TITLE: A Phase II study of MRI based functional imaging for the evaluation of bone metastasis in men with castrate resistant prostate cancer receiving XL184

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SUMMARY

Study Design: In this single arm, open label phase II study, 25 patients with metastatic to the bone, castrate resistant prostate cancer will be treated with 60mg XL184 daily, p.o. Patients will undergo two baseline screening MRI of the abdomen and pelvis prior to initiating study, and have a third set of MRI at 2 weeks on study. Subsequently, patients will be followed with MRI of the abdomen/pelvis along with CT scan of the chest every 12 weeks for disease monitoring. In addition, circulating tumor cells, standard laboratories, and pain assessments will be collected according to the schema below.

Eligible Patients: Patients must have histologically confirmed prostate cancer with evidence of castration resistance defined as rising PSA or clinical/radiographic progression following androgen deprivation, as well as anti-androgen therapy and anti-androgen withdrawal. Patients must have bone metastases identifiable on screening MRI studies. Patients must have an ECOG performance status of 0 or 1 and have adequate bone marrow, liver and renal function.

Primary Objective: To determine the effect of XL184 on the functional MRI metrics K^{trans} and apparent diffusion coefficient (ADC) within castrate resistant prostate cancer bone metastases. Specifically, we will use dynamic contrast MRI (DCE-MRI) to measure the volume transfer constant of the MRI contrast reagent, K^{trans}, and diffusion weighted imaging (DWI) to calculate the ADC at baseline and while on therapy with the hypothesis that XL184 will inhibit bone marrow vascular permeability and stroma proliferation, causing early changes in K^{trans} and ADC.

Secondary Objectives: In addition to characterizing the change in the functional MRI metrics, we will be correlating the pre-treatment ADC/K^{trans} values, at baseline and according to change over time, with standard disease metrics including RECIST tumor measurement criteria, PSA, circulating tumor cell numbers (CTC, CellSearch), and pain (Pain questionnaire and analgesic log). As such, these metrics will be secondary objectives of the study. We will also be performing an exploratory analysis of c-MET expression within circulating tumor cells.

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1. BACKGROUND

1.1. Castrate Resistant Prostate Cancer (CRPC)

Although most men are diagnosed with early stage, curable prostate cancer, unfortunately, prostate cancer recurrence is seen in ~40% of patients over time[1]. Although typically effective initially, in most cases hormone responsiveness is finite and patients typically fail first line androgen deprivation within 2-3 years, progressing to CRPC. This transition represents an important clinical landmark of an evolving disease that correlates with an increased risk of death and morbidity[2]. This year ~32,000 men are projected to die from prostate cancer, the vast majority of whom will die from metastatic castration resistant disease (mCRPC) with bone metastases[3]. The effective therapies for progressive CRPC are limited with docetaxel and cabazitxel chemotherapies along with the novel immunotherapy sipuleucel-T as the only currently FDA approved therapies shown to improve patient survival in the CRPC setting [4, 5, 6, 7]. The approximate survival after standard therapies in this setting is bleak and in the order of months. In addition to death from the disease, CRPC, especially when metastatic to the bones, leads to substantial disability in men who suffer from the disease with a high incidence of pain, bone fractures, abnormal blood counts and fatigue. There are no targeted therapies proven to be effective for CRPC, as the precise biology of castration resistance remains elusive. There is thus a desperate need for novel therapies focused on new targets implicated in bone metastasis biology.

1.2. MET and CRPC bone metastases

Although the androgen receptor (AR) remains a critical driver of prostate cancer, even in the setting of castration resistance, and novel therapies targeting the AR are showing promise in the mCRPC setting[8-10], disease progression despite the most formidable androgen axis inhibition is eventual. Multiple therapies that target castrate resistant biology beyond the AR are in development. One of the most exciting targets implicated in CRPC progression is the tyrosine kinase c-MET. c-Met protein is over-expressed or mutated in many tumor cell types and plays key roles in tumor cell proliferation, survival, invasion, metastasis, and angiogenesis[11, 12]. In prostate cancer, c-MET expression is variable and over-expressed in 40-80% of prostate cancer tissues[13, 14]. c-MET was found to be expressed in particularly high levels (86%) of lymph node and bone metastases[15]. Furthermore, c-MET expression was found to be upregulated in prostate cancer models following castration implicating a mechanistic role in castration resistance[13, 16]. In addition to potentially regulating prostate cancer cell survival and proliferation, c-Met and its ligand HGF are reported to stimulate osteoblast and osteoclast proliferation[17-19]. Given c-MET's potential stimulatory effects on prostate cancer and bone stroma, and prostate cancer's predilection for bone metastases, c-MET is an intriguing molecule to target in mCRPC.

1.3. XL184 (Cabozantinib)

XL184 is an orally bioavailable small molecule inhibitor of several receptor tyrosine kinases, most notably c-MET,VEGFR2 and RET with IC_{50} of 1.8 nM, 0.035nM and 3.8 nMrespecvitvely.XL184 caused tumor regression in multiple *in vivo* tumor models. Treatment with XL184 shows rapid effects on the tumor endothelium, resulting in breakdown of the vasculature beginning 24 hours after administration of XL184, thus suggesting potent anti-

angiogenic effects of XL184. These effects translate into significant tumor growth inhibition after XL184 treatment in multiple tumor models including human MTC, human breast cancer, human lung carcinoma, and rat glioblastoma (Table 1). Overall, the data generated in vivo demonstrate that the target profile of XL184 translates to potent anti-angiogenic activity and potent antitumor efficacy.

Table1: XL184 ED_{50} Values in Tumor Models

Tumor Line	Species	Tissue of Origin	ED_{50}[a] (mg/kg/day)	Treatment Duration
TT	Human	Medullary thyroid carcinoma	11	qd× 21
MDA-MB-231	Human	Breast	2	qd× 14
H441	Human	Lung	3	qd× 14
C6	Rat	Brain	<1	qd× 12

ED_{50}, dose associated with 50% tumor growth inhibition; qd, once daily.
[a] $AUC_{0\text{-}inf}$ or $AUC_{0\text{-}24\ h}$ values are about 5.16 µg·h/mL for 3 mg/kg/day in mice, 23.3 µg·h /mL for 1 mg/kg/day in rats, and 38.9 µg·h/mL for 175 mg/day in humans.

Over 1000 patients to date have been treated at various doses, in multiple clinical trials with XL184. With the capsule formulation, the maximum tolerated dose was 175mg daily with reported dose limiting toxicities of plantar/palmar erythema, elevated lipase, elevations in AST/ALT and mucositis. The most common AEs considered either possibly or probably related to XL184 (frequency ≥ 15% of subjects, N=483 patients from pooled studies) consisted of fatigue (46%), diarrhea (42%), decreased appetite (27%), nausea (28%), vomiting (17%), palmar-plantar eryhtrodysaesthesia syndrome (17%) increased AST/ALT (16%), hypertension (16%), and rash (15. Most AEs (80%, regardless of relation) were of Grade 1 or 2. These events were generally reversible or manageable with dose interruptions or reductions. A complete description of the adverse event profile associated with XL184 is available within the investigator's brochure[20, 21]

Recently, 171 patients with metastatic castrate resistant prostate cancer were treated with XL184 at 100mg (free base) oral daily dosing in the context of a phase II randomized discontinuation trial conducted in multiple tumor types, with an expanded prostate cancer cohort (NCT00940225). XL184 was shown to have a remarkable impact on bone metastases with 82/108 (76%) of patients with evaluable bone scans showing a partial or complete response, and the majority a concomitant improvement in bone pain[20, 22]. Significant and lasting changes in measures of bone turnover were also observed. Many of these patients achieved concomitant improvements in their PSA and hemoglobin. There was a much more modest change in measurable disease, with only 3/34 (9%) confirmed responses according to RECIST criteria[22].

Upon review of the data from NCT00940225, it was noted that overall rate of dose reduction from 100 mg to 60 mg was 51%. Only 14% required an additional reduction in dose from 60 mg to the next lowest dose of 40 mg, which is consistent with an overall improvement in tolerability profile at the 60-mg dose level. The majority (69%) of subjects with pain at baseline who experienced early dose reduction (before Week 6) to 60 mg went on to report pain improvement at Week 6. Moreover, 80% of these subjects remained progression-free and continued to report pain relief at the Week 12 time point. Thus the dose of 60 mg daily appears to offer improved tolerability while maintaining efficacy in a patient population with advanced CRPC and cancer-related pain at

baseline. As such, this study, as well as the pending phase III studies in CRPC, will adopt a starting cabozantinib dose of 60 mg daily.

Based on the preliminary PK data from 46 subjects participating in a phase I open-label, single-dose crossover study to assess the effect of food on the bioavailability of XL184 (study XL184-004), a high-fat meal did not appear to alter the terminal $t_{1/2, z}$ of XL184 [mean $t_{1/2, z}$: 131 hours (fed) vs 128 hours (fasted)]. The high-fat meal significantly increased the median $t_{max}$to 6 hours from 4 hours (fasted). The high-fat meal also significantly increased both the XL184 $C_{max}$and AUC values by 39% and 56%, respectively. The geometric mean ratio of C_{max} fed/fasted was 1.39 (90% CI: 1.16-1.67), and the geometric mean ratio of $AUC_{0\text{-last}}$ fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, XL184 should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each dose).

1.4. Functional MRI

The current standard bone imaging employed in mCRPC is technitium based nuclear medicine bone scintigraphy, based on uptake of the radionuclide in metabolically active bone. It is not specific for tumor induced changes, and is not quantitative at the lesion level. In fact, according to Prostate Cancer Working Group Criteria 2.0[23], bone scans should only be evaluated for presence or lack of new lesions. State of the art MRI technologies have several advantages over traditional bone scintigraphy and CT. MRI is not hampered by X-ray attenuation by sclerotic bone and can thus allow accurate and precise measurement of intra-bone lesions that can be measured over time. For prostate cancer bone metastases, 65% of patients will have reproducibly measurable bone lesions according to RECIST criteria when imaged with standard MRI, compared to <30% with standard CT scan[24, 25]. Thus a higher percentage of bone lesions can be assessed over time in the context of therapy and measured for response. Functional MRI imaging has the additional benefit of allowing biologic characterization of the bone metastases. Diffusion weighted imaging measures waters movement within the imaged region. It can be used to accurately measure cellularity, proliferation, apoptosis and early responses to treatment[26]. More specifically, by measuring the apparent diffusion coefficient (ADC), it is possible to characterize biologic changes within a tumor before any apparent change in size of the tumor is appreciated[26, 27]. The other functional MRI pharmacodynamic marker that has particular relevance in studies of anti-angiogenic agents is K^{trans}, obtained using DCE-MRI. K^{trans} is a measurement calculating the volume transfer constant of the contrast reagent and essentially is a measurement of vascular perfusion. Investigators at the University of Chicago and others have shown that VEGF targeted agents that alter angiogenesis are known to significantly decrease K^{trans}[28]. Importantly, our group has demonstrated that K^{trans} can be reliably and reproducibly measured in CRPC bone metastases[29].

1.5. Circulating Tumor Cells

Recently, many technologies have been investigated for detection and isolation of circulating tumor cells (CTC) from the peripheral blood[30-39]. The most commonly used technology, immunomagnetic cell separation (CellSearch (Veridex, LLC)), has been utilized to enumerate CTC from men with CRPC and is an FDA approved device. Several investigators have shown that absolute and change in CTC number can be prognostic and predictive of patient outcome[40, 41]. Using cutting edge resources available at the University of Chicago, the Szmulewitz laboratory

has successfully used fluorescence activated cell sorting (FACS) followed by multiplex IF to isolate and interrogate CTC from men with CRPC. Seven out of fifteen patients in the first cohort had >200 presumptive CTC events by flow cytometry. All of these patients with >200 events had at least 10 CTC identified by imaging with the median of 22 (range 10-25) and an average of 19.4 (+/- 5.1). With these techniques, it is possible to probe CTC from patients with mCRPC for c-MET and phospho-c-MET (activated c-MET) in real-time.

1.6. Rationale

XL184 is an inhibitor of c-MET and VEGFR2 with potent anti-angiogenesis properties in preclinical models. An ongoing multi-tumor phase II clinical trial has shown a tremendous impact on nuclear medicine bone scan, however the biology underpinning these changes is unknown. To understand the changes within the bone indicated by the initial XL184 study, more sensitive and precise bone imaging is necessary. MRI based imaging, both traditional and functional, is an exciting tool that can potentially illuminate the mechanism of affect of XL184 on mCRPC to the bones by allowing sensitive interrogation of bone lesion biology. This study proposes to utilize functional bone imaging to test the hypothesis that XL184, through inhibition of c-MET and VEGFR2 in the tumor cells and stromal cells, will have a potent affect on the microenvironment, causing an early inhibition of angiogenesis and subsequent intra-tumoral cell death and tumor shrinkage. To confirm this hypothesis, potent changes in K^{trans} should be seen at 2 weeks, a very early time point, followed next by intra-tumoral cellular changes, characterized by ADC changes at 12 weeks, finally followed by tumor shrinkage at subsequent imaging.

1.7 Interim Safety Analysis

After the first 13 patients (approximately 50% accrual) were treated on this trial, an unplanned safety analysis was performed to review XL184 tolerability at the current dose and schedule, due to concern for frequent toxicity requiring dose modification. Although largely well tolerated at 60mg/day up to week 4, nearly all patients required subsequent dose reduction (12/13, with 1 patient dose reduced at week 12) before their first on study disease evaluation at 12 weeks. On average patients were either held or dose reduced for toxicity between weeks 4-6. The most commonly reported toxicity requiring dose reductions were fatigue, decreased appetite, hand-foot syndrome, and hypertention. The vast majority of these were persistent moderate toxicities (grade 2) that interfered with patient quality of life. As such, the dosing schema has been modified to include a scheduled dose reduction after 4 weeks on study. As the primary endpoint of the study is MRI changes at 2 weeks, this change will not affect the primary scientific endpoint.

2. OBJECTIVES

2.1. Primary Objective

- The primary objective of the study is to determine effect of XL184 on the functional MRI metrics K^{trans} and apparent diffusion coefficient (ADC) within castrate resistant prostate cancer bone metastases.

2.2. Secondary Objectives

- To quantify progression free survival in men with CRPC treated with XL184 according to Prostate Cancer Working Group criteria[23]

- To correlate and changes in MRI based functional metrics with bone scan, PSA, RECIST response criteria, CTC number and with changes in pain.
- To explore c-MET, phospho-c-MET staining on circulating tumor cells as a predictive biomarker for response and duration of response to XL-184.

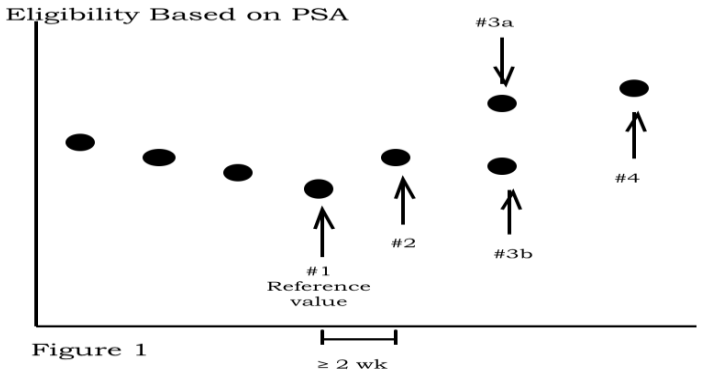
3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Histologically or cytologically confirmed prostate cancer with progressive disease defined as either:

- Bone scan: 2 or more new lesions
- Nodal/visceral: According to RECIST criteria (20% increase in sum of diameters)[42]
- Rising PSA: PSA evidence for progressive prostate cancer consists of a PSA level of at least 2 ng/ml which has risen on at least 2 successive occasions, at least 2 weeks apart. If the confirmatory PSA (Fig 1 #3) value is less (Fig 1 #3b) than the screening PSA (Fig 1 #2) value, then an additional test for rising PSA (Fig 3 #4) will be required to document progression.

Figure 1: Eligibility Based on PSA



3.1.2. Evidence of castration resistance defined as disease progression despite a testosterone level <50ng/dL (or surgical castration)

3.1.2.1. Antiandrogen withdrawal:

- Patients who are receiving an antiandrogen (e.g. bicalutamide, nilutamide, flutamide) as part of primary androgen ablation must demonstrate disease progression following discontinuation of antiandrogen.
- Disease progression after antiandrogen withdrawal is defined as 2 consecutive rising PSA values, obtained at least 2 weeks apart, or documented osseous or soft tissue progression.
- For patients receiving flutamide, at least one of the PSA values must be obtained 4 weeks or more after flutamide discontinuation.

- For patients receiving bicalutamide or nilutamide, at least one of the PSA values must be obtained 6 weeks or more after antiandrogen discontinuation.
- No antiandrogen withdrawal response is expected in patients in whom antiandrogen therapy did NOT result in a decline in PSA or in those patients in whom the response to antiandrogens was <3 months. Therefore, it is not necessary to wait for AAWD in pts w/out PSA decline on an anti-androgen or in those in whom a PSA response lasted <3 months. In this instance, progression after withdrawal is not necessary. A 4 week wash out alone is sufficient.

3.1.3. Evidence of metastatic disease to the bones within the lumbar spine, sacrum, or pelvic bones that is identifiable on screening pelvic MRI.

- If patient has had prior pelvis RT, then bone metastases must be out of radiated port (e.g. lubar or sarcral spine).

3.1.4. Any prior therapy for castrate disease acceptable other than prior XL184 with a minimum washout of 2 weeks for any other anticancer therapy.

- Prior palliative radiotherapy to the pelvis must be documented and requires a minimum of 6-week washout. Any other radiotherapy or radionuclide requires a 2 week washout.
- Denosumab or zoledronic acid are allowed provided they are initiated prior to study initiation.

3.1.5. ECOG performance status ≤2 (**Appendix A**).

3.1.6. Patients must have normal organ and marrow function as defined below:

– Absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– Hemoglobin	≥9.0g/dL
– Total bilirubin	≤1.5 x the upper limit of normal. (≤3 if known Gilbert's)
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– Creatinine clearance	Calculated (traditional Cockroft-Gault) GFR ≥60ml/min.
– Lipase	<1.5 x the upper limit of normal
– Urine protein/creatinine ration	≤1
– Serum phosphorus	≥lower limit of normal

3.1.7. Patients who are capable of sexual intercourse that may lead to fertilization must agree to avoid insemination either by abstinence or with an adequate form of contraception.

3.1.8. Ability to understand and the willingness to sign a written informed consent document.

3.2. Exclusion Criteria

3.2.1. Patients who have had chemotherapy or radiotherapy within 2weeks prior to entering

the study or those who have not recovered from adverse events due to agents administered more than 2weeks earlier.

- Patients on LHRH-Agonists/antagonists should be maintained on these agents.
- Concomitant bone strengtheners (e.g. zoledronic acid, denosumab) are allowed provided they have been started prior to study initiation.

3.2.2. Patients who are receiving herbal supplements known to increase bleeding risk including fish oil, flaxseed oil, clove, red clover, ginger, ginkgo biloba, St. John's Wart and tumeric.

3.2.3. Patients who are receiving any other investigational agents.

3.2.4. Prior treatment with other c-MET targeted therapies.

3.2.5. Patients with known untreated brain metastases are excluded from this clinical trial because of their poor prognosis and because of the unknown cerebral bleeding risk associated with XL184 angiogenesis inhibition.

3.2.6. The patient has experienced any of the following within 3 months of the first dose of study treatment:

a. clinically-significant hematemesis or gastrointestinal bleeding
b. hemoptysis of ≥ 0.5 teaspoon (2.5ml) of red blood
c. any other signs indicative of pulmonary hemorrhage

3.2.7. Patients with documented bladder invasion with prostate cancer and active gross hematuria are excluded due to the increased risk of bleeding due to the study medication XL 184.

3.2.8. The patients has radiographic evidence of cavitating pulmonary lesion or encasing a major blood vessel.

3.2.9. The subject has uncontrolled or significant inercurrent illness including, but not limited to:

1) Cardiovascular disorders: Decompensated congestive heart failure, uncontrolled hypertension (>150mm Hg systolic or >100mm Hg diastolic), unstable angina, myocardial infarction within 6 months, cerebrovascular event within 6 months.
2) Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
   i. Any of the following at the time of screening
      - intra-abdominal tumor/metastases invading GI mucosa
      - active pepticulcerdisease not controlled with antacids,
      - inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
   ii. Any of the following within 6 months before the first dose of study treatment:
      (1) history of abdominal fistula
      (2) gastrointestinal perforation

(3) bowel obstruction or gastric outlet obstruction
(4) intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more that 6 months ago.

iii. GI surgery (particularly when associated with delayed or incomplete healing) within 28 days. Note: Complete healing following abdominal surgery must be confirmed prior to initiating treatment with cabozantinib even if surgery occurred more that 28 days ago.

3) Other disorders associated with a high risk of fistula formation including PEG tube placement within 3 months before the first dose of study therapy or concurrent evidence of intraluminal tumor involving the trachea and esophagus.
3) Other clinically significant disorders such as:
i) active infection requiring systemic treatment
(1) Chronic, but inactive hepatitis C or HIV are allowed, however an undetectable viral load must be documented.
ii) serious non-healing wound/ulcer/bone fracture
iii) history of organ transplant
iv) concurrent uncompensated hypothyroidism or thyroid dysfunction
v) history of major surgery within 4 weeks or minor surgical procedures within 1 week before initiation of study

3.2.10. Inability to swallow tablets.

3.2.11. The patient has a corrected QT interval of >500ms.

3.2.12. History of other active second malignancies.

3.2.13. The patient requires concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (e.g.,clopidogrel).

Low dose aspirin (≤ 81 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

3.3. Inclusion of Minorities

Men of all races and ethnic groups are eligible for this trial.

4. REGISTRATION AND DATA COLLECTION/MANAGEMENT

The University of Chicago Comprehensive Cancer Center maintains a secure, password protected, and regularly backed up commercial clinical trials database called "Velos." All patients on the trial will be enrolled at a single institution, the University of Chicago, and will be subsequently entered into the Velos clinical trial database. Data will be entered by the study coordinator and stored within the database using a unique identifier number.

Study Coordinator:

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Eligible patients will be entered on study centrally at the University of Chicago by the Study Coordinator. Forms are available to NorthShore co-investigator on the University of Chicago Cancer Research Center website.

- http://cancer.uchicago.edu
- Click on the **Intranet** (top right corner).
- Enter your site specific user name and password
- Click on **Phase II Website**
- Click on **Forms**

The following baseline clinical variables will be collected and stored in the database using data entry forms all available in the Velos database (**Appendix B**):

- Demographics
- Age
- Race
- Performance status
- Primary tumor data
- Diagnosis date
- Baseline staging
- Baseline PSA
- Gleason grade
- Primary tumor treatment
- Systemic therapy administered
- Date of androgen ablation start
- Dates of anti-androgen therapy, and withdrawal
- Dates and types of other systemic therapy
- Dates and types of systemic radiotherapy
- Sites of metastatic disease

The pain assessment questionnaire and analgesic usage forms (**Appendix C**) will be collected and stored within each patient's research chart along with all source documentation. Research charts will be stored in a locked room at the University of Chicago only accessible by members of the research team. All imaging data will be collected and annotated by Dr. Oto within the HIRO radiology database at the University of Chicago.

Patients can be registered only after the initial IRB approval for the participating site has been forwarded to the Coordinating Center, University of Chicago.

All patients must be registered with the University of Chicago Study Coordinator.The following

documents should be completed by the research nurse or data manager and faxed to **(773) 702-4889** or emailed to the study coordinatora minimum of 48 hours prior to expected study med start date:

- Provider of information
- Treating Physician (NCI investigator number)
- Patient name and hospital ID number
- Patient's zip code of residence
- Date & copy of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- Complete **Phase II Consortium Affiliate Clinical Trial Patient Registration Form**
- Source documentation for eligibility and pre-study procedures
- Prior authorization and documentation of abiraterone availability

The research nurse or data manager at the participating site will then call the study coordinator to confirm all selection criteria listed in Section 3.

To complete the registration process, the UCMC Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Fax or e-mail, within 28 hours of completed registration, the assigned treatment arm
- Call the research nurse or data manager at the participating site and verbally confirm registration.

5. CLINICAL ASSESSMENTS

5.1. Screening Assessments

Patients who sign informed consent and are being considered for study participation will undergo pre-study screening evaluations within 28 days of initiation of study drug. Tumor assessment including CT of the chest or chest x-ray, MRI of the abdomen and pelvis with contrast (including research related images-see section 8), and nuclear medicine bone scan should be performed within this period. In addition, to confirm eligibility, patients should have screening CBC (white blood cell count, hemoglobin, platelet count, white blood cell differential), serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, alkaline phophatase, albumin, lipase, amylase, phosphorus), thyroid function tests (TSH, free T4), creatine kinase (CK), INR and Urine Protein/Creatinine ratio. As described in the correlative section (Section 8.2), an additional 15 mL of blood will also be collected during screening for CTC analysis by the Szmulewitz laboratory (for University of Chicago patients only). The ECOG performance status and concomitant medications will also be noted during screening for eligibility purposes.

5.2. Baseline (Day 1-Cycle 1, week 0) Assessments

Eligible patients who have signed informed consent and have had eligibility confirmed will be seen in the outpatient clinic on Day 1of study. They will undergo a history and physical examination, have ECOG performance status, concomitant medications, and baseline toxicity documented at this visit. The subject will also complete the pain assessment questionnaire and analgesic intake log at this visit. In addition to CBC and chemistries (phosphorus, amylase, lipase not required), and PSAwill also be recorded at baseline. Subjects will subsequently receive their first 30 day supply of study drug (refer to Section 6 for further treatment plan information). A second baseline CTC sample for the Szmulewitz laboratory will also be obtained (for University of Chicago patients only). Finally, as described in the correlative section (Section 8.1), a second baseline MRI of the pelvis will be obtained at the Day 1 visit (or within 72hours prior)

5.3. On-Study Assessments

Clinical visits will occur every two weeks for the first three months and then every 4 weeks thereafter. Cycles are 4 weeks long and each 4 week visit will be the start of a new cycle. A three day grace period will be allowed for each visit, however, every attempt should be made to prescribe to the study calendar. At each of these visits, subjects will undergo a history and physical examination, have ECOG performance status, concomitant medications, and toxicity documented at each visit. The subject will also complete the pain assessment questionnaire and analgesic intake log at these visits. All screening chemistries, CBC, thyroid studies and urine studies, will be performed at all on study visits. An EKG will be checked at week 4 visit to assess for prolongation of QTc prolongation once the study drug is at steady state. The final CTC sample for the Szmulewitz lab will be collected at the week 2 visit. A pelvis MRI and bone scan will be performed at the week 2 visit, otherwise all radiologic examinations with bone scan, chest imaging, MRI abdomen/pelvis will be performed at 12 week intervals. Likewise, PSA as measureof disease burden will be measured every 12 weeks.

5.4. Off Study Assessments

Patients will be followed with these assessments until taken off study (Section 7.3 for duration of therapy details). Within 30 days of study medication discontinuation, subjects will undergo a complete evaluation with a history and physical examination, ECOG performance status, concomitant medications, and baseline toxicity documented at this visit. The subject will also complete the Present Pain Intensity and analgesic intake log, have CBC, chemistries, Urine studies, PSA, and have radiologic tumor assessments performed, unless already performed within two weeks of being taken off study. Study participant refusal or inability to undergo these evaluations should be noted.

5.5. Study Calendar

Evaluations	Screening (w/in 4 weeks)	Cycle 1, Day 1 of study (Week 0)	Cycle1, D15(Week 2)	Each Cycle start (Week 4, 8, 12, 16, 20, etc.) Cycle 2, D15(Week 6) Cycle 3 Day 15, (Week 10)	Week 12, then every 12 weeks	Off study
History& Physical exam (w/vitals)		X	X	X		X
Informed Consent	X					
ECOG Performance status	X	X	X	X		X
Concomitant medications	X	X	X	X		X
Adverse Events & Toxicity		X	X	X		X
Pain Assessment[a]		X	X	X		X
Tumor Assessments						
Chest imaging[b]	X				X	X
Bone Scan	X		X		X[c]	X
MRI Pelvis w/contrast-Researchimages	X	X	X		X	X
MRI Abd/Pelvis w/contrast	X				X	X
Laboratory Assessments						
CBC with platelets and differential	X	X	X	X		X
Serum chemistries[d]	X	X[f]	X	X		X
INR	X					
TSH, free T4	X		X	X		X
EKG[e]	X			X		
Urine protein/creatinine	X		X	X		X
PSA		X			X	X
CTC-Szmulewitz lab[g]	X	X	X			

[a]Present Pain Intensity Score and analgesic intake log (Appendix C)
[b] Either chest x-ray or CT of the chest are acceptable
[c]If new lesions seen on 12 week bone scan in absence of other metrics of progression, bone scan should be repeated 6 week later to rule out bone scan flare.
[d]Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, alkaline phophatase, albumin, phosphorus, amylase, lipase, creatine kinase (CK)
[e]EKG should be performed during screening period and at week 4 only, then as clinically indicated
[f] Phosphorus, amylase, lipase not to be repeated at day 1 of study
[g]University of Chicago Patients only

6. TREATMENT PLAN

6.1. Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 8. All patients will be treated with XL184 at a starting dose of

60mg oral daily dosing. Due to observed toxicity (see Section 1.6 above) after 4 weeks of treatment at 60mg/day, the dose will be decreased for all patients to 40mg/day for subsequent dosing. Patients dose reduced to 40mg prior to week for will stay at this dose level. Appropriate further dose modifications are described in Section 6.3. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy with the exception of patients who are chemically castrated who should continue to receive their LHRH agonist while on this clinical trial. Medications for bone health (e.g. zoledronic acid or denosumab) should likewise be continued (Section 3.1.5).

A supply of doses will be administered at the clinical site at each 4 week visit during the On-Study Treatment period. Subjects should fast (with exception to water) 2 hours before through 1 hour after each dose. Subjects will be provided with sufficient study treatment and instructions for self-administration. Any unused study treatment must be returned to the study site for drug accountability and disposal.

6.2. Description of Drug/Pharmaceutical Information

XL184

Chemical Name: Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (l)-malate salt

How Supplied: Exelixis will provide each investigator with adequate supplies of cabozantinib, which will be supplied as 60-mg, and 20-mg yellow film-coated tablets. The 60-mg tablets are oval, and the 20-mg tablets are round. The components of the tablets are listed in table 2.

Storage and Disposal: All study drug will be shipped and stored at room temperature (15-30 degrees Celsius. Inventories of XL184 will be kept by the investigational pharmacy at the University of Chicago. Any unused, previously dispensed XL184 will be returned to the investigational pharmacy and discarded at the discretion of the pharmacist in a manner that prevents accidental ingestion. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

Agent Accountability/Ordering: The investigational pharmacist will keep a careful log of XL184 supply and maintain the drug accountability log. When a patient is enrolled, the pharmacist will enter into the log: the subject identification number, the number of the pill bottle dispensed and the date. The research nurse will retrieve pill-bottles from the investigational pharmacy, dispense the bottle to the patient, and collect used bottles. The nurse will also keep a careful record of unused capsules and return unused drug to the investigational pharmacy for dispensing. The investigational pharmacy will procure XL184 directly from Exelixis and will ensure that adequate supplies are maintained.

Table 2: XL184 Tablet Components

Ingredient	Function	% w/w
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.7
Microcrystalline Cellulose (Avicel PH-102)	Filler	38.9
Lactose Anhydrous (60M)	Filler	19.4

Hydroxypropyl Cellulose (EXF)	Binder	3.0
Croscarmellose Sodium (Ac-Di-Sol)	Disenegrant	6.0
Colloidal Silicon Dioxide,	Glidant	0.3
Magnesium Stearate	Lubricant	0.75
Opadry Yellow Film Coating which includes: - HPMC 2910 / Hypromellose 6 cp - Titanium dioxide - Triacetin - Iron Oxide Yellow	Film Coating	4.00

6.3. Dose Reductions or Treatment Delay for Toxicity

Subjects will be monitored for adverse events (AE's) continuously throughout the study and for 30 days after the last dose of study medication. Subjects will have treatment withheld if they develop unacceptable toxicity defined as:

- Intolerable Grade 2 toxicity that cannot be adequately managed
- Grade 3 or greater non-hematological toxicity (including nausea, vomiting, or diarrhea despite optimal management)
- Urine protein/creatinine ratio > 2
- Grade 4 hematological toxicity

If a subject experiences unacceptable study treatment related "unacceptable toxicity" (per the criteria above), study treatment may be withheld at the investigator's discretion if clinically necessary. XL 184 therapy will be permanently discontinued for any patient who experiences any XL184-related "unacceptable toxicity" who do not recover from the XL184 related toxicity to ≤ 1 Grade within four weeks (one cycle). Any patient who requires more than two weeks to recover from an XL-184 related unacceptable toxicity will have the dose reduced one level [table 3, Section 6.3] to 40mg. If the patient was at 40mg already, then the appropriate dose reduction would be to 20mg. Dose reductions are at the discretion of the investigator for drug holds <2 weeks. Dose escalation from 40mg to 60mg is not permitted for safety reasons. If apatient at 20mg/day does not experience further toxicity after completing one cycle (4 weeks) at the reduced dose, the XL184 dose may be re-escalated and the patient monitored at two weeks and one month for recurrence of unacceptable toxicity.Upon dose re-escalation, if the increased dose is not tolerated, the patient should be maintained at the lower, tolerated dose.If study treatment is withheld, the subject should be instructed not to "shift" or make up the withheld doses unless the missed dose can be taken within 12 hours of the normal dosing time.

- For example, if doses are withheld on Days 11-15 of a 28-day daily-dosing cycle, dosing would resume (if indicated) on Day 16 and the cycle would end as scheduled on Day 28.
- If doses are withheld on Days 1-4 of a 28-day cycle, dosing would resume (if indicated) on Day 5 and the cycle would end as scheduled on Day 28. (Except for Cycle 1, wherein the first day of Cycle 1 is defined as the date the first dose of study treatment is administered).

Table 3: Dose Reductions

First Dose Level Reduction	Second Dose Level Reduction
XL184 40 mg oral daily	XL184 20 mg oral daily

6.2.1. Warnings and Precautions

The general adverse event profile of cabozantinib includes GI symptoms (such as nausea, vomiting, and diarrhea), fatigue, anorexia, palmar-plantar erythrodysesthesia (PPE) syndrome, skin rash, elevated ALT and AST, increased pancreatic enzymes with rare cases of pancreatitis, as well as side effects associated with inhibition of VEGF signaling such as thrombotic events (e.g., pulmonary embolism [PE] and deep vein thrombosis [DVT]), hypertension, proteinuria, hemorrhagic events, and rare cases of gastrointestinal [GI] perforation and rectal/perirectal abscess. Arterial thromboembolism (transient ischemic attack [TIA], myocardial infarction [MI]) have been reported rarely. A complete description of the adverse event profile associated with XL184 is available within the investigator's brochure[20, 21].

Subjects with severe diarrhea who are unresponsive to anti-diarrheals such as loperamide or who become dehydrated may require temporary interruption of therapy followed by dose reduction. Subjects with nausea can be managed according to accepted practice (e.g., with prochlorperazine).

Adverse events potentially related to inhibition of VEGFR should be carefully monitored. Subjects who develop GI perforation, wound dehiscence requiring medical intervention, serious bleeding, nephrotic syndrome, hypertensive crisis, or thromboembolic events must be discontinued from the study.

6.2.2. General Guidelines for Non-Hematologic and Hematologic Adverse Events

General guidelines for the management of non-hematologic and hematologic toxicities are provided in Table 5 and Table 6, respectively. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity.

Table 5. General Approach to the Management of Non-Hematologic Toxicities

CTCAE Version 4 Grade	Guidelines/Intervention
Grade 1:	Add supportive care as indicated. Continue study treatment at the current dose levels.
Grade 2:	
Grade 2 AEs considered related to study treatment that are subjectively tolerable or easily managed	Add supportive care as indicated. Continue study treatment at the current dose levels.
Grade 2 AEs considered related to study treatment that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected	Dose reduce • If the AE dose not resolve to Grade ≤ 1 or baseline in 7 to 10 days or worsens at any time, cabozantinib dosing should then be interrupted. Then upon resolution to baseline or Grade ≤ 1, the reduced dose should be restarted. • If the AE does resolves to resolves to Grade ≤ 1 or baseline without a dose interruption, continue the reduced dose.
Grade 3:	
Grade 3 AEs considered related to study treatment which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly	• Interrupt study treatment and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤ 1 within 24 hours, treatment may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced

	• For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤ 1, treatment should be restarted with a dose reduction. Note: if the investigator believes the likelihood of a reoccurrence of the same Grade 3 AE is small due to continued prophylaxis or other effective intervention, treatment may be resumed without a dose reduction and with very careful monitoring of the subject.
Grade 3 AEs considered related to study treatment that occurred despite optimal prophylaxis or is not easily managed by medical intervention	Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction
Grade 4:	
Grade 4 AEs considered related to study treatment	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator.

Dose reductions or delays may occur in the setting of lower grade toxicity than defined above if the investigator believes that it is in the interest of the subject's safety.

Table 6. General Approach to the Management of Hematologic Toxicities

CTCAE Version 4 Grade	Intervention
Neutropenia	
Grade 3 neutropenia with documented infection Grade 3 neutropenia ≥ 5 days Grade 4 neutropenia	Interrupt cabozantinib treatment until resolution to Grade ≤ 1, and resume cabozantinib treatment at a reduced dose.
Thrombocytopenia	
Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia	Interrupt cabozantinib treatment until resolution to ≤ Grade 1, and resume cabozantinib treatment at a reduced dose
Febrile Neutropenia	
Grade 3 febrile neutropenia	Interrupt cabozantinib treatment until recovery of ANC to Grade ≤ 1 and temperature to ≤ 38.0°C and resume cabozantinib treatment at a reduced dose.
Grade 4 febrile neutropenia	Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator.

ANC, absolute neutrophil count; LLN, lower limit of normal
Neutropenia: Grade 1 (LLN ≤ ANC < 1.5×10^9/L; Grade 2 (1×10^9/L ≤ ANC <1.5 x 10^9/L),
Grade 3 (0.5×10^9/L ≤ ANC < 1×10^9/L), Grade 4 (ANC < 0.5×10^9/L).
Febrile Neutropenia: Grade 3 (present); Grade 4 (Life-threatening consequences; urgent intervention indicated).
Thrombocytopenia: Grade 1 (<LLN – 75 x 10^9/L); Grade 2 (<75.0 – 50.0 x 10^9/L);
Grade 3 (Platelet count ≤ 50 - 25 × 10^9/L); Grade 4 (Platelet count < 25×10^9/L).

6.2.3. Treatment-Emergent Hypertension

Hypertension is a relatively common complication of other VEGF-pathway inhibitors and has been observed in cabozantinib clinical studies.

Decisions to decrease or hold the dose of study treatment must be based on BP readings taken by a medical professional and must be confirmed with a second measurement at least 5 minutes following the first measurement. Other than for hypertension requiring immediate therapy, the presence of new or worsened hypertension should be confirmed at a second visit before taking new therapeutic action. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine. Cabozantinib dosing should be interrupted in subjects with severe hypertension (180 mm Hg systolic or 120 mm Hg diastolic; or sustained ≥ 160 mm Hg systolic or ≥ 110 diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy (Table 7).

Table 7. Management of Hypertension Related to Cabozantinib

Criteria for Dose Modifications	Treatment/cabozantinib Dose Modification
Subjects not receiving optimized anti-hypertensive therapy	
> 140 mm Hg (systolic) and < 160 mm Hg OR > 90 mm Hg (diastolic) and < 110 mm Hg	• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Maintain dose of cabozantinib • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced.
≥ 160 mm Hg (systolic) and < 180 mm Hg OR ≥ 110 mm Hg (diastolic) and < 120 mm Hg	• Reduce cabozantinib by one dose level. • Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications) • Monitor subject closely for hypotension. • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.
≥ 180 mm Hg (systolic) OR ≥ 120 mm Hg (diastolic)	• Interrupt treatment with cabozantinib Add new or additional anti-hypertensive medications and/or increase dose of existing medications. • Monitor subject closely for hypotension. • When SBP < 140 and DBP < 90, restart cabozantinib treatment at one dose level lower • If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure < 140 systolic or < 90 diastolic, dose of cabozantinib should be reduced further.

BP, blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure
NOTE: If SBP and DBP meet different criteria in table, manage per higher dose-modification criteria

6.2.4. **Treatment-Emergent Proteinuria**

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Table 8 provides a recommended algorithm for treatment-emergent proteinuria management.

Table 8: Management of Treatment-Emergent Proteinuria

Urine Protein/Creatinine Ratio	Treatment/Dose Modification
≤ 1	• No change in treatment or monitoring
> 1 and < 2	• Repeat urine protein/creatinine within 7 days • If > 1 and < 2 on repeat, decrease study treatment dose to 125 mg. Check urine protein/creatinine every 2 weeks. If

	urine protein/creatinine remains > 1 and < 2 for 1 month, continue reduced dose of study treatment and check urine protein/creatinine per protocol. If urine protein/creatinine is < 1 on 2 consecutive readings resume treatment with full dose study treatment (the second reading is a confirmatory reading and can be done within a week of the first reading).
≥ 2	• Repeat urine protein/creatinine ratio within 7 days • If > 2 on repeat, hold treatment and check urine protein/creatinine ratio every 14 days. If urine protein/creatinine remains > 2 and stable (≤ 20% change) for 1 month, can monitor per protocol. Resume treatment if urine protein/creatinine ratio is < 2 on 2 consecutive readings (the second reading is a confirmatory reading can be done within a week of the first reading). Restart full dose if urine P/C decreases to < 1. Restart study treatment at 75 mg if urine P/C decreases to > 1 but < 2 (dose level -1, Table 4). • If urine protein/creatinine remains > 2 for 5weeks (>4 weeks after holding XL 184), subject must come off study treatment.

6.2.5. **Pancreatic Conditions**

Amylase and lipase elevations have been observed in clinical studies with cabozantinib. The clinical significance of asymptomatic elevations of enzymes is not known but in general have not been associated with clinically apparent sequelae. It is recommended that subjects with lipase elevation and/or symptoms of pancreatitis have more frequent laboratory monitoring of lipase and/or amylase (2-3 times per week). Subjects with symptomatic pancreatitis should be treated with standard supportive measures.

Asymptomatic Lipase or Amylase Elevations

Asymptomatic Lipase or Amylase Elevations	
Grade 1 or Grade 2	Continue at current dose level. More frequent monitoring is recommended
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 elevations recur, then treatment must be interrupted again and till lipase and amylase levels have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 4	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline and if resolution occurred within 4 days, cabozantinib may be restarted at the same dose or a reduced dose. If resolution took more than 4 days, the dose must be reduced upon retreatment provided that resolution occurred within 6 weeks. • If retreatment following Grade 4 lipase or amylase elevation is at the same dose and Grade 3 or 4 elevations recur, then treatment must be interrupted again until lipase and amylase have resolved to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.

Symptomatic Pancreatitis

Pancreatitis	
Grade 1	Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended
Grade 2	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline , cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 6 weeks. • If retreatment following Grade 2 pancreatitis is at the same dose and Grade 2 pancreatitis recurs, then treatment must be interrupted again and till resolution to Grade ≤ 1 or baseline and retreatment must be at a reduced dose.
Grade 3	• Interrupt treatment • Monitor lipase and amylase twice weekly • Upon resolution to Grade ≤ 1 or baseline , cabozantinib may be restarted at a reduced dose if resolution occurred within 6 weeks
Grade 4	Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy, treatment may resume at a reduced dose per investigator judgment.

6.2.6. **Skin Disorders**

Palmar-plantar erythrodysesthesia syndrome (PPE; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water

leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

The onset of PPE is variable with paresthesia (tingling, numbness) being the characteristic initial manifestation, which can be accompanied by slight redness or mild hyperkeratosis. PPE advances with symmetrical painful erythema and swollen areas (edema) on the palms and soles. The lateral sides of the fingers or periungual zones may also be affected. Adequate interventions are required to prevent worsening of skin symptoms such as blisters, desquamations, ulcerations, or necrosis of affected areas.

Aggressive management of symptoms is recommended, including early dermatology referral. Subjects with skin disorders should be carefully monitored for signs of infection (e.g., abscess, cellulitis, or impetigo).

In the case of study treatment-related skin changes (e.g., rash, hand-foot syndrome), the investigator may request that additional assessments be conducted with the subject's consent. These assessments may include digital photographs of the skin changes and/or a biopsy of the affected skin and may be repeated until the skin changes resolve.

Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)	
No apparent toxicity	Prophylaxis with Ammonium lactate 12% cream (Amlactin®) twice daily OR heavy moisturizer (e.g. Vaseline) twice daily
Grade 1	Continue treatment at current dose if tolerable or reduce to the next lower dose if intolerable. Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 2 PPE
Grade 2	Reduce study treatment to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Assess subject at least weekly for changes in severity. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis or affects self-care) or if there is no improvement after 2 weeks, proceed to the management guidelines for Grade 3 PPE. If the dose was reduced, then upon resolution to Grade 0 or Grade 1, treatment may continue at the reduced dose. If the dose was only interrupted but not reduced, then treatment may be restarted at one dose level lower.
Grade 3	Interrupt study treatment until severity decreases to Grade 1 or 0. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Pain control with NSAIDs/GABA agonists/narcotics. Treatment may restart at one dose level lower when reaction decreases to Grade 1 or 0. Permanently discontinue subject from study if reactions worsen or do not improve within 6 weeks.

GABA, γ-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

6.2.7. Diarrhea, Nausea, Vomiting, Stomatitis and Mucositis

Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal agents is recommended at the first sign of diarrhea as initial management.

Loperamide is recommended as standard first line therapy. Alternatively, diphenoxylate/atropine can be used. Additional agents to consider in subjects with diarrhea that is refractory to the above include deodorized tincture of opium and octreotide (Benson et al. 2004). Some subjects may require concomitant therapy with loperamide, diphenoxylate/atropine, and deodorized tincture of opium to control diarrhea. When combination therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, a dose reduction and/or dose interruption of cabozantinib should be implemented as described in Table 3 (dose reduction table). In addition, general supportive measures should be implemented including continuous oral hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high fat meals and alcohol.

Nausea and Vomiting

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. A dose reductions and/or dose interruption of cabozantinib may be required as described in Table 3 if antiemetic treatment and/or prophylaxis alone is not adequate.

Agents classified as having a high therapeutic index (such as 5-HT3 receptor antagonists, or NK-1 receptor antagonists) per ASCO or MASCC/ESMO guidelines for anti-emetics in oncology or dexamethasone are recommended (Hesketh et al. 2008, ASCO 2006; Roila et al, Annals of Oncology, 2010). Caution is recommended with the use of aprepitant or fosaprepitant and nabilone as cabozantinib exposure may be affected by concomitant administration because aprepitant and fosaprepitant are both inhibitors and inducers of CYP3A4, and nabilone is a weak inhibitor of CYP3A4.

Stomatitis and Mucositis

Preventive measures may include a comprehensive dental examination to identify any potential complications before study treatment is initiated. Appropriate correction of local factors should be instituted as indicated, such as modification of ill-fitting dentures and appropriate care of gingivitis. During treatment with cabozantinib, good oral hygiene and standard local treatments such as non-traumatic cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. The oral cavity should be rinsed and wiped after meals, and dentures should be cleaned and brushed often to remove plaque. Local treatment should be instituted at the earliest onset of symptoms. When stomatitis interferes with adequate nutrition and local therapy is not adequately effective, dose reduction or temporary withholding of cabozantinib should be considered.

Hepatobiliary Disorders

Elevations of transaminases have also been observed during treatment with cabozantinib. In general, it is recommended that subjects with elevation of ALT, AST, and/or bilirubin have more frequent laboratory monitoring of these parameters. If possible, hepatotoxic concomitant medications and alcohol should be discontinued in subjects who develop elevated transaminases.
Since subjects may enter the study with elevations of AST/ALT at baseline, the following guideline should be used for dose modifications:

Transaminase elevation	
CTCAE v4.0	**Intervention**

Subjects with AST and ALT less than or equal to the ULN at baseline	
Grade 1	Continue study treatment with weekly monitoring of liver function tests (LFTs) for at least 4 weeks.. Then resume the standard protocol-defined monitoring of LFTs.
Grade 2	Continue study treatment with at least twice weekly monitoring of LFTs for 2 weeks. Then weekly for 4 weeks. If LFTs continue to rise within Grade 2, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator
Subjects with AST or ALT above the ULN but ≤ 3.0 x ULN (i.e., Grade 1) at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and still Grade 1 or Grade 2	Continue study treatment with at least twice weekly monitoring of LFTs for 4 weeks. If LFTs continue to rise, interrupt study treatment. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until Grade ≤ 2. Then continue with at least weekly LFTs until resolution to Grade ≤ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator.
Subjects AST or ALT > 3.0 but ≤ 5.0 x ULN at baseline	
≥ 1.5 fold transaminases increase (at least one of AST or ALT) and still Grade 2 or Grade 3	Interrupt study treatment and monitor with at least twice weekly LFTs until LFTs resolve to baseline and Grade ≤ 2. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib.
Grade 4	Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade ≤ 1. If the subject was unequivocally deriving clinical benefit, the subject may be able to resume treatment at a lower dose as determined by the investigator.

Cabozantinib treatment should also be interrupted when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (e.g., International Normalized Ratio [INR]). Should elevated transaminases be observed (grade 1 or higher), the INR should be checked. Should an elevated transaminase level be accompanied by bilirubin and/or INR monitoring of transaminases should be intensified (2–3 times per week) and cabozantinib should be held until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels (INR < 1.5 × ULN, total bilirubin < 1.5 × ULN, aminotransferases < 2.5 × ULN or baseline).

Subjects must have cabozantinib permanently discontinued if transaminase elevations are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase

[ALP]) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), as the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe liver injury.

All subjects who develop isolated bilirubin elevations of Grade 3 should have study treatment held until recovered to Grade ≤ 1 or baseline (or lower). If this occurs within 6 weeks of the dosing delay, study treatment may continue at a reduced dose. In subjects without biliary obstruction and Grade 4 bilirubin elevation, or with recurrence of Grade 3 bilirubin elevation after a dose reduction, study treatment must be discontinued.

6.2.8. **Hemorrhage**

Hemorrhagic events have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. As preventive measures, subjects should be evaluated for potential bleeding risk factors prior to initiating cabozantinib treatment and monitored for bleeding events with serial complete blood counts and physical examination while on study. Risk factors for hemorrhagic events may include (but may not be limited to) the following:

- Tumor lesions of the lung with cavitations or tumor lesions which invade, encase, or abut any major blood vessels; non-small cell lung cancer (NSCLC) with squamous cell differentiation is known for significant lung cavitations and centrally located tumors that may invade major blood vessels. The anatomic location and characteristics of tumor as well as the medical history should be carefully reviewed in the selection of subjects for treatment with cabozantinib.
- Recent or concurrent radiation to the thoracic cavity
- Active peptic ulcer disease, ulcerative colitis, and other inflammatory GI diseases
- Underlying medical conditions which affect normal hemostasis (e.g., deficiencies in clotting factors and/or platelet function, or thrombocytopenia)
- Concomitant medication with anticoagulants or other drugs which affect normal hemostasis

Based on the described predisposing risk factors for hemoptysis, many studies with antiangiogenic drugs exclude subjects with NSCLC and squamous cell differentiation. Although enrollment of subjects with NSCLC with squamous cell differentiation has been allowed on cabozantinib studies, cabozantinib studies exclude NSCLC subjects with any of the following: tumors abutting, encasing, or invading a major blood vessel; cavitating lesions; history of clinically significant hemoptysis; or recent (within 3 months) radiation therapy to the thoracic cavity including brachytherapy unless radiation therapy targets bone metastasis.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 0.5 teaspoon (2.5ml) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and may be restarted after the cause of hemorrhage has been identified and the risk of bleeding has subsided. Therapy of bleeding events should include supportive care and standard medical interventions.

Furthermore, subjects who develop tumors abutting, encasing, or invading a major blood vessel or who develop cavitation of their pulmonary tumors while on study treatment must be discontinued from cabozantinib treatment.

6.2.9. Rectal and Perirectal Abscess

Rectal and perirectal abscesses have been reported, sometimes in subjects with concurrent diarrhea. These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place.

6.2.10. Guidelines for Prevention of GI Perforation/Fistula and Non-GI Fistula Formation

GI perforation/fistula and Non-GI fistula formation have been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Carefully monitor for episodes of abdominal pain, especially in subjects with known risk factors for developing GI perforation/fistula or non-GI fistula, to allow for early diagnosis. Such risk factors include (but may not be limited to) the following:

GI-perforation/fistula:

- Intra-abdominal tumor/metastases invading GI mucosa
- Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis or symptomatic cholangitis, or appendicitis
- History of abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess
- Prior GI surgery (particularly when associated with delayed or incomplete healing). Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Additional risk factors include concurrent chronic use of steroid treatment or non-steroidal anti-inflammatory drugs. Constipation indicative of bowel obstruction should be monitored and effectively managed.

Non-GI fistula:

- Radiation therapy has been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with such agents (e.g., bevacizumab). Radiation therapy to the thoracic cavity (including mediastinum) should be avoided within 3 months of starting treatment with cabozantinib. Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy.

Discontinue all study treatment in subjects who have been diagnosed with GI or non-GI perforation/fistula.

6.2.11. Wound healing and Surgery

VEGF inhibitors can cause wound healing complications and wound dehiscence which may occur even long after a wound has been considered healed. Therefore, surgical and traumatic wounds

must have completely healed prior to starting cabozantinib treatment and be monitored for wound dehiscence or wound infection while the subject is being treated with cabozantinib.
Treatment with cabozantinib must be interrupted for any wound healing complication which needs medical intervention. Treatment with cabozantinib can be resumed once wound healing has occurred unless otherwise prohibited in specific protocols. Cabozantinib should be discontinued in subjects with serious or chronic wound healing complications.
The appropriate dose hold interval prior to elective surgery to reduce the risk for wound healing complications has not been determined. In general, cabozantinib should be stopped at least 3 weeks (5 half lives) prior to elective surgery.

6.2.12. **Endocrine Disorders**

Prospective studies of markers of thyroid functions are currently ongoing in two single-agent studies to characterize the effects of cabozantinib on thyroid function. Preliminary data indicate that cabozantinib affects thyroid function tests (TFTs) in a high number of subjects. In Study XL184-203, 17 of 34 (50%) euthyroid subjects with castration-resistant prostate cancer (CRPC) developed abnormal thyroid-stimulating hormone (TSH) levels 6 weeks after initiation of cabozantinib treatment (6% showed TSH levels between 5 and 7 mU/L, 44% had TSH > 7 mU/L). The median TSH level at week 6 was 5.2 mU/L (range, 0.02-29.7 mU/L). In a Phase 1 combination study of rosiglitazone and cabozantinib (XL184-008) to determine the potential for a clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are enrolled. Among 11 evaluable subjects, the AE of hypothyroidism was reported in 55% of subjects. Currently available data are insufficient to determine the cause of TFT alterations and its clinical relevance. Routine monitoring of thyroid function and assessments for signs and symptoms associated with thyroid dysfunction is recommended for subjects treated with cabozantinib. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

Other endocrine disorders such as hypocalcemia and hyperglycemia, and associated laboratory changes, have been observed in less than 10% of subjects. Monitoring with standard laboratory tests for endocrine disorders and clinical examination prior to initiation and during treatment with cabozantinib is recommended. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

6.2.13. **Guidelines for Prevention of Osteonecrosis of the Jaw**

Osteonecrosis of the jaw (ONJ) has been reported with use of antiangiogenic drugs and bisphosphonates and denosumab in cancer patients. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, dental or orofacial surgery procedures, and cancer disease itself. Three cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of IB. As a preventive measure, invasive dental procedures should be avoided if possible in subjects who have previously been treated with or concomitantly receive bisphosphonates or denosumab. In cases where dental procedures are unavoidable, the risks and benefits of a dental procedure and the extent of the procedure as well as the risk of developing osteonecrosis of the jaw need to be considered when deciding on the duration of a temporary

treatment interruption of cabozantinib. If clinically possible, treatment with cabozantinib should be held for at least 2 weeks prior to a dental procedure and resumed after complete wound healing occurred. Subjects with any documented case of osteonecrosis should have study treatment interrupted, and appropriate clinical management should be initiated. Reinitiation of study treatment must be discussed with and approved by the Sponsor on a case by case

6.3. Concomitant Medication and Treatment

If the subject must use a concomitant medication during the study, it is the responsibility of the investigator to ensure that details regarding the medication are recorded.

Chemotherapy and Radiotherapy
If possible, alternative anticancer treatment should not be initiated until PD has been observed by standard guidelines and study treatment has been discontinued. If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention (e.g. nephrostomy tube placement, TURP) is discouraged unless medically unavoidable. Subjects receiving local intervention are allowed to continue to receive study treatment at the investigator's discretion as long as they continue to meet study eligibility criteria.

Other Medications
Anti-emetics and anti-diarrheal medications should not be administered prophylactically prior to the first dose of study drug. After the first dose of study drug, at the discretion of the investigator and after the onset of symptoms, treatment (or prophylaxis) with anti-emetic and anti-diarrheal medications may be undertaken per standard clinical practice.

Pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. Colony stimulating factors (e.g. granulocyte colony-stimulating factors) administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically before the first dose of study treatment. Erythropoietin should not be used based on a recent report of increased risk of tumor recurrence/progression associated with erythropoietin[43].

No concurrent investigational agents will be permitted.

6.4. Potential Drug Interactions

Cytochrome P450: Preliminary data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the AUC of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce cytochrome P450 enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 μM).

Cabozantinib is a CYP3A4 substrate (but not a CYP2C9 or CYP2D6 substrate), based on data from in vitro studies using CYP-isozyme specific neutralizing antibodies. Preliminary results from

a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 80% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended. In addition, caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib, as this could significantly increase the exposure to cabozantinib.

Preliminary results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 33-39% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir) may increase cabozantinib concentrations. Grapefruit / grapefruit juice and Seville oranges may also increase plasma concentrations of cabozantinib. Strong CYP3A4 inhibitors and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.
Because in vitro studies only assessed the metabolizing capacity of the CYP3A4, CYP2C9, and CYP2D6 pathways, the potential for drugs that inhibit/induce other CYP450 pathways (e.g., CYP2C8, CYP2C19, CYP2B6, CYP1A2) to alter cabozantinib exposure is not known. Therefore, these drugs should be used with caution when given with cabozantinib.

Please refer to the Flockhart drug interaction tables for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways (Flockhart 2007; *http://medicine.iupui.edu/clinpharm/ddis/table.aspx*).

Protein Binding: Cabozantinib is highly protein bound (approximately 99.9%) to human plasma proteins. Therefore, highly protein bound drugs should be used with caution with cabozantinib because there is a potential displacement interaction that could increase free concentrations of cabozantinib and/or a co-administered highly protein-bound drug (and a corresponding increase in pharmacologic effect). Factors that influence plasma protein binding may affect individual tolerance to cabozantinib. Therefore, concomitant medications that are highly protein bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol) should be used with caution. Because warfarin is a highly protein bound drug with a low therapeutic index, administration of warfarin at therapeutic doses should be avoided in subjects receiving cabozantinib due to the potential for a protein binding displacement interaction.

Other Interactions: In a relative bioavailability study in dogs cabozantinib exposure was not significantly affected by drugs that alter gastric pH. Nevertheless, drugs such as proton pump inhibitors (PPIs) and H_2-antagonists produce profound suppression of gastric acid secretion and significant increases in gastric pH. By elevating gastric pH, PPIs and H_2-antagonists may decrease

cabozantinib plasma exposure levels and its effectiveness in vivo, resulting in clinically significant drug interactions. The use of PPIs (e.g., omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole) and/or H_2-antagonists (e.g., ranitidine, famotidine, and nizatidine) is discouraged during this study. If antacids are not adequate, the use of H_2 blockers is preferred over PPIs (Note: Cimetidine should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib). Antacids, H_2 blockers, or PPIs should be taken at least 2 hours (preferably 4 hours) after taking cabozantinib but at least 14 hours before the next dose of cabozantinib if possible.

In vitro data suggest that cabozantinib is unlikely to be a substrate for P glycoprotein (P-gp), but it does appear to have the potential to inhibit the P-gp transport activity.

Additional details related to these overall conclusions are provided in the Investigators Brochure

7. SAFETY

7.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation of a subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study drug treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Abnormal laboratory values, ECG findings, or vital signs that are considered clinically significant by the investigator, and pre-existing medical conditions that worsen during a study, should be recorded as AEs.

For the purpose of data collection, all AEs that occur after informed consent through 30 days after last dose of study treatment (or until a subject is determined to be a screening failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

Assessment of the relationship of the AE to the study treatment by the investigator will be based on the following two definitions:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Assessment of toxicities and adverse events will be graded according to the Common Toxicity Criteria (CTC), version 4.03:

- V4.03 (CTCAE): publish date June 14, 2010: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-

14_QuickReference_8.5x11.pdf

7.2. Serious Adverse Events

The serious adverse event (SAE) definition and reporting requirements are in accordance with the International Conference of Harmonisation (ICH) Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in death.
2. Is immediately life-threatening (ie in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity.
   - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
5. Is a congenital anomaly or birth defect.
6. Is an important medical event (IME)
   - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of Serious Adverse Event. Examples of IMEs include: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

ALL Serious Adverse Events, whether or not they are considered related to the study treatment MUST be reported to the sponsor-investigator and to the University of Chicago Comprehensive Cancer Center (UCCCC). Refer to Section 7.5 for reporting guidelines.

7.3. Serious and Unexpected Suspected Adverse Reactions (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction if there evidence to suggest a causal relationship to the adverse event. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls.

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, FDA-approved package insert, or elsewhere in the current IND application. This includes adverse events listed in the protocol, consent or IND as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with this investigational agent.

ALL SUSARS occurring on this clinical trial must be reported to the FDA. Refer to Section

7.5.3 for reporting guidelines.

7.4. Serious Adverse Event Reporting to Exelixis

As soon as an investigator becomes aware of an adverse event that meets the definition of 'serious,' this should be documented to the extent that information is available. This report must be submitted by the study site to Exelixis or designee within 24 hours even if the event is not felt to be drug related.

Email: drugsafety@exelixis.com;
Fax: 650-837-7392

This study will be using Form FDA 3500A (MedWatch form) for SAE reporting.

MedWatch forms and information: http://www.fda.gov/medwatch/getforms.htm

The minimum information required for SAE reporting includes identity of investigator, site number, patient number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (ie the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Exelixis Drug Safety personnel or designee.

When reporting serious adverse events, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death should not be reported as an SAE, but as an *outcome* of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then Death may be used as an event term and should be reported as "death, cause unknown". If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair.
    - Procedures for pre-existing conditions that have not worsened after initiation of treatment.
    - Pre-specified study hospitalizations for observation.
    - Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics.

- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
- All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to the FDA by the investigator as required by 21 CFR 312.32 (See **Section 7.4.2** below).
  - These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form).
  - The final MedWatch must be submitted by the study site to Exelixis within 1-2 business days of submisison to the FDA to allow Exelixis time to cross-report to Exelixis' IND. Email: drugsafety@exelixis.com; Fax 650-837-7392

7.5. Other Reporting Requirements

7.5.1. University of Chicago Comprehensive Cancer Center (UCCCC)

7.5.1.1. Events Occurring at the University of Chicago

All serious adverse events and protocol deviations must also be reported to the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO).

The Research Nurse or other designated individual should report the SAE/deviation to the UCCCC Quality Assurance (QA) Coordinator by the end of the business day when s/he becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12pm (noon) the next business day. Each event report must indicate where the event meets the IRB's Unanticipated Problem reporting criteria.

7.5.1.2. Events Occurring at Participating Site(s)

For serious and unexpected adverse events occurring at a participating site it is the responsibility of the research nurse, study coordinator, or other designated individual at the site where the event occurs to notify the UCCCC of the adverse event. Events should be reported to the UCCCC QA Coordinator at: (773) 834 2461 or qaccto@bsd.uchicago.edu.

For unexpected and serious suspected adverse reactions which FDA require reporting as a single occurrence, Form 3500A (MedWatch) must be completed by the designated site personnel and returned to the UCCCC QA Coordinator according to the timeframes in Section 2.4.

7.5.2. The Institutional Review Board

When appropriate, the IRB's Unanticipated Problem electronic submission form must be completed by the research nurse or other designated individual and submitted by the investigator via the IRB's electronic submission system within **the IRB's designated reporting timeframes**. Details of the IRB's current policy can be found on their website at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html

Events occurring at a participating site should be reported to the local IRB of record according to their policies and procedures and may be reported to the University of Chicago IRB if they meet current reporting criteria.

7.5.3. FDA

This study will be conducted under an IND held by Dr. Russell Szmulewitz at the University of Chicago.

Per 21 CFR 312.32, the sponsor-investigator is required to notify the FDA and all participating investigators of potential serious risks within 15 calendar days of determining the information meets FDA reporting requirements. Unexpected fatal or life-threatening suspected adverse events must be reported to the FDA by the sponsor-investigator via phone or fax within 7 calendar days.

Current FDA regulations require that all SUSARs (see definition in section 7.3) occurring on this trial, other findings that suggest a significant risk to humans exposed to the investigational drug (e.g. information from pooled analysis of multiple studies), and any clinically significant increase in the rate of an expected serious adverse reaction be reported as an IND Safety Report.

In order to meet these requirements, the sponsor-investigator will review all reported serious adverse events as they occur and will conduct a literature search to seek new safety information and review and analyze all safety information from this clinical trial at least annually and more frequently as appropriate.

Table A: Reporting Requirements

Report Type	Method of Report	Responsible Party	Timeline[1]	
			Fatal/Life-Threatening Event	
			Yes	No
Individual Report	Form 3500A (MedWatch)[7]	RN/CRA	4 calendar days[5]	10 calendar days[5]
Other Findings that Suggest *Significant Risk*[2]	Narrative[3]	PI	4 calendar day[6]	10 calendar days[6]
Clinically Significant Increased Frequency of Suspected Adverse Reactions[4]	Narrative	PI	4 calendar days[6]	10 calendar days[6]

1:	Report Due to CCTO IND Coordinator regardless of whether or not all information regarding the event is available. If applicable, a follow-up report should be provided to the IND Coordinator once additional information on the event is available.
2:	An IND Protocol Amendment is also required to describe any changes to the protocol, consent, or overall conduct of the study made as a result of this information. All revised documents should be made available to the CCTO IND Coordinator at the time of IRB submission.
3:	Copy of relevant publication(s) should be included if applicable.
4:	Details of individual cases should be included as appropriate
5:	From date event was reported to the sponsor-investigator
6:	After information is received by the investigator and determined to meet reporting criteria
7:	Copy should be maintained in the subject research chart and master IND file in the CCTO.

All other events (e.g. protocol deviations or other safety concerns) not meeting the requirements for IND Safety Reporting (per 21 CFR 312.32) but which require reporting to the IRB as an Unanticipated Problem will be reported to the FDA as an informational amendment or with the annual report as appropriate.

The CCTO IND coordinator will report all reportable events to the FDA within the designated timelines and provide a copy of the final report to Exelixis at the time of submission to the FDA. **(Section 7.3)**.

7.5.4. Reports to Participating Institution(s)

It is the responsibility of the designated Regulatory Manager on behalf of the sponsor-investigator to notify all participating sites of all unexpected and serious suspected adverse reactions that occur on this clinical trial and which are reported to the FDA as an IND Safety Report (21 CFR 312.32). A copy of the completed Form 3500A (MedWatch) and/or IND Safety Report Narrative will be provided to the responsible Regulatory Manager by the IND Coordinator for distribution to all participating sites.

7.6. Other Safety Considerations

7.6.1. Laboratory Data

All laboratory data obtained during the course of the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an adverse event or serious adverse event as appropriate, unless this value is consistent with the patient's present disease state or is consistent with values obtained prior to entry into the study.

7.6.2. Pregnancy

Use of medically accepted methods of contraception is very important during the study and up to 3 months post-study treatment. If a subject's partner becomes pregnant during the study, she will be followed through the end of her pregnancy and the infant should have a follow-up at least 6 months after birth. If a female partner of a male subject becomes pregnant during the study, the pregnant female partner will be asked to be followed through the end of her pregnancy. The outcome of a pregnancy (for a subject or for the partner of a subject) and the

medical condition of any resultant offspring must be reported to Exelixis or designee. Any birth defect or congenital anomaly must be reported as a serious adverse event and any other untoward events occurring during the pregnancy must be reported as adverse events or serious adverse events, as appropriate.

7.6.3. Medication Errors

Any medication error that results in an adverse event, even if it does not meet the definition of serious, requires reporting within 24 hours to Exelixis or designee.

7.6.4. Follow-Up of Adverse Events

Any SAE or AE assessed as possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to possibly-related serious adverse events that occur *greater than 30 days after last dose* of study treatment. The status of all other continuing adverse events will be documented as of 30 days after last dose of study treatment.

7.6.5. Safety Monitoring

According to University of Chicago Cancer Center Guidelines, this protocol will be classified as moderate risk. Data and Safety Monitoring (DSM) will occur at the weekly University of Chicago Genitourinary Oncology DSM meeting. At each meeting, the study will be reviewed for safety and progress toward completion. Toxicities and adverse events will also be reviewed and a DSM form will be completed at each meeting. Twenty percent of research charts will be audited annually for protocol compliance items including eligibility, completion of procedures, administration of treatment, reporting of toxicities, documentation of response, follow-up, data-collection, record keeping, and the collection of correlative studies.

8. CORRELATIVE/SPECIAL STUDIES

8.1. Functional MRI

8.1.1. Axial free-breathing images will be collected with 3mm thickness utilizing a 1.5T phased array surface coil using a field-of view 30-35 cm for all acquisitions.

8.1.2. Screening MRI (MRI #1) will be within 14 days prior to initiating therapy with second baseline MRI (MRI #2) performed at least 1 week since MRI #1 and within 24 hours of study initiation.

8.1.3. Bone lesions adequate for analysis must be a minimum of 2 x 2 cm.

8.1.4. Lesions must be free of MR artifacts (e.g. metal).

8.1.5. If more than one lesion meets all imaging criteria, the ADC and K^{trans} for each lesion

will be recorded.

8.1.6. **Dynamic Contrast Images**

- Imaged lesions must be in an area where the scanning plane will contain a low blood flow tissue (e.g. muscle) and/or a high blood flow area (e.g. kidney, liver, spleen) as a tissue control.

The sequences that will be used for image acquisition are as follows:

- A scout scan to determine optimal plane of scanning through the lesion (axial, coronal, or sagital) will be obtained. This plane will be used for all subsequent scans.
- A pre-infusion T1-weighted scan through the entire anatomical region will be obtained with the following parameters: 2D fast SPGR, TR 100 ms, TE 1.7 ms, flip angle 60, bandwidth 15.63 MHz, slice thickness 8 mm, slice spacing 1 mm, acquisition matrix 256 x 128. Scan duration is approximately 1 min.
- A pre-infusion T2-weighted scan through the entire anatomical region will be obtained with the following parameters: 2D FSE, TR 3500 ms, TE 85 ms, echo train length 12, bandwidth 20.83 MHz, and acquisition matrix 192 x 160. Scan duration is approximately 2.5 min.
- Pre-infusion T1-weighted limited scans through the center of the lesion and a reference tissue will be obtained with the following parameters: 2D fast SPGR, multiphase, TR 8 ms, TE 1.7ms, flip angle 60, bandwidth 15.63 MHz, slice thickness 8 mm, slice spacing 1 mm, acquisition matrix 256 x 160, 60 acquisitions, 2 slices per acquisition. Scan duration 125 s.
- Dynamic infused T1-weighted limited scans through the center of the lesion and a reference tissue will be obtained using the following parameters:Breath-hold T1 3D TFE (e-thrive), 400x338x200 mm FOV, 2x2x4/2 (acquired/reconstructed) mm voxel size (200x169 matrix), SENSE factor 2, 10° flip angle, TR/TE 7.8/2.5 ms, partial Fourier, 432 Hz/pixel bandwidth, SPAI). The gadolinium-based contrast agent (0.1 mM/kg of patient weight of Omniscan^{TM}(GE Healthcare) or 0.05mM/kg Multihance^{TM}(Bracco, Italy) will be injected 60 s after scanning begins at a rate such that the total duration of injection is 10 s. Total scan duration 9 min.
- Post-infusion T1-weighted scan through the entire lesion. 2D fast SPGR, TR 100 ms, TE 1.7 ms, flip angle 60, bandwidth 15.63 MHz, slice thickness 8 mm, slice spacing 1 mm, acquisition matrix 256 x 128. Scan duration approximately 1 min.
- In some instances, contrast washout may be assessed by a return to the slower multiple slice T1-weighted imaging (TR ~ 175 ms, TE ~ 3.1 ms). These images, which allow a larger volume of tissue to be examined, will be acquired from several minutes after contrast media injection.
- K^{trans} will be calculated from DCE-MRI images using the multiple tissue reference method as we have described[28, 29]

8.1.7. **Diffusion Weighted Images (ADC)**

- DWI sequence parameters will be as follows:Navigated 2D single shot spin echo EPI, 400x400x255 mm FOV, 2x2 mm acquired voxel size (reconstructed 1.25 mm), 32 x7 mm slices, SENSE factor 2, spectrally selective fat

suppression (SPAIR), inversion time 100 ms, partial Fourier (0.6), b factors 0, 800 s/mm^2, TR/TE 3578/67 ms, 13.4 Hz/pixel bandwidth, 4 averages, nominal scan duration 3:27 min (without counting respiratory navigator triggering).

- ADC maps will be generated from DW images using diffusion-analysis software (Philips view forum, Philips Healthcare). A region of interest (ROI) covering the entire lesion with as large as possible diameter, will be drawn on magnified images for each visualized bone metastases as determined by Dr. Oto. The average ADC for within each ROI will be calculated.

8.1.8. The intra-patient within lesion mean ADC and K^{trans}values will be determined by averaging the values from the two baseline examinations.

8.1.9. The overall intra-patient and inter-patient variability will be calculated using a components of variance model in conjunction with the biostatistics core at the University of Chicago. The investigators have used these models previously to describe the variability in K^{trans} for mCRPC to the bone[29].

8.1.10. The first post therapy MRI evaluation will occur after 14 days of therapy (Section 5.5). 72 hours (3 days) of latitude will be allowed for this evaluation. Patients who do not have a completed day 14 MRI will not be evaluable for the primary endpoint of the study (Section2.1). All subsequent functional MRI capture will occur at 12 week intervals±7 days (Section 5.5).

8.1.11. Changes in ADC and K^{trans}values over time will be calculated by subtracting subsequent values from the baseline lesion means. Each evaluable bone metastasis will be analyzed with respect to these metrics separately.

8.1.12. All imaging data will be collected by Dr. Oto within the HIRO radiology database at the University of Chicago. Imaging data collected at participating institutions will be captured according to the above guidelines, saved as DICOM images on a transferable medium (e.g. CD-ROM, DVD, jump drive) and mailed to the study coordinator at the University of Chicago. The outside images will be anonymized within HIRO for analysis by Dr. Oto and his team.

8.2. Circulating Tumor Cell Characterization

As discussed in Section 1.5, the Szmulewitz laboratory has developed methodologies to isolate and interrogate CTC from patients with mCRPC. As a secondary objective to this study, these methodologies will be utilized to isolate CTC before and after XL184 administration and characterize those CTC for c-MET and phospho (active) c-MET expression. Given the limitations of the procedure, with respect to the necessity for immediate processing, this correlative will only be collected and performed on samples collected at the University of Chicago.

Sample Acquisition
Circulating tumor cells will be isolated from the following:

1. Peripheral venous blood (15ml per collection) will be collected in **2**BD VacutainerCPT® tubes (Becton Dickenson, Franklin Lakes, NJ) as described in the study calendar (Section 5.5).

2. Upon collection, samples will be taken to the Szmulewitz laboratory within 30 minutes of blood draw for subsequent mononuclear cell isolation

Mononuclear Cell Isolation

CTC's- CPT tubes will be centrifuged at 1500g for 20minutes at room temperature. Following centrifugation, the uppermost plasma layer will be removed and discarded. Mononuclear cell layer will be then transferred from both tubes into one new 15ml conical tube. Phosphate buffered saline (PBS) will be added to a total volume of 15ml. The cells will be centrifuged at 450g for 5 minutes at room temperature. The supernatant will be discarded and the washed mononuclear cells will be resuspended in 10ml of PBS for further processing.

CTC Identification and Characterization

Once mononuclear cell fraction isolated, prostate cancer cells will be identified and further characterized using Fluorescence Activated Cell Sorting (FACS). The pellet of cells will be resuspended in cell separation buffer (PBS with 2mM EDTA, 0.5% serum albumin), FcR blocking buffer (Miltenyi), EpCAM (to bind epithelial cells) and CD45 (to bind white blood cells) primary antibodies conjugated to specific fluorescent markers (Miltenyi and Invitrogen, repectively). Cells will then by analyzed in conjunction with the flow cytometry core facility gating and sorting the EpCAM positive, CD45 negative population.

Once isolated, the cells will be characterized using multiplex fllourescentImmunocytochemistry (ICC). According to the data gathered in the initial patient cohort, visualization of CTC's with immunofluorescnence is optimally feasible for patients with a minimum of 100 events detected in the EpCAM+/CD45- gate. Therefore, only these samples will be utilized for ICC studies. Cells are directly FACS sorted onto charged glass chamber slides, and then fixed with 3% formalin and stained with the following antibodies for multiplex fluorescence along with DAPI nuclear counterstain:

Total c-Met:	**eBioscience Cat. # 14-8858-80**	**1:100 Overnight**		
Phospho c-MET	**Invitrogen Cat.# 44888-G**	**1:50 Overnight**		
Anti-Rat Secondary-Texas Red Conjugated		**Santa Cruz Biotech**	**1:100**	**1 hour**
Anti-Rabbit Secondat-Alexa 633 Conjugated		**Invitrogen**	**1:100**	**1 hour**

The slides will be imaged using Axiovert 200 microscope. Captured images will be analyzed for fluorescence intensity and digitally scored using ImageJ software. Positive and negative control cells stained concomitantly will also be digitally analyzed and will provide the reference for staining intensity analysis.

8.3. Pain Questionnaire and Analgesic Inventory

Pain assessments will consist of subject-reported responses to a questionnaire (see **Appendix C**) in which subjects will be asked to rate their pain and degree of interference in daily activities due to pain at its worst over the prior 24 hours (adapted from the MD Anderson Symptom Assessment Inventory)[44], as well as their pain relative to their prior assessment (adapted from the Subjective Significance Question)[45]. The subject will complete this pain questionnaire and analgesic log at the study visits according to the study calendar (Section 5.5).

9. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria[23, 42, 46] (**Appendix D**). For the purposes of this study, patients should be re-evaluated every 12 weeks.

9.1. Outcome Measures based on PSA Decline

The following parameters will be recorded after the initial 12 weeks of therapy and at 12-week intervals thereafter.

- PSA decline will be measured according to PCWG-2 (2008) criteria[23].
- PSA changes from baseline will be calculated for all patients.
- Time to progression (TTP) based on revised PSA Working Group-2 criteria (2008 version).
- PSA progression free survival: PSA measurements will be taken at screening (baseline) and subsequently at time points as indicated in the schedule of visits. Any unscheduled PSA measurement will be utilized in the periodic assessment of PSA progression.
- The maximal decline in PSA for each patient will be recorded for each patient.
- The date of the maximal PSA decline (nadir date) will be recorded for each patient, as will the duration from the start of therapy to the nadir PSA.

9.2. Radiographic Tumor Response

Change in measurable disease, when applicable, will be determined according to RECIST 1.1 and PSAWG-2 criteria (Appendix E)[23, 42]. For the purposes of this study, imaging will be repeated according to the study calendar (Section 5.5) every 12 weeks unless otherwise indicated clinically.

Lymph nodes[46]*:* To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). Lymph nodes that are at least 10 mm but less than 15 mm in short axis may be pathologic and can be considered non-measurable/non-target lesions (that are not measured). At baseline and in follow-up, only the short axis will be measured and followed.

Bone lesions: Bone lesions are by definition non-measurable. If bone lesions are identified on MRI that have soft tissue components that are identifiable and accurately measurable, the bi-dimensional measurements of these lesions will be recorded as soft tissue measurable disease. Of note, progression based on bone scan will be assessed according to PCWG-2 criteria[23]. Isolated

new lesions on bone scan at the 12-week scan will be confirmed with a repeat bone scan at 6 weeks to rule out bone scan flair. If no new lesions are seen at the 6-week confirmation, it will be considered flair. All subsequent bone scans will follow standard criteria with regards to progression (two new lesions necessary for progression).

9.3. Duration of Response

The duration of overall response is measured from the time measurement criteria are met for complete or partial response until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

9.4. Progression-Free Survival

Time to progression or progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size/Primary Endpoint

The primary endpoint statistically will be vascular permeability as captured by the K^{trans} parameter at the two week time-point, as we have already established the intra and inter-patient variability of this metric. The effect of treatment with XL184 will be tested by subtracting the average of the two baseline K^{trans}measurements from the post-two week treatment value and performing a paired t-test. A 95% confidence interval for the magnitude of the mean change will also be generated. In our previous study[29], the mean K^{trans} was estimated to be 0.088 (min^{-1}) with a coefficient of variation of approximately 15%, corresponding to a standard deviation (SD) of the within-patient differences of 0.018. To allow for additional variability due to heterogeneity of the treatment effect, we assume a 50% greater SD of 0.027. In order to have 80% power to detect a 20% reduction in K^{trans} (from 0.088 to 0.070), which has been observed with VEGF pathway directed agents in other malignancies, n=20 patients will be required for a two-sided test at the alpha=0.05 significance level. Allowing for 20% of the patients to be non-evaluable, n=25 subjects will be enrolled in the study. Patients in whom there are incomplete data for week 2, week 12 MRI time points will be considered non-evaluable for the primary endpoint and replacement patients will be enrolled.

10.2. Analysis of Secondary Endpoints

Correlation of Functional MRI Changes with Standard Response Metrics
$K^{trans}$and ADC will be calculated as described Section 8.1. In addition, tumor measurements will be recorded at baseline and over the course of therapy. Pain will be monitored with the pain assessment questionnaire (**Appendix C**) and analgesic intake score and the scores analyzed per

patient over time as well as for the entire population using standard comparative statistics. CTC have recently been shown to be a sensitive predictive marker of treatment response in mCRPC[47]. Thus, CTC will be enumerated centrally by Quest diagnostics using the FDA approved CellSearch platform. In addition, standard prognostic laboratory studies including hemoglobin, and PSA, will be collected as per the schema above. PSA PFS and overall PFS will be calculated (Section 9). The association of PFS with K^{trans} and ADC will be established using the Cox proportional hazards approach using standard progression criteria[23]. In addition percent change in the functional MRI metrics will be correlated to changes in bone scan, RECIST tumor measurements, PSA, CTC and pain scale changes using a non-parametric Pearson correlation coefficient, all in conjunction with the biostatistics core at the University of Chicago.

c-MET and phospho-c-MET CTC staining
The expression of c-MET and phospho c-MET within each CTC within one patient sample will be averaged and the cumulative expression will be scored as low if at or below that of the negative control, intermediate if between negative and positive control and high if at or above positive control level. The percentage of CTC with low, intermediate, high expression level will be calculated. Standard comparative statistics (median/range, mean/standard deviation) will be used to describe c-MET and phospho c-MET staining within each patient and for the entire cohort based on the numeric staining intensity after background subtraction (Section 8.2). The association of c-MET and phospho-c-MET staining with PFS will be established using the Cox proportional hazards approach if possible based on sample size with adequate staining. In addition, c-MET and phospho-c-staining will be correlated with the PSA and RECIST response rates using a non-parametric Pearson correlation coefficient to explore the role of these CTC metrics as predictive biomarkers.

Safety Evaluation and Analysis
Safety analysis will be conducted on the full analysis set. All AEs occurring on study will be listed by subject in a data listing. The type of adverse events (AEs), intensity and incidence rates will be presented in all treated subjects."

11. PUBLICATION PLAN

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the Principal Investigator will provide any such publication to Exelixis, Inc. for review at least sixty (60) days prior to submission and also comply with any provisions regarding publication as are agreed to between the Principal Investigator's institution (e.g., University of Chicago.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 12 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. In any event, a full report of the outcomes should be made public no later than three (3) years after the end of data collection. Authorship for abstracts and manuscripts resulting from this study will be determined according to guidelines established by the International Committee of Medical Journal Editors.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Sample Data Capture Forms

Patient Baseline Data

Diagnostic PSA: ☐

Use PSA value closest to the date of the initial local tumor therapy.

Clinical T stage: ☐ Surgery date: ☐

Clinical N stage: ☐ Surgical T stage: ☐

Biopsy date: ☐ Surgical N stage: ☐

Biopsy primary Gleason score: ☐ Surgical primary Gleason score: ☐

Biopsy secondary Gleason score: ☐ Surgical secondary Gleason score: ☐

☐ Capsule invasion ☐ Seminal vesical invasion ☐ Margin positive

Primary Tumor Therapy

Primary tumor therapy #: ☐

Primary tumor therapy type: ☐

Primary tumor therapy start: ☐

Primary tumor therapy end: ☐

Assoc hormone therapy? ○ Yes ○ No

Assoc hormone therapy type: ☐

Assoc hormone therapy start: ☐

Assoc hormone therapy stop: ☐

Androgen Ablation

INSTRUCTION

The use of an anti-androgen (e.g. bicalutamide) as part of combined androgen ablation should be recorded on the 'Other Hormonal Therapy' form.

Androgen ablation start: [ ]

Androgen ablation administered for local disease should be entered under 'Tumor Therapy' form

Intermittant androgen ablation? ○Yes ○No

If yes, continuous androgen ablation start: [ ]

Other Hormonal Therapy

INSTRUCTION

Each additional hormonal therapy should be listed separately. Anti-androgren therapy (e.g. bicalutamide) administered with androgen ablation should be listed here.

Other hormonal therapy #: [ ]

Other hormone type: [ ]

Therapy start: [ ]

Therapy stop: [ ]

Withdrawal response? ○Yes ○No

Treatment History

Form Name: Treatment History Form

Treatment Details

Therapy Code* * Select Therapy

Therapy Start Date

Approximate?

If approximate, enter the exact month (if known) and the year Month: Year:

Therapy Start Date*

Therapy End Date

Approximate?

If approximate, enter the exact month (if known) and the year Month: Year:

Therapy End Date

Agent Select Agent

Cumulative Dose Units

If applicable, site of therapy: Primary Other

Timing:

Palliative?

Best Response:

Resection:

Notes

APPENDIX C

Analgesic Intake:
Please list each medication you have used to treat pain **over the last twenty-four hours** including the dose and the number of pills taken over the twenty-four hour period. For transdermal patches, please list the dose of patch and frequency of changing the patch.

Medication	**Dose**	**Times taken**
Example 1: Morphine sulfate IR	*30mg*	*6*
Example 2: Fentanyl patch	*50mcg/h*	*Every 72 hours*

Pain Questionnaire :

1. People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										As Bad As You Can Imagine
	0	1	2	3	4	5	6	7	8	9	10
a. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
b. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

2. Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	1	2	3	4	5	6	7	8	9	10
a. **General activity**?	○	○	○	○	○	○	○	○	○	○	○

3. Compared to the last time I completed this questionnaire, my **pain**in the last 24 hours was
   A. Very much worse
   B. Moderately worse
   C. A little worse
   D. About the same
   E. A little better
   F. Moderately better
   G. Very much better

Appendix D

PROSTATE-SPECIFIC ANTIGEN WORKING GROUP CRITERIA[23]

Progressive Disease after Androgen Deprivation Eligibility Criteria:

PSA evidence for progressive prostate cancer consists of a PSA level of at least 5 ng/ml which has risen on at least 2 successive occasions, at least 2 weeks apart. If the confirmatory PSA (#3 below) value is less (i.e., #3b) than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression.

Procedures for Assessing PSA Progression Post Study Treatment

PSA measurements will be taken on a monthly basis. PSA increases and decreases will be tracked in order to assess disease response.

PSA partial response is defined by at least a 50% decline from screening (baseline) PSA value. The declined must be confirmed by a second PSA value obtained 4 or more weeks later.

PSA progressive disease may be defined in both patients who have not shown a decrease in their PSA and those who have. For patients who have not shown a decrease, progressive disease is defined as an increase of 25% over the screening (baseline) PSA value and in increase in the absolute-value PSA level by at least 5ng/mL. This increase should be confirmed by a second value.

For those patients whose PSA have decreased but has not reached response criteria, progressive disease is defined as 25% increase over the nadir PSA value provided that the increase is at least 5ng/mL and is confirmed.

Duration of PSA Response

Duration of PSA Response is measured from the time when the PSA value first declines by at least 50% of the screening (baseline) and that was eventually confirmed by a second value. It is calculated until the time at which there is an increase of 50% of PSA nadir, provided the absolute increase is at least 5 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 50% above the nadir.

If the PSA never shows a 50% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Time to Disease Progression

For patients who have achieved a $\geq$ 50% decrease from the screening (baseline) PSA, assessment of time to disease progression is when the PSA has increased 50% above the nadir and at a minimum of 5ng/mL. For patients without a PSA decrease of this magnitude or without a decrease, the time for progression is calculated at the time a 25% increase from screening (baseline) PSA has been achieved.

Appendix E

RESPONSE EVALUATION CRITERIA in SOLID TUMORS (RECIST 1.1) [42, 46]

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Lymph nodes*:* To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). Lymph nodes that are at least 10 mm but less than 15 mm in short axis may be pathologic and can be considered non-measurable/non-target lesions (that are not measured). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Evaluation: Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as

having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

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