Cancer Therapy: Clinical

A Dose-Ranging Study of Cabozantinib in Men with Castration-Resistant Prostate Cancer and Bone Metastases

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Abstract

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

Experimental Design: An adaptive design was used to determine the lowest active daily dose among 60, 40, and 20 mg. 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 (CTC).

Results: Among 11 evaluable subjects enrolled at 40 mg, there were 9 partial responses (PR), 1 complete response, and 1 stable disease (SD). Of 10 subjects subsequently enrolled at 20 mg, there were 1 PR, 5 SDs, and 4 with progressive disease. Among 13 subjects enrolled on the 40 mg 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 40 mg, median treatment duration was 27 weeks. 58% of subjects with ≥5 CTCs/7.5mL at baseline converted to <5.

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

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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 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 (VEGFR). Osteoclasts also secrete HGF, suggesting that MET signaling may play a role in pathologic 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 140 mg daily dose (11). In a phase II randomized discontinuation study (XL184-203), 171 subjects with mCRPC and measurable disease received cabozantinib 100 mg 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...
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 prespecified 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 2 phase III studies.

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 post hoc study outcome. Of subjects with pain at baseline, 67% 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 (AE). The most common grade III toxicities during the lead-in stage were fatigue, hypertension, and hand-foot syndrome (12). The most common serious AE was pulmonary embolism (6%; ref. 12).

The high rate of bone scan improvement coupled with clinical benefit warranted 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 ≥ 1,500/mm³, platelets ≥ 100,000/mm³, hemoglobin ≥ 9g/dL), hepatic function [total bilirubin ≤ 1.5 × the upper limit of normal (ULN), transaminases ≤ 2.5 × ULN], and renal function [serum creatinine ≤ 1.5 × ULN]. Patients were required to have undergone bilateral orchiectomy 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 posttreatment change in ⁹⁹ᵐTc-MDP bone scan from baseline to week 6. Bone scans were conducted at 6 and 12 weeks and every 12 weeks thereafter. BSR was assessed using an automated U.S. Food and Drug Administration (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 (CTC). CTC data are reported herein. CTCs were assessed by the CellSearch assay (Veridex). 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 7.5 mL of blood, respectively (16). Posttreatment 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 3 dose levels (+1, 0, and −1; 60, 40, and 20 mg, respectively). At each dose level, Sargent single-stage 3-outcome design was used (17). The study assumptions are that a promising response rate would be ≥75% and a nonpromising 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, nonpromising 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 (CI) would not be wider than 35% if at least a 63% response rate is achieved. Per protocol, dose level +2 (100 mg daily, to match the randomized discontinuation study dose) was possible for dose escalation in the event of low response rate at dose level 0, 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 (60 mg), 0 (40 mg), and −1 (20 mg; Fig. 1). The primary endpoint was week 6 BSR.

**Cohort 1.** Twelve subjects were enrolled at dose level 0 (40 mg 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, 2–57 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 40 mg daily, a second cohort of 11 subjects was enrolled at dose level −1 (20 mg 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 (100 mg 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

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Table 1. Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Dose level 0 (40 mg)</th>
<th>Dose level −1 (20 mg)</th>
<th>Expansion (40 mg)</th>
<th>All subjects</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects consented</td>
<td>12</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Median (range) age, y</td>
<td>68 (50–83)</td>
<td>64 (48–72)</td>
<td>65 (53–74)</td>
</tr>
<tr>
<td>Number who received prior chemotherapy</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Number with measurable disease</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Median bone scan lesion area</td>
<td>761</td>
<td>711</td>
<td>290</td>
</tr>
<tr>
<td>Median (range) baseline PSA, ng/mL</td>
<td>54 (2–182)</td>
<td>78 (10–647)</td>
<td>59 (1–557)</td>
</tr>
</tbody>
</table>
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 20 mg daily, an expansion cohort of 13 subjects was enrolled at dose level 0 (40 mg 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, 6–51 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 40 mg daily (cohort 1 and expansion cohort), given the low BSR rate at 20 mg 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 posttreatment 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 40 mg 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, 1 had PR on bone scan and remained on study for 27 weeks; the other 2 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 posttreatment changes in CTC number and conversion from unfavorable to favorable categories. CTC analyses were restricted to subjects treated at 40 mg 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

Figure 2. Representative bone scan changes in 2 subjects from cohort 1 (40 mg 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).

Figure 3. Waterfall plot of BSLA change at 6 weeks compared with baseline. BSR is defined as ≥30% decrease in BSLA. A, cohort 1, 40 mg daily. ‘’, subjects with confirmed BSR at 12 weeks. B, cohort 2, 20 mg daily. ‘’, subjects who achieved BSR at 12 weeks after dose escalation to dose level +2. C, expansion cohort, 40 mg daily. ‘’, subjects with BSR at 12 weeks. PO, per os.
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 40 mg 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 II) at 2 weeks and 2 subjects with venous thromboembolic events (VTE, grade III) 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 II anorexia and weight loss), another at 33 weeks (grade II diarrhea, anorexia, and weight loss), and the last at 57 weeks (grade III weight loss and neutropenia, without documented fever or infection).

For subjects enrolled at 20 mg 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 III VTEs were receiving 100 mg 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 100 mg 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 40 mg but not 20 mg daily dose. At 40 mg 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 100 mg dose (12).

Cabozantinib at 40 mg 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. Posttreatment bone scan changes in clinical trials of mCRPC have typically been used per PCGW2 to describe disease progression, based on appearance of at least 2 new lesions (13). Posttreatment improvements in bone scans have not been addressed by PCGW2. Our study shows the potential for CAD-based, quantitative bone scan assessment of posttreatment response. Further development will require validation of BSLA compared with other clinically relevant outcome measures.

Posttreatment 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 3 nuclear medicine–specialized physicians (22). None of the 6 subjects showed 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 radiotherapy. The proportion of subjects who previously received docetaxel increased with each successive cohort (Table 1). The impact of prior chemotherapy on biologic 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.

Posttreatment 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 impact cancer viability more completely than inhibition of either pathway individually. Indeed, trials targeting either MET or VEGF pathways individually have not shown clinical benefit in mCRPC. Phase III trials of angiogenesis/VEGF-targeted therapies bevazicu- mab (23), sunitinib (24), lenalidomide (25), or afliibercept (sponsor press release, 2012) in men with mCRPC have not improved OS. Bilotumumab, 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 the effect of cabozantinib.

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 40 mg dose in mCRPC subjects, in an intermediate expansion cohort of cabozantinib in subjects with mCRPC. The nonrandomized expansion cohort of cabozantinib in subjects with mCRPC at 40 mg daily is associated with a high BSR rate in men with mCRPC and potentially different targets to the effect of cabozantinib.

Disclosure of Potential Conflicts of Interest

R.J. Lee has research support from Exelixis, Inc. J.G. Goldin is the founder of MedQIA LLC. M.R. Smith has research support from Exelixis, Inc. and is a consultant for Exelixis, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

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Development of methodology: R.J. Lee, J.G. Goldin

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.J. Lee, P.J. Saylor, M.D. Michaelson, S.M. Rothenberg, M.E. Smas, D.T. Miyamoto, C.A. Gurski, S. Maheswaran, D.A. Haber, J.G. Goldin, M.R. Smith


Writing, review, and/or revision of the manuscript (i.e., reporting data, constructing databases): R.J. Lee, P.J. Saylor, M.D. Michaelson, D.T. Miyamoto, S. Maheswaran, J.G. Goldin, M.R. Smith

Administrative, technical, or material support (i.e., reporting data, constructing databases): M.R. Smith


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