable disease (SD). Of 10 subjects subsequently enrolled at 20mg, there were 1 PR, 5 SDs, and 4 with progressive disease. Among 13 subjects enrolled on the 40mg expansion cohort, there were 6 PRs and 7 SDs. No subjects required dose reduction or treatment interruption at 6 or 12 weeks; 3 subjects at dose level 0 discontinued due to AEs by 12 weeks. At 40mg, median treatment duration was 27 weeks. 58% of subjects with ≥5 CTCs/7.5mL at baseline converted to <5.

Conclusions
Cabozantinib 40mg daily was associated with a high rate of bone scan response. Cabozantinib 40mg daily was associated with better tolerability than previously reported for cabozantinib 100mg daily. These observations informed the design of phase III studies of cabozantinib in mCRPC.
Introduction.

Bone metastases occur in 90% of men with fatal prostate cancer and are associated with significant morbidity and mortality(1, 2). Bone metastasis involves complex interactions between prostate cancer cells, osteoblasts, osteoclasts, bone matrix, and endothelial cells. Despite advances in the management of metastatic castration-resistant prostate cancer (mCRPC), effective management of bone metastases remains an important unmet medical need.

The MET receptor tyrosine kinase and vascular endothelial growth factor (VEGF) signaling pathways are thought to play important roles in prostate cancer progression and bone metastasis. MET expression is regulated by the androgen receptor, and androgen deprivation increases MET expression in prostate cancer cells(3, 4). Androgen deprivation also increases tumor and stromal expression of the MET ligand, Hepatocyte Growth Factor (HGF). Increased expression of MET and/or HGF correlate with prostate cancer progression(3, 5). Plasma and urine VEGF levels are independent predictors of overall survival (OS) in mCRPC(6, 7). Osteoblasts and osteoclasts express MET and VEGF receptors (VEGFRs). Osteoclasts also secrete HGF, suggesting that MET signaling may play a role in pathological bone remodeling(8). In prostate cancer cells, VEGF activates MET via neuropilin-1, which may protect against apoptosis(9). Together, these observations provide a strong rationale for dual inhibition of VEGFR and MET in men with mCRPC and bone metastases.

Cabozantinib (XL184) is an oral, small molecule tyrosine kinase inhibitor (TKI) whose targets include VEGFR2, MET, KIT, and mutationally activated RET(10). Cabozantinib is approved for treatment of metastatic medullary thyroid cancer at 140mg daily dose(11). In a phase II
randomized discontinuation study (XL184-203), 171 subjects with mCRPC and measurable disease received cabozantinib 100mg daily during a 12-week lead-in stage. Subsequent treatment was based on response at 12 weeks: subjects with response by modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria continued open-label cabozantinib, subjects with progressive disease discontinued therapy, and subjects with stable disease were randomized to either placebo or continued cabozantinib. Randomization was suspended after 122 subjects due to unexpected changes on bone scans and clinical improvement; an additional 49 subjects were enrolled in a nonrandomized expansion cohort. Bone disease was present at baseline in 87% of subjects, and 43% previously received docetaxel. The mRECIST response rate was 5%, although most subjects had minor improvements in measurable disease. Unexpectedly, 68% of subjects had partial or complete resolution of bone scans, a posthoc study outcome. 67% of subjects with pain at baseline reported a decrease in pain. Prostate specific antigen (PSA) and bone scan changes were discordant in 40%. By week 12, dose reductions occurred in 51% of subjects, with 12% discontinuing treatment due to adverse events (AEs). The most common grade 3 toxicities during the lead-in stage were fatigue, hypertension, and hand-foot syndrome(12). The most common serious AE was pulmonary embolism (6%)(12).

The high rate of bone scan improvement coupled with clinical benefit warrant further development of cabozantinib in men with mCRPC and bone metastases. This study was designed to determine the efficacy and tolerability of cabozantinib at lower starting doses. The prespecified primary outcome was bone scan response (BSR), defined as ≥30% decrease in bone scan lesion area (BSLA) using a computer-aided detection (CAD) system.
Materials and Methods.

Patients.

Eligible patients had pathologically confirmed mCRPC with metastases on bone scan, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate bone marrow function (absolute neutrophil count ≥1500/mm³, platelets ≥100,000/mm³, hemoglobin ≥9g/dL), hepatic function (total bilirubin ≤1.5 x the upper limit of normal (ULN), transaminases ≤2.5 x ULN), and renal function (serum creatinine ≤1.5 x ULN). Patients were required to have undergone bilateral orchiectomies or receive ongoing treatment with a GnRH agonist or antagonist. Patients were required to have mCRPC based on progression in bone and/or PSA progression per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria(13). Patients were excluded if they had radiation therapy within 2 weeks of study entry, radionuclide treatment within 6 weeks, initiation of denosumab or bisphosphonates within 4 weeks, more than 2 prior chemotherapy regimens, brain metastasis, uncontrolled intercurrent illness, therapeutic treatment with anticoagulants, or estimated life expectancy <3 months. All subjects were required to be able to understand the study requirements and provide written informed consent. In accordance with the Helsinki Declaration, study protocol and informed consent documents were approved by the Institutional Review Board.

Study Outcomes.

The primary outcome measure was post-treatment change in ⁹⁹ᵐTc-MDP bone scan from baseline to week 6. Bone scans were performed at 6 weeks, 12 weeks, and every 12 weeks thereafter. BSR was assessed using an automated FDA 510(k)-approved CAD system and
independent nuclear medicine physician review(14, 15). A decrease in total BSLA of ≥30% was defined as a partial response (PR). Complete response (CR) was defined as complete resolution of bone scan abnormalities; stable disease (SD) as <30% increase or decrease in BSLA; and progressive disease (PD) as ≥30% increase in BSLA.

Secondary outcome measures included bone turnover markers and effects on circulating tumor cells (CTCs). CTC data are reported herein. CTCs were assessed by the CellSearch assay (Veridex, Raritan, NJ). CTCs were measured every 3 weeks through week 15. CTCs at 6 and 12 weeks were compared against baseline values for correlation with BSR. CTCs were considered unfavorable or favorable at ≥5 or <5 CTCs per 7.5mL of blood, respectively(16). Post-treatment changes in CTC number and conversion from unfavorable to favorable categories were evaluated.

**Study Design and Statistical Analyses.**

The primary objective was to determine the lowest effective cabozantinib dose among three dose levels (+1, 0, and -1; 60mg, 40mg, and 20mg, respectively). At each dose level, Sargent single-stage three-outcome design was employed(17). The study assumptions are that a promising response rate would be ≥75% and a non-promising response rate would be ≤50%. At 82% power, the probability of accepting or rejecting an ineffective dose would be 0.10 or 0.80, respectively. Under these assumptions, 11 subjects were required at each dose level. The investigated dose level is considered promising if ≥8 subjects achieve a response, non-promising if ≤6 subjects achieve a response, and inconclusive if 7 responses are observed.
Eleven subjects would be treated at the starting dose level 0. Per the adaptive response schema, one additional dose level (-1 or +1) would be selected for further evaluation based on the response rate at dose level 0. Once the lowest active dose level was identified (or if inconclusive), 13 additional subjects (expansion cohort) would be treated for a total of 24 subjects (11 + 13) at that dose level. The total projected sample size was 35 subjects (11 + 11 + 13). With 24 subjects treated at the lowest active dose level, the 90% exact binomial confidence interval would not be wider than 35% if at least a 63% response rate is achieved. Per protocol, dose level +2 (100mg daily, to match the randomized discontinuation study dose) was possible for dose escalation in the event of low response rate at dose level -1, after week 6 evaluation.

**Results.**

**Patient characteristics.**

The study completed enrollment of 36 subjects. Subjects initiated therapy between May, 2011, and December, 2011. Table 1 summarizes the baseline characteristics of the subjects. Data were evaluated as of December 4, 2012.

**Bone Scan Response.**

An adaptive response scheme was used to determine the lowest active daily cabozantinib dose among dose levels +1 (60mg), 0 (40mg), and -1 (20mg) (Fig. 1). The primary endpoint was week 6 BSR.

*Cohort 1.* Twelve subjects were enrolled at dose level 0 (40mg daily). One subject discontinued treatment after 2 weeks due to worsening of baseline fatigue and anorexia. An additional subject
was enrolled to allow for 11 evaluable subjects. Ten of 11 (91%) evaluable subjects exhibited BSR at 6 weeks, with 1 CR, 9 PR, and 1 SD. The median decrease in BSLA was 62%. Figure 2 illustrates examples of CR and PR from cohort 1.

The waterfall plot depicts changes in BSLA at week 6 (Fig 3A). Responses were durable. Nine of 10 (90%) evaluable subjects had confirmed BSR at 12 weeks (3 CR, 6 PR, 1 SD). No subjects required dose reduction or delay at 6 or 12 weeks. The median time on study was 30 weeks (range, 2 to 57 weeks). Treatment was discontinued due to PD in 6 subjects, intercurrent illness considered unrelated to cabozantinib in 2 subjects, and drug-related AEs in 4 subjects.

Cohort 2. Per the study design, with ≥8 responses at 40mg daily, a second cohort of 11 subjects was enrolled at dose level -1 (20mg daily). Ten subjects were evaluable at 6 weeks. One of 10 (10%) subjects exhibited PR, 5 had SD, and 4 had PD. Changes in BSLA at week 6 are shown (Fig 3B). No subjects required dose reduction or delay at 6 or 12 weeks from the original dose level.

Five subjects were dose-escalated to dose level +2 (100mg daily) after week 6, per protocol. Three of these 5 subjects achieved PR at 12 weeks. Thus, the best response in this cohort was 4 of 11 (36%) subjects with PR by 12 weeks.

The median time on study was 26 weeks (range, 4-45 weeks, inclusive of subjects who underwent dose escalation). Treatment was discontinued due to PD in 7 subjects, intercurrent illness considered unrelated to cabozantinib in 2 subjects, and drug-related AEs in 2 subjects.
Expansion cohort. With fewer than 6 responses at 20mg daily, an expansion cohort of 13 subjects was enrolled at dose level 0 (40mg daily). Six of 13 (46%) subjects exhibited PR at 6 weeks, and 7 subjects had SD. Changes in BSLA at 6 weeks are depicted in the waterfall plot (Fig 3C). At 12 weeks, 6 of 10 (60%) evaluable subjects had PR. Three subjects with SD at 6 weeks had PR at 12 weeks. Thus, the best response by 12 weeks was PR in 9 of 13 subjects (69%).

No subjects required dose reduction or delay at 6 or 12 weeks. The median time on study was 19 weeks (range, 6 to 51 weeks). Treatment was discontinued due to PD in 8 subjects, intercurrent illness considered unrelated to cabozantinib in 1 subject, withdrawal of consent in 1 subject (after 41 weeks on protocol), and drug-related AEs in 2 subjects.

PSA.

Serum PSA was measured at baseline and every 3 weeks on study. PSA changes are reported for subjects treated at 40mg daily (cohort 1 and expansion cohort), given the low BSR rate at 20mg daily. BSLA and PSA change per subject at 6 weeks are depicted in pairs in the waterfall plot (Fig. 4). BSLA and PSA change were discordant in 13 of 24 evaluable subjects (54%). One subject exhibited a post-treatment PSA decline of >50%.

Measurable Disease.

Measurable metastatic disease was not required for study entry. Evaluation of measurable disease was not a prospectively-defined endpoint. Measurable disease was assessed with
abdominal/pelvic computed tomography concurrent with bone scans. Evaluation was restricted to subjects treated at 40mg daily. Six subjects had measurable disease at baseline. Five subjects were evaluable at 6 weeks (one subject discontinued study at 2 weeks): 3 had stable measurable disease and 2 had progressive measurable disease. Of the 3 subjects with stable measurable disease, one had PR on bone scan and remained on study for 27 weeks; the other two had SD on bone scan and remained on study for 15 and 21 weeks. Of the 2 subjects with progressive measurable disease at 6 weeks, 1 had PR on bone scan and remained on study for 19 weeks, and the other had SD on bone scan and discontinued therapy at 6 weeks (data not shown).

Circulating Tumor Cells.

CTCs were prospectively collected to evaluate post-treatment changes in CTC number and conversion from unfavorable to favorable categories. CTC analyses were restricted to subjects treated at 40mg daily. Prior studies have correlated improved prognosis with conversion from unfavorable to favorable CTC categories on other prostate cancer therapies(16, 18).

Twelve of 21 evaluable subjects had unfavorable baseline CTC levels. Eleven of the 12 subjects (92%) had >30% decline in CTCs by 12 weeks, with 7 subjects (58%) converting to favorable (Fig. 5). Six of the 7 subjects (86%) who converted to favorable had BSR at 6 weeks, compared with 3 of the 5 subjects (60%) who did not convert. Subjects with favorable CTC conversion received study drug for median 24 weeks, compared with 12 weeks for those who did not convert.

Safety and tolerability.
There were no dose reductions during the first 12 weeks at any dose level. In total, 2 of 36 (5.6%) subjects discontinued treatment due to drug-related AEs by 6 weeks, and 4 of 36 (11%) discontinued due to drug-related AEs by 12 weeks.

For all 25 subjects enrolled at 40mg daily, 3 (12%) discontinued treatment by 12 weeks due to drug-related AEs. These included 1 subject with worsening of baseline fatigue and anorexia (both grade 2) at 2 weeks, and 2 subjects with venous thromboembolic events (VTEs, grade 3) at 6 and 12 weeks. Three other subjects developed drug-related AEs prompting discontinuation after prolonged (>12 weeks) exposure to cabozantinib: one at 19 weeks (grade 2 anorexia and weight loss), another at 33 weeks (grade 2 diarrhea, anorexia, and weight loss), and the last at 57 weeks (grade 3 weight loss and neutropenia, without documented fever or infection).

For subjects enrolled at 20mg daily, there were no drug-related AEs leading to treatment discontinuation at the original dose level. Five subjects were dose-escalated per protocol. Two subjects who eventually discontinued treatment due to drug-related grade 3 VTEs were receiving 100mg daily at the time, at 11 and 26 weeks.

Discussion.

VEGFR and MET pathways are thought to play important roles in prostate cancer progression and bone metastasis. Dual inhibition of VEGFR and MET by cabozantinib has shown promise in mCRPC(19) and other malignancies, including medullary thyroid cancer(11, 20). In the randomized discontinuation trial of subjects with mCRPC, cabozantinib 100mg daily was associated with high rates of bone scan improvement, but was limited by AEs requiring dose
reduction and treatment discontinuation(19). When this study was initiated, there were no efficacy or tolerability data to support lower starting doses of cabozantinib in mCRPC.

In this prospective study, we observed high BSR rates at the 40mg but not 20mg daily dose. At 40mg daily, 16 of 25 subjects (64%; 90% CI: 46%-80%) exhibited BSR at 6 weeks. By 12 weeks, the best response was 16 PR and 3 CR in 19 of 25 subjects (76%; 90% CI: 58%-89%). These findings are comparable with the 68% BSR rate at the 100mg dose(12).

Cabozantinib at 40mg daily was well tolerated. Subjects were treated for median of 27 weeks (range, 2-57 weeks). No subjects required dose reduction or delay by 12 weeks, compared with 51% at 12 weeks in the randomized discontinuation study(12). Discontinuation due to drug-related AEs occurred in 12% by 12 weeks.

To the best of our knowledge, this is the first reported study to use BSR as the prespecified primary study outcome. Post-treatment bone scan changes in clinical trials of mCRPC have typically been used per PCGW2 to describe disease progression, based on appearance of at least two new lesions(13). Post-treatment improvements in bone scans have not been addressed by PCGW2. Our study demonstrates the potential for CAD-based, quantitative bone scan assessment of post-treatment response. Further development will require validation of BSLA compared with other clinically relevant outcome measures.

Post-treatment improvements in bone scans have been noted with another TKI, sunitinib, in mCRPC. In post-hoc analyses of a phase II study of sunitinib in mCRPC(21), 6 of 25 subjects
(24%) had a response on bone scan, evaluated by consensus opinion of three nuclear medicine-specialized physicians(22). None of the 6 subjects demonstrated response by PSA or mRECIST criteria.

Bone scan and PSA changes were discordant in 54% in our study, suggesting that PSA alone is not a reliable marker for clinical outcome following cabozantinib treatment. We prospectively evaluated CTCs as a measure of tumor burden. While most subjects (92%) with unfavorable levels at baseline exhibited a decline in CTCs, 58% converted to favorable levels on therapy. Subjects with conversion exhibited higher BSR rates at 6 weeks and longer median time on study compared with subjects whose CTC levels remained unfavorable.

Our study has limitations. This study was not designed to control for factors that could influence response to therapy such as prior chemotherapy or radionuclides. The proportion of subjects who previously received docetaxel increased with each successive cohort (Table 1). The impact of prior chemotherapy on biological responsiveness of prostate cancer cells and the bone microenvironment to cabozantinib is unknown, although a recent report of a phase II nonrandomized expansion cohort of cabozantinib in subjects with docetaxel-pretreated mCRPC showed high rates (60%) of BSR(19). Larger studies are required to validate BSR as an intermediate endpoint. We did not formally assess pain response. Establishment of CTC conversion as a predictive marker of treatment response would require larger studies.

Post-treatment bone scan changes reflect altered osteoblast activity due to changes in tumor perfusion, tumor cell death, direct downregulation of osteoblast function, or a combination of
factors. Together, decrease in bone turnover (19), decrease in CTCs, and clinical benefit such as pain improvement suggest that the bone scan improvements after cabozantinib therapy are unlikely to simply reflect an imaging phenomenon. The coordinated downregulation of MET and VEGFR signaling on prostate cancer cells, osteoblasts, osteoclasts, and vascular cells may disrupt the bone microenvironment and impair cancer viability more completely than inhibition of either pathway individually. Indeed, trials targeting either MET or VEGF pathways individually have not demonstrated clinical benefit in mCRPC. Phase III trials of angiogenesis/VEGF-targeted therapies bevacizumab (23), sunitinib (24), lenalidomide (25), or aflibercept (sponsor press release, 2012) in men with mCRPC have not improved OS. Rilotumumab, a monoclonal antibody to HGF, did not improve OS in men with mCRPC in a randomized phase II trial (26). Further studies are required to dissect the contributions of different cell lineages or potentially different targets to cabozantinib’s effect.

Our findings have informed the design of ongoing trials of cabozantinib in mCRPC. The nonrandomized expansion cohort of trial XL184-203 (NCT00940225) was amended to include a 40mg dose in mCRPC subjects, in addition to the original 100mg dose. Two phase III trials of cabozantinib at 60mg daily starting dose are currently enrolling patients with mCRPC and prior treatment with docetaxel and either abiraterone or enzalutamide. COMET-1 (NCT01605227) compares cabozantinib with prednisone, with the primary outcome measure of OS. COMET-2 (NCT01522443) compares cabozantinib with mitoxantrone and prednisone in subjects with symptomatic disease, with the primary outcome measure of durable pain response from weeks 6 to 12.
In summary, cabozantinib at a starting dose of 40mg daily achieves a high BSR rate in men with mCRPC and bone metastases. Cabozantinib at 40mg daily is associated with better tolerability than previously reported for the 100mg daily dose. These results support further prospective study of cabozantinib at lower doses.
References.


**Table 1.** Baseline characteristics of subjects.

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Figure Legends.

**Fig. 1.** Adaptive response design(17).

**Fig. 2.** Representative bone scan changes in two subjects from cohort 1 (40mg daily). The left panel of each pair represents the baseline bone scan; the right panel is the scan from week 6. BSLA change was -100% for subject 1 (CR) and -97% for subject 2 (PR).

**Fig. 3.** Waterfall plot of BSLA change at 6 weeks compared with baseline. BSR is defined as $\geq 30\%$ decrease in BSLA. A. Cohort 1, 40mg daily. Asterisks indicate subjects with confirmed BSR at 12 weeks. B. Cohort 2, 20mg daily. Asterisks indicate subjects who achieved BSR at 12 weeks after dose-escalation to dose level +2. C. Expansion cohort, 40mg daily. Asterisks indicate subjects with BSR at 12 weeks.

**Fig. 4.** Waterfall plot of BSLA change and PSA change at 6 weeks compared with baseline, in subjects treated at 40mg daily (cohort 1 and expansion cohort). Each pair of bars represents one subject. Blue bars indicate BSLA change; red bars indicate PSA change. Thirteen of 24 evaluable subjects demonstrated discordance of bone scan and PSA change.

**Fig. 5.** Waterfall plot of CTC change by 12 weeks in subjects with unfavorable CTC levels at baseline. Green bars indicate subjects whose CTCs converted to favorable levels at 6 weeks; blue bars indicate subjects whose CTCs did not convert.
Fig. 2

Subject 1
Baseline Week 6

Subject 2
Baseline Week 6

-100%

-97%
Fig. 4

![Graph showing percent change from baseline for Cabozantinib 40 mg daily]

Legend:
- PSA
- BSLA
Clinical Cancer Research

A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases


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