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A dose finding clinical trial of cabozantinib (XL184) administered in combination with abiraterone acetate in metastatic castration-resistant prostate cancer

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Abstract

Background: Cabozantinib can enhance the effect of abiraterone in preclinical prostate cancer models. This study aimed to define the recommended phase 2 dose (RP2D) and preliminary efficacy of abiraterone+cabozantinib in mCRPC.

Methods: Patients with progressive mCRPC with 0–2 prior chemotherapy regimens but no prior CYP17A1 or MET inhibitor received abiraterone acetate at 1000mg daily with prednisone 5mg BID in combination with cabozantinib at 20mg, 40mg, or 60mg daily in a dose-escalation 3+3 open-label phase 1 design (Part A). After tolerable doses were defined, cohorts were expanded to better define toxicity and efficacy (Part B).

Results: There were no dose-limiting toxicities (DLTs) in the first 4 weeks at any of the 3 dose levels in Part A. Two of the 3 patients at the 60mg dose level required dose reductions beyond cycle 2 due to fatigue. In Part B, 9 more patients were accrued to each of the 20mg and 40mg doses. Of the 12 patients treated at the 40mg dose, only one DLT (grade 3 lipase elevation) was observed in cycle 1. The median time to radiographic progression was 12.88 months (95% CI: 5.42- not estimated [NE]) in the 20mg cohort and 22.01 months (95% CI:15.44-NE) in the 40mg cohort. Median overall survival was 23.29 months (95% CI:19.06-NE) in the 20mg cohort and 39.08 months (95% CI:17.38-NE) in the 40mg cohort.

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Conclusions: Based on tolerability and preliminary efficacy, 40mg cabozantinib plus 1000mg abiraterone daily is the RP2D.

Keywords

prostate cancer; abiraterone; cabozantinib; castration-resistant; XL184

Introduction

While most men diagnosed with prostate cancer do not die of their disease, prostate cancer is the third most common cause of cancer death among men in the United States[1]. The initial systemic treatment for metastatic prostate cancer is androgen deprivation therapy (ADT), but eventually prostate cancer cells become resistant to this intervention and transition to a state of castration resistance[2]. In a significant number of patients, castration-resistant prostate cancers remain dependent on signaling through the androgen receptor (AR)[3–5]. Abiraterone acetate is an inhibitor of 17α-hydroxylase/C17, 20-lyase (CYP17A1) that blocks the synthesis of androgens by the adrenal glands[6] and prostate cancer cells themselves[7], thus depriving these cells of non-testicular sources of androgens. Abiraterone is approved for the treatment of mCRPC both in patients who have been previously treated with docetaxel chemotherapy[8], and in patients who are chemotherapy naïve[9]. More recently, abiraterone has been reported to prolong overall survival in patients with treatment-naïve metastatic hormone sensitive prostate cancer (mHSPC) when combined with initial ADT.[10,11] Thus, therapeutic strategies to enhance and prolong the anti-cancer activity of abiraterone are critical to optimize outcomes in patients with metastatic prostate cancer. A variety of mechanisms of resistance to abiraterone have been described in the literature[12], including maintaining hormonal signaling through amplification, mutations, and/or splice variants of the AR, or overexpression of CYP17A1[7]; transdifferentiation to a non-AR dependent state[13] (including neuroendocrine prostate cancer); and activation of alternate survival signaling pathways.

Cabozantinib is a multi-kinase inhibitor with activity against MET and VEGFR2[14], as well as multiple other kinases including RET, KIT, FLT-1/3/4, TIE2, and AXL[15]. Single agent cabozantinib has demonstrated meaningful clinical activity in metastatic CRPC, with results of a Phase II study demonstrating improvements in bone scans, pain, and even measurable soft tissue disease in some patients[16]. In the randomized Phase III COMET-1 trial[17], cabozantinib did not improve overall survival compared with prednisone, however, it did improve bone scan response and progression-free survival.

As such, cabozantinib has shown some activity in very late stage mCRPC but further development would require identification of predictive biomarkers or rational therapeutic combinations likely earlier in the disease process. One such potential therapeutic combination is cabozantinib with abiraterone. In pre-clinical models of CRPC, abiraterone treatment led to a compensatory increase in phosphorylation of the insulin-like growth factor I receptor (IGFIR) pathway with downstream activation of MEK1/2 and ERK1/2[18], suggesting this pathway as an alternate signaling pathway conferring resistance to abiraterone. *In vivo*, cabozantinib inhibited abiraterone induction of IGFIR and downstream

activation of p-MEK1/2 and p-ERK1/2 and enhanced the anti-tumor activity of abiraterone. [18] These studies would suggest that cabozantinib plus abiraterone could be an effective therapeutic strategy for mCRPC or metastatic hormone sensitive prostate cancer. Thus, we conducted a Phase I study to define the recommended phase 2 dose (RP2D) or MTD of cabozantinib when combined with abiraterone, as well as to assess the toxicity and preliminary anti-tumor activity of abiraterone in combination with cabozantinib in mCRPC.

Patients and Methods

Study design and treatments

This two-stage study consisted of a dose-escalation stage (Part A) followed by a dose-expansion stage (Part B). Part A employed a standard 3 + 3 design to evaluate three dose levels of cabozantinib (20, 40 and 60mg/day orally) in combination with abiraterone acetate 1000mg orally daily and prednisone 5mg orally twice daily to establish the recommended phase 2 doses (RP2D) of the combination. Part B was an expansion phase including up to 3 dose levels determined to be safe and tolerable in Part A. The cohorts could be expanded to a maximum of 12 subjects at each dose level (including the subjects from Part A). Treatment in all cohorts was continued until disease progression, unacceptable toxicity, initiation of another cytotoxic or investigational agent, or discontinuation at the investigator's discretion.

Study population

The study enrolled patients with mCRPC with symptomatic or radiographic progression from prior therapy. Patients may have received 0–2 prior chemotherapy regimens for CRPC; thus, patients could be docetaxel-naïve or refractory. Patients who received prior Met or VEGFR inhibitors were excluded. While treatment with prior CYP17A1 inhibitors was exclusionary, prior ketoconazole was allowed if >120 days elapsed since discontinuation. Continuation of androgen deprivation therapy with a luteinizing hormone-releasing hormone agonist or antagonist was required in patients who were not surgically castrate. Patients were required to have an Eastern Cooperative Oncology Performance Status (ECOG PS) of 2 or less, and demonstrate no major organ dysfunction or uncontrolled hypertension (defined as systolic blood pressure greater than 140 mmHg, or diastolic blood pressure greater than 90 mmHg).

The study was conducted at a single institution in the United States. The study protocol (Dana-Farber/Harvard Cancer Center protocol # 11–441) and its amendments were approved by the Institutional Review Board and all patients provided written informed consent prior to participating in the study. The study was conducted under the principles of the World Medical Association, Declaration of Helsinki, and Good Clinical Practice guidelines of the International Conference on Harmonization.

Pharmacokinetic studies

Samples to determine steady state trough concentrations (C_{min}^{ss}) of abiraterone and cabozantinib in plasma were collected shortly before dosing on days 8, 15, and 21 of cycle 1 and day 1 of cycle 2. Patients were instructed to take both drugs at the same time every day, at least 2 h after food consumption, and at a time that would allow them to arrive at the

outpatient clinic for collecting a blood sample before dosing. They were also asked to maintain a diary to record the date and time that each daily dose was taken. At each time point, peripheral venous blood was collected into two tubes containing potassium ethylenediaminetetraacetic acid which were promptly centrifuged (1,300 g, 15 min, 4°C). The plasma was stored in polypropylene cryovials at −80°C until packaged on dry ice for shipment to the analytical laboratories.

Abiraterone was measured by the Clinical Pharmacology Core of the Dana-Farber/Harvard Cancer Center (Boston, MA) using a liquid chromatography/mass spectrometry assay as previously reported with minor modifications, including the use of abiraterone methyl ether as an internal standard.[19] The analytical method was validated and applied to the analysis of study samples as recommended in the applicable FDA Guidance for Industry.[20] Abiraterone was determined at concentrations ranging from 0.25–100 ng/mL with an interday accuracy of 96.1–105.3% and precision ranging from 2.9–11.2%. The determination of cabozantinib was performed under the direction of Exelixis, Inc. (San Francisco, CA) using a validated liquid chromatography/tandem mass spectrometry assay with a 0.5 ng/mL lower limit of detection.[21]

Prior clinical pharmacokinetic studies found that steady state pharmacokinetics for repeated daily dosing was achieved within 8 days for abiraterone (mean terminal half-life, 10.3 h) and 15 days for cabozantinib (mean terminal half-life, 111–131 h).[22–24] Mean C_{min}^{ss} values were calculated for each patient as the geometric mean of the evaluable results for all four time points for abiraterone and the three time points beginning with day 15 of cycle 1 for cabozantinib. The actual time that samples were collected relative to prior dose had to be known and within 24 ± 4 h of the prior dose for an assay result to be evaluable. Samples collected after the dose of either drug was reduced were inevaluable. The geometric mean C_{min}^{ss} was calculated from the values for individual patients at each dose level and reported with the SD as estimated by the jacknife technique.[25] Routines provided in Microsoft Office Excel 2007 (12.0.6715.5000) SP3 MSO (12.0.6683.5000) (Redmond, WA) were used for descriptive statistics.

Safety and antitumor assessments

Safety—Patients were evaluated weekly for the first cycle (DLT assessment period), then every 2 weeks in the second cycle, and then every 28 days until study drug discontinuation. Safety and tolerability were determined by assessment of adverse events (AE), physical examinations, ECOG PS, vital signs, and laboratory tests. The severity of abnormal laboratory values and AEs were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For assessment of dose-limiting toxicities (DLTs), patients must have completed at least 28 days of therapy and be assessable for toxicity, i.e. any patient who stopped therapy prior to receiving 85% of planned dose in the first four weeks for any reason other than a DLT was required to be replaced.

Antitumor Effect – Serologic Response—PSA responses are reported as the percentage change from the time of their first treatment with therapy. PSA levels were

assessed before study entry then every 4 weeks thereafter. The maximum decline in PSA that occurred at any point after treatment is reported using a waterfall plot. PSA progression was the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir was documented, which was confirmed by a second value obtained 3 or more weeks later.

Antitumor Effect – Radiographic Response—As a secondary endpoint, measurable and/or non-measurable disease were assessed by RECIST 1.1 criteria using [99mTc]-MDP skeletal scintigraphy and contrast-enhanced diagnostic CT of the abdomen and pelvis. Imaging studies were obtained at baseline, and participants were initially reevaluated every 8 weeks (within 7 days prior to day 1 of the subsequent cycle). After the completion of 12 cycles of therapy, participants underwent radiographic evaluation every 12 weeks (within 7 days prior to day 1 of the subsequent cycle). Confirmatory scans were obtained at least 4 weeks following initial documentation of an objective response. Radiographic progression as defined by RECIST 1.1 and Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria[26] and response assessments were prospectively performed by independent radiologist in the DF/HCC imaging core.

Analysis Methods

All disease outcomes or response assessments were performed on an intent-to-treat (ITT) population, i.e., all patients received response assessments to the initial assigned dose levels. Patient characteristics were summarized descriptively. Discrete variables were summarized as number and percent (%) while continuous variables were summarized by median (interquartile range [IQR]). The safety population included all patients who had taken at least one dose of abiraterone and cabozantinib. The frequency and percent of toxicities measured by the maximum grade a patient experienced is summarized overall and according to cabozantinib dose levels.

The sample size of 12 patients for each dose level in expansion cohort was based on constructing a 2-stage exact binomial confidence interval by the method of Atkinson and Brown[27] on the rate of DLTs: if 2 of 12 patients have a DLT (either 0 of 3 in Part A and then 2 of 9 in the expansion cohort , or 1 of 6 in Part A and then 1 of 6 in the expansion cohort), this corresponds to a 16.7% observed DLT rate, and has a 90% confidence interval of either (0.05, 0.63) or (.06, .58).

Per the original protocol, patients were discontinued from study for progressive disease due to radiographic progression by PCWG2 criteria,[26] or in the absence of radiographic progression if there was symptomatic progression or changes in the participant's condition rendering the participant unacceptable for further treatment in the opinion of the treating investigator. This latter group of patients were defined on retrospective analysis as having progressed due to "no longer clinically benefiting" (NLCB) as suggested by PCWG3 criteria,[28] which were published after this study was conducted. Time to event outcomes, such as (i) time to PSA progression, (ii) time to radiographic progression by PCWG2 criteria[26] per original protocol, (iii) time to progression as defined as the earlier of

radiographic progression (PCWG2)[26] or clinician assessment of NLCB[28] and (iv) overall survival (OS) were estimated using the Kaplan-Meier method.

Results

Description of Enrolled population

Between May 17, 2012, and May 27, 2014, the study enrolled total of the 27 patients. Nine patients were enrolled in the dose escalation phase (Part A) with 3 at each cabozantinib dose level of 20mg, 40mg and 60mg daily; an additional 9 patients were in each of the two expansion cohorts at 20mg and 40mg cabozantinib dose levels (Part B) (Figure 1). The median age was 64 (IQR, 61–70) and the median baseline PSA was 20 ng/mL (IQR 6–45). Eleven of 27 patients (40.7%) had previously received docetaxel chemotherapy, and 4/27 patients (14.8%) had visceral metastases (Table 1).

Dose-limiting toxicities

There were no DLTs in first 4 weeks from the 3 dose levels in Part A (the dose escalation phase); however two of the 3 patients at the 60mg cabozantinib dose level required dose reduction beyond cycle 2 due to fatigue. For Part B, dose expansion was performed at the 20mg and 40mg dose levels given a more favorable long term tolerability profile compared to 60mg. An additional 18 patients were enrolled in Part B, 9 patients at each of the 20mg and 40mg dose levels, for a total of 12 patients treated at each of these doses including the patients treated in Part A. During the first cycle for the expansion cohorts, 0 of 9 patients experienced a DLT at the 20mg dose level, and 1 of 9 patients experienced a DLT (grade 3 asymptomatic lipase elevation requiring dose reduction) at the 40mg dose level. The 2-stage 90% exact binomial confidence intervals on the rate of DLTs are 0.0 (90%CI: 0.01–0.63) for the 20mg dose and 0.08 (90%CI: 0.02–0.86) for the 40mg dose.

Adverse events

Of the 27 patients included in the safety population, 13 patients (48%) experienced maximum grade 3 AEs, and 4 patients (15%) experienced grade 4 AEs: two from the cabozantinib 40mg cohort and two from the 60mg cohort (Table 2.1). All four grade 4 events (renal disorder and appendicitis at the 40mg dose level; aortic valve disease and hyperglycemia at the 60mg dose level) seen in this study were indicated by the treating investigator to be unrelated to abiraterone and cabozantinib. Twenty-six of 27 patients reported treatment related AEs (Table 2.2); 15 patients had maximum grade 3 treatment-related AEs of which 12 (80%) were felt related to cabozantinib: 3 patients at 20mg dose, 7 at 40mg dose and 2 at 60mg dose.

The most common treatment-related grade 2 AEs (all cohorts) were hypertension (22.2%), hypophosphatemia (18.5%), elevated AST (11.1%), palmar-plantar erythrodysesthesia (11.1%) and musculoskeletal and connective tissue disorders (11.1%: 1 herniated disc, 2 muscle weakness). Treatment-related Grade 3 AEs experienced by more than one patient (all cohorts) included infections (11.1%), hypophosphatemia (11.1%), thromboembolic events (n=2), anemia (n=2), elevated lipase (n=2), and elevated ALT (n=2) (Table 2.3). A total of 14 of 27 (52%) of patients on trial had cabozantinib dose reductions or discontinuations due to

toxicity: 3 of 12 at the 20mg starting dose, 8 of 12 at the 40mg starting dose, and 3 of 3 at the 60mg starting dose.

Pharmacokinetics

The geometric mean C_{min}^{ss} for abiraterone 1,000 mg QD was similar in patients receiving cabozantinib at doses of 20 mg QD (14.1 ± 4.5 ng/mL, n=11) and 40 mg QD (15.2 ± 7.6 ng/mL, n=8). Data was available for only 2 patients treated with 60 mg cabozantinib precluding meaningful comparisons with data from the other two dose levels. The median C_{min}^{ss} for abiraterone for all 21 patients was 16.0 ng/mL (range, 5.9–29.8 ng/mL). The geometric mean C_{min}^{ss} for cabozantinib given once daily was 213 ± 109 ng/mL for the 20 mg QD dose (n=11) and 434 ± 146 ng/mL for patients treated with 40 mg QD (n=8). The geometric mean dose-normalized C_{min}^{ss} of cabozantinib for all 21 patients was 11.1 ± 4.9 ng/mL/mg.

Description of efficacy results

As of data lock October 24, 2017, twenty-six (26) patients had been discontinued from study treatment, while 1 patient remained on treatment. The median follow-up was 33.8 months (IQR: 16.9–43.2 months). Maximum PSA declines of >50% were seen in 58.3%, 58.3% and 100% of the patients in the 20mg, 40mg and 60mg cohorts, respectively (Figure 2). For the patients treated at the 20mg and 40mg dose levels, Kaplan-Meier curves for time to PSA progression, time to radiographic progression, time to progression (by earlier of radiographic progression or "no longer clinically benefiting"[28]), and overall survival are shown in Figure 3. The estimated median time to radiographic progression was 12.88 months (95% CI 5.42 – not estimated [NE]) in the 20mg cohort and 22.01 months (95% CI 15.44 - NE) in the 40mg cohort, and median overall survival was 23.29 months (95% CI 19.06 - NE) in the 20mg cohort and 39.08 months (95% CI 17.38 - NE) in the 40mg cohort (95% CI 0.21 – 1.53). Based on tolerability and preliminary efficacy, abiraterone acetate 1000mg daily with cabozantinib 40mg daily is the recommended phase 2 dose (RP2D).

Discussion

The development of rational therapeutic combinations to enhance the anti-tumor activity and prolong clinical benefit from abiraterone acetate treatment is an important unmet clinical need in prostate cancer. Here we demonstrate that abiraterone can be safely combined with cabozantinib in patients with mCRPC. Though there were no dose-limiting toxicities for cabozantinib 20mg, 40mg or 60mg at 4 weeks after starting treatment, the 40mg and 20mg doses were favored for dose expansion given better long-term tolerability compared to cabozantinib 60mg. While 10 of the 12 patients treated at the 40mg dose experienced grade 3 or higher toxicities, these were mostly asymptomatic (such as hypertension and alteration in laboratory parameters) and were easily managed pharmacologically or with dose delays and/or reductions. None of the grade 4 toxicities seen in this study were felt to be related to abiraterone or cabozantinib, and there was no treatment-related mortality. There was a suggestion of greater clinical benefit with the 40mg dose as compared to the 20mg dose – while the initial PSA response rate to both doses was similar, there was a trend towards longer time to progression and overall survival with the 40mg dose. These findings are in

consonance with a prior study suggesting greater pharmacodynamic activity of 40mg compared to 20mg with respect to bone scan response.[29] Moreover, patients treated with 40mg of cabozantinib with abiraterone had longer median radiographic progression free-survival (22.01 months) and overall survival (34.7 months) versus the outcome seen in patients treated with abiraterone alone in the COU-AA-302 study (16.5 months and 39.08 months respectively)[30,31] despite the fact that our study allowed patients with visceral metastases and prior chemotherapy exposure. These poorer prognosis patients were excluded from the COU-302 trial. Our findings suggest that combining cabozantinib at 40mg with abiraterone was tolerable and could lead to prolonged benefit compared to abiraterone alone.

The development of abiraterone acetate as a therapeutic agent in prostate cancer has been transformative to management of these patients. With results of the LATITUDE[10] and STAMPEDE[11] trials demonstrating a survival benefit to the addition of abiraterone to initial androgen deprivation therapy for metastatic hormone-sensitive prostate cancer, the contexts in which meaningful clinical benefit from abiraterone have been demonstrated continue to expand. A major ongoing research effort is focusing on incorporating abiraterone acetate in treatment paradigms for localized disease, including concurrent treatment with external beam radiation therapy[32], or in the neoadjuvant[33,34] and neoadjuvant/adjuvant (NCT02903368) settings. If abiraterone decreases metastatic relapse in these settings, this will lead to further decreases in the death rate attributable to prostate cancer[35], as well as decrease suffering related to symptoms of recurrent disease and its treatment.

In this context, elucidating and therapeutic targeting of resistance mechanisms to abiraterone are critical to further enhance clinical benefits derived from this agent. Specifically, resistance to abiraterone could involve compensatory signaling through alternate survival pathways, and co-targeting of these pathways would be expected to lead to superior clinical outcomes, as has been demonstrated with the addition of the MEK inhibitor trametinib to the RAF inhibitor dabrafenib in the first line treatment of BRAF-mutated melanoma[36,37].

Cabozantinib is an intriguing partner for combination treatment with abiraterone given its mechanism of action. As a multi-kinase inhibitor, it can simultaneously target critical signaling pathways as well as compensatory pathways. For example, inhibition of compensatory upregulation of MET signaling with blockade of the VEGF pathway has been implicated as its major mechanism of action in renal cell carcinoma[38,39]. Two of the major targets of cabozantinib, MET and VEGFR2, have both been mechanistically implicated in the development of castration resistance in patients[40]. Interestingly, in a PTEN/p53-deficient genetically engineered mouse model, the anti-tumor activity of cabozantinib was demonstrated not to be related to inhibition of MET but rather to activation of a neutrophil-mediated anticancer innate immune response[41]. In a preclinical model of prostate cancer, it has been demonstrated that cabozantinib can inhibit compensatory upregulation of the IGF1R/MEK/ERK pathway in prostate cancer cells induced by abiraterone treatment[18]. Clearly, further investigation is needed to clarify the mechanism by which cabozantinib may enhance the activity of abiraterone in patients.

Cabozantinib demonstrated interesting single-agent clinical activity in a Phase 2 nonrandomized expansion study in castration-resistant prostate cancer (CRPC), demonstrating bone scan response rates of 73% and 45% in 100mg (N=93) and 40mg (N=51) cohorts, respectively.[16] In addition, there were improvements seen in measurable soft tissue disease, circulating tumor cells and bone biomarkers, along with improvements in pain and analgesic use.[42] In these studies, the 100mg dose of cabozantinib was associated with significant toxicity so a 60mg dose was chosen for the subsequent Phase 3 COMET-1 study, where patients were randomized to cabozantinib vs. prednisone with primary endpoint of overall survival. The COMET-1 study demonstrated improvements in bone scan response, radiographic progression-free survival, symptomatic skeletal events, CTC conversions, and bone biomarkers but not PSA outcomes or overall survival. Because the COMET-1 study did not demonstrate an OS benefit, the Phase 3 COMET-2 study comparing pain palliation with cabozantinib vs. a control arm of mitoxantrone/prednisone was discontinued early. Final results of COMET-2 demonstrated that in the 119 patients randomized prior to discontinuation, pain response rates were 15% for cabozantinib and 17% for mitoxantrone/prednisone; bone scan response rates were 31% for cabozantinib and 5.2% for mitoxantrone/prednisone.[43] Why the COMET-1 and COMET-2 studies demonstrated improvements in intermediate parameters but not their primary endpoints remains unclear. One possibility is that these intermediate parameters do not reflect a change in disease biology that leads to prolongation of survival. In addition, we hypothesize that part of the reason that the Phase 3 studies did not meet their primary endpoints is that these patients were heavily pre-treated with both taxane and androgen-receptor targeted therapies (all patients were required to have failed docetaxel as well as abiraterone and/or enzalutamide), whereas in the Phase 2 study cited above[16] only 44% of patients had received prior abiraterone and 4% received prior enzalutamide. It has been suggested that upregulation of c-Met is an early compensatory event with androgen ablation[44] that can be therapeutically targeted with inhibitors of c-Met.[45] These studies would suggest that agents that inhibit the MET pathway, such as cabozantinib, may have increased activity earlier in the disease course, particularly in combination with androgen-receptor targeted therapy.

CYP3A4/5 is the major cytochrome P450 (CYP) isozyme involved in the hepatic metabolism of both abiraterone and cabozantinib in humans, with minimal involvement of other CYP isozymes.[24,46] *In vitro* studies using human hepatic microsomes showed that abiraterone is a moderate inhibitor of CYP3A4/5 and that cabozantinib inhibits the isozyme weakly. Cabozantinib is not a potent inducer of CYP3A4/5 and the induction potential of abiraterone on CYP isozymes has not been reported. The pharmacokinetics of cabozantinib are readily altered by agents that significantly inhibit or induce CYP3A4 activity.[21] Systemic exposure to abiraterone was decreased by 55% when given to subjects that had been pretreated with the strong CYP3A4 inducer rifampin but not significantly affected when coadministered with the strong CYP3A4 inhibitor ketoconazole.[47] The plasma pharmacokinetics of erlotinib, an approved anticancer drug for which CYP3A4 metabolism represents a prominent route of its elimination, was not affected by the coadministration of cabozantinib in a phase I study in patients with solid tumors.[24] The current understanding of the pharmacokinetics and metabolism of abiraterone and cabozantinib therefore suggests

that there is a relatively low potential for a clinically relevant alteration in the plasma pharmacokinetics of either drug when given concurrently.

Two different dosage forms for oral administration have been used during the course of the clinical development of cabozantinib, the original capsule and a newer tablet formulation. While publically accessible information on the C_{min}^{ss} of cabozantinib is available from several clinical trials in which patients with solid tumors received 140 mg QD doses of the capsule formulation,[48] similar data is not available for the tablet formulation used in this trial. The two dosage forms are not strictly bioequivalent, primarily due to differences in the rate of absorption following administration of a single 140 mg dose that gives rise to statistically different maximum concentrations of the drug in plasma, although they otherwise provide nearly indistinguishable plasma concentration-time curves when administered over a broad range of clinically relevant doses.[49] Linear pharmacokinetics has been demonstrated for the tablet formulation at single doses ranging from 20–140 mg. Thus, although a formal comparison of the steady state pharmacokinetics for the two dosage forms have not been undertaken, there appears to be sufficient justification to use dose-normalized C_{min}^{ss} values to compare data from the present study with data from prior clinical trials of single agent cabozantinib that employed the capsule formulation.

Consistent with the known linear pharmacokinetic behavior of cabozantinib for the tablet dosage form,[49] the geometric mean C_{min}^{ss} of cabozantinib in patients treated with doses of 40 mg QD (434 ± 146 ng/mL, n=11) was 2.04 times greater than in patients treated with 20 mg QD (213 ± 109 ng/mL, n=8), when given together with abiraterone 1,000 mg QD. The geometric mean (±SD) dose-normalized C_{min}^{ss} of cabozantinib (i.e. C_{min}^{ss} divided by dose in mg) for all 21 patients with evaluable data in the current study, 11.1 ± 4.9 ng/mL/mg, was within the 7.7 –34.1 ng/mL/mg range of dose-normalized mean C_{min}^{ss} values of the drug in CRPC patients treated with 100 mg QD of the capsule formulation as a single agent (data on file at Exelixis). These findings suggest that the steady state pharmacokinetics of cabozantinib were not affected by the co-administration of abiraterone.

The overall median C_{min}^{ss} of abiraterone in the present study for the entire group of 21 patients with evaluable pharmacokinetic data was 16.0 ng/mL (range, 5.9–29.8 ng/mL), compared to 11.1 ng/mL (range not reported) in 119 patients evaluated in the Phase 3 COU-AA-301 trial[46] and 10.5 ng/mL (range, 2.6–26.9 ng/mL) over the first 3 months of treatment in a group of 55 patients in another recently reported study.[50] The range of abiraterone concentrations seen in combination with cabozantinib in our study overlaps with ranges of C_{min}^{ss} in previous reports. The median abiraterone concentration seen in our study is numerically different from prior studies, though it is entirely possible that other unknown factors, such as differences in patient characteristics or their diets, the time that samples were collected relative to the prior dose, consistency in the daily dosing time, the analytical methods used to measure the drug concentration, or interpatient variability in the pharmacokinetics of the drug, contributed to the differences seen here. A more formal drug-drug interaction study would be needed to definitively determine if cabozantinib affects abiraterone levels. If cabozantinib were shown to mitigate the likelihood of low systemic abiraterone exposure in some patients, this could also increase the chance of clinical benefit as low abiraterone levels have previously been correlated with inferior outcomes.[50,51]

However, there is no evidence that this is the mechanism mediating potentially greater clinical benefit seen at the 40mg dose level in this study compared to the 20mg dose level as the abiraterone concentrations were nearly equivalent in these groups: 14.1 ± 4.5 ng/mL (n=11) at the 20mg dose and 15.2 ± 7.6 ng/mL (n=8) at the 40mg dose.

In conclusion, we have demonstrated safety, tolerability, and preliminary evidence of clinical activity with the combination of abiraterone and cabozantinib. The results of this trial provide important information to guide the design of a definitive comparative trial, which will more fully assess the ability of cabozantinib to increase duration of cancer control and overall survival in combination with abiraterone in patients with prostate cancer.

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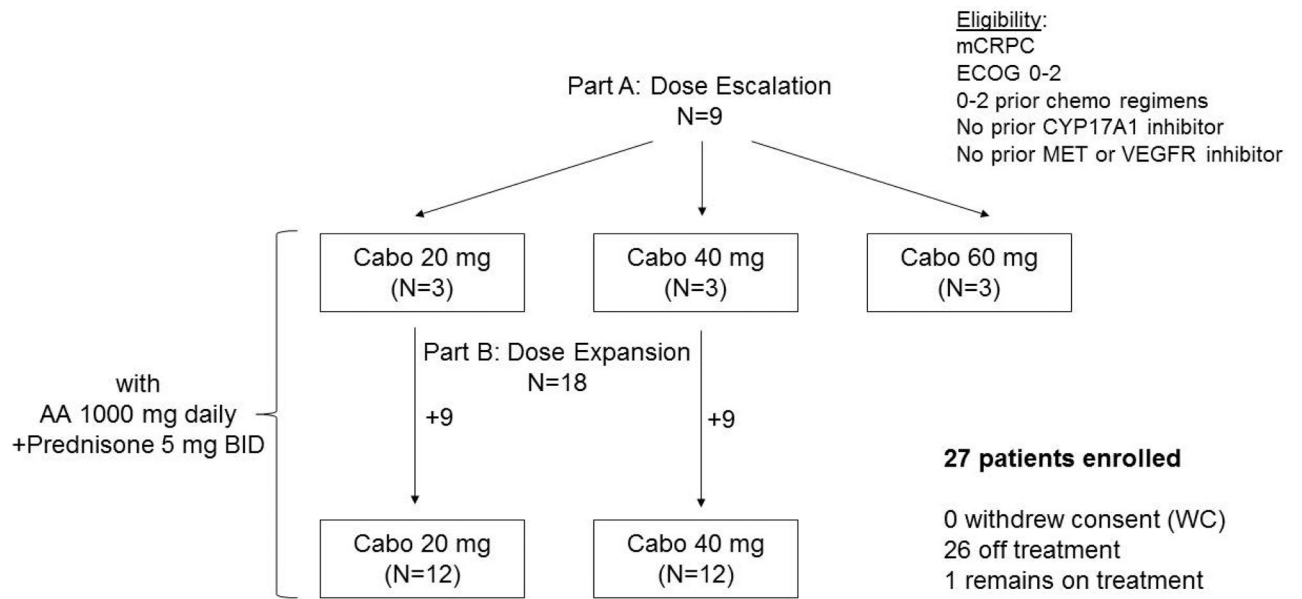
Figure 1.
Schema of patient cohorts in the dose escalation (Part A) and dose expansion (Part B) phases
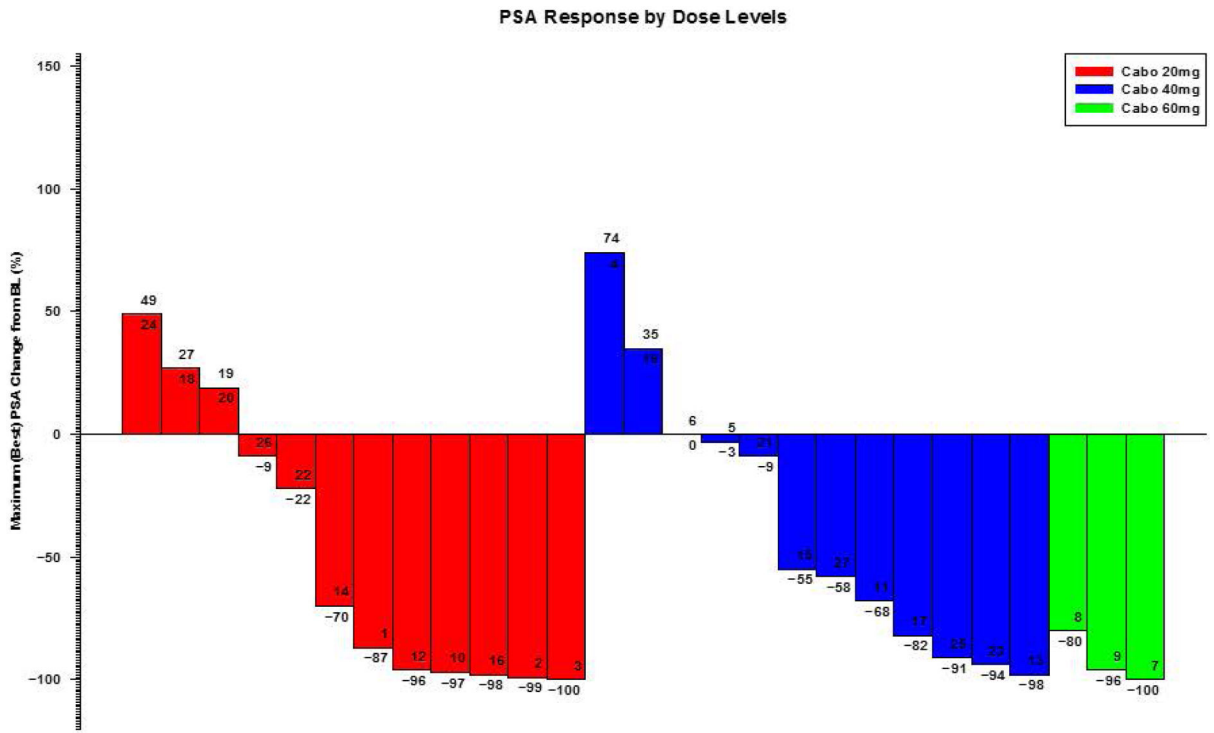of this study. Cabo=cabozantinib, AA=abiraterone acetate.

Figure 2.
Waterfall plot of maximal PSA change (%) from baseline by cabozantinib dose level.
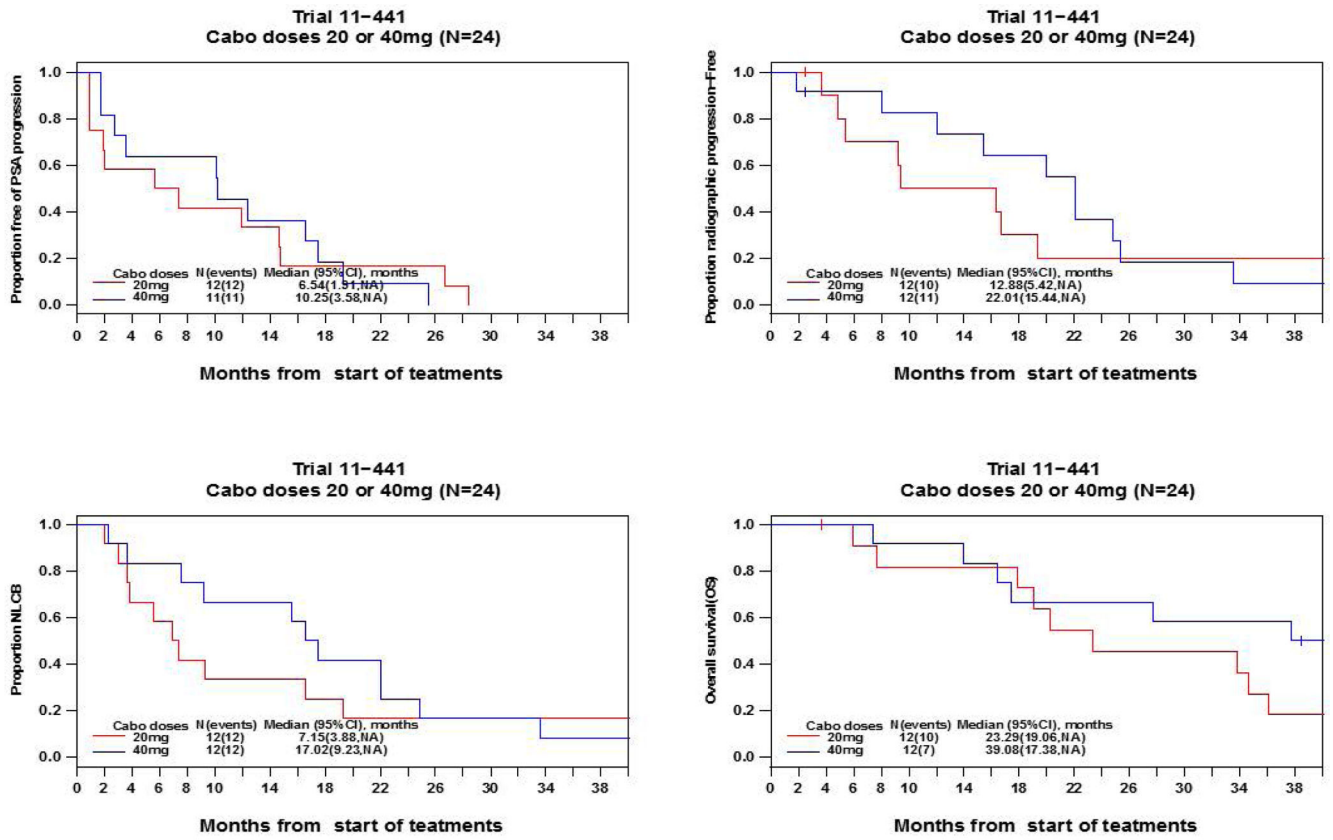
Figure 3.
Kaplan-Meier curves for **A.** time to PSA progression **B.** time to radiographic progression **C.** time to progression by the earlier of radiographic progression or no longer clinically benefiting (NLCB) and **D.** overall survival in patients treated at 20mg and 40mg dose levels.

Table 1.

Patient characteristics according to cabozantinib dose level

Factor	Stat	cabozantinib, 20mg, N=12	cabozantinib, 40mg, N=12	cabozantinib, 60mg, N=3*	Total N=27
Follow-up (months)	Median (IQR)	21.8 (15.4,35.0)	38.1 (17.1,41.8)	55.8 (31.1,56.9)	33.8 (16.9,43.2)
		[3.6,60.4]	[7.4,58.5]	[6.3,58.0]	[3.6,60.4]
Age at diagnosis (year)	Median (IQR)	62 (59,66)	60 (57,62)	57 (55,59)	60 (57,64)
	Range	[50,74]	[49,68]	[53,61]	[49,74]
Age at start of study (year)	Median (IQR)	66 (61,72)	62 (61,67)	65 (60,68)	64 (61,70)
	Range	[52,76]	[53,75]	[56,71]	[52,76]
Race (White)	N (%)	12(100.0)	11(91.7)	3(100.0)	26(96.3)
Baseline ECOG PS N (%)	0	11(91.7)	11(91.7)	3(100.0)	25(92.6)
	1	1(8.3)	1(8.3)	0(0.0)	2(7.4)
Gleason at Dx, N (%)	6	0(0.0)	1(8.3)	1(33.3)	2(7.4)
	7	2(16.7)	2(16.7)	0(0.0)	4(14.8)
	8–10	10(83.3)	9(75.0)	2(66.7)	21(77.8)
Baseline testosterone level (ng/dL)	Median (IQR)	7 (0,10)	11 (10,17)	7 (7,7)	9 (7,12)
	Range	[0,16]	[7,24]	[7,7]	[0,24]
Baseline PSA (ng/mL)	Median (IQR)	31 (19,72)	14 (2,47)	8 (6,9)	20 (6,45)
	Range	[1,376]	[0,783]	[4,11]	[0,783]
Prior docetaxel use	N (%)	5(41.7)	5(41.7)	1(33.3)	11(40.7)
Prior opiate use	N (%)	5(41.7)	6(50.0)	1(33.3)	12(44.4)
Visceral metastases	N (%)	2(16.7)	1(8.3)	1(33.3)	4(14.8)
LDH >1xULN, N (%)	Yes	2(16.7)	1(8.3)	1(33.3)	4(14.8)
	No	10(83.3)	11(91.7)	2(66.7)	23(85.2)
Normal Albumin (3.7–5.4 g/dL)	N (%)	12(100.0)	12(100.0)	3(100.0)	27(100.0)
HGB (<12.5 g/dL) N (%)	Low	5(41.7)	4(33.3)	2(66.7)	11(40.7)
	Normal	7(58.3)	8(66.7)	1(33.3)	16(59.3)
Alkaline Phosphatase (>118 U/L), N (%)	High	4(33.3)	4(33.3)	0(0.0)	8(29.6)
	Normal	8(66.7)	8(66.7)	3(100.0)	19(70.4)

Table 2.1

Number of Patients with ALL Adverse Events (AEs) according to cabozantinib dose level

	cabozantinib dose level							
	cabozantinib 20mg, abiraterone 1000mg		cabozantinib 40mg, abiraterone 1000mg		cabozantinib 60mg, abiraterone 1000mg		TOTAL	
	N	%	N	%	N	%	N	%
Maximum Grade [*]								
1	2	16.7	1	8.3	-	-	3	11.1
2	5	41.7	1	8.3	1	33.3	7	25.9
3	5	41.7	8	66.7	-	-	13	48.1
4	-	-	2	16.7	2	66.7	4	14.8
Total	12	100.0	12	100.0	3	100.0	27	100.0

[*] maximum grade consolidates reports of all AEs of same type for a patient.

Table 2.2

Number of Patients with **Treatment-Related** AEs according to cabozantinib dose level

| | cabozantinib dose level | | | | | | | |
| | cabozantinib 20mg, abiraterone 1000mg | | cabozantinib 40mg, abiraterone 1000mg | | cabozantinib 60mg, abiraterone 1000mg | | TOTAL | |
	N	%	N	%	N	%	N	%
Maximum Grade								
1	3	27.3	1	8.3	-	-	4	15.4
2	3	27.3	3	25.0	1	33.3	7	26.9
3	5	45.5	8	66.7	2	66.7	15	57.7
Total	11	100.0	12	100.0	3	100.0	26	100.0

*maximum grade consolidates reports of all AEs of same type for a patient.

Table 2.3

Frequency and proportion of most commonly reported AEs that were indicated as possibly, probably, or definitely related to protocol therapy

Maximum Grade 2+ (with N>1 patients)	N (%)	Maximum Grade 3 (with N>1 patients)	N (%)
Hypertension	6(22)	Infection	3(11)
Hypophosphatemia	5(19)	Hypophosphatemia	3(11)
AST	3(11)	Anemia	2(7)
Palmar-plantar erythrodysesthesia syndrome	3(11)	ALT	2(7)
Musculoskeletal and connective tissue	3(11)	Lipase increase	2(7)
Anemia	2(7)	Thromboembolic event	2(7)
ALT	2(7)		
Thromboembolic event	2(7)		