

**Abbreviated Title:** Phase I/II XL184 in mCRPC

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**Title:** A Phase I and Randomized Phase II Multicenter Study of Cabozantinib (XL184) plus Docetaxel and Prednisone in Metastatic Castrate Resistant Prostate Cancer

**Coordinating Center:** Center for Cancer Research

**Principal Investigator:** William Dahut, M.D. <sup>A-F</sup>  
Genitourinary Malignancies Branch (GMB)  
Center for Cancer Research  
National Cancer Institute  
Building 10, Room 3-2571  
9000 Rockville Pike  
Bethesda, MD 20892  
Phone: 240-760-6187  
Email: [dahutw@mail.nih.gov](mailto:dahutw@mail.nih.gov)

**Co-Investigators:**

Fatima Karzai, M.D., NIMHD <sup>A-F</sup>  
10 Center Drive, Room 13N240  
Bethesda, MD 20892  
Phone: 301-402-9134  
Email: [Fatima.karzai@nih.gov](mailto:Fatima.karzai@nih.gov)

Ravi Madan, M.D., GMB, CCR, NCI <sup>A-F</sup>  
10 Center Drive, Room 13N240  
Bethesda, MD 20892  
Phone: 301-480-7168  
Email: [madanr@mail.nih.gov](mailto:madanr@mail.nih.gov)

Andrea Apolo, M.D., GMB, CCR, NCI <sup>A-F</sup>  
10 Center Drive, Room 13N240  
Bethesda, MD 20892  
Phone: 301-480-0536  
Email: [andrea.apolo@nih.gov](mailto:andrea.apolo@nih.gov)

James Gulley, M.D., Ph.D., GMB, CCR, NCI <sup>A-F</sup>  
10 Center Drive, Room 13N240  
Bethesda, MD 20892  
Phone: 301-480-7164  
Email: [gulleyj@mail.nih.gov](mailto:gulleyj@mail.nih.gov)

Howard Parnes, M.D. <sup>A-F</sup>  
Prostate and Urologic Cancer Research Group  
Division of Cancer Prevention, NCI  
9609 Medical Center Dr, Room 5E302  
Rockville MD 20850  
Phone: 240-276-7045  
Email: [parnesh@mail.nih.gov](mailto:parnesh@mail.nih.gov)

John Wright, M.D., Ph.D. <sup>A-F</sup>  
Investigational Drug Branch, CTEP, DCTD, NCI  
9609 Medical Center Dr, Room 5W454  
Rockville MD 20850  
Phone: 240-276-6565  
Email: [wrightj@ctep.nci.nih.gov](mailto:wrightj@ctep.nci.nih.gov)

\*Liang Cao, Ph.D. GB, CCR, NCI<sup>E, F</sup>  
37 Convent Drive, Room 6134  
Bethesda, MD 20892-1906  
Phone: 301-435-9039  
E-mail: [caoli@mail.nih.gov](mailto:caoli@mail.nih.gov)

\*William Figg, Pharm.D., GMB, CCR, NCI<sup>E, F</sup>  
10 Center Drive, Room 5A01  
Bethesda, MD 20892  
Phone: 240-760-6179  
Email: [wdfigg@mail.nih.gov](mailto:wdfigg@mail.nih.gov)

\*Donald P Bottaro, PhD, UOB, CCR, NCI<sup>E, F</sup>  
10 Center Drive, Room 1W-5832  
Bethesda, MD 20892  
Phone: 301-402-0922  
Email: [bottarod@mail.nih.gov](mailto:bottarod@mail.nih.gov)

\*Cindy Chau, Pharm.D., Ph.D., GMB, CCR, NCI<sup>E, F</sup>  
10 Center Drive, Room 5A01  
Bethesda, MD 20892  
Phone: 301-402-3622  
Email: [chauc@mail.nih.gov](mailto:chauc@mail.nih.gov)

\*Jane Trepel, Developmental Therapeutics  
Branch, (DTB), CCR, NCI<sup>E, F</sup>  
10 Center Drive, Room 2N230  
Bethesda MD, 20892  
Phone: 301-496-1547  
Email: [trepelj@mail.nih.gov](mailto:trepelj@mail.nih.gov)

\*Douglas Price, Ph.D., GMB, CCR, NCI<sup>E, F</sup>  
10 Center Drive, Room 5A01  
Bethesda, MD 20892  
Phone: 301-451-5860  
Email: [dkprice@mail.nih.gov](mailto:dkprice@mail.nih.gov)

Anna Couvillon, N.P., GMB, CCR, NCI<sup>A-F</sup>  
10 Center Drive, Room 13N224  
Bethesda, MD 20892  
Phone: 301-443-6211  
Email: [couvilla@mail.nih.gov](mailto:couvilla@mail.nih.gov)

Guinevere Chun, R.N., OCD, CCR, NCI<sup>A, B, C, E, F</sup>  
10 Center Drive, Room 12N226  
Bethesda, MD 20892-1906  
Phone: 240-760-6065  
Email: [gchun@mail.nih.gov](mailto:gchun@mail.nih.gov)

Helen Owens, R.N., OCD, CCR, NCI<sup>A, B, C, E, F</sup>  
10 Center Drive, Room 12N226  
Bethesda, MD 20892-1906  
Phone: 240-760-6068  
Email: [howens@mail.nih.gov](mailto:howens@mail.nih.gov)

\*Seth Steinberg, PhD<sup>E, F</sup>  
Biostatistics and Data Management Section  
National Cancer Institute  
9609 Medical Center Drive, Room 2W334  
Rockville, MD 20850  
Phone: 240-276-5563  
Email: [steinbes@mail.nih.gov](mailto:steinbes@mail.nih.gov)

**Responsible Research Nurse:**

Helen Owens, R.N., OCD, CCR, NCI

**Referral Contact/Study Coordinator:**

Helen Owens, R.N., OCD, CCR, NCI  
10 Center Drive, Room 12N226  
Bethesda, MD 20892-1906  
Phone: 240-760-6068  
Email: [howens@mail.nih.gov](mailto:howens@mail.nih.gov)

\* not responsible for patient care

- A. Obtain information by intervening or interacting with living individuals for research purposes
- B. Obtaining identifiable private information about living individuals
- C. Obtaining the voluntary informed consent of individuals to be subjects
- D. Makes decisions about subject eligibility
- E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes
- F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
- G. Some/all research activities performed outside NIH

### Multi-Institution Contacts:

Institutional PI:

Joseph Kim, M.D.  
Prostate and Urologic Cancers Program,  
Signal Transduction Program  
Institution: Yale Comprehensive Cancer Center  
Institution FWA #: 2577  
Yale School of Medicine  
333 Cedar St, Fitkin 1, Rm 121  
New Haven, CT 06520  
Phone Number: 203-737-1600  
E-mail: [joseph.kim@yale.edu](mailto:joseph.kim@yale.edu)

IRB Contact:

Christine Early  
IRB of Record Name: Yale University Human  
Investigations Committee IORG #: 4296  
55 College Street  
New Haven, CT 06510  
Phone Number: 203-785-4688  
Email: [hrpp@yale.edu](mailto:hrpp@yale.edu)

Pharmacy Contact:

Thomas Ferencz, RPh, BCOP  
Smilow Cancer Center at Yale New Haven Hospital  
266 So, Frontage Road, Room 8-110  
New Haven, CT, 06510  
Phone Number: 203-200-4455  
Email: [Thomas.ferencz@ynhh.org](mailto:Thomas.ferencz@ynhh.org)

Institutional Contact:

Matthew Piscatelli, BS CCRP  
2 Church Street South, Suite 507  
New Haven, CT, 06519  
Phone Number: 203-737-8367  
Email: [matthew.piscatelli@yale.edu](mailto:matthew.piscatelli@yale.edu)

**CTEP Supplied Agents:**

|               |                      |
|---------------|----------------------|
| Drug Name:    | Cabozantinib (XL184) |
| IND Number:   | 116059               |
| NSC Number:   | 761968               |
| Sponsor:      | CTEP                 |
| Manufacturer: | Exelixis             |

**Commercially available agents:**

Docetaxel and prednisone will be supplied by the local site pharmacy.

**Subjects of Study:**

| Number | Sex  | Age-Range       |
|--------|------|-----------------|
| 81     | Male | $\geq 18$ - 100 |

## **PRÉCIS**

### **Background:**

- Docetaxel is established as first-line chemotherapy in patients with metastatic castrate resistant prostate cancer (CRPC). However; it is increasingly recognized that combining docetaxel with other agents of clinical activities without overlapping toxicities could simultaneously target different cellular signaling pathways vital for tumor survival, producing either additive or synergistic activities.
- Inhibition of angiogenesis, either as a stand-alone approach or in combination with chemotherapy, has demonstrable antitumor efficacy against CRPC and there are several antiangiogenic agents that are now in clinical trials in this population of patients.
- Cabozantinib (XL184) was developed as an inhibitor of both angiogenesis and of its resistance mechanism. It is an inhibitor of multiple receptor tyrosine kinases including c-Met, VEGFR2 and RET.
- In single agent clinical studies, cabozantinib demonstrated, broad anti-tumor activities across many solid tumor types.

### **Objectives:**

- To determine the safety profile of cabozantinib in combination with docetaxel and prednisone, and to determine the maximal tolerated dose (MTD) as recommended phase II dose in combination with docetaxel.
- To determine the relative efficacy (in terms of PFS) of docetaxel and cabozantinib compared to docetaxel alone

### **Eligibility:**

- Patients must have progressive metastatic CRPC. There must be radiographic evidence of disease after primary treatment with surgery or radiotherapy. If patients had been on flutamide, they must have disease progression at least 4 weeks after withdrawal. Patients on bicalutamide or nilutamide must have progression at least 6 weeks after withdrawal. Withdrawal criteria apply only to patients on the above anti-androgens for at least the prior 6 months.
- Patients must be at least 18 years of age and able to give informed consent.
- Patients in the Phase II portion of the study must have progressed on abiraterone or enzalutamide

### **Design:**

- The initial phase I portion of this study will test fixed dose docetaxel and prednisone in combination with cabozantinib at three escalating doses. Using a standard 3 + 3 design, three patients will initially be treated at each dose level until MTD has been defined.
- An expansion cohort will then be enrolled at the MTD to further characterize safety, toxicity and pharmacokinetic data and to obtain preliminary information on the efficacy of the combination treatment.

- In Phase II, patients will be enrolled to a randomized two-arm cohort comparing docetaxel in combination with cabozantinib to docetaxel alone with a primary endpoint of PFS.
- The accrual ceiling for the study, including the Phase I dose escalation and the expansion phases as well as the Phase II randomized phase, is set at 81.

**SCHEMA**

| <b>Phase I portion</b>  |                             |
|---|-----------------------------|
| <b>Dose Escalation Schedule to determine MTD</b>  |                             |
| <b>Dose Level</b>   | <b>Dose of cabozantinib</b> |
| Level -1  | 20 mg PO every other day    |
| Level 1   | 20 mg PO daily              |
| <b>Level 2</b>  | <b>40* mg PO daily</b>      |
| Level 3   | 60 mg PO daily              |
| <p>At all dose levels, subjects will also take:</p> <ul style="list-style-type: none"> <li>• Docetaxel: 75 mg/m<sup>2</sup> IV day 1 of each 21 day cycle</li> <li>• Prednisone: 5 mg PO, twice daily</li> <li>• *40mg PO daily has been determined to be the MTD for the dose expansion cohort.</li> </ul> |                             |

| <b>Randomized Phase II Portion</b> |  |
|------------------------------------|--|
| Unblinded Randomization            |  |
| Arm A*                             | Docetaxel 75 mg/m <sup>2</sup><br>Prednisone 5 mg BID                                |
| Arm B                              | Docetaxel 75 mg/m <sup>2</sup><br>Prednisone 5 mg BID<br>Cabozantinib 40 mg PO daily |
|                                    | Patients treated until radiographic progression                                      |

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## 1 OBJECTIVES

### 1.1 PRIMARY OBJECTIVE

- To determine the safety profile of cabozantinib in combination with docetaxel and prednisone, and to determine the maximal tolerated dose (MTD) as the recommended phase II dose in combination with docetaxel
- To determine the relative efficacy (in terms of progression free survival) of docetaxel and cabozantinib compared to docetaxel alone

### 1.2 SECONDARY OBJECTIVES

- To assess pharmacokinetics of each agent during combination therapy.
- To evaluate antitumor activities of combination therapy via measurable disease as determined by Response Evaluation Criteria in Solid Tumors (RECIST) and Prostate Cancer Clinical Trials Working Group Criteria 2<sup>1</sup>.
- To assess changes in molecular biomarkers in the pathways of receptor tyrosine kinases and angiogenesis, as well as the biomarkers for bone metabolism.

## 2 BACKGROUND

### 2.1 CASTRATE RESISTANT PROSTATE CANCER

Prostate cancer is the most common malignancy and the second leading cause of cancer-related deaths in American men. It is estimated that 217,730 men were diagnosed with prostate cancer and 32,050 died from this disease in 2010.<sup>2</sup> Although the disease is initially responsive to androgen deprivation therapy, it invariably progresses and becomes resistant to androgen ablation in the majority of patients. This leads to the development of CRPC, which is defined as tumor growth despite castrate levels of androgens (serum testosterone < 50 ng/dL).<sup>1</sup> Advanced CRPC carries significant morbidity and mortality, and often necessitates a transition to the treatment with chemotherapy to control tumor growth and prevent disseminated organ involvement. The role of chemotherapy in metastatic CRPC was limited until 2004 when two pivotal phase III randomized trials, TAX 327 and SWOG 99-16, demonstrated an overall survival benefit of docetaxel (with prednisone or estramustine) compared to mitoxantrone and prednisone.<sup>3,4</sup> Based on its modest survival benefit, docetaxel obtained FDA approval and was established as first-line chemotherapy in patients with metastatic CRPC.

#### Strategies to improve clinical efficacy of docetaxel

It is increasingly recognized that combining docetaxel with other agents of clinical activities without overlapping toxicities could simultaneously target different cellular signaling pathways vital for tumor survival, producing either additive or synergistic activities. Given the survival benefit conferred by docetaxel, it is encouraging that further studies using docetaxel-based combination therapies targeting multiple cellular mechanisms concurrently could be a viable option for this patient population. In fact, numerous trials have been conducted combining docetaxel with different agents of distinct mechanisms of action, including TKIs, angiogenic inhibitors, bone-targeted agents, BCL-2 inhibitors, immunologic agents, and vitamin D analogs.<sup>5</sup>

The available data so far has produced inconsistent results. Several phase II trials of combination treatment have indicated enhanced anti-tumor activity beyond docetaxel alone, whereas others have been proven to be futile. To consolidate the conflicting results published on docetaxel-based therapies, a recent meta-analysis from 12 randomized combination trials with 2,244 patients was performed. The trials were selected in the meta-analysis if they were randomized control trials studying first-line chemotherapy of histologically confirmed CRPC with docetaxel plus prednisone as the control arm. It demonstrated higher PSA response rate and longer overall survival in favor of docetaxel-based combinational therapies,<sup>6</sup> thus, provided evidence for further endeavor to pursue docetaxel-based combination therapies. This opens up to a question that which molecular pathways are the most appropriate targets which can be incorporated into docetaxel-based regimen for metastatic CRPC patients.

### Anti-angiogenic Agents as Potential Partners for Docetaxel in Combination Therapy

#### *Targeting angiogenesis in combination therapy*

The significance of angiogenesis in promoting prostate cancer growth and metastasis has been well established. Microvessel density was reported to be substantially higher in prostate cancer samples from patients with metastatic disease when compared with those without metastatic disease.<sup>7</sup> Elevated plasma and urine levels of VEGF-A was found to be associated with metastatic progression and reduced survival in patients with prostate cancer,<sup>8</sup> thus demonstrated the potential to serve as an independent prognostic factor in men with metastatic prostate cancer.<sup>9</sup> Blocking tumor neovascularization via anti-angiogenic agents, e.g. bevacizumab, has been determined as an appealing approach in reducing proliferation and metastatic potential of various tumors, including prostate cancer.<sup>10</sup> In an attempt to improve patient's outcome in the first-line treatment setting, the benefit of addition of bevacizumab was assessed in the CALGB phase III trial (90401), where docetaxel, prednisone and bevacizumab was compared with docetaxel and prednisone in 1,050 men with metastatic CRPC. Although addition of bevacizumab led to significant improvements in PFS and PSA response rate but no significant difference in overall survival was noted.<sup>11</sup> The negative result from this seemingly promising combination indicates refractoriness and resistance do occur during the course of anti-angiogenic treatment. Multiple mechanisms for acquired resistance have been postulated with supportive preclinical and clinical evidence.

#### *Controlling the escape from anti-angiogenesis*

Angiogenesis is a complex process and multiple mediators are involved at different cellular interface. The examples of these molecules are the families of VEGF, PDGF, FGF, ANG and TIE signaling system, TGF- $\beta$  signaling, and the NOTCH and WNT signaling pathway, etc.<sup>12</sup> Resistance to VEGF inhibitor, such as bevacizumab, usually ensues as inhibition of angiogenesis via a single target which can be potentially overcome by shifting the balance to the production of other pro-angiogenic mediators given the redundancy of angiogenic system.<sup>12</sup> Indeed, blocking neovascularization by VEGF antibody was found to induce hypoxia which in turn up-regulate angiogenic factors such as bFGF, chemokines and ephrin, and angiopoietin families, leading to anti-angiogenesis rescue.<sup>13</sup> To overcome the hurdle of multiple pre-existing or induced pro-angiogenic factors, we previously took the strategy of dual inhibition of angiogenesis by combining docetaxel, prednisone with two other agents of distinct anti-angiogenic properties, thalidomide and bevacizumab, in chemotherapy-naïve CRPC patients in a single arm phase II trial. Striking results were observed in that 90% of patients achieved PSA decline of > 50% with a 60% objective response rate among patients with measurable disease.<sup>14</sup> The median time to

progression was 18.2 months and median OS was 28.2 months, comparing favorably to what was observed in TAX 327 and SWOG 9916.<sup>14</sup> Subsequent ongoing phase II trial utilizing same strategy of dual angiogenic inhibition (phase II trial of docetaxel, bevacizumab, lenalidomide and prednisone in patients with metastatic CRPC) yielded similar activity as of last analysis in August 2011 (unpublished data). All patients developed Grade  $\frac{3}{4}$  neutropenia, due to overlapping toxicity profiles of docetaxel and thalidomide, in the first trial, which necessitate the use of pegfilgrastim in the second trial. The superior antitumor activities from these two trials supports further research into this strategy, however, new targets lacking overlapping toxicities with docetaxel need to be sought to improve tolerability profile.

Another mechanism of VEGF-independent tumor angiogenesis was elucidated by Pennacchietti et al. in cultured cells and mouse xenograft tumor model. Receptor tyrosine kinase c-Met, a protooncogene capable of cell invasion and metastasis upon binding to hepatocyte growth factor (HGF), was found overexpressed under hypoxic condition and this overexpression was inversely proportional to the blood vessel proximity.<sup>15</sup> The up-regulation of c-Met sensitized it to HGF stimulation and resulted in increased cell motility and invasiveness (invasive switch).<sup>15</sup> Hypoxia-inducible factors (HIFs)-induced c-Met overexpression is considered a cellular coping mechanism in response to low oxygen levels upon selective inhibition of VEGF pathway. However, it potentially can serve as an effective outlet for tumor to escape anti-angiogenesis. In fact, a paracrine mechanism for HGF stimulation of c-Met has been largely implicated in the progression of prostate cancer.<sup>16</sup> Upregulation of c-Met expression is frequently observed in prostate cancer tissues, particularly in metastatic tumor samples.<sup>16</sup> Interestingly, the bone metastases expressed significantly more c-Met than did the lymph node metastases.<sup>17</sup> AR signaling appears to negatively regulate the expression of c-Met as significantly elevated c-Met expression was observed during androgen deprivation therapy.<sup>18</sup> This may potentiate c-Met-driven metastasis resulting in the development of more aggressive CRPC. The fact that suppression of c-Met via RNA interference resulted in loss of hypoxia-enhanced, HGF-stimulated cell branching,<sup>15</sup> supports the use of combination of anti-angiogenic agents with c-Met blocking agents for the prevention of both angiogenic and invasive switch and overcome the resistance to anti-angiogenesis.

## 2.2 IND AGENT - CABOZANTINIB (XL184)

The search for dual inhibition of both angiogenesis and its resistance mechanism led to the development of XL 184 (Cabozantinib), a potent inhibitor of multiple receptor tyrosine kinases including c-Met, vascular endothelial growth factor receptor 2 (VEGFR2) and RET. Cabozantinib is orally bioavailable as demonstrated by PK studies in rodent and non-rodent models. In vitro assays showed that cabozantinib was a substrate of CYP3A4-mediated metabolism. It 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. It is highly protein-bound (99%) to human plasma proteins and its terminal-phase half-life ( $t_{1/2, z}$ ) values are 59.1 to 136 hours. In in-vivo target modulation studies, administration of cabozantinib to mice resulted in dose-dependent inhibition of MET, and VEGFR2 with  $IC_{50}$  values of 1.8 nM and 0.035 nM (Investigator Brochure).

## 2.2.1 Nonclinical Development of cabozantinib

### 2.2.1.1 *In Vivo* Activity

Inhibition of VEGF signaling pathway was previously shown to result in more invasive tumors in the transgenic RIP-Tag2 mouse model of pancreatic neuroendocrine cancer that spontaneously develops aggressive tumors<sup>19</sup>. In RIP-Tag2 transgenic mice, tumors treated with XL184 were smaller ( $P < 0.05$ ) than in mice treated with vehicle or an anti-VEGF antibody, but were also less invasive ( $P < 0.05$ ) and had no liver metastases<sup>20</sup>. All mice treated with XL184 ( $n = 6$ ) survived until 20 weeks, but none treated with vehicle ( $n = 14$ ) or anti-VEGF antibody ( $n = 8$ ) reached that endpoint. Tumor vascularity decreased after treatment, with reductions ranging from 67% at 3 mg/kg to 83% at 30 mg/kg for 7 days<sup>21</sup>. Tumors were 35% smaller after XL184 treatment than corresponding values for vehicle control mice. c-Met protein expression in tumors was slightly decreased, but phosphorylated c-Met was markedly reduced after treatment for 7 days.

Mice bearing MDA-MB-231 cells (expressing MET and VEGF) were administered four oral doses of 100 mg/kg<sup>22</sup>. XL184 increased tumor hypoxia (13-fold) and apoptosis (TUNEL; 2.5-fold) at 8 and 4 hours after the first and second doses, respectively, when compared to vehicle-treated tumors. In addition, XL184 disrupted tumor vasculature by inducing endothelial cell death that negatively affected tumor viability. XL184 treatment resulted in significant tumor growth inhibition of MDA-MB-231 tumors ( $P < 0.001$ ) at all doses (1, 3, 10, 30, or 60 mg/kg) when compared to vehicle-treated tumors. Dose-dependent inhibition was observed for the 3 and 10 mg/kg doses ( $P < 0.01$ ), and complete inhibition was observed at the 30 and 60 mg/kg doses. A single 100 mg/kg dose resulted in sustained MDA-MB-231 tumor growth inhibition for ~8 days after which tumors began growing at a rate similar to vehicle-treated control tumors. In addition, XL184 inhibited tumor growth ( $P < 0.001$ ) in the MET-expressing rat C6 glioma cell line for all doses (1, 3, 10, 30, or 60 mg/kg) when compared with vehicle-treated tumors. The 3 mg/kg and 10 mg/kg doses resulted in significant tumor regression (62% and 85%,  $P < 0.0001$ ) when compared with predose tumor weights. Subchronic administration of XL184 was well tolerated in mice and rats with no signs of toxicity, as determined by stable and/or increasing body weights during the treatment period.

ARCaP-M is a human prostate cancer model which expresses both c-Met and VEGF co-receptor NP-1 used in a human prostate tumor xenograft study in mouse bone<sup>23</sup>. ARCaP-M cells were injected into the tibia of nude mice on Day 1, and on Day 31 animals with established bone lesions were randomized to receive XL184 or vehicle daily (qd) for 7 weeks of treatment<sup>24</sup>. Tibiae from vehicle-treated animals exhibited both osteoblastic and osteolytic lesions, whereas tibiae from XL184 treated animals appeared mostly normal. Thus, XL184 treatment blocked both osteoblastic and osteolytic progression of ARCaP-M xenograft tumors in bone.

### 2.2.1.2 Nonclinical Pharmacodynamics

In mice, the effective dose resulting in 50% inhibition ( $ED_{50}$ ) of targets was achieved at well tolerated doses of XL184 and at plasma exposures comparable to exposure observed in clinical trials<sup>25</sup>. XL184 produced prolonged inhibition of receptor phosphorylation, such as sustained inhibition of c-Met and VEGFR2 for 10 hours after administration of a single dose of XL184. This extended inhibition occurred in a manner that was generally predicted by plasma exposure, *i.e.*, inhibition was diminished when plasma levels fell below approximately 20  $\mu\text{M}$  for c-Met, 5  $\mu\text{M}$  for VEGFR2, and 23  $\mu\text{M}$  for TIE-2.

Once daily administration of XL184 resulted in significant inhibition of c-Met phosphorylation in TT tumors, relative to tumors from vehicle control-treated mice, with maximal inhibition of 70% seen at 60 mg/kg.<sup>25</sup> Dose-dependent inhibition of phosphorylation of c-Met and RET was observed among the 3, 10, and 30 mg/kg dose groups as well.

c-Met phosphorylation was inhibited by a single 100 mg/kg oral dose of XL184, 2–8 hours post dose in H441 tumors (human lung papillary adenocarcinoma) that harbor constitutively phosphorylated c-Met<sup>22</sup>. This effect was reversible, as c-Met phosphorylation returned to basal levels by 48 hours after treatment.

### 2.2.1.3 Nonclinical Pharmacokinetics

In the various xenograft models, plasma exposures were similar and plasma concentrations in the range of 3 to 27  $\mu\text{M}$  were associated with efficacy<sup>25</sup>. In rats, plasma concentrations in the range of 5 to 15  $\mu\text{M}$  were associated with maximal anti-tumor activity. Despite the apparent requirement for high peak concentrations, trough concentrations as low as 0.1  $\mu\text{M}$  were observed at highly efficacious doses in mice. These results were consistent with *in vivo* target modulation studies in mice which demonstrated long (4- to 10-hour) durations of action, and indicated that continuous high exposure was not required to maintain efficacy.

Dose proportional increases in exposure occurred at oral doses of 3–100 mg/kg in mice and at 3–30 mg/kg in rats<sup>25</sup>. In rats, the oral bioavailability of XL184 dosed as a solid was approximately 100% of XL184 dosed as a liquid. In comparison, oral bioavailability was much lower in dogs (20%) and monkeys (18%) for the solid versus liquid dosage forms.

Systemic drug exposure parameters (maximum plasma concentration [ $C_{\text{max}}$ ] and area under the time-concentration curve from 0 to t hours post-dose [ $\text{AUC}_{0-t}$ ] values) associated with single XL184 oral doses in rats increased less than dose-proportionally with increasing dose (100–900 mg/kg)<sup>25</sup>. With repeat daily oral dosing in rats, systemic exposure ( $\text{AUC}_{0-t}$  values) increased generally dose-proportionally following 14 and 178 dosing days (dose ranges 1–15 mg/kg/day and 0.1–1 mg/kg/day, respectively). The  $C_{\text{max}}$  and  $\text{AUC}_{0-t}$  values in rats administered 100 mg/kg were approximately 2-fold and 3-fold higher, respectively, than for dogs given 2000 mg/kg; therefore, the higher systemic exposure to XL184 in rats correlated with the greater toxicity observed in this species at lower administered doses.

Systemic drug exposure parameters ( $C_{\text{max}}$  and  $\text{AUC}_{0-t}$  values) associated with single XL184 oral doses in dogs increased less than dose-proportionally with increasing XL184 dose (400–2000 mg/kg), suggesting possible saturation of systemic absorption<sup>24</sup>. With repeat daily dosing, exposure ( $C_{\text{max}}$  and  $\text{AUC}_{0-24}$  values) both increased greater than dose-proportionally from 10 to 100 mg/kg and less than dose proportionally from 100 to 1000 mg/kg following 14 dosing days.

### 2.2.1.4 Toxicology

In rodents and non-rodents, histopathological changes associated with XL184 administration were observed in gastrointestinal (GI) tract, bone marrow, lymphoid tissues, kidney, and adrenal and reproductive tract tissues<sup>24</sup>. Histopathological changes present in the bone and pancreas were considered secondary to XL184 administration. Adverse effects following oral exposure to XL184 were generally dose-related, clinically monitorable, and self-resolving upon discontinuation of dosing. In 6-month chronic toxicity studies, treatment-related changes were present only in kidney (rats) and reproductive tissues (dog). In reproductive/developmental toxicity studies, XL184 administration resulted in decreased fertility in male and female rats, in

embryotoxicity when given to pregnant rats, and in a visceral tissue malformation (small spleen) when given to pregnant rabbits. The no-observable-adverse-effect-levels (NOAELs) for the chronic toxicity and reproductive/developmental toxicity studies occurred at plasma exposures (AUC) below steady-state values measured in subjects with solid tumors administered 175 mg XL184 capsule form daily (Study XL184-001).

In definitive genotoxicity bioassays, XL184 was negative in an *S. typhimurium/E.coli* bacterial mutagenicity study, an *in vitro* chromosome aberration study using human peripheral blood lymphocytes, and an *in vivo* mouse bone marrow micronucleus study<sup>25</sup>. In safety pharmacology studies, no adverse effects occurred on neurobehavioral or respiratory functions in XL184-treated rats or on cardiovascular function in XL184-treated dogs.

### 2.2.2 Clinical Experience

As of May 4, 2011, 1003 patients have been studied in 12 ongoing Exelixis-sponsored clinical trials with XL184 treatment 1) as a single agent at doses ranging from 0.08 to 11.52 mg/kg on an intermittent dosing schedule, 2) from 25 to 265 mg (19.7-209 mg freebase equivalent weight) on a fixed daily dosing schedule and 3) in combination with temozolomide (TMZ) and radiation therapy (RT), or with erlotinib (Exelixis Communication, 2011). The maximum tolerated dose (MTD) on once daily (qd) by mouth (PO) dosing schedule was determined to be 175 mg L-malate salt (or approximately 138 mg freebase equivalent weight).

Detailed information for each of these studies, including pharmacokinetic data, can be found in the Investigator's Brochure (2011)<sup>24</sup>. Safety and efficacy information, from the 2011 Investigator's Brochure, is summarized below.

#### 2.2.2.1 Phase I Studies

Study **XL184-001** was a phase 1 dose-escalation study in subjects with solid tumors. Eighty-five subjects, across 13 dosing levels (DL) ranging from 0.08 mg/kg qd (using powder-in-bottle [PIB] suspension on a 5 days on, 9 days off schedule) to 265 qd (using capsules [25 and/or 100mg] for two, 14-day cycles) were enrolled. The capsule MTD was determined to be 175 mg qd<sup>26</sup>. Of the 35 subjects with medullary thyroid cancer (MTC) and measureable disease enrolled in the dose expansion phase, 10 (29%, 95% CI) had confirmed partial responses (cPR) (with a duration up to 48+ months), 17 (49%) had tumor shrinkage of  $\geq 30\%$ , and stable disease (SD) of at least 6 months was observed in 15/37 (41%) of the MTC subjects.

In Study **XL184-002**, treatment of subjects with newly diagnosed glioblastoma (GB) consisted of cabozantinib in combination with TMZ with or without radiation therapy. Enrollment has been terminated and no clinical efficacy data is presented in the 2011 Investigator's Brochure. All adverse events (AEs) were assessed with respect to combination treatment and not the individual components. Nineteen patients were evaluated for AEs, the most common grade 3 or higher included neutropenia (21%), thrombocytopenia (16%), leucopenia (16%), and hypertension (11%). Myelosuppression, including prolonged pancytopenia, is a dose-limiting toxicity (DLTs) associated with TMZ use. The frequency at which bone marrow toxicity was observed in this study is consistent with the TMZ prescribing information.

Study **XL184-004** is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover study to assess the effect of food on the bioavailability of cabozantinib in healthy adult subjects. According to a randomization scheme, 56 subjects received single oral doses of the assigned treatment of Test (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg



capsules 30 minutes after administration of a high-fat breakfast) or Reference (175 mg cabozantinib, dosed as one 100-mg capsule and three 25-mg capsules under fasting conditions). Blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib pharmacokinetics. See “Pharmacokinetics” section for results.

Study **XL184-005** is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg cabozantinib, dosed as one 100-mg tablet) or Reference (100 mg cabozantinib, dosed as two 50-mg capsules), according to a randomization scheme. Each dosing was administered under fasting conditions, and blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib PK. See “Pharmacokinetics” section for results.

In Study **XL184-008**, subjects with advanced solid tumors (particularly renal cell carcinoma [RCC] and differentiated thyroid cancer [DTC]) are evaluated for any potential clinically significant drug-drug interaction of cabozantinib on the CYP isozyme CYP2C8. The effect of qd dosing of 175 mg cabozantinib and a single dose of rosiglitazone will be evaluated. In 11 patients evaluated for AEs, the most common grade 3 or higher AEs were fatigue (9%), hypophosphatemia (27%), blood amylase increase (9%), and hyponatremia (9%).

In a phase 1 study, **CA205-001**, Japanese subjects with advanced or metastatic solid tumors for whom the standard of care is ineffective or inappropriate, received cabozantinib at a starting dose of 75 mg PO qd. Two of the three subjects in the first cohort experienced DLTs of proteinuria and thrombocytopenia. Because of a change in study sponsor, this study was reinitiated as **XL184-014**. One additional subject was enrolled as of May 2011 at 50 mg PO qd.

Study **XL184-202** was a phase 1b/2 trial that evaluated the safety and tolerability of cabozantinib and erlotinib administered in combination in non-small-cell lung cancer (NSCLC) subjects. Of the 64 subjects enrolled in the phase 1 dose-escalation portion of the study, all but two had been previously treated with and progressed on erlotinib therapy. A cPR was observed in 5 subjects (8%) and 24 subjects (37%) had SD/PR  $\geq 4$  months. The most common grade 3 or higher AEs in the phase 1 portion included diarrhea (44%), fatigue (22%), hypokalemia (11%), decreased appetite (6%), dyspnea (14%), lipase increase (6%), hypomagnesemia (6%), and dehydration (5%). Twenty-eight subjects were enrolled in the phase 2 portion of the study, in which subjects who had received clinical benefit from erlotinib and subsequently experienced progressive disease (PD), received single-agent cabozantinib or cabozantinib with erlotinib. AEs  $\geq$  grade 3 included dehydration (8%) and hypertension (8%). One patient, who was treated with single-agent cabozantinib, had a cPR.

In the phase I part of this trial (study 9243/12C0204), 20 patients were treated at 3 dose levels (4 at 20 mg, 8 at 40 mg, and 7 at 60 mg) of cabozantinib in combination with docetaxel and prednisone. The MTD of cabozantinib in combination with docetaxel and prednisone was determined to be 40mg. Two DLTs occurred in the 60 mg cabozantinib cohort. One DLT was febrile neutropenia and the other was grade 2 intolerable hand/foot syndrome. The median age was 68 years old (44-84 yrs). The median baseline PSA was 94.7 ng/mL (0.01-754.1 ng/mL). Median Gleason score was 9 (7-10). Median number of cycles was 9.5 (1-33). Common grade 2 and grade 3 adverse events possibly related to cabozantinib were: hand/foot syndrome (4/16), oral mucositis (4/16), hypophosphatemia (4/16), and fatigue (3/16).

#### 2.2.2.2 Phase 2 Studies

In a phase 2 study, **XL184-201**, subjects with progressive or recurrent GB in first or second relapse were enrolled to receive cabozantinib qd as a single agent. Group A received an initial dose of 175 mg (Group A), subsequent cohorts (Groups B and C) received an initial dose of 125 mg. Forty-six subjects were enrolled in Group A, and a total of 176 subjects were enrolled in Groups B/C. Fifty-seven subjects experienced one or more serious adverse events (SAEs) that were assessed to be related to treatment, including five fatal related.

Study **XL184-203** is a phase 2 randomized discontinuation trial. Subjects are enrolled into one of nine tumor-specific cohorts: breast cancer, gastric/gastroesophageal (GEJ) cancer, hepatocellular carcinoma (HCC), melanoma, NSCLC, ovarian cancer, pancreatic cancer, prostate cancer, and small cell lung cancer (SCLC). Eligible subjects with advanced solid tumors receive open-label cabozantinib at starting dose of 100 mg qd for 12 weeks. Of the 531 subjects enrolled in this study as of May 2011, 92 experienced one or more SAEs that were assessed to be related to treatment with cabozantinib, including seven fatal related SAEs. Randomization was suspended in the CRPC and ovarian cancer cohorts based on observed high rates of clinical activity, and randomized subjects were unblinded. At the last interim analysis, 171 patients with CRPC had been accrued to the study. DCR at week 12 was 68% with 0 of 171 subjects achieving CR, 7 achieving confirmed PR and the remainder with stable disease. Given the encouraging result, a non randomized extension (NRE) cohort was opened for CRPC patients to be evaluated at 100 mg and 40 mg daily doses sequentially. As of June 2012, results were available for 93 CRPC patients treated at 100 mg daily cabozantinib in the extension cohort, 62 (67%) had a bone scan response<sup>27</sup>. 4 were CRs and 58 were PRs. 15 of these patients also showed stable disease on bone scan. The median duration of response was 5.4 (5.0 – 6.9) months. 84 % of patients experienced at least one dose reduction due to adverse events. One patient with extensive liver disease experienced a related grade 3 portal vein thrombosis with grade 5 liver failure. Preliminary evidence supports clinical activity at 40 mg<sup>28</sup>. Study **XL184-205** is a randomized phase 2 trial for subjects with grade IV astrocytic tumors in first or second relapse. Subjects received one of four regimens: 25 mg qd (Arm 1) continuously, 75 mg qd (Arm 2) continuously, 125 mg qd for 2 weeks followed by 50 mg qd continuously (Arm 3), and 125 mg qd on an intermittent 3 week on/1 week off schedule (Arm 4). A total of 19 subjects were accrued before the study was terminated. Three subjects were rolled over to maintenance Study XL184-900. One subject experienced an SAE assessed to be related to treatment with cabozantinib.

Study **XL184-301** is a blind trial for subjects with unresectable, locally advanced or metastatic MTC, randomized 2:1 to cabozantinib or placebo. SAEs reported in Study XL184-301 are: one grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), one grade 5 cardiac arrest following asystolic vagal reaction after aspiration on study medication, and three SAEs of acquired trachea-esophageal fistula (two grade 3, one grade 5).

#### 2.2.2.3 Phase 3 Studies

COMET-1 is a randomized, double blind phase 3 trial of cabozantinib in men with metastatic castration-resistant prostate cancer (mCRPC) who had previously been treated with and progressed after treatment with docetaxel, abiraterone and/or enzalutamide. The primary endpoint of the trial was overall survival, and the secondary endpoint was bone scan response as assessed by an independent radiology committee. All patients in the trial had bone metastases,

and there was no limit to the number or type of prior treatments. Patients were randomized 2:1 to receive cabozantinib (60 mg daily) or prednisone (5 mg twice daily). The trial did not meet its primary endpoint of demonstrating a statistically significant increase in overall survival for patients treated with cabozantinib as compared to prednisone. The median overall survival for the cabozantinib arm of the trial was 11.0 months versus 9.8 months for the prednisone arm (hazard ratio 0.90; 95% confidence interval 0.76 – 1.06; p value 0.212).<sup>29</sup>

In the randomized, double-blind phase 3 COMET-2 trial ((NCT01522443), 119 men with progressive mCRPC after treatment with docetaxel, abiraterone, and/or enzalutamide, with moderate to severe pain were randomized in a 1:1 fashion to cabozantinib 60 mg po once daily or mitoxantrone and prednisone (12 mg/m<sup>2</sup> every 3 weeks and prednisone 5 mg every 12 hours).<sup>30</sup> The primary endpoint was pain response. The secondary endpoints were bone scan response and overall survival. The primary endpoint of improving pain was not achieved with pain response rates of 15% for cabozantinib vs. 17% for mitoxantrone and prednisone (P = 0.773). The bone scan response rates were 31% for cabozantinib vs. 5.2 % for mitoxantrone and prednisone. The median overall survival was 9 months for cabozantinib vs 7.9 months for mitoxantrone and prednisone.

While the results of both the COMET-1 and COMET-2 trials were negative, both of these studies utilized cabozantinib as a single agent. We hypothesize the addition of the multikinase inhibitor cabozantinib to docetaxel and prednisone could potentially minimize tumor resistance by targeting different cellular signaling pathways without overlapping toxicities. Additionally, emerging clinical data suggests mCRPC patients treated with anti-androgen therapy like abiraterone or enzalutamide have decreased responses to subsequent therapy with docetaxel due to cross-resistance in the androgen pathway targeted by docetaxel, abiraterone, or enzalutamide.<sup>31</sup>

#### **2.2.2.4 Adverse Events**

The clinical studies with XL184 are ongoing and thus the AE data from the clinical database as of March 1, 2011 and May 4, 2011 do not yet include all SAEs (Exelixis Communication, 2011). As of March 2011, AE data are available for 913 subjects who have been dosed with XL184 (806 in single-agent studies and 107 in combination studies of XL184 with erlotinib, rosiglitazone, or TMZ ± radiation) (Investigator's Brochure, 2011). Data from the 806 subjects who received single-agent XL184 show that the most frequently (>20%) observed AEs regardless of causality were fatigue, diarrhea, nausea, decreased appetite, constipation, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, dysphonia, and hypertension. Effects that may be related to the inhibition of VEGF, including hypertension, thromboembolic events, GI perforation, fistula formation, hemorrhage, wound dehiscence, and proteinuria, have been observed in the single-agent and combination XL184 studies. The most commonly reported SAEs that were assessed as related to study treatment with XL184 (as a single-agent or combination) were pulmonary embolism (PE), diarrhea, dehydration, deep vein thrombosis (DVT), vomiting, nausea, thrombocytopenia, fatigue, wound dehiscence, and PPE syndrome.

Grade 5 AE data are available for 1404 subjects who have been dosed with cabozantinib as a single agent (1286) or in combination (118) through June 1, 2012. There have been 27 grade 5 AEs related to study treatment: GI hemorrhage (two subjects), pulmonary hemorrhage (one subject), esophageal hemorrhage (one subject), PE (two subjects), respiratory failure (three subjects), respiratory disorder (one subject), hemoptysis (one subject), death due to unknown

cause (four subjects), intracranial hemorrhage (one subject), intestinal perforation (one subject), enterocutaneous fistula (one subject), tracheo-esophageal fistula (one subject), esophageal fistula (one subject), hemorrhage (two subjects), hepatic failure (one subject), bronchopneumonia (one subject) cardiac arrest (one subject), sepsis (one subject), and diverticular perforation, peritonitis (one subject) (Exelixis Communication). The initial daily doses of drug in these subjects were 100 mg (8 subjects), 125 mg (8 subjects), 175 mg (11 subjects). In 2 subjects, the initial dose of 125 mg was reduced to 50 and 75 mg respectively prior to death.

#### 2.2.2.5 Pharmacokinetics

Pharmacokinetic analysis of 74 patients in trial **XL184-001** showed dose proportional increases in maximum plasma concentration ( $C_{max}$ ) and AUC both for PIB (dose range 0.08-11.52 mg/kg) and the capsule formulation (dose range: 125 to 175 mg)<sup>26</sup>. Terminal-phase half-life ( $t_{1/2,z}$ ) values were 59.1 to 136 hours (Investigator's Brochure, 2011). After repeat dosing,  $t_{1/2,z}$  values (mean  $\pm$  standard deviation) for XL184 were  $91.3 \pm 33.3$  hours ( $n = 23$ ), and apparent steady-state plasma levels were reached by Day 15<sup>26</sup>. Steady-state clearance for the 175 mg capsule dose derived from repeat dose data was  $4.2 \pm 1.5$  L/h. Patients who received 175 mg capsules had four- to five-fold higher steady-state exposure (AUC) compared with Day 1 ( $7.68 \pm 2.85$  mcg·h/mL;  $n = 23$  vs.  $41.6 \pm 15.3$  mcg·h/mL;  $n = 23$ ), indicating that XL184 accumulated with repeat daily dosing. There was no significant difference in exposure between patients with MTC and those without MTC.

Based on the preliminary PK data from 23 subjects in **XL184-005** who completed both treatments, after a single oral dose of cabozantinib at 100 mg, the terminal  $t_{1/2,z}$  of cabozantinib appeared to be similar for both tablet and capsule formulations, with approximately mean values of 110 hours (Exelixis Communication, 2012). The median time to the maximum plasma concentration ( $t_{max}$ ) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for  $C_{max}$  and the area under the plasma drug concentration time curve (AUC) values were observed for both formulations (coefficient of variation [CV]%  $C_{max}$ : 51% for the tablet formulation, 61% for the capsule formulation; CV% for the AUC from time zero to the last quantifiable timepoint or to infinity [ $AUC_{0-last}$  or  $AUC_{0-inf}$ ]: 40-43% for the tablet formulation, 43% for the capsule formulation). The geometric mean  $C_{max}$  of the tablet formulation was approximately 39% higher than the value observed for the capsule formulation. The geometric mean  $AUC_{0-last}$  and  $AUC_{0-inf}$  values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high within-formulation variability observed, no statistical difference in exposure between the two formulations was apparent.

Based on the preliminary PK data from 46 subjects who completed both treatments on trial **XL184-004**, a high-fat meal did not appear to alter the terminal  $t_{1/2,z}$  of cabozantinib [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 cabozantinib  $C_{max}$  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  $AUC_{0-last}$  fed/fasted was 1.56 (90% CI: 1.34-1.80). Based on this result, cabozantinib must be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

## 2.3 OTHER AGENTS

### 2.3.1 Docetaxel with prednisone

#### Docetaxel as first-line treatment in metastatic CRPC

Docetaxel, a semi-synthetic taxane with the ability to disrupt microtubule dynamics, possesses potent antitumor activity in a variety of malignancies. Its mechanism in prostate cancer is thought to be two-fold. First, it acts as a microtubule stabilizer by binding preferentially to Beta-tubulin, leading to assembly of microtubules without GTP and other various cofactors. This leads to static polymerization, which disrupts the normal mitotic process, causing cell arrest in G2/M phase and ultimately leads to apoptosis. A second mechanism involves BCL-2, which is an oncoprotein that enhances tumor activity via inhibition of apoptosis. The stabilization of microtubule structure by docetaxel results in inactivation of BCL2 function via phosphorylation, which prevents binding to BAX. Increased free BAX induces activation of the caspase cascade leading to apoptosis.<sup>32</sup>

In 2004, both Tannock et al. and Petrylak et al. simultaneously published positive results from two randomized trials using docetaxel as backbone in metastatic CRPC. In TAX 327, the median survival improved from 16.5 months to 18.9 months in patients receiving docetaxel and prednisone every three weeks, as compared to patients who received mitoxantrone and prednisone. Docetaxel also effectively decreased PSA ( $P < 0.001$ ), relieved pain associated bone metastases ( $P = 0.01$ ), as well improved quality of life ( $P = 0.005$ ).<sup>33</sup> With an extended follow-up, this survival benefit has persisted. In an updated report, median survival was 19.2 months in the docetaxel arm, as compared to 16.3 months in the mitoxantrone arm. More patients survived at 3 years in the docetaxel arm (18.6%) compared with those in the mitoxantrone arm (13.5%).<sup>4</sup> Similar benefit was also observed in SWOG 9616 where the median survival in docetaxel and estramustine arm surpassed that of mitoxantrone arm by 1.9 months (17.5 vs. 15.6 months;  $P = 0.02$ ).<sup>3</sup>

These two large randomized studies were the first to demonstrate survival benefit after long battle for active chemotherapeutic agents for men with metastatic CRPC. Undoubtedly, docetaxel is effective in this disease. However, the survival improvement is modest with only 5.9% (86.5% vs. 81.4%) reduction in the rate of death at 3 years with limited survival advantage of 2.9 months<sup>4</sup>. New strategies are clearly needed to increase the number and duration of the response.

More recently, trials have examined the use of intermittent taxane therapy as a possible mechanism to overcome resistance to these agents<sup>33,34</sup>. Perhaps more practically, “drug holidays” may improve the quality of life for patients and allow them to recover from the cumulative toxicity of the chemotherapeutic agents during this period<sup>35-37</sup>. There have been several trials in prostate cancer that have examined this intermittent approach to chemotherapy and have seen favorable results. In a study of 250 patients randomized to 36 mg/m<sup>2</sup> of docetaxel weekly with high dose calcitriol vs. placebo, arbitrary guidelines were set to have a PSA decline  $> 50\%$  and  $PSA \leq 4$  in order to qualify for a drug holiday. Of the 20% of patients who qualified, 90.9% were responsive to docetaxel up resumption of treatment<sup>38</sup>. The NCI results from a phase II study involving docetaxel combined with antiangiogenic agents report a median OS of  $> 28$  months, which exceeds any contemporary trial that does not employ this intermittent strategy<sup>11,14</sup>.

Extensive preclinical and clinical research is ongoing in the identification of the drivers of disease progression. Multiple novel agents with distinct cellular or molecular targets or implications in tumor microenvironment are being assessed in clinical trials either as single agent or in combination with other effective agents.

## 2.4 RATIONALE

Given the superior clinical activity and unique molecular mechanism of cabozantinib in CRPC patients, we hypothesize that addition of cabozantinib to docetaxel and prednisone, in patients with metastatic CRPC, will bear acceptable toxicity profile given significant non-overlapping range of AEs and potentially minimize tumor resistance and improve survival by targeting different cellular pathways simultaneously. This combinational therapy with allowances for the incorporation of treatment holidays will represent a safe and effective strategy to maximize patients' benefit and further extend their survival.

In phase II randomized discontinuation trial, cabozantinib, as a single agent, was dosed at 100 mg once daily. No recommended dose for combination therapy has been defined. At 100 mg dose level, high incidence of fatigue (9%), hand-foot syndrome (8%), and HTN (5%) were noted in all advanced solid tumors patients<sup>39</sup>. Similar rate of adverse events (AEs) were also observed in CRPC cohort with Grade 3/4 AEs being fatigue (11%), HTN (7%), and hand-foot syndrome (5%).<sup>40</sup> The rate of dose reductions and permanent discontinuations of cabozantinib for AEs occurred in 41% and 12% of all patients, and 51% and 10% in CRPC cohort, respectively.<sup>39,40</sup> Thus, we propose to conduct a phase I study to define the MTD of cabozantinib when in combination with docetaxel and prednisone. In particular, cabozantinib will be examined at three dose levels (20 mg, 40 mg, and 60 mg qd) with an expansion cohort at MTD. A dose (-1) of 20 mg qod will be studied if DLT is seen at the 20 mg dose level.

### 2.4.1 Rationale for evaluating Docetaxel and prednisone vs. Docetaxel and Prednisone with Cabozantinib

Emerging clinical data suggests that mCRPC patients treated with modern anti-androgen therapy such as enzalutamide or abiraterone have decreased responses to subsequent therapy. This is likely due to cross-resistance in the androgen pathway which is targeted by these agents as well as docetaxel<sup>31</sup>. Three separate retrospective analyses demonstrated a median progression free survival of 4.6 months or less in patients who were treated with docetaxel after progression on abiraterone<sup>41-43</sup>. The median overall survival in two of these studies was found to be less than 13 months<sup>41,42</sup>. Although these studies are small and retrospective, they share a consistent and uniform finding that docetaxel and prednisone have limited benefits after disease progression on abiraterone.

On the phase I portion of this study, a total of 19 patients were enrolled. Seventeen patients were evaluable (one patient withdrew due to travel and a second patient was not evaluable due to a fall injury). For the 17 patients, median progression free survival is 12.1 months; 6 month PFS is 76.0% (95% CI: 52.0%-90.3%), 12 month PFS is 55.3% (95% CI: 31.9% - 76.6%). For the 14 patients who received abiraterone or enzalutamide, median PFS is 13.6 months; 6 month PFS is 77.9% (95% CI: 51.3% - 92.2%), 12 month PFS is 62.3% (95% CI: 36.3% - 82.8%). PFS results seen in this trial compare favorably to historical previously published data of treatment with docetaxel after progression on abiraterone in mCRPC, suggesting the addition of

cabozantinb to docetaxel may help overcome acquired resistance. Further studies will assess if there is a molecular signature that identifies patients benefiting from the cabozantinib plus docetaxel combination.

#### **2.4.2 CHAARTED Trial (Rationale for Modification of Exclusion Criteria)**

High-volume hormone-sensitive metastatic prostate cancer has historically been treated using hormonal therapy followed by chemotherapy. The disease however remained poorly prognostic in nature. A shift in the treatment paradigm of these patients occurred with the results of the Eastern Cooperative Oncology Group (ECOG) phase III randomized CHAARTED trial, which looked at whether the addition of upfront chemotherapy to hormonal therapy improved overall survival in patients with hormone-sensitive metastatic prostate cancer.

A retrospective subanalysis from this trial was reported by Dr. Christopher Sweeney from the Dana Farber Cancer Institute, at the 2014 American Society of Clinical Oncology (ASCO) Plenary Session.<sup>44</sup> In the CHAARTED trial, men with metastatic castrate-sensitive prostate cancer were randomized 1:1 to receive androgen deprivation therapy (ADT) alone or to ADT with chemotherapeutic drug docetaxel at 75 mg/m<sup>2</sup> every 3 weeks for 6 cycles to be started within 4 months of starting ADT. ADT plus docetaxel resulted in a median overall survival of 57.6 months (HR= 0.61; P = .0003) compared to 44 months in the ADT arm. Patients were stratified according to high-volume vs low-volume disease and the benefit for docetaxel therapy was found to be more apparent in the high-volume metastatic group vs the low-volume metastatic group.

Most patients with metastatic castrate-sensitive prostate cancer will progress to a castrate-resistant state. Previous evidence has also shown that upon progression, docetaxel confers an overall survival benefit.<sup>33</sup> However, it is unlikely that such survival benefit would be achieved in cases where a patient has already been treated with 6 cycles of docetaxel while castrate-sensitive. Given the very positive results of the CHAARTED trial and current shift towards initial treatment with docetaxel for high-volume hormone-sensitive metastatic disease, we propose amending protocol 12-C-0204 to address the initial treatment with docetaxel. If a patient has progressed on docetaxel chemotherapy in the castrate-sensitive state, then they will be excluded from this trial on the basis that re-treatment with docetaxel will not confer benefit to the metastatic castrate resistant patient. Additionally, if a patient has progressed to a castration-resistant state and received docetaxel, they will be excluded from this trial as re-treatment with docetaxel has not found to be of benefit in this patient population. Lastly, a time period of 6 months will be required between a patient's completion of the 6th cycle of docetaxel based on CHAARTED and the first dose of study treatment (cycle 1, day 1). This time period is based upon data seen in other solid tumor types, such as retreatment in ovarian cancer with platinum-based chemotherapies.

## **2.5 CORRELATIVE STUDIES BACKGROUND**

In addition to the studies listed below, eligible subjects on this protocol may participate in NCI protocol 12-C-0080. Participants in this study will undergo F-18 NaF PET/CT scanning at baseline (within 7 days prior to starting therapy). A subset of these patients (approximately 20) will undergo a second baseline scan within 2-5 days of the initial scan. All participants will then undergo subsequent NaF PET/CT scanning at week 8. These research imaging procedures will

be conducted in addition to the clinical imaging procedures listed in the study calendar in section **10**. The research radiation risks are discussed in the imaging protocol.

### **2.5.1 Genetic biomarkers:**

Single nucleotide polymorphisms (SNPs) in genes that play an important role in the drug metabolism and disposition of docetaxel and cabozantinib (via cytochrome P450 3A4 and ABCB1-mediated pathways) will be evaluated to correlate with efficacy and clinical outcomes. Functional SNPs in the *VEGFR2* gene could alter antiangiogenic treatment response or outcome by affecting the VEGF signaling pathways. Thus, we will determine if *VEGFR2* genetic variants may be correlated to toxicity and clinical outcomes as we have previously shown in patients treated with bevacizumab and sorafenib.<sup>45</sup>

### **2.5.2 Pharmacodynamic biomarkers:**

Plasma levels of several angiogenic biomarkers, including vascular endothelial growth factor-A (VEGF-A), soluble VEGFR2 (sVEGFR2), soluble c-Met (sMET), and placental growth factor (PIGF), have been shown to be significantly altered after single agent cabozantinib treatment (Investigator's Brochure). Plasma samples will be obtained to measure changes in the molecular markers of angiogenesis, as well as c-Met before and after administration of the combination. Urinary levels of c-met will also be measured as previous studies have reported it to be a potential marker of metastatic prostate cancer. The change in HGF, which is the only known ligand of c-Met, will be also measured as a marker for c-Met inhibition. The potential relationship between biomarker expression and tumor/PSA response will be explored.

### **2.5.3 Markers for bone activities:**

Crosslinked C-telopeptide of type I collagen (CTx) is a marker of osteoclast activity and bone resorption, while total Alkaline phosphatase (t-ALP) is a marker for osteoblast activity. The significant reduction of serum CTx and t-ALP by cabozantinib was reported in the CRPC cohort from a phase II randomized discontinuation trial.<sup>40</sup> Osteoclast mediated bone resorption can also be assessed by measuring urine N-telopeptide (uNTx), which has been reported as an independent prognostic factor for overall survival in patients with bone metastases from CRPC.<sup>46</sup> Samples will be obtained to determine changes in bone turnover from activation of both osteoblasts and osteoclasts.

### **2.5.4 Circulating Tumor Cells (CTC)**

The changes in CTC counts have been shown to be the most accurate and independent predictor of OS in CRPC. CTC enumeration at baseline and post-treatment is prognostic of survival and the shedding of cells into the circulation represents an intrinsic property of the tumor, distinct from extent of disease. Thus, CTC will be investigated before and after drug administration as an experimental endpoint. The data will be used to correlate with clinical response. Molecular determinants can also be identified and characterized in CTCs as potential predictive biomarkers of tumor sensitivity to therapeutic treatments. CTCs will be isolated at baseline and genetic analysis will be performed to determine androgen receptor (AR) expression and activity in tumor cells to further understand the clinical response to the combination treatment.



### 3 PATIENT SELECTION

#### 3.1 ELIGIBILITY CRITERIA

##### 3.1.1 Inclusion Criteria

**3.1.1.1** Must have metastatic, progressive, castrate resistant prostate cancer (CRPC). There must be radiographic evidence of disease after primary treatment with surgery or radiotherapy that has continued to progress radiographically or biochemically (rising PSA levels on successive measurements) despite adequate androgen-deprivation therapy, which is defined as having undergone bilateral surgical castration or continued treatment on GnRH agonists or antagonists..

Progression must be evidenced and documented by any of the following parameters:

1. Two consecutively rising PSA values, above the baseline, at a minimum of 1-week intervals
2. Appearance of one or more new lesions on bone scan
3. Progressive measurable disease by RECIST 1.1

The use of androgen receptor inhibitors is not required prior to study entry. For those patients receiving an anti-androgen agent (flutamide, bicalutamide, or nilutamide), for at least 6 consecutive months immediately prior to study entry, and are entering the trial due to a rise in PSA, they must demonstrate a continued rise in PSA within 4 weeks after stopping flutamide and within 6 weeks after stopping bicalutamide or nilutamide. Flutamide, nilutamide and bicalutamide disease progression requirements only apply to patients who have been on these drugs for at least the prior 6 months.

**3.1.1.2** Histopathological confirmation of prostate cancer by the Laboratory of Pathology of the NCI, Pathology Department of the Walter Reed National Military Medical Center or Yale is required prior to entering this study. Patients whose pathology specimens are no longer available may be enrolled if the patient has a clinical course that is consistent with prostate cancer and available documentation from an outside pathology laboratory of the diagnosis. All efforts should be made to have the material forwarded to the research team for use in correlative studies in cases where original tissue blocks or archival biopsy material is available.

**3.1.1.3** Patients must have metastatic disease, defined as at least one lesion on bone scan or at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as  $\geq 20$  mm with conventional techniques or as  $\geq 10$  mm with spiral CT scan, MRI, or calipers by clinical exam.

**3.1.1.4** Patients must have a performance status of 0 to 2 according to the ECOG criteria (see [Appendix A](#))

**3.1.1.5** Patients must have adequate bone marrow, hepatic, and renal function with:

- Hemoglobin  $\geq 9$  g/dL
- Leukocytes  $\geq 3000/\mu\text{L}$
- ANC  $\geq 1500/\mu\text{L}$ , without CSF support

- Platelets  $\geq 100,000/\mu\text{L}$
  - AST(SGOT)  $\leq 2.5 \times$  upper limit of normal (ULN);
  - ALT(SGPT)  $\leq 2.5 \times$  upper limit of normal (ULN);
  - Total serum bilirubin  $\leq$  the upper limit of normal (ULN).
  - Serum albumin  $\geq 2.8 \text{ g/dL}$
  - Serum phosphorus, calcium, magnesium, and potassium  $\geq$  LLN
  - Lipase  $< 2.0 \times$  the upper limit of normal and no radiologic or clinical evidence of pancreatitis
  - Creatinine  $\leq 1.5 \times$  institutional upper limits of normal
- OR
- Creatinine clearance of  $\geq 50 \text{ ml/min/1.73 m}^2$  for patients with creatinine levels above institutional normal by 24 hour urine.
  - Urine protein/urine creatinine ratio (UPCR)  $\leq 1$

**3.1.1.6** Patients must be at least 18 years of age. Because no dosing or adverse event data are currently available on the use of cabozantinib in combination with docetaxel and prednisone in patients  $< 18$  years of age, children are excluded from this study, but may be eligible for future pediatric trials.

**3.1.1.7** Patient must be capable of understanding and complying with protocol requirements and is willing to give informed consent

**3.1.1.8** Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of XL184 administration.

Sexually active subjects and their female partners must agree to use medically accepted barrier methods of contraception (eg, male or female condom) during the course of the study and for 4 months after the last dose of study drug(s), even if oral contraceptives are also used. All subjects of reproductive potential must also agree to use both a barrier method and a second method of birth control during the course of the study and for 4 months after the last dose of study drug(s). Should a woman become pregnant or suspect she is pregnant while her partner is participating in this study, she should inform her treating physician immediately.

**3.1.1.9** Patients enrolled on the randomized portion of the study must have had disease progression on arbiraterone or enzalutamide.

### **3.1.2 Exclusion Criteria**

- 3.1.2.1** The subject has had evidence within 2 years of the start of study treatment of another malignancy which required systemic treatment
- 3.1.2.2** The subject is unable to swallow tablets.
- 3.1.2.3** The subject has tumor invading (or there is concern for invasion of) major blood vessel.
- 3.1.2.4** The subject has active brain metastases or epidural disease. Subjects with brain metastases previously treated with whole brain radiation or radiosurgery or subjects with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 2 weeks before starting study treatment are eligible. Neurosurgical resection of brain metastases or brain biopsy is permitted if completed at least 3 months before starting study treatment. Baseline brain scans are not required to confirm eligibility.
- 3.1.2.5** The subject 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 ( $\leq 81$  mg/day), low-dose warfarin ( $\leq 1$  mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.
- 3.1.2.6** The subject has a corrected QT interval calculated by the Fridericia formula (QTcF)  $> 500$  ms within 28 days before initiation of protocol therapy. Note: if initial QTcF is found to be  $> 500$  ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is  $\leq 500$  ms, the subject meets eligibility in this regard.
- 3.1.2.7** Patients with contraindication to steroid use
- 3.1.2.8** Prior treatment with cabozantinib
- 3.1.2.9** The patient has received cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies) within 3 weeks, or nitrosoureas or mitomycin within 6 weeks before the first dose of study treatment.
- 3.1.2.10** The subject has received prior treatment with a small molecule kinase inhibitor or a hormonal therapy (including investigational kinase inhibitors or hormones) within 14 days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment with the exception of patients receiving prior abiraterone or ketoconazole. For patients receiving prior abiraterone or ketoconazole, they must discontinue the medication within 5 half-lives of the compound before the first dose of study treatment in order to participate in this study. Note: Subjects with prostate cancer currently receiving LHRH or GnRH agonists must be maintained on these agents.
- 3.1.2.11** The subject has received any other type of investigational agent within 28 days before the first dose of study treatment.
- 3.1.2.12** The subject has received radiation therapy:
- to the thoracic cavity or gastrointestinal tract within 3 months before the first dose of study treatment

- to bone or brain metastasis within 14 days before the first dose of study treatment
  - to any other site(s) within 28 days before the first dose of study treatment
- 3.1.2.13** The subject has received radionuclide treatment within 6 weeks prior to the first dose of the study treatment
- 3.1.2.14** The subject has not recovered to baseline or CTCAE  $\leq$  Grade 1 from toxicity due to all prior therapies, including surgery, except alopecia and other non-clinically significant AEs.
- 3.1.2.15** The subject has prothrombin time (PT)/ International Normalized Ratio (INR) or partial thromboplastin time (PTT) test results at screening  $\geq 1.3 \times$  the laboratory ULN within 7 days before the first dose of study treatment.
- 3.1.2.16** The subject has experienced any of the following:
- clinically-significant hematemesis or gastrointestinal bleeding within 6 months before the first dose of study treatment
  - hemoptysis of  $\geq 0.5$  teaspoon (2.5 mL) of red blood within 3 months before the first dose of study treatment
  - any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment
- 3.1.2.17** The subject has evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib.
- 3.1.2.18** The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
- a. Cardiovascular disorders including
    - i. Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening
    - ii. Concurrent uncontrolled hypertension defined as sustained BP  $>140$  mm Hg systolic, or  $> 90$  mm Hg diastolic despite optimal antihypertensive treatment (BP must be controlled at screening)
    - iii. Any history of congenital long QT syndrome
    - iv. Any of the following within 6 months before the first dose of study treatment:
      - unstable angina pectoris
      - clinically-significant cardiac arrhythmias
      - stroke (including TIA, or other ischemic event)
      - myocardial infarction
      - thromboembolic event requiring therapeutic anticoagulation (Note: subjects with a venous filter (e.g. vena cava filter) are not eligible for this study)
  - b. Gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
    - i. Any of the following within 28 days before the first dose of study treatment

- intra-abdominal tumor/metastases invading GI mucosa
  - active peptic ulcer disease
  - inflammatory bowel disease (including ulcerative colitis and Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis
  - malabsorption syndrome
- 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 than 6 months ago.
- c. 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.
- d. Other clinically significant disorders such as:
- i. active infection requiring intravenous treatment within 10 days of starting protocol treatment
  - ii. serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment
  - iii. history of organ transplant
  - iv. concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment
  - v. history of major surgery as follows:
    - (1) Major surgery within 3 months of the first dose of cabozantinib if there were no wound healing complications or within 6 months of the first dose of cabozantinib if there were wound complications
    - (2) Minor surgery within 1 months of the first dose of cabozantinib if there were no wound healing complications or within 3 months of the first dose of cabozantinib if there were wound complications

**In addition**, complete wound healing from prior surgery must be confirmed at least 28 days before the first dose of cabozantinib irrespective of the time from surgery

**3.1.2.19** HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with the study agents. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

**3.1.2.20** Patients who require taking drugs that are strong inhibitors/inducers of CYP3A4 and cannot be switched to an alternative medication.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as <http://medicine.iupui.edu/clinpharm/ddis/>; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Please refer to patient information sheet in **Appendix B**.

**3.1.2.21** Patients with greater than or equal to grade 2 peripheral neuropathy at baseline.

**3.1.2.22** The subject has had treatment with docetaxel for the treatment of metastatic castrate-sensitive prostate cancer within 6 months before the first dose of study treatment.

**3.1.2.23** The subject has had progression of prostate cancer during 6 cycles of prior docetaxel treatment for castrate sensitive disease.

**3.1.2.24** The subject has received chemotherapy for castration-resistant prostate cancer.

### **3.1.3 Inclusion of Women and Minorities**

Men of all races and ethnic groups are eligible for this trial. Women are excluded as prostate cancer does not exist in this population.

### **3.1.4 Recruitment Strategies**

The study will be posted on the CCR website and on clinicaltrials.gov

## **3.2 SCREENING EVALUATION**

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening before study treatment administration. Screening evaluations may be performed as part of an NIH Screening protocol. This does not include the baseline correlative studies that will only be performed after the patient has signed the consent form.

- To be performed 1 week prior to enrollment
  - History and physical exam including weight and vital signs
  - Tumor marker profile: PSA
- To be performed within 16 days prior to enrollment
  - CBC with differential and platelet count, prothrombin time/INR, activated partial thromboplastin time
  - Urinalysis and UPCR

- Electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH, ionized calcium, amylase, lipase, total protein, GGT
- Thyroid function tests – TSH, total T3, T4
- 12 lead ECG
- To be performed within 4 weeks prior to enrollment
  - CT scan of chest, abdomen, and pelvis
  - Technetium 99 bone scintigraphy scan
  - Testosterone (baseline only, test must be repeated if more than 8 weeks have elapsed between evaluation and C1D1); not required for patients with prior bilateral orchiectomy

## 4 REGISTRATION AND RANDOMIZATION PROCEDURES

### 4.1 REGISTRATION

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) [ncicentralregistration-1@mail.nih.gov](mailto:ncicentralregistration-1@mail.nih.gov). After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

#### 4.1.1 For Participating Site Registration

Registration will be a two-part process as patients are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section [5.9.2](#).

### 4.2 RANDOMIZATION (PHASE II ONLY)

After confirming eligibility, patients will be randomized on a 1:1 basis to receive either docetaxel alone or docetaxel with cabozantinib. Randomization will be performed by the CRO.

## 5 TREATMENT PLAN

### 5.1 PHASE I (CLOSED TO ACCRUAL AS OF AMENDMENT DATED 06-11-2014)

There are two components to this study. A Phase 1, single-arm, open-label, dose-escalation component will study cabozantinib combined with fixed dose docetaxel and prednisone in subjects with metastatic CRPC. This component will consist of two parts:

- A Dose Escalation part to determine the maximum tolerated dose (MTD). Subjects will accrue using a “3 plus 3” design. The evaluation of dose-limiting toxicity (DLT) as defined in Section 5.4 occurring within the first 6 weeks of treatment will be used to determine changes in dose levels. However, all available safety, PK, and pharmacodynamic data will be considered in the decision to dose escalate, dose de-escalate, or expand the current cohort. All patients will be treated with docetaxel at 75 mg/m<sup>2</sup> intravenously every three weeks on day 1 of each cycle as a cycle, and prednisone 5 mg PO BID on days 1-21. Patients will receive a daily cabozantinib dose of 20 mg in dose level 1, 40 mg in dose level 2, and 60 mg in dose level 3 throughout the cycle. If there are 2 or more DLTs at dose level 1, subjects will be enrolled on dose level -1 at 20 mg every other day. All patients will receive 8 mg of oral dexamethasone, 12 hours, 3 hours, and 1 hour before docetaxel infusion.
- An Expansion Stage. Once the MTD is determined, the study will enter the Expansion Stage in which up to an additional 6 subjects will be accrued (to a total of up to 24) in order to obtain additional safety, PK, and pharmacodynamic data at the MTD.

Patients will continue to receive study treatment as long as they do not experience disease progression and/or unmanageable side effects from the treatment.

### 5.2 PHASE II

A second component of this study will attempt to determine the relative efficacy of docetaxel, prednisone and cabozantinib at the MTD as compared to docetaxel and prednisone (standard of care) in mCRPC patients. In this study patients will be randomized to either of the two treatment regimens and then treated until disease progression.

### 5.3 AGENT ADMINISTRATION

Treatment will be administered primarily on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

| Dose Escalation Schedule |                       |
|--------------------------|-----------------------|
| Dose Level               | Dose Cabozantinib     |
| Level -1                 | 20 mg every other day |
| Level 1                  | 20 mg daily           |
| Level 2                  | 40* mg daily          |
| Level 3                  | 60 mg daily           |



**\*40mg daily has been determined to be the MTD and will be the dose in the dose escalation phase and the phase II randomized phase.**

| <b>REGIMEN DESCRIPTION</b>   |   |                     |                |                             |                      |
|--|---|---------------------|----------------|-----------------------------|----------------------|
| <b>Agent</b>   | <b>Premedications;<br/>Precautions</b>                                    | <b>Dose</b>         | <b>Route</b>   | <b>Schedule</b>             | <b>Cycle Length</b>  |
| Cabozantinib***  | none  | ** mg               | PO             | ** every other day or daily | 21 days<br>(3 weeks) |
| Docetaxel  | 8 mg of oral dexamethasone, 12 hours, 3 hours, and 1 hour before infusion | 75mg/m <sup>2</sup> | IV over 1 hour | Day 1 of each cycle         |                      |
| Prednisone   | Take with food or with milk to reduce stomach irritation.                 | 5 mg                | PO             | Twice daily                 |                      |
| <p>**Doses and intervals as appropriate for assigned dose level.</p> <p>*** Not all patients in the phase II portion will be treated with Cabozantinib – 20 patients will be on the combination arm and 20 on the single agent docetaxel arm</p> |   |                     |                |                             |                      |

### 5.3.1 Cabozantinib

Subjects will be instructed to take cabozantinib orally at the appropriate dose level once daily or every other day on a 21 day cycle. As indicated in section 9.1, the first dose of cabozantinib should be withheld until the last PK blood draw 24 hours after the docetaxel infusion; the cycle 2 day 1 dose should be taken just prior to the docetaxel infusion before PK samples are drawn. If a dose is missed, subjects should be instructed *not* to make it up on the following day. Cabozantinib should be taken on an empty stomach, 2 hours before taking cabozantinib and 1 hour after each cabozantinib dose patients should not eat. Subjects should be instructed not to crush or chew and to avoid both grapefruit and Seville orange products while on the study drug. Subjects will be instructed to notify their physician immediately of any and all AEs. Subjects experiencing one or more AEs due to the study treatment may require a dosing delay or reduction(s) in their dose in order to continue with study treatment.

### 5.3.2 Docetaxel

Prepare as indicated in section 8.2.1.3.

Docetaxel 75mg/m<sup>2</sup> will be administered intravenously over approximately 60 minutes on cycle 1 day 1 and repeated every 21 days (i.e. a 3-week cycle). All patients will receive 8 mg of dexamethasone orally 12 hours 3 hours and 1 hour prior to docetaxel infusion. If a patient misses a pretreatment dose of dexamethasone, he may receive dexamethasone 8 mg intravenously prior to docetaxel.

In the event of a hypersensitivity reaction, infusion times may be longer. Hypersensitivity reactions may be managed clinically according to PI discretion. Please see [Appendix C](#) for suggested management guidelines (optional).

To minimize patient exposure to phthalate plasticizers (e.g., DEHP), which may be leached from PVC containers and administration sets, administer docetaxel only through polyethylene-lined administration sets

### **5.3.3 Prednisone**

Prednisone should be taken orally twice a day, at 5mg for each dose. Prednisone should be taken at approximately the same time every day. The doses should be taken about 12 hours apart  $\pm$  2 hours. Gastric irritation may be reduced if taken before, during, or immediately after meals or with milk. If a dose of prednisone is missed (more than 14 hours have passed since the last dose), patients should be instructed not to make up the dose and to resume taking prednisone at the next scheduled dose.

### **5.3.4 Study Drug Accountability & Compliance**

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice.

The investigator will maintain accurate records of receipt of all cabozantinib, including dates of receipt (compliance form available in [Appendix D](#)). In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all unused cabozantinib will be reconciled, returned or destroyed in accordance with applicable state and federal regulations.

Drug accountability and subject compliance will be assessed with drug dispensing and return records.

## **5.4 DEFINITION OF DOSE-LIMITING TOXICITY**

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (v4.0). Dose limiting toxicities (DLTs) are defined as adverse events occurring during the first two cycles of therapy and related to the study medications (attributions: possible, probable, and definite) while fulfilling one of the following criteria:

1. Any Grade 3 or greater non-hematologic toxicity except asymptomatic grade 3 hypertension, hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, and asymptomatic grade 4 uric acid.
2. A treatment delay of > 2 weeks due to an adverse event (delays due to dental procedures are not included)
3. Grade 4 neutropenia (ANC<500/uL) lasting >5 days.
4. Febrile neutropenia

5. Grade 3 thrombocytopenia lasting for 7 days or more or thrombocytopenia < 50K/uL requiring platelet transfusion for bleeding will be considered dose limiting.
6. Any treatment related AEs that lead to dose reduction of either agent (duration or dose) in cycles 1 and 2 will be considered a DLT.

Anemia will not be considered a DLT.

Hypertension will only be considered a DLT if it is a grade 4 or if clinical management of hypertension as defined in **6.1.7.1** mandates a dose reduction.

With the exception of grade  $\leq 3$  fatigue and grade  $\leq 3$  reversible asymptomatic labs, the occurrence of a cabozantinib related DLT will lead to removal from protocol therapy unless patients can recover to grade 1 or baseline within 2 weeks. In such cases, patients may continue with protocol treatment with a dose reduction. In the cases of these exceptions, only 1 dose reduction will be permitted during the DLT evaluation period.

A subject will be replaced if the subject does not have a DLT but is not fully evaluable for DLT due to missing more than 25% in total of the dosing days due to progressive disease or reasons other than cabozantinib-related toxicity.

Because of the long half-life of cabozantinib, DLTs will be monitored for the first 6 weeks (during the first two cycles).

Management and dose modifications associated with the above adverse events are outlined in Section **6**.

Dose escalation will proceed in cohorts of 3–6 patients as defined in the table below. Patients may be accrued concurrently within a single dose level. Patients may be enrolled on the next higher dose level, provided that at least three patients on the previous dose level have completed at least 6 weeks of the combination treatment, and none have experienced a DLT. If one instance of DLT is observed among the initial 3 patients, 3 additional patients must be treated at this dose level without further DLT before escalation can proceed to the next dose level. If two instances of DLT are observed at a dose level, the MTD has been surpassed, and a total of 6 patients must be treated at the previous dose level. The MTD is defined at the dose level at which no more than 1 of 6 patients experiences DLT at the level below that which had two instances of DLT.

If a patient did not experience DLT and did not finish treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level.

Inpatient dose escalation may be allowed at the discretion of the principal investigator if the following conditions are met:

- a. there is no drug-related toxicity > grade 2 after 3 courses of study treatment at the initial dose level;
- b. the higher dose level has been completed by all patients in that cohort and no patients experienced a DLT
- c. there is no evidence of disease progression.

In addition, patients who have their dose escalated will not be evaluated for DLTs as they will have previously been evaluated for DLT at their initial dose level and will be more than 3 cycles into therapy.

Dose Escalation Table

| Number of Patients with DLT at a Given Dose Level                             | Escalation Decision Rule   |
|---|--|
| 0 out of 3  | Enter 3 patients at the next dose level.   |
| $\geq 2$  | Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.  |
| 1 out of 3  | Enter at least 3 more patients at this dose level. <ul style="list-style-type: none"> <li>• If 0 of these 3 patients experience DLT, proceed to the next dose level.</li> <li>• If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.</li> </ul> |
| $\leq 1$ out of 6 at highest dose level below the maximally administered dose | This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.   |

**5.5 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES**

Subjects must inform the investigators of the current or planned use of all other medications during the study (including prescription medications, vitamins, herbal and nutritional supplements, and over-the-counter medications).

**5.5.1 Concurrent Medications/Interventions**

**5.5.1.1 Anticancer Therapy**

If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention is discouraged unless medically unavoidable. Subjects receiving local intervention (e.g., palliative radiation) are allowed to continue to receive study treatment at the investigator's discretion.

**5.5.1.2 Other Medications**

Subjects must be instructed to inform the investigators of the current or planned use of all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements). It is the responsibility of the investigator to ensure that details regarding all medications are documented.

Bisphosphonates started prior to screening activities or initiated during the course of the study to control bone pain may be used with caution.

Colony stimulating factors (*e.g.*, erythropoietin and granulocyte colony-stimulating factors) administered as dictated by safety purposes are acceptable while the subject is enrolled on study. Pain medications administered as dictated by standard practice are acceptable while the patient is enrolled on the study.

No concurrent investigational agents are permitted.

### 5.5.1.3 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]/K<sub>i</sub> values compared to CYP2C8 (*i.e.*, 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. Strong CYP3A4 inducers such as rifampin, carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, St. John's wort and troglitazone 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 should be avoided 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.

Please consult a frequently-updated list such as <http://medicine.iupui.edu/clinpharm/ddis/> for a list of agents that interact with CYP3A4.

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/>).

**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.

**Drugs Associated with QTc Prolongation:** Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Caution should be used when treating subjects on cabozantinib with other drugs associated with QTc prolongation (see <http://www.qtdrugs.org>). Additional QTc monitoring is suggested for subjects who are treated concomitantly with QTc prolonging drugs.

**Other Interactions:** H<sub>2</sub> blockers may be taken concomitantly with cabozantinib with the exception of cimetidine, which should be avoided because of its potential to interfere with CYP3A4 mediated metabolism of cabozantinib. 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.

### **5.5.2 Supportive Care**

General guidelines for the management of cabozantinib related non-hematologic toxicities are provided in Section 6.1.1. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, skin disorders (PPE), embolism and thrombus, and hypertension, see below.

#### **5.5.2.1 Prophylaxis**

See section 5.3.2 for information on dexamethasone prophylaxis with docetaxel administration.

#### **5.5.2.2 Neutropenia**

Growth factors may be used as medically indicated if patient develops fever and neutropenia. Dose reduction or interruption of docetaxel is also recommended as described in section 6.2. Grade 4 febrile neutropenia will result in being removed from protocol therapy. See section 5.4.

### 5.5.2.3 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<sup>47</sup>. 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 Section 6.1.2.1. 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 not including cabozantinib, high fat meals and alcohol.

### 5.5.2.4 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 Section 6.1.2 if antiemetic treatment and/or prophylaxis alone is not adequate.

Agents classified as having the highest therapeutic index (such as 5-HT<sub>3</sub> receptor antagonists) per ASCO or MASCC/ESMO guidelines for anti-emetics in oncology or dexamethasone are recommended<sup>48-50</sup>. 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.

### 5.5.2.5 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.

### 5.5.2.6 Hepatobiliary Disorders

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. See section 6.1.3.1 for additional information.



### 5.5.2.7 Skin Disorders

All subjects on study should be advised on prophylactic measures for hand-foot syndrome including the use of emollients (Ammonium lactate 12% cream or heavy moisturizer twice daily), 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.

Urea 20% cream twice daily and clobetasol 0.05% cream once daily should be used in subjects that exhibit toxicity. NSAIDS, GABA agonists and opioids may be used for pain control.

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.

### 5.5.2.8 Embolism and Thrombosis

Low molecular weight heparin should be used to establish full anticoagulation in subjects on the first occurrence of a PE and/or DVT. Full anticoagulation with warfarin is not permitted and venous filters are not recommended. Treatment can be restarted at the discretion of the investigator. Subjects should permanently discontinue after a second thrombotic event.

Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

### 5.5.2.9 Hypertension

See instructions in Section [6.1.7.1](#)

## 5.6 ON STUDY ASSESSMENTS

Please see study calendar (section [10](#)) for schedule of the study assessments.

### 5.6.1 *Electrocardiogram (ECG) Assessments*

ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures. At any time point, if there is an increase in QTc interval to an absolute value > 500 msec using the Fridericia correction formula, two additional ECGs should be performed approximately 2 minutes apart, within 30 minutes. If the average QTc interval calculated by the Fridericia formula from the three ECGs is > 500 msec, study treatment must be withheld and a cardiology consultation is recommended for evaluation and subject management. Study treatment may only be continued if the QTc resolves to 500msec or less and per investigator



judgment that continued treatment is appropriate. Abnormalities in the ECG that lead to a change in subject management (e.g., dose reduced or withheld, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE CRF. If values meet criteria defining them as serious, they must be reported as SAEs. When an ECG time point coincides with other activities, the blood draw will be obtained at the scheduled time point, and the ECG will be collected first, followed by vital signs.

### **5.6.2 Vital Signs**

Vital signs (body temperature, respiratory rate, and blood pressure and pulse) will be conducted at regular intervals. Blood pressure and pulse will be measured after the subject has been sitting for at least 5 minutes.

When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled time point, and the vitals will be obtained as close to the scheduled blood draw as possible.

### **5.6.3 Physical Examinations**

A physical examination will include assessments of general appearance, skin, HEENT, thorax/lungs, cardiovascular, abdominal, genitourinary, musculoskeletal and neurological findings. Any pertinent findings should be documented either in the subject's medical history (if determined to be prior to the first dose of cabozantinib) or as an AE (if new or worsening after the first dose of cabozantinib).

### **5.6.4 Laboratory Assessments**

Laboratory assessments will include the following:

- Hematology:
  - CBC with differential
  - Reticulocytes (if indicated)
  - Erythrocyte sedimentation rate (if indicated)
- Serum chemistries:
  - Hepatic panel (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin)
  - Acute care panel (Sodium, Potassium, Chloride, Total CO<sub>2</sub> (Bicarbonate), Creatinine, Glucose, Urea nitrogen)
  - Mineral panel (Albumin, Calcium total, Magnesium total, Phosphorus)
  - Ionized calcium
  - Amylase
  - Lipase
  - Lactate dehydrogenase (LDH)
  - Total protein
  - $\gamma$ -glutamyltransferase (GGT)
- Urinalysis and UPCR
- Thyroid function tests - TSH, total T3 and T4
- PT/INR or PTT
- PSA

## 5.7 DURATION OF THERAPY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

## 5.8 DURATION OF FOLLOW UP

Once the patient is no longer receiving treatment (as per section 5.9.1), follow up evaluations as listed in the study calendar in section 10 will be conducted as appropriate per standard of care at the NCI or by the patient's physician. The patient may also receive follow-up calls to monitor his well-being and progress.

For patients who are taken off treatment due to treatment toxicities, a follow up evaluation will be conducted within a month and if appropriate, the subject will be taken off study.

## 5.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

### 5.9.1 *Criteria for removal from protocol therapy*

Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject from study treatment or from the study if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

In addition, any of the following conditions require withdrawal of the subject from study treatment:

- An AE or intercurrent illness that in the opinion of the investigator warrants the subject's withdrawal from treatment
- Necessity for treatment with other investigational drug or other anticancer medications prohibited by protocol
- Noncompliance with the protocol schedule
- Participation in another clinical study using anticancer agent(s)
- Occurrence of cabozantinib related DLT as defined in section 5.4 with the exceptions of grade 4 neutropenia lasting > 5 days, grade ≤ 3 fatigue and grade ≤ 3 reversible asymptomatic laboratory abnormalities
- Occurrence of any grade 3 or grade 4 non hematologic AE (except asymptomatic grade 3 hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, and asymptomatic grade 4 uric acid) during cycles 3 and beyond unless the subject is unequivocally deriving clinical benefit

- Occurrence of grade 4 febrile neutropenia
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under this protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 4 months following discontinuation of study treatment
- Inability to tolerate the administration of cabozantinib
- Cabozantinib treatment delays > 2 weeks during the DLT evaluation period
- Cabozantinib treatment delays > 2 weeks during cycles 3 and beyond unless the subject was unequivocally benefitting from cabozantinib treatment
- Progressive disease (PD)
- Investigator Discretion

The reason for study treatment discontinuation will be documented. For subjects who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol-specified follow-up procedures and end-of-treatment assessments, if possible, unless consent to participate in the study is also withdrawn.

If a subject fails to return for the protocol-defined visits, an effort must be made to determine the reason. If the subject cannot be reached by telephone, at the minimum a registered letter should be sent to the subject (or the subject's legal guardian) requesting contact with the clinic.

If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 30 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

### **5.9.2 Off Study Criteria**

- Investigator Discretion
- Manufacturer no longer able to supply study agent
- Completion of all study procedures
- Participant requests to be withdrawn from study
- Death
- Screen failure

If a subject withdraws consent to participate in the study, the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject, other than the determination of survival status from public records such as government vital statistics or obituaries.

### **5.9.3 Off Study Procedure**

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) main page must be completed and

sent via encrypted email to: NCI Central Registration Office (HOIS) [ncicentralregistration-l@mail.nih.gov](mailto:ncicentralregistration-l@mail.nih.gov).

### For Participating Sites

All subjects must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. An off-study form will be supplied by the CCR study coordinator. Send the completed off-study form to the CCR study coordinator.

## **6 DOSING DELAYS/DOSE MODIFICATIONS**

In general, the PI will attempt to attribute the toxicity to the most likely agent. In cases of overlapping toxicities (with the exception of hematologic toxicities) of cabozantinib and docetaxel, toxicities will be attributed to cabozantinib. Hematologic toxicities will be attributed to docetaxel due to the infrequency of their occurrence in studies with single agent cabozantinib.

Patients who require a treatment delay of >2 weeks, due to toxicities related to treatment, will permanently discontinue treatment on study.

Patients will remain on study in the case of unavoidable dental procedures that require a treatment delay of >2 weeks.

### **6.1 CABOZANTINIB**

Subjects will be monitored continuously for AEs throughout the study. **Subjects must be instructed to notify their physician immediately for any and all toxicities.**

General guidelines for the management of non-hematologic are provided in Table **6.1.1**. As a general approach, it is suggested that all AEs be managed with supportive care when possible at the earliest signs of toxicity. Calcium, magnesium, potassium and phosphorus should be kept above the lower limits of the laboratory normal values. For more specific guidelines on gastrointestinal AEs (diarrhea, nausea/vomiting, stomatitis/mucositis), hepatobiliary disorders, pancreatic disorders including lipase and amylase elevations, skin disorders (PPE), embolism and thrombus, hypertension, proteinuria, hemorrhage, rectal and perirectal abscess, gastrointestinal (GI) perforation and GI fistula, non-GI fistula, wound healing and surgery, osteonecrosis of the jaw (ONJ), endocrine disorders and management of treatment-emergent prolongation of the QTc interval, refer to the appropriate below. Guidance for the management of fatigue, anorexia, weight loss, eye disorders, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory/thoracic/mediastinal disorders and congenital, familial and genetic disorders can be found in the Cabozantinib Investigator's Brochure.

Dosing may need to be interrupted for AEs considered not related to cabozantinib if this is clinically indicated or if causality is initially uncertain. Study treatment may be resumed at the same dose (or a lower dose per investigator judgment) if the AE is determined not to be related to cabozantinib once the investigator determines that retreatment is clinically appropriate and the subject meets the protocol re-treatment criteria.

Dosing delays and modification instructions for cabozantinib non-hematologic toxicities are below. If study treatment of cabozantinib is restarted after being withheld or interrupted, the subject should be instructed not to make up the missed doses of cabozantinib.

If the subject does not recover from his or her toxicities to tolerable Grade  $\leq 2$  within  $\leq 2$  weeks, the subject will have study treatment permanently discontinued.

The minimum dose of study treatment will be 20 mg every other day. Subjects who cannot tolerate 20 mg every other day will have study treatment discontinued.

The reason for treatment delay and reduced dose must be recorded on the case report form (CRF).

### 6.1.1 General Guidelines for the Management of Cabozantinib-Related non-Hematologic Toxicities

| CTCAE Version 4 Grade  | Guidelines/Intervention   |
|--|---|
| <b>Grade 1:</b>  | Add supportive care as indicated. Continue cabozantinib at the current dose level   |
| <b>Grade 2:</b>  |   |
| Grade 2 AEs considered related to cabozantinib that are subjectively tolerable or easily managed   | Add supportive care as indicated. Continue cabozantinib at the current dose level.  |
| Grade 2 AEs considered related to cabozantinib that are intolerable to the subject or deemed unacceptable in the investigator's judgment; or are not easily managed or corrected | Dose Interruption and/or Dose Reduction <ul style="list-style-type: none"> <li>After dose reduction, if the AE does not resolve to Grade <math>\leq 1</math> or baseline in 7 to 10 days or worsens at any time, cabozantinib dosing should then be interrupted.</li> <li>If the AE resolves to baseline or Grade <math>\leq 1</math>, after dose interruption, cabozantinib may be resumed at either the same reduced dose or with another dose reduction at the discretion of the investigator.</li> <li>If this is a recurring event the dose should be reduced. If the AE resolves to Grade <math>\leq 1</math> or baseline without a dose interruption, continue the reduced dose.</li> </ul>  |
| <b>Grade 3:</b>  |   |
| Grade 3 AEs considered related to cabozantinib which occurred without optimal prophylaxis or which is easily managed by medical intervention or resolved quickly                 | <ul style="list-style-type: none"> <li>Interrupt cabozantinib and add supportive care as indicated</li> <li>For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade <math>\leq 1</math> within 24 hours, cabozantinib 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</li> <li>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 <math>\leq 1</math>, cabozantinib 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</li> </ul> |
| 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 $\leq$ Grade 1 or baseline, and resume treatment with a dose reduction  |
| <b>Grade 4:</b>  |   |
| Grade 4 AEs considered related to study treatment  | Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit and the subject is not within the DLT evaluation period (cycles 1 & 2). In this case, upon recovery to Grade $\leq 1$ or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator and sponsor but only with sponsor approval.   |

***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.***

## **6.1.2 Diarrhea, Nausea, Vomiting, Stomatitis, and Mucositis**

### **6.1.2.1 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. The dose modification guidance in Table 6.1.1 should be followed. 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.

### **6.1.2.2 Nausea and Vomiting**

Anti-emetic agents along with supportive care are recommended as clinically appropriate at the first sign of nausea and vomiting. The dose modification guidance in Table 6.1.1 should be followed.

The 5-HT<sub>3</sub> receptor antagonists are recommended over chronic use of NK-1 receptor antagonists and dexamethasone (NK-1 receptor antagonists can induce or inhibit CYP3A4, and glucocorticoids induce CYP3A4 and thus could lower cabozantinib exposure. Caution is also recommended with the use of nabilone, which is a weak inhibitor of CYP3A4.

### **6.1.2.3 Dehydration**

As of 26 August 2013 dehydration events have been identified with comparable incidence (9%) and occurring in a shorter time to onset in the blinded prostate cancer studies (median time to onset 38-46 days) than previously experienced with cabozantinib in the MTC development program (median time to onset 114.6 days). Extra monitoring/medical management including electrolyte monitoring and/or early dose reduction of patients exhibiting dehydration symptoms and those with risk factors for dehydration is indicated.

### **6.1.2.4 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.

### 6.1.3 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:

#### 6.1.3.1 Transaminase Elevations

| <b>Transaminase elevation<br/>CTCAE v4.0</b>                               | <b>Interventions</b>   |
|--|--|
| <b>Subjects with AST and ALT less than or equal to the ULN at baseline</b> |  |
| <b>Grade 1</b>   | Continue cabozantinib with weekly monitoring of liver function tests (LFTs) for at least 4 weeks. Then resume the standard protocol-defined monitoring of LFTs.  |
| <b>Grade 2</b>   | Continue cabozantinib 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 cabozantinib treatment. Then continue with at least weekly LFTs until resolution to Grade $\leq$ 1. Study treatment may then be resumed at a one-dose-level reduction of cabozantinib   |
| <b>Grade 3</b>   | Interrupt cabozantinib treatment and monitor with at least twice weekly LFTs until Grade $\leq$ 2. Then continue with at least weekly LFTs until resolution to Grade $\leq$ 1. Cabozantinib may then be resumed at a one-dose-level reduction.   |
| <b>Grade 4</b>   | Discontinue study treatment permanently. LFTs should be monitored as clinically indicated, at least 2-3 times per week, until resolution to Grade $\leq$ 1. If the subject was unequivocally deriving clinical benefit and the subject is not within the DLT evaluation period (cycles 1 & 2), the subject may be able to resume treatment at a lower dose of cabozantinib as determined by the investigator and sponsor but only with sponsor approval. |



| <b>Subjects with AST or ALT above the ULN at baseline</b>  |   |
|--|---|
| ≥ 1.5 fold increase of AST or ALT AND both AST and ALT are ≤ 5.0 x ULN   | Continue cabozantinib treatment with at least twice weekly monitoring of LFTs for 4 weeks and weekly 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 increase of AST or ALT and at least one of AST or ALT is Grade 3 (i.e. AST or ALT > 5.0 but ≤ 20.0 x ULN) | 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.  |
| <b>Grade 4</b>   | 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 and the subject is not within the DLT evaluation period (cycles 1 & 2), the subject may be able to resume treatment at a lower dose as determined by the investigator and sponsor but only with sponsor approval. |

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]). 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 2 weeks after 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.

#### **6.1.4 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 has 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.

### 6.1.4.1 Asymptomatic Lipase or Amylase Elevations

| <b>Asymptomatic Lipase or Amylase Elevations</b> |  |
|--|--|
| Grade 1 or Grade 2                               | Continue at current dose level. More frequent monitoring is recommended  |
| Grade 3  | <ul style="list-style-type: none"><li>• Interrupt treatment</li><li>• Monitor lipase and amylase twice weekly</li><li>• Upon resolution to Grade <math>\leq</math>1 or baseline, cabozantinib may be restarted at the same dose or at a reduced dose provided that this occurs within 2 weeks.</li><li>• If retreatment following Grade 3 lipase or amylase elevation is at the same dose and Grade 3 or Grade 4 elevations recur, then treatment must be interrupted again until lipase and amylase levels have resolved to Grade <math>\leq</math>1 or baseline and retreatment must be at a reduced dose</li></ul>  |
| Grade 4  | <ul style="list-style-type: none"><li>• If occurring within the DLT evaluation period, permanently discontinue cabozantinib</li></ul> Otherwise: <ul style="list-style-type: none"><li>• Interrupt treatment</li><li>• Monitor lipase and amylase twice weekly</li><li>• Upon resolution to Grade <math>\leq</math> 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 2 weeks.</li><li>• 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 <math>\leq</math> 1 or baseline and retreatment must be at a reduced dose.</li></ul> |

### 6.1.4.2 Pancreatitis

| Pancreatitis                    |   |
|---------------------------------|---|
| Grade 2 and asymptomatic        | Continue at current dose level. More frequent monitoring of lipase and amylase and radiographic evaluation is recommended   |
| Grade 2 symptomatic and Grade 3 | <ul style="list-style-type: none"> <li>• If grade 3 pancreatitis occurs during DLT evaluation period, permanently discontinue cabozantinib</li> </ul> Otherwise: <ul style="list-style-type: none"> <li>• Interrupt treatment</li> <li>• Monitor lipase and amylase twice weekly</li> <li>• Upon resolution to Grade <math>\leq</math>1 or baseline, cabozantinib may be restarted at a reduced dose if resolution occurred within 2 weeks</li> </ul> |
| Grade 4                         | Permanently discontinue treatment. However, if the subject was unequivocally deriving benefit from cabozantinib therapy and the subject is not within the DLT evaluation period (cycles 1 & 2), treatment may resume at a reduced dose agreed to by the investigator and sponsor but only with sponsor approval.  |

### 6.1.5 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 in cabozantinib-treated subjects. All subjects on study should be advised to use prophylactic measures for skin care. These measures include the use of hypoallergenic moisturizing creams, ointment for dry skin, sunscreen with SPF  $\geq$ 30; avoidance of exposure of hands and feet to hot water; protection of pressure-sensitive areas of hands and feet; and use of thick cotton gloves and socks to prevent injury and to keep the palms and soles dry. Subjects with skin disorders should be carefully monitored for signs of infection (*e.g.*, abscess, cellulitis, or impetigo).

Early signs of hand-foot syndrome can include tingling, numbness, and slight redness or mild hyperkeratosis. Early manifestations include painful, symmetrical red and swollen areas 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.

Treatment guidelines for PPE related to study treatment are presented in the table below.

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.

| <b>6.1.5.1 Hand-Foot Skin Reaction and Hand Foot Syndrome (PPE)</b> |   |
|---|---|
| Grade 1   | Continue cabozantinib at current dose. 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.  |
| Grade 2   | If tolerable, continue cabozantinib at current dose. If intolerable, reduce cabozantinib dose to next lower level and/or interrupt dosing. Start/continue urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Add analgesics for pain control with NSAIDs/GABA agonists/narcotics if needed. Assess subject at least weekly for changes in severity. If treatment was interrupted (but not reduced), treatment may be restarted at the same dose or at one dose level lower when reaction decreases to Grade 1 or 0. If a treatment interruption is again required, the dose must be reduced when treatment resumes. Subjects should be instructed to notify investigator immediately if severity worsens. If severity worsens at any time, or affects self-care, proceed to the management guidelines for Grade 3 PPE. |
| 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 unless the subject was unequivocally deriving clinical benefit. In this situation, the subject may be able to resume treatment at a lower dose as determined by the investigator / principal investigator and Sponsor, but only with Sponsor approval.  |

GABA,  $\gamma$ -aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drugs; PPE, palmar-plantar erythrodysesthesia

### 6.1.6 Thromboembolic Events

Deep vein thrombosis and PE have been observed in clinical studies with cabozantinib; including fatal events (please refer to the IB). Unless DLT as defined in Section 5.4, subjects who develop a PE or DVT should have study treatment held until therapeutic anticoagulation with heparins is established. Study treatment may be resumed with a one dose-level reduction in subjects who have uncomplicated PE or DVT and are deriving clinical benefit from study treatment. During treatment with anticoagulants, subjects need to be monitored on an ongoing basis for bleeding risk and signs of bleeding. Subjects with life-threatening PE or DVT should have study treatment discontinued unless toxicity can be managed and subject is deriving clear clinical benefit as determined by the investigator and agreed by the Sponsor. Venous filters (*e.g.* vena cava filters) are not recommended due to the high incidence of complications associated with their use. Once a subject is fully anticoagulated, treatment can be restarted per investigator judgment at one dose lower. Subjects should permanently discontinue after a second thrombotic event. Although routine prophylactic anticoagulation is not necessary for all subjects, prophylactic anticoagulation is allowed for individual subjects at the discretion of the investigator.

Arterial thrombotic events (*e.g.*, transient ischemic attack, myocardial infarction) have been observed rarely in studies with cabozantinib. Cabozantinib should be discontinued in subjects

who develop an acute MI or any other clinically significant arterial thromboembolic complication.

### 6.1.7 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. Subjects with known hypertension should be optimally managed prior to study entry. Clinical judgment should be used in deciding whether new or worsened hypertension emerging during treatment with cabozantinib requires immediate therapy, or whether therapeutic intervention can be delayed in order to confirm the finding of new or worsened hypertension at a second visit before taking new therapeutic action. It is recommended that this second visit occur within 1 week. 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 ( $\geq 180$  mm Hg systolic or  $\geq 120$  mm Hg diastolic; or sustained  $\geq 160$  mm Hg systolic or  $\geq 110$  diastolic) who cannot be controlled with medical interventions and discontinued in subjects with hypertensive crises or hypertensive encephalopathy. (See next Table below).

#### 6.1.7.1 Management of Hypertension Related to Cabozantinib

| Criteria for Dose Modifications   | Treatment/cabozantinib Dose Modification  |
|---|---|
| <b>Subjects not receiving optimized anti-hypertensive therapy</b>                                 |   |
| > 150 mm Hg (systolic) and < 160 mm Hg<br>OR<br>> 100 mm Hg (diastolic) and < 110 mm Hg           | <ul style="list-style-type: none"> <li>• Increase antihypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications)</li> <li>• Maintain dose of cabozantinib</li> <li>• If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure &lt; 150 systolic or &lt; 90 diastolic, or if the subject is symptomatic, the dose of cabozantinib should be reduced</li> </ul>  |
| $\geq 160$ mm Hg (systolic) and < 180 mm Hg<br>or<br>$\geq 110$ mm Hg (diastolic) and < 120 mm Hg | <ul style="list-style-type: none"> <li>• Interrupt and/or reduce cabozantinib by one dose level;</li> <li>• Increase antihypertension therapy (ie, increase dose of existing medications and/or add new antihypertensive medications);</li> <li>• Monitor subject closely for hypotension;</li> <li>• If optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure &lt; 150 systolic or &lt; 100 diastolic, dose of cabozantinib should be reduced further.</li> </ul> |
| $\geq 160$ mm Hg (systolic) OR<br>$\geq 100$ mm Hg (diastolic)                                    | <ul style="list-style-type: none"> <li>• Interrupt treatment with cabozantinib</li> <li>• Increase anti-hypertension therapy (i.e., increase dose of existing medications and/or add new antihypertensive medications)</li> <li>• Monitor subject closely for hypotension.</li> <li>• When SBP &lt;150 and DBP &lt;100, restart cabozantinib</li> </ul>   |

| Criteria for Dose Modifications   | Treatment/cabozantinib Dose Modification  |
|---|---|
|   | treatment at the same dose level. <ul style="list-style-type: none"> <li>• Once treatment is restarted, if optimal antihypertensive therapy (usually to include 3 agents) does not result in blood pressure &lt; 150 systolic or &lt; 100 diastolic, cabozantinib should be held and restarted at a lower dose when SBP &lt;150 and DBP &lt;100.</li> </ul> |
| Hypertensive crisis or hypertensive encephalopathy  | <ul style="list-style-type: none"> <li>• Discontinue all study treatment</li> </ul>   |
| 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 |   |

### 6.1.8 Proteinuria

Proteinuria has been reported with approved drugs that inhibit VEGF pathways as well as with cabozantinib. Any level of proteinuria diagnosed by dipstick should be quantified by a UPCR (mg/dL protein / mg/dL creatinine). When a UPCR exceeds 1, a repeat UPCR or a 24-hour urine protein and creatinine should be performed to confirm the result. Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria >3.5 g/day in combination with hypoalbuminemia, edema and hyperlipidemia) or any other relevant renal disease. Also, given the nephrotoxic potential of bisphosphonates, these agents should be used with caution in patients receiving treatment with cabozantinib. Details of management are described in Table 6.1.8.1 below.

### 6.1.8.1 Management of Treatment Emergent Proteinuria

| Urine Protein/Creatinine Ratio             | Action To Be Taken  |
|--|---|
| ≤ 1  | <ul style="list-style-type: none"> <li>No change in treatment or monitoring</li> </ul>  |
| > 1 and < 3.5                              | <ul style="list-style-type: none"> <li>No change in study treatment required</li> <li>Consider confirming with a 24-hour protein excretion within 7 days</li> <li>Repeat UPCR within 7 days and once every week. If UPCR is &lt; 1 on two consecutive readings, then UPCR monitoring can revert to protocol specific time points. (The second reading is a confirmatory reading and can be done within 1 week of the first reading.).</li> </ul>  |
| ≥ 3.5                                      | <ul style="list-style-type: none"> <li>Hold cabozantinib immediately and confirm with 24 hour urine protein excretion.</li> <li>If proteinuria of ≥ 3.5 g/24 hours is confirmed without diagnosis of nephrotic syndrome, continue to hold cabozantinib and monitor UPCR weekly. If UPCR decreases to &lt; 2, restart cabozantinib at a reduced dose. Continue monitoring UPCR once every week until two consecutive readings are &lt; 1, then revert to UPCR monitoring frequency specified in the protocol.</li> </ul> |
| Nephrotic Syndrome                         | <ul style="list-style-type: none"> <li>Discontinue cabozantinib treatment.</li> </ul>   |
| UPCR; urine protein/urine creatinine ratio |   |

### 6.1.9 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
- History of clinically significant hemoptysis

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis ( $\geq 0.5$  teaspoon (2.5ml) of red blood). Treatment with cabozantinib should be interrupted if less severe forms of clinically significant hemorrhage occur and, if it does not meet DLT criteria as defined in Section 5.4, 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 invading a major blood vessel while on study treatment must be discontinued from cabozantinib treatment.

#### **6.1.10 Rectal and Perirectal Abscesses**

These should be treated with appropriate local care and antibiotic therapy. Cabozantinib should be held until adequate healing has taken place unless  $\geq$  grade 3 and occurring in the first 2 cycles in which case cabozantinib should be permanently discontinued.

#### **6.1.11 Gastrointestinal Perforation and GI fistula**

Complete healing following abdominal surgery or resolution of intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

#### **6.1.12 Wound Healing and Surgery**

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 meeting DLT criteria as defined in Section 5.4. 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.

#### **6.1.13 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 (see Cabozantinib Investigator's Brochure). 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 required. Cabozantinib should be discontinued in subjects with severe or life-threatening endocrine dysfunction.

#### **6.1.14 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. Cases of osteonecrosis have been reported in subjects treated with cabozantinib, the details of which are provided in the current version of Investigator's Brochure. 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. Study treatment may be reinitiated if it does not meet DLT criteria as defined in section 5.4; however, reinitiation must be discussed with and approved by the Sponsor on a case by case basis.

#### **6.1.15 Guidelines for Management of Treatment-Emergent Corrected QT (QTc) Prolongation**

Treatment with cabozantinib has been associated with a mild prolongation of the QTc interval. Other factors which may contribute to QTc prolongation include

- Treatment with other drugs associated with QTc prolongation (see <http://www.qtdrugs.org>).
- Treatment with CYP 3A4 inhibitors (which may increase cabozantinib drug levels)
- Electrolyte changes (hypokalemia, hypocalcemia, hypomagnesemia).
- Medical conditions which can alter electrolyte status e.g., severe or prolonged diarrhea.

Subjects having any of these additional risk factors while on cabozantinib must have ECGs performed approximately one week after the onset of these factors.

If at any time on study there is an increase in QTc interval to an absolute value >500 msec, two additional ECGs should be performed within 30 minutes after the initial ECG with intervals not less than 3 minutes apart. If the average QTcF from the three ECGs is >500 msec, study treatment must be permanently withheld if this occurs during the DLT evaluation period. Otherwise, the following actions should be taken:

- Check electrolytes, especially potassium, magnesium and calcium. Correct abnormalities as clinically indicated.
- If possible, discontinue any QTc-prolonging concomitant medications.
- Repeat ECG triplets hourly until the average QTcF is  $\leq 500$  msec or otherwise determined by consultation with a cardiologist.

The Sponsor should be notified immediately of any QTc prolongation event.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation has resolved. Cardiology consultation is recommended for evaluation and subject management. Symptomatic subjects must be treated according to standard clinical practice. No additional study treatment is to be given to the subject until after the event has resolved, the subject has been thoroughly evaluated, and further treatment has been agreed to by the Sponsor. If any additional study treatment is given (e.g., after correction of electrolyte abnormalities and normalization of QTcF), it will be at a reduced dose as agreed to by the investigator and the Sponsor.

**6.1.16 Additional information for dose delays or dose reductions:**

Dose delays for reason(s) other than AEs related to cabozantinib, such as surgical procedures with no anticancer therapy intent, may be allowed with investigator approval. The acceptable length of interruption will be determined by the investigator.

**6.2 DOCETAXEL DOSE MODIFICATIONS**

Patients should have an ANC  $\geq 1500$  cells/mm<sup>3</sup>, a platelet count  $\geq 75,000$  cells/mm<sup>3</sup> (grade 1 hematologic toxicity) and resolution of any grade 3 or higher non-hematologic toxicity to  $\leq$  grade 1 or baseline in order to initiate another treatment cycle of docetaxel.

For febrile neutropenia developed within a prior cycle, docetaxel can be continued during future cycles at a dosage decreased by 25% and if indicated, with the addition of filgrastim support. For grade 4 neutropenia lasting greater than 5 days docetaxel will be held and patients will be treated with filgrastim support. Docetaxel will be resumed at the same dose once neutropenia has resolved to  $\leq$  grade 1 or baseline.

**Docetaxel Dose Modifications for Neutropenia without Fever:**

| When Neutrophils fall to            | for a Duration of  | Recommended Course  |
|-------------------------------------|--------------------|---|
| <1000 but $\geq 500$ /mcL (Grade 3) | Any length of time | No dose reduction for future cycles.  |
| <500/mcL (Grade 4)                  | $\leq 5$ days      | No dose reduction for future cycles.  |
| <500/mcL (Grade 4)                  | > 5 days           | No dose reduction. DOCETAXEL will be held and patients will be treated with filgrastim support. DOCETAXEL will be resumed at the same dose once neutropenia has resolved to $\leq$ grade 1 or baseline. |

For grade 3 constipation or grade 3 fatigue, treatment can resume with a 25% dose reduction after resolution of toxicity to  $\leq$  grade 1 or baseline. Patients will be allowed to continue docetaxel treatment at successively reduced doses as long as they do not have progressive disease, regardless of the time required for recovery from ADEs. For dose-limiting toxicities related to docetaxel that lead to withholding docetaxel temporarily, cabozantinib may be withheld along with docetaxel at the discretion of the investigators for the best interest and safety of patients. However, prednisone should not be interrupted.

### 6.3 STUDY DRUG DOSE HOLIDAYS

Patients may receive treatment indefinitely, but may have the doses of one or all drugs (docetaxel, cabozantinib or prednisone) withheld temporarily for resolution of toxicities or taking drug holidays, and potentially resume treatment as long as they do not fulfill the criteria for removal from protocol therapy outlined in section 5.9.1. The determination of a drug holiday will be at the discretion of the investigator.

## 7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2.1.1) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

### 7.1 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST (CAEPR) FOR

#### CABOZANTINIB S-MALATE (XL184, NSC 761968)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. *Frequency is provided based on 2438 patients.* Below is the CAEPR for XL184 (Cabozantinib s-malate).

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 4, 2016<sup>1</sup>

| Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438] |                     |                        | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|--|---------------------|------------------------|---|
| Likely (>20%)  | Less Likely (<=20%) | Rare but Serious (<3%) |   |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS   |                     |                        |   |
|  | Anemia              |                        |   |
| ENDOCRINE DISORDERS  |                     |                        |   |
|  | Hypothyroidism      |                        | <b><i>Hypothyroidism (Gr 2)</i></b>                         |
| GASTROINTESTINAL DISORDERS   |                     |                        |   |
|  | Abdominal pain      |                        | <b><i>Abdominal pain (Gr 3)</i></b>                         |
|  | Constipation        |                        | <b><i>Constipation (Gr 2)</i></b>                           |
| Diarrhea   |                     |                        | <b><i>Diarrhea (Gr 3)</i></b>                               |

| Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438] |   |   | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|--|---|---|---|
| Likely (>20%)  | Less Likely (<=20%)   | Rare but Serious (<3%)                            |   |
|  | Dry mouth   |   | <i>Dry mouth (Gr 2)</i>                                     |
|  | Dyspepsia   |   | <i>Dyspepsia (Gr 2)</i>                                     |
|  |   | Gastrointestinal fistula <sup>2</sup>             |   |
|  |   | Gastrointestinal hemorrhage <sup>3</sup>          |   |
|  |   | Gastrointestinal perforation <sup>4</sup>         |   |
|  | Mucositis oral  |   | <i>Mucositis oral (Gr 3)</i>                                |
| Nausea   |   |   | <i>Nausea (Gr 3)</i>  |
|  | Oral pain   |   | <i>Oral pain (Gr 2)</i>                                     |
| Vomiting   |   |   | <i>Vomiting (Gr 3)</i>                                      |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS   |   |   |   |
|  | Edema limbs   |   |   |
| Fatigue  |   |   | <i>Fatigue (Gr 3)</i>                                       |
| INFECTIONS AND INFESTATIONS  |   |   |   |
|  | Infection <sup>5</sup>  |   |   |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS   |   |   |   |
|  |   | Wound complication                                |   |
| INVESTIGATIONS   |   |   |   |
|  | Alanine aminotransferase increased                                      |   | <i>Alanine aminotransferase increased (Gr 3)</i>            |
|  | Aspartate aminotransferase increased                                    |   | <i>Aspartate aminotransferase increased (Gr 3)</i>          |
|  | Lipase increased  |   | <i>Lipase increased (Gr 4)</i>                              |
|  | Platelet count decreased  |   | <i>Platelet count decreased (Gr 3)</i>                      |
| Weight loss  |   |   | <i>Weight loss (Gr 3)</i>                                   |
| METABOLISM AND NUTRITION DISORDERS   |   |   |   |
| Anorexia   |   |   | <i>Anorexia (Gr 3)</i>                                      |
|  | Dehydration   |   |   |
|  | Hypocalcemia  |   |   |
|  | Hypokalemia   |   |   |
|  | Hypomagnesemia  |   |   |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS  |   |   |   |
|  | Arthralgia  |   |   |
|  | Musculoskeletal and connective tissue disorders - Other (muscle spasms) |   |   |
|  |   | Osteonecrosis of jaw                              |   |
|  | Pain in extremity   |   |   |
| NERVOUS SYSTEM DISORDERS   |   |   |   |
|  | Dizziness   |   |   |
| Dysgeusia  |   |   | <i>Dysgeusia (Gr 2)</i>                                     |
|  | Headache  |   |   |
|  |   | Reversible posterior leukoencephalopathy syndrome |   |

| Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 4.0 Term) [n= 2438] |   |                                  | Specific Protocol Exceptions to Expedited Reporting (SPEER)                       |
|--|---|----------------------------------|---|
| Likely (>20%)  | Less Likely (<=20%)   | Rare but Serious (<3%)           |   |
| RENAL AND URINARY DISORDERS  |   |                                  |   |
|  | Acute kidney injury   |                                  |   |
|  |   | Proteinuria                      |   |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS  |   |                                  |   |
|  | Cough   |                                  |   |
|  | Dyspnea   |                                  |   |
|  |   | Pneumothorax <sup>6</sup>        |   |
|  |   | Respiratory fistula <sup>7</sup> |   |
|  | Respiratory hemorrhage <sup>8</sup>                                 |                                  |   |
| Voice alteration   |   |                                  | <i>Voice alteration (Gr 3)</i>  |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS   |   |                                  |   |
|  | Alopecia  |                                  |   |
|  | Dry skin  |                                  | <i>Dry skin (Gr 2)</i>  |
| Palmar-plantar erythrodysesthesia syndrome   |   |                                  | <i>Palmar-plantar erythrodysesthesia syndrome (Gr 3)</i>                          |
|  | Rash maculo-papular   |                                  | <i>Rash maculo-papular (Gr 3)</i>   |
|  | Skin and subcutaneous tissue disorders - Other (hair color changes) |                                  | <i>Skin and subcutaneous tissue disorders - Other (hair color changes) (Gr 2)</i> |
| VASCULAR DISORDERS   |   |                                  |   |
| Hypertension   |   |                                  | <i>Hypertension (Gr 3)</i>  |
|  | Thromboembolic event <sup>9</sup>                                   |                                  |   |

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

<sup>3</sup>Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

<sup>4</sup>Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

<sup>5</sup>Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

<sup>6</sup>Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

<sup>7</sup>Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

<sup>8</sup>Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

<sup>9</sup>Thromboembolic event includes pulmonary embolism which may be life-threatening.

**Adverse events reported on XL184 (Cabozantinib s-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib s-malate) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome  
**CARDIAC DISORDERS** - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Supraventricular tachycardia  
**EAR AND LABYRINTH DISORDERS** - Hearing impaired; Vertigo  
**ENDOCRINE DISORDERS** - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism  
**EYE DISORDERS** - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)  
**GASTROINTESTINAL DISORDERS** - Abdominal distension; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Hemorrhoids; Ileus; Pancreatitis; Rectal pain; Rectal ulcer  
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (implant site inflammation); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain  
**HEPATOBIILIARY DISORDERS** - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatitis toxic); Portal vein thrombosis  
**IMMUNE SYSTEM DISORDERS** - Allergic reaction; Anaphylaxis; Autoimmune disorder  
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture  
**INVESTIGATIONS** - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (D-dimer); Investigations - Other (eosinophil count increased); Investigations - Other (glucose urine present); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; White blood cell decreased  
**METABOLISM AND NUTRITION DISORDERS** - Glucose intolerance; Hyperglycemia; Hyponatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)  
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Back pain; Buttock pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (muscle hemorrhage); Musculoskeletal and connective tissue disorders - Other (osteonecrosis); Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Myalgia; Neck pain; Osteoporosis  
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Neoplasms benign,

malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain

**NERVOUS SYSTEM DISORDERS** - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (cerebral hematoma); Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks

**PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

**RENAL AND URINARY DISORDERS** - Chronic kidney disease; Hematuria; Renal and urinary disorders - Other (azotemia); Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Vaginal fistula

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hypoxia; Laryngeal edema; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Erythema multiforme; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (splinter hemorrhages); Skin ulceration

**VASCULAR DISORDERS** - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

**Note:** XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

### **7.1.1 Adverse Event List(s) for Commercial Agent(s)**

#### **7.1.1.1 Docetaxel**

(See package insert for complete list of side effects)

The most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia

#### **7.1.1.2 Prednisone**

(See package insert for complete list of side effects)

Serious side effects of prednisone include hypertension, hyperglycemia, infections, ruptured tendons, psychotic reactions, glaucoma, severe edema, gastrointestinal bleeding and allergic reactions. Short term side effects may include headaches and insomnia while long term side effects may cause weight gain, exophthalmos, osteoporosis, acne and truncal fat distribution.

#### Allergic Reactions

anaphylactoid or hypersensitivity reactions, anaphylaxis, angioedema.

#### Cardiovascular System

bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, ECG changes caused by potassium deficiency, edema, fat embolism,

hypertension or aggravation of hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, necrotizing angitis, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

#### Dermatologic

acne, acneiform eruptions, allergic dermatitis, alopecia, angioedema, angioneurotic edema, atrophy and thinning of skin, dry scaly skin, ecchymoses and petechiae (bruising), erythema, facial edema, hirsutism, impaired wound healing, increased sweating, Kaposi's sarcoma, lupus erythematosus-like lesions, perineal irritation, purpura, rash, striae, subcutaneous fat atrophy, suppression of reactions to skin tests, striae, telangiectasis, thin fragile skin, thinning scalp hair, urticaria.

#### Endocrine

Adrenal insufficiency-greatest potential caused by high potency glucocorticoids with long duration of action (associated symptoms include; arthralgias, buffalo hump, dizziness, life-threatening hypotension, nausea, severe tiredness or weakness), amenorrhea, postmenopausal bleeding or other menstrual irregularities, decreased carbohydrate and glucose tolerance, development of cushingoid state, diabetes mellitus (new onset or manifestations of latent), glycosuria, hyperglycemia, hypertrichosis, hyperthyroidism, hypothyroidism, increased requirements for insulin or oral hypoglycemic agents in diabetics, lipids abnormal, moon face, negative nitrogen balance caused by protein catabolism, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness), suppression of growth in pediatric patients.

#### Fluid and Electrolyte Disturbances

congestive heart failure in susceptible patients, fluid retention, hypokalemia, hypokalemic alkalosis, metabolic alkalosis, hypotension or shock-like reaction, potassium loss, sodium retention with resulting edema.

#### Gastrointestinal

abdominal distention, abdominal pain, anorexia which may result in weight loss, constipation, diarrhea, elevation in serum liver enzyme levels (usually reversible upon discontinuation), gastric irritation, hepatomegaly, increased appetite and weight gain, nausea, oropharyngeal candidiasis, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis, vomiting.

#### Hematologic

anemia, neutropenia (including febrile neutropenia).

#### Metabolic

negative nitrogen balance due to protein catabolism.

#### Musculoskeletal

arthralgias, aseptic necrosis of femoral and humeral heads, increase risk of fracture, loss of muscle mass, muscle weakness, myalgias, osteopenia, osteoporosis, pathologic fracture of long



bones, steroid myopathy, tendon rupture (particularly of the Achilles tendon), vertebral compression fractures.

### Neurological/Psychiatric

amnesia, anxiety, benign intracranial hypertension, convulsions, delirium, dementia (characterized by deficits in memory retention, attention, concentration, mental speed and efficiency, and occupational performance), depression, dizziness, EEG abnormalities, emotional instability and irritability, euphoria, hallucinations, headache, impaired cognition, incidence of severe psychiatric symptoms, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, increased motor activity, insomnia, ischemic neuropathy, long-term memory loss, mania, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders including steroid psychoses or aggravation of pre-existing psychiatric conditions, restlessness, schizophrenia, verbal memory loss, vertigo, withdrawn behavior.

### Ophthalmic

blurred vision, cataracts (including posterior subcapsular cataracts), central serous chorioretinopathy, establishment of secondary bacterial, fungal and viral infections, exophthalmos, glaucoma, increased intraocular pressure, optic nerve damage, papilledema.

### Other

abnormal fat deposits, aggravation/masking of infections, decreased resistance to infection, hiccups, immunosuppression, increased or decreased motility and number of spermatozoa, malaise, insomnia, moon face, pyrexia.

## **7.2 DEFINITIONS**

### **7.2.1 Adverse Event**

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

### 7.2.1.1 Adverse Event Characteristics:

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
- For expedited reporting purposes only:
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section Error! Reference source not found.) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- **Attribution** of the AE:
  - 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.

### 7.2.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 7.2.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. “Unexpected”, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 7.2.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

### **7.2.5 Serious Adverse Event**

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### **7.2.6 Disability**

A substantial disruption of a person's ability to conduct normal life functions.

### **7.2.7 Life-threatening adverse drug experience**

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

### **7.2.8 Protocol Deviation (NIH Definition)**

Any change, divergence, or departure from the IRB approved research protocol.

### **7.2.9 Non-compliance (NIH Definition)**

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

### **7.2.10 Unanticipated Problem**

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 7.3 EXPEDITED ADVERSE EVENT REPORTING TO CTEP

#### 7.3.1 Reporting via CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (<http://ctep.cancer.gov>). The reporting procedures to be followed are presented in the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” which can be downloaded from the CTEP Web site (<http://ctep.cancer.gov>). These requirements are briefly outlined in the tables below (Section 7.3.4).

#### 7.3.2 In the Event of Lost Internet Connectivity

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

#### 7.3.3 Multi-institutional Studies

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

#### 7.3.4 Expedited Reporting Guidelines

Use the CC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.**

Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

**Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention**<sup>1,2</sup>

#### FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for  $\geq$  24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Hospitalization                                | Grade 1 and Grade 2 Timeframes | Grade 3-5 Timeframes    |
|--|--------------------------------|-------------------------|
| Resulting in Hospitalization $\geq$ 24 hrs     | 10 Calendar Days               | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization $\geq$ 24 hrs | Not required                   |                         |

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

<sup>1</sup>Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

<sup>2</sup> For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

#### 7.4 ROUTINE ADVERSE EVENT REPORTING TO CTEP

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

## **7.5 NHLBI IRB AND NHLBI CLINICAL DIRECTOR (CD) REPORTING**

### **7.5.1 NHLBI-IRB and NHLBI CD Expedited Reporting of Unanticipated Problems and Deaths**

The Protocol PI will report in the NIH Problem Form to the NHLBI-IRB and NHLBI CD:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

### **7.5.2 NHLBI-IRB Requirements for PI Reporting at Continuing Review**

The protocol PI will report to the NHLBI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
  - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
  - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
  - All Grade 5 events regardless of attribution;
  - All Serious Events regardless of attribution.

**NOTE:** Grade 1 events are not required to be reported.

### **7.5.3 NHLBI-IRB Reporting of IND Safety Reports**

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NHLBI IRB.

### **7.5.4 NCI Guidance for Reporting Expedited Adverse Events for Multicenter Trials**

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 48 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies. A blank participating site problem form can be found in [Appendix F](#).

## 7.6 SECONDARY MALIGNANCY

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

## 7.7 SECOND MALIGNANCY

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

## 7.8 DATA AND SAFETY MONITORING PLAN

### 7.8.1 *Principal Investigator/Research Team*

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB using iRIS and if applicable to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

### 7.8.2 *Sponsor Monitoring Plan*

Please see section [12.2](#).

## 8 PHARMACEUTICAL INFORMATION

### 8.1 CABOZANTINIB (XL184) (NSC# 761968)

#### 8.1.1 Availability:

Cabozantinib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

#### 8.1.2 Toxicity:

Please see section 7.1.1.

#### 8.1.3 Formulation and preparation:

Cabozantinib is supplied by Exelixis and distributed by the DCTD. Cabozantinib is available in 20 mg and 60 mg tablets. The tablets are yellow film coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantinib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 tablets per bottle. Cabozantinib should be dispensed in its original container; however, cabozantinib tablets can be dispensed in a pill cup with an expiration date not to exceed 24 hours. It can also be repackaged in a pharmacy dispensing bottle with expiration date not to exceed 7 days. The components of the tablets are listed the table below.

#### Cabozantinib Tablet Components and Composition

| Ingredient  | Function          | % w/w |
|---|-------------------|-------|
| Cabozantinib malate (25% drug load as cabozantinib) | 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                                  | Film Coating      | 4.00  |
| - Triacetin   |                   |       |
| - Iron Oxide Yellow                                 |                   |       |

#### 8.1.4 Storage:

Store intact bottles of cabozantinib at controlled room temperature, 20° to 25°C.

#### 8.1.5 Stability:

Stability testing of the intact bottles is on-going. XL184 is stable up to 24 hours when dispensed in an open container such as a pill cup, and up to 7 days when dispensed in a closed container such as a pharmacy bottle other than the original container.



### **8.1.6 Administration procedures:**

See section **5.3.1**

### **8.1.7 Incompatibilities:**

Potential Drug Interactions: XL184 is a substrate of CYP3A4. Coadministration of XL184 with medications that are strong inhibitors/inducers of CYP3A4 should be avoided. Strong CYP3A4 inducers are rifampin, carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, St. John's wort, and troglitazone. Strong CYP3A4 inhibitors include ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, and ritonavir. (See the frequently updated <http://medicine.iupui.edu/clinpharm/ddis/> for current list agents that interact with CYP3A4). Use alternative medications. Avoid grapefruit/ grapefruit juice and Seville oranges while participating in this trial.

In-vitro data indicate that XL184 is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Additional details related to these overall conclusions can be found in the investigator brochure.

XL184 is highly protein bound, 99.9%. Use caution when coadministering XL184 with medications that are highly protein-bound (e.g., diazepam, furosemide, dicloxacillin, and propranolol). Avoid administration of warfarin with XL184 as warfarin is highly protein-bound and has a very narrow therapeutic index.

### Potential Food Effect

The effect of food on the bioavailability of cabozantinib was evaluated in healthy adult subjects in a Phase 1, open-label, randomized, single-dose, two-treatment, two way crossover study (Study XL184-004). Based on the preliminary PK data, a high fat meal did not appear to alter the terminal t<sub>1/2</sub>, but significantly increased the median t<sub>max</sub> to 6 hours from 4 hours (fasted). The high fat meal also significantly increased both the cabozantinib C<sub>max</sub> and AUC values by 41% and 57%, respectively. Based on this result, cabozantinib should be taken on an empty stomach (fasting is required 2 hours before and 1 hour after each cabozantinib dose).

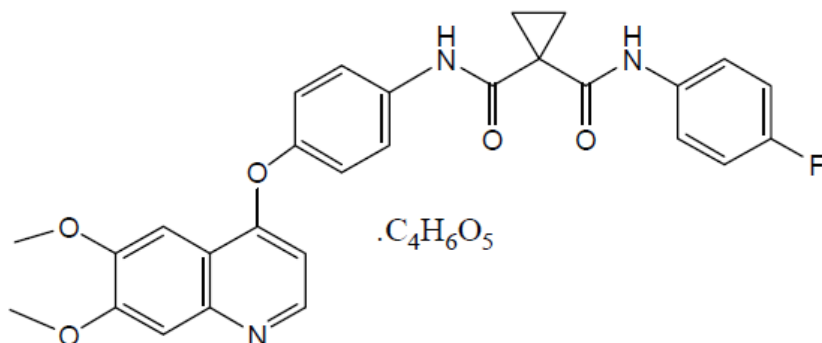
Patient Care Implications: Do not take grapefruit/ grapefruit juice or Seville oranges while participating in this trial. Inform physician and study healthcare team about current medications including over the counter drugs, herbals, or natural medicines. Do not use cimetidine for dyspepsia or indigestion.

Molecular Weight: 635.6

Chemical Name: N-[4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl]-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate

Molecular Formula: C<sub>28</sub>H<sub>24</sub>FN<sub>3</sub>O<sub>5</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>5</sub>

Chemical Structure:



Mechanism of action:

Cabozantinib is a tyrosine kinase inhibitor. It inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis, and targets primarily MET and VEGFR2. Other targets are RET, AXL, KIT, TIE-2, and FLT-3.

**8.1.8 Agent Ordering and Agent Accountability**

**8.1.8.1** NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email [PMBAfterHours@mail.nih.gov](mailto:PMBAfterHours@mail.nih.gov) anytime.

**8.1.8.2** Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

## **8.2 COMMERCIAL AGENTS**

### **8.2.1 Docetaxel (TAXOTERE®)**

(Please see package insert for complete drug information)

#### **8.2.1.1 Source**

Docetaxel will be obtained from commercial sources by the local site pharmacy.

#### **8.2.1.2 Toxicity: See section 7.1.1.1**

#### **8.2.1.3 Formulation and Preparation**

##### **8.2.1.3.1 Formulation**

TAXOTERE® (docetaxel) Injection Concentrate, Intravenous infusion (IV) is a sterile, non-pyrogenic, pale yellow to brownish-yellow, non-aqueous solution in single-use vials containing 20 mg docetaxel (anhydrous), 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol solution per milliliter in two presentations:

1. TAXOTERE® (docetaxel) Injection Concentrate 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol in a blister pack in one carton (NDC 0075-8003-01)
2. TAXOTERE® (docetaxel) Injection Concentrate 80 mg docetaxel in 4 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol in a blister pack in one carton (NDC 0075-8004-04)

##### **8.2.1.3.2 Preparation**

Dilute the concentrated drug product:

1. After removing Taxotere® from refrigeration, allow them to stand at room temperature approximately 5 minutes before proceeding
2. Use only a 21-Gauge needle to withdraw the drug product from a vial
  - Larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and introduce particulate matter into the drug product
3. Aseptically withdraw the amount of concentrated docetaxel solution required for a patient’s dose with a calibrated syringe and transfer it into an appropriate parenteral product bag or bottle containing a volume of either 0.9% NS or D5W sufficient to produce a final docetaxel concentration within the range 0.3 – 0.74 mg/mL
  - Product concentrations must not exceed 0.74 mg docetaxel per milliliter
  - To minimize patient exposure to phthalate plasticizers (e.g., DEHP), which may be leached from PVC containers, prepare and store docetaxel injection for administration to patients in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin)
4. Thoroughly mix the admixture by manual rotation and by gently inverting the product container

- When prepared as described and stored between 2° – 25°C, docetaxel solutions are stable for 4 hours

#### **8.2.1.4 Storage and Stability**

Store between 2°C and 25°C. Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

#### **8.2.1.5 Administration Procedures**

See section **5.3.2**. To minimize patient exposure to phthalate plasticizers (e.g., DEHP), which may be leached from PVC containers and administration sets, administer docetaxel only through polyethylene-lined administration sets

#### **8.2.1.6 Incompatibilities**

- Hypersensitivity to docetaxal or polysorbate 80; neutrophil counts of <1500/ $\mu$ L.
- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism.

### **8.2.2 Prednisone**

(Please see package insert for complete drug information)

#### **8.2.2.1 Source:**

For patient administration oral tablets will be purchased by the local site pharmacy from commercial sources.

#### **8.2.2.2 Toxicity:** See section **7.1.1.2**

#### **8.2.2.3 Formulation and preparation:**

Prednisone is supplied as 5 mg tablets.

#### **8.2.2.4 Stability and storage:**

Store at 15 - 30°C, protected from moisture and light.

#### **8.2.2.5 Administration procedures:**

See section **5.3.3**.

#### **8.2.2.6 Incompatibilities:**

Systemic fungal infections and known hypersensitivity to components.

## **9 PHARMACOKINETIC, BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES (NCI SITE ONLY)**

All patients enrolling at NCI on phase I (dose-escalation) and on the cabozantinib arm in the dose expansion will have blood samples drawn for PK studies. All patients enrolling at NCI will have samples collected for the other studies as described below. Samples will not be collected on patients enrolled outside NCI.

## 9.1 PHARMACOKINETIC STUDIES

Blood samples for determination of plasma levels of cabozantinib and docetaxel will be obtained from each patient on Day 1 of Cycles 1 and 2 (C1D1, C2D1) at the following time points: before infusion, at approximately 5 minutes prior to the end of docetaxel infusion, 15 minutes, 30 minutes, 3h, 6h, 12h and 24h after the end of docetaxel infusion. The first dose of cabozantinib has to be administered on Day 2 of Cycle 1 after blood collection of the last time point (24h) to compare docetaxel exposure on C1D1 to C2D1, with and without XL184. XL184 should be taken at the beginning of the docetaxel infusion, prior to drawing PK blood samples on day 1 of cycle 2.

The plasma concentration-time data will be analyzed using WinNonlin software (Pharsight, Mountain View, CA). The maximum concentration, time to maximum concentration, the area under the curve extrapolated to infinity, and clearance will be calculated. An assessment of a PK interaction of cabozantinib with docetaxel will be made by comparison of the derived PK parameters of cabozantinib in this study to those for historical data when cabozantinib was given alone. These assessments will be conducted according to the assay technology SOP utilized and validated by Exelixis and shared with Dr. Figg's laboratory for the purpose of conducting this study.

### 9.1.1 Collection of Specimens

One 6mL sodium heparin tube (BD, Franklin Lakes, NJ) is collected from each patient on Day 1 of Cycles 1 and 2 (C1D1, C2D1) at the following time points: before drug administration, at approximately 5 minutes prior to the end of docetaxel infusion, and at 15 minutes, 30 minutes, 3h, 6h, 12h and 24h after the end of docetaxel infusion.

### 9.1.2 Handling and Processing of Specimen(s)

The samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet.

Please e-mail Julie Barnes at [Julie.barnes@nih.gov](mailto:Julie.barnes@nih.gov) and Paula Carter [pcartera@mail.nih.gov](mailto:pcartera@mail.nih.gov) at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

Upon arrival in the Blood Processing Core (BPC), samples will be centrifuged, and the plasma transferred into cryovials for storage at -80C until the time of analysis. In addition, samples will be barcoded as described in section 9.3.1.

### 9.1.3 Site Performing the Study

The pharmacokinetic analysis will be performed on a research basis in the BPC.

## 9.2 BIOMARKER STUDIES

### 9.2.1 Genetic Biomarkers

Dr. Figg's laboratory has extensive experience and expertise in performing pharmacogenetic analyses of genes involved in angiogenesis and drug metabolism pathways. Towards this end, polymerase-chain reaction (PCR) followed by either restriction fragment length polymorphism (RFLP), direct sequencing, or gene array analysis will be used to genotype the single nucleotide polymorphisms.

#### 9.2.1.1 Collection of Specimen(s)

One 6ml EDTA tube (BD, Franklin Lakes, NJ) will be collected from patients at baseline (after consent, prior to treatment initiation).

#### 9.2.1.2 Handling and Processing of Specimens(s)

Immediately after collection, invert the blood tube 8-10 times. Place the tube on wet ice and then store at 4°C in the refrigerator. The date and exact time of each blood draw should be recorded on the tube. Please page 102-11964 for immediate pick-up.

Please e-mail Julie Barnes at [Julie.barnes@nih.gov](mailto:Julie.barnes@nih.gov) and Paula Carter [pcartera@mail.nih.gov](mailto:pcartera@mail.nih.gov) at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

Upon arrival in the BPC, genomic DNA will be extracted and analyzed for genetic polymorphisms.

#### 9.2.1.3 Site(s) Performing Correlative Study

The genotyping will be performed on a research basis in the Molecular Pharmacology Section.

### 9.2.2 Pharmacodynamic biomarkers:

The analyses will be performed with assays developed and validated in Dr. Liang Cao's laboratory using electrochemiluminescence technology that provides ultra-high sensitivity and very large signal dynamic range. The c-met assay utilized by Dr. Don Bottaro has been previously validated in his laboratory and published in studies<sup>54,56</sup>. Purified protein standards will be used for generating standard curves for concentration determination.

#### 9.2.2.1 Collection of Specimens

##### Plasma levels of VEGF, PlGF, HGF:

One 5mL EDTA plasma tube (BD, Franklin Lakes, NJ) is collected from each patient prior to drug administration on C1D1 (baseline), C2D1, C3D1 to measure VEGF and PlGF for anti-VEGFR2 activity and HGF for anti-c-MET activity.

Immediately after collection, invert the blood tube 8-10 times. Place the tube on wet ice and then store at 4°C in the refrigerator. The date and exact time of each blood draw should be recorded on the tube.

Please e-mail Julie Barnes at [Julie.barnes@nih.gov](mailto:Julie.barnes@nih.gov) and Paula Carter [pcartera@mail.nih.gov](mailto:pcartera@mail.nih.gov) at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

#### Plasma and urinary levels of soluble met:

One 5mL EDTA plasma tube (BD, Franklin Lakes, NJ) is collected from each patient prior to drug administration on C1D1 (baseline), C2D1, C3D1 to measure soluble c-met. Immediately after collection, invert the blood tube 8-10 times. Place the tube on wet ice and then store at 4°C in the refrigerator. The date and exact time of each blood draw should be recorded on the tube.

Urine samples (at least 5 mL) will be collected prior to drug administration on C1D1 (baseline), C2D1, and C3D1 to measure soluble met.

Please e-mail Julie Barnes at [Julie.barnes@nih.gov](mailto:Julie.barnes@nih.gov) and Paula Carter [pcartera@mail.nih.gov](mailto:pcartera@mail.nih.gov) at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

#### **9.2.2.2 Sample Processing**

Plasma levels of VEGF, PIGF, HGF:

Upon arrival in the BPC, blood samples will be centrifuged for 5 minutes at 1200 x g at 4°C. Plasma will be aliquoted into 2 cryovials and stored at -80°C until the time of analysis. The samples will be transferred to Dr. Liang Cao's lab at Bldg 37/Rm6134 (301-435-9039) for analysis.

Plasma and urinary levels of soluble met:

Upon arrival in the BPC, blood samples will be centrifuged for 10 minutes at 1300 x g at RT. Plasma will be aliquoted into 2 cryovials and stored at -80°C until the time of analysis.

Urine samples will be adjusted to pH 7.5 with Trizma-HCl (Sigma, St. Louis, MO), 2 mol/L, pH 7.5 using 50 microliters per 2 ml urine volume. Centrifuge urine samples at 3000 x g for 10 min at room temperature to remove cells and debris; store samples in appropriately sized plastic cryovials (Nunc or Sargent) at -80C. Determine urine creatinine value per standard clinical laboratory testing protocol for every sample collected prior to freezing and storage. The samples will be transferred to Dr. Don Bottaro's lab at Bldg 10/Rm 1W-5832 (301-402-0922) for analysis.

#### **9.2.2.3 Site Performing the Assay**

The pharmacodynamic biomarker analysis studies will be performed on a research basis in the laboratories of Dr. Liang Cao (Bldg 37/Room 6134) and Dr. Don Bottaro at Bldg 10/Room 1W-5832.



### **9.2.3 Markers for Bone Activities**

#### **9.2.3.1 Collection of Specimen(s)**

Samples will be collected as part of the routine laboratory testing to measure the levels of total ALP and bone-specific ALP, and urine samples will be collected to measure uNTx prior to drug administration on C1D1 (baseline), C2D1, C3D1, and C5D1 (week 12). Blood will be collected in a 4 mL SST tube and urine will be collected in a 5 mL urine tube. Please request these assessments in CRIS by checking the box “Other Mayo” and listing the test names (Alkaline Phosphatase, Bone specific; NTx-Telopeptide, Urine) in the description box.

#### **9.2.3.2 Sample Processing**

The processing will be performed by the Clinical Center Laboratory.

#### **9.2.3.3 Site Performing the Assay**

The analysis will be performed by the Clinical Center Laboratory.

### **9.2.4 Circulating Tumor Cells**

#### CTC enumeration:

CTCs will be investigated using immunofluorescence techniques and CTC identification by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers. Jane Trepel has extensive experience in working with CTC technology and has developed a platform for accurate detection of CTC enumeration. The Veridex CTC analysis is an FDA-approved platform for the capture, analysis, and enumeration of CTCs in monitoring metastatic prostate cancer.

#### AR analysis in CTC:

Dr. Liang Cao has expertise in developing new CTC technologies capable of isolating live CTCs for molecular analyses. CTCs will be isolated using a novel and patented CTC microchip-based technology. The purified CTC will be used for the analysis of androgen receptor expression and activity. All the downstream molecular analytic assays have been established and validated.

#### **9.2.4.1 Collection of Specimen(s)**

CTC enumeration: Two 7cc lavender top tubes for flow-based CTC analysis will be collected at C1D1 pre and C5D1 pre (week 12). Up to nine patients may have peripheral blood collected at the same time points (C1D1 pre and C5D1 pre) in one 7.5cc CellSave Preservative Tube for Veridex CTC analysis.

AR analysis in CTCs: One 5 ml K2ETDA tube will be collected at pre-drug on C1D1 (baseline) and forward to Dr. Liang Cao’s laboratory within two hours. CTCs will be isolated using a novel and patented CTC microchip-based technology. The purified CTC will be used for the analysis of androgen receptor expression and activity. All the downstream molecular analytic assays have been established and validated. These studies will be performed by Liang Cao, Head of Molecular Targets Core.

#### **9.2.4.2 Handling and Processing of Specimens(s)**

CTC enumeration: As soon as possible after the patient is scheduled please send email notification to the Trepel lab: Jane Trepel at [trepel@helix.nih.gov](mailto:trepel@helix.nih.gov); Min-Jung Lee at [leemin@mail.nih.gov](mailto:leemin@mail.nih.gov) that the sample is scheduled. After the sample is drawn please call the



Trepel lab at 301-496-1547 to communicate that the sample is ready. Keep the sample on the unit at room temperature. The sample will be picked up by the lab and processed for CTC enumeration.

AR analysis in CTCs: As soon as possible after the patient is scheduled please send email notification to the Cao lab: Liang Cao at caoli@helix.nih.gov that the sample is scheduled. After the sample is drawn please call the Cao lab (Mr. Yunkai Yu at 301.443.2799) to communicate that the sample is ready. Keep the sample on the unit at room temperature. The sample needs to be picked up by the lab within 2 hours. The blood will be processed for CTC isolation.

#### **9.2.4.3 Site(s) Performing Correlative Study**

The flow cytometric analyses will be performed by the Trepel laboratory. The Trepel lab will deliver CellSave tubes to the research nursing staff and arrange for sending the tubes for Veridex analysis.

AR analysis in CTCs will be performed by Dr. Liang Cao's laboratory in the Molecular Targets Core, Genetics Branch, Building 37, Room 6134.

### **9.3 SAMPLE STORAGE, TRACKING AND DISPOSITION**

Samples will be ordered and tracked through the CRIS Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA.

#### **9.3.1 Blood Processing Core (BPC) - Storage**

All samples will be bar-coded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number; time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Bar-coded samples are stored in bar-coded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused

samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

### ***9.3.2 Handling and Storage for Research Samples Managed by Jane Trepel's Laboratory***

Using a secure laboratory computerized database and a backup hardcopy process, all specimen collection and processing steps are documented and the specific location of each specimen is tracked. Each new specimen collected is assigned a unique 2D barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. De-identified labels will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only de-linked specimens will be stored.

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents is restricted to appropriate personnel only. SOPs ensure that any changes in the informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel are trained to adhere to SOPs and are monitored for high-quality performance.

### ***9.3.3 Molecular Targets Core (Dr. Cao's Lab) - Storage***

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers. De-identified labels will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Samples are labeled with printed consecutive numbers, frozen on dry ice, and stored in a -80°C freezer located at the NCI Research Facility, Building 37. The freezer is locked and monitored 24/7 for temperature control. Samples will be tracked using a limited access Excel database.

Access to the inventory system and associated documents will be restricted to appropriate personnel only. Requests to use specimens stored in the repository must be approved by the IRB. SOPs ensure that any changes in the informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance. The PI will submit a report to the IRB in the event that samples are lost or destroyed.

## 10 STUDY CALENDAR

| Protocol Activities  | Screening/Eligibility<br>(Timepoints relative to enrollment) |                 |                | Study Treatment Period<br>(1 cycle = 3 weeks) | End of Treatment               |
|--|--|-----------------|----------------|---|--------------------------------|
|  | ≤4 weeks prior   | ≤ 16 days prior | ≤ 1 week prior | Day 1 of every cycle                          | Within 30 days after last dose |
| Informed consent   |  |                 | X              |   |                                |
| Demographics   | X  |                 |                |   |                                |
| Medical & Oncology History   | X  |                 | X              |   |                                |
| Dental Examination <sup>1</sup>  |  | X               |                |   |                                |
| Physical examination <sup>5</sup>  |  |                 | X              | X   | X                              |
| Weight   | X  |                 |                | X   | X                              |
| Vital signs  | X  |                 |                | X   | X                              |
| ECOG performance status  | X  |                 |                | X   | X                              |
| Clinical laboratory tests <sup>2</sup>   |  | X               |                | X   | X                              |
| Urinalysis and UPCR  |  | X               |                | X   | X                              |
| PSA  |  |                 | X              | X <sup>2</sup>                                | X                              |
| PT/INR and PTT   |  | X               |                | X   |                                |
| Thyroid Function tests   |  | X               |                | X   |                                |
| Serum testosterone   | X  |                 |                |   |                                |
| 12-lead ECG  |  | X               |                | X   | X                              |
| Tumor assessment: CT scan <sup>3</sup> (chest, abdomen and pelvis), <sup>99</sup> Tc bone scintigraphy | X  |                 |                | X<br>(every 3 cycles)                         |                                |
| Cabozantinib administration  |  |                 |                | X<br>(daily or every other day)               |                                |
| Docetaxel administration   |  |                 |                | X<br>(day 1 of each cycle)                    |                                |
| Prednisone administration  |  |                 |                | X<br>(twice daily)                            |                                |
| Pharmacokinetics <sup>7</sup>  |  |                 |                | Cycles 1 & 2 only                             |                                |
| Correlative studies  |  |                 |                | X <sup>4</sup>                                |                                |
| Concomitant medications  |  |                 |                | Continuous                                    | X                              |
| Adverse events   |  |                 |                | Continuous                                    | X <sup>6</sup>                 |

ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; UPCR, urine protein/urine creatinine ratio

<sup>1</sup>Dental examination required in patients that have been treated with or are currently taking bisphosphonates

<sup>2</sup>Clinical laboratory tests include: CBC, acute care panel, mineral panel, hepatic panel, ionized calcium, amylase, lipase, LDH, total protein, GGT. Refer to section 5.6.4. In the event the patient's condition is

deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of next cycle of therapy.

<sup>3</sup> In order to minimize radiation exposure, if there is no evaluable soft tissue disease on baseline CT, future CT scans will not be obtained unless clinically indicated.

<sup>4</sup> Correlative blood and urine samples collected at baseline, C1D1, C2D1, C3D1 and C5D1. See section [9.2](#) for additional instructions.

<sup>5</sup> Height does not need to be repeated unless there is a clinical indication<sup>6</sup> If treatment related toxicity is present, adverse event must be followed until resolution, stable or irreversible per investigator discretion.

<sup>7</sup> NCI patients enrolled on phase I and on the cabozantinib arm of phase II. See section [9](#) for instructions.

## 11 MEASUREMENT OF EFFECT

### 11.1 ANTITUMOR EFFECT – SOLID TUMORS

Although response is not the primary endpoint of this trial, patients with metastatic disease will be assessed primarily by CT scan of the chest, abdomen and pelvis and by <sup>99</sup>Tc bone scintigraphy. For the purposes of this study, patients should be re-evaluated every 3 cycles.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)<sup>59</sup> and Prostate Cancer Clinical Trials Working Group criteria (PCWG2)<sup>1</sup>. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

#### 11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study agents.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

#### 11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm by chest x-ray or as  $\geq 10$  mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### ***11.1.3 Methods for Evaluation of Measurable Disease***

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of

MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.



**FDG-PET** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

#### **11.1.4 Response Criteria**

##### **11.1.4.1 Evaluation of Target Lesions**

- Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

#### 11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

#### 11.1.4.3 Metastatic Bone Lesions

Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen by the end of cycle 3 or before cycle 4 (after the first staging bone scan) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required in next scheduled staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after cycle 3, but no additional lesions are seen on confirmatory scans, the scans from after cycle 3 would serve as the baseline scan to evaluate for disease progression<sup>1</sup>.

#### 11.1.4.4 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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

**For Patients with Measurable Disease (i.e., Target Disease)**

| <b>Target Lesions</b>   | <b>Non-Target Lesions</b>   | <b>New Lesions</b> | <b>Overall Response</b> | <b>Best Overall Response when Confirmation is Required*</b> |
|---|-----------------------------|--------------------|-------------------------|---|
| CR  | CR                          | No                 | CR                      | $\geq 4$ wks. Confirmation**                                |
| CR  | Non-CR/Non-PD               | No                 | PR                      | $\geq 4$ wks. Confirmation**                                |
| CR  | Not evaluated               | No                 | PR                      |   |
| PR  | Non-CR/Non-PD/not evaluated | No                 | PR                      |   |
| SD  | Non-CR/Non-PD/not evaluated | No                 | SD                      | Documented at least once $\geq 4$ wks. from baseline**      |
| PD  | Any                         | Yes or No          | PD                      | no prior SD, PR or CR                                       |
| Any   | PD***                       | Yes or No          | PD                      |   |
| Any   | Any                         | Yes                | PD                      |   |
| <p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration.</i>” Every effort should be made to document the objective progression even after discontinuation of treatment.</p> |                             |                    |                         |   |

**For Patients with Non-Measurable Disease (i.e., Non-Target Disease)**

| <b>Non-Target Lesions</b>  | <b>New Lesions</b> | <b>Overall Response</b> |
|--|--------------------|-------------------------|
| CR   | No                 | CR                      |
| Non-CR/non-PD  | No                 | Non-CR/non-PD*          |
| Not all evaluated  | No                 | not evaluated           |
| Unequivocal PD   | Yes or No          | PD                      |
| Any  | Yes                | PD                      |
| * 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised |                    |                         |

**11.1.5 Duration of Response**

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: 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.

**12 DATA COLLECTION / DATA REPORTING**

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

**12.1 DATA COLLECTION**

Data will be collected prospectively and entered into NCI CCR C3D database within 14 days of collection. The NCI principal investigator is responsible for the collection, maintenance and quality control of study data.

Quality assurance complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g.: laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment

- Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)
- Toxicity was assessed according to protocol (laboratory report slips, etc)
- Response was assessed according to protocol (X-ray, scan, lab reports, date noted on clinical assessment, as appropriate)

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

**End of study procedures:** Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

## 12.2 DATA REPORTING

### 12.2.1 *Method*

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (<http://ctep.cancer.gov/reporting/cdus.html>).

**Note:** If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

### 12.2.2 *Responsibility for Data Submission*

Study participants are responsible for submitting CDUS data and/or data forms to either the Coordinating Center quarterly. The date for submission to the Coordinating Center will be set by them. CDUS does not accept data submissions from the participants on the study. When setting the dates, allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP by the quarterly deadlines (see Section 12.2.1).

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

### 12.3 CTEP MULTICENTER GUIDELINES

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in [Appendix E](#).

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.
- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

### 12.4 COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” ([http://ctep.cancer.gov/industryCollaborations2/intellectual\\_property.htm](http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
  - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
  - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said

- other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
- c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator ([http://ctep.cancer.gov/industryCollaborations2/intellectual\\_property.htm](http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: [ncicteppubs@mail.nih.gov](mailto:ncicteppubs@mail.nih.gov)

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

## **13 STATISTICAL CONSIDERATIONS**

### **13.1 STUDY DESIGN/ENDPOINTS**

The single arm phase I study of fixed dose of docetaxel and prednisone in combination with cabozantinib will enroll patients at a maximum of three escalating doses using a standard 3 + 3 design. The primary objective is to determine the safety profile of cabozantinib in combination with docetaxel and prednisone, and to determine the maximal tolerated dose (MTD) as recommended phase II dose in combination with docetaxel. Once the MTD has been determined, 6 additional patients will be enrolled as an expansion at MTD level to further characterize the safety, toxicity and pharmacokinetics, as well as to obtain preliminary data on the efficacy of the combination treatment.

After completing the phase I portion, a randomized phase II portion of the trial will be conducted to compare docetaxel, prednisone and cabozantinib at the MTD as compared to docetaxel and prednisone (standard of care) in mCRPC patients. Based upon results in the literature, patients who would be eligible to be randomized on this part of the trial would be expected to have an estimated 5 month median progression free survival from docetaxel and prednisone. The goal of this portion of the study will be to determine if the use of cabozantinib, docetaxel, and prednisone will result in patients having an improved progression free survival, with a 9 month median progression free survival. Kaplan-Meier curves and a two-tailed log-rank test will be the primary analysis methods. Assuming exponential progression free survival curves, the hazard rate for docetaxel and prednisone alone would be 0.1386, or approximately a 14% probability of progressing each month when the median PFS is approximately 5 months. If we assume that adding cabozantinib will increase the median progression free survival time to approximately 9 months, this corresponds to a hazard rate of 0.0770 and the resulting hazard ratio for the comparison of the two overall actuarial curves would be 1.80. Following the principles of a phase 2.5 design, to compare these curves and detect a difference with a 0.10 one-tailed log-rank test, a total of 29 evaluable subjects per arm (58 total) will need to be randomized over a two year period and followed for an additional 18 months from the date of entry of the last patient, with occurrence of 52 total progressions in both arms combined, in order to have 80% power to compare the curves.

As a futility rule for early stopping, when 50% of the anticipated events have occurred (26 total progressions), the hazard ratio will be determined. If this hazard ratio favors docetaxel and prednisone, then no further patients will be randomized as soon as this has been determined.

### **13.2 SAMPLE SIZE/ACCRUAL RATE**

Up to 18 subjects may be required to reach the MTD, with an additional 6 subjects required for the expansion phase. Thus, an enrollment of up to 24 subjects is anticipated prior to the randomized portion. For the phase II portion, 58 patients will be enrolled with an additional 4 patients allowed for randomized patients who are not evaluable. Currently, we have 19 patients enrolled. If we enroll an additional 62, this will bring the total accrual required to 81.

Based on previous efforts and experience in recruiting patients with this disease onto trials at the NCI, it is anticipated that 2 to 3 patients will be enrolled to this trial per month. Thus, it is expected that accrual for Phase I can be completed in approximately 1 year and the accrual of 62 patients for Phase II can be completed in 2 years. Men of all races will be eligible for this study. Prostate cancer is not present in women; therefore, they will be excluded from this study.



| <b>Accrual Targets</b>                        |                   |   |              |              |
|---|-------------------|---|--------------|--------------|
| <b>Ethnic Category</b>                        | <b>Sex/Gender</b> |   |              |              |
|   | <b>Females</b>    |   | <b>Males</b> | <b>Total</b> |
| Hispanic or Latino                            | 0                 | + | 4            | = 4          |
| Not Hispanic or Latino                        | 0                 | + | 77           | = 77         |
| <b>Ethnic Category: Total of all subjects</b> | 0 (A1)            | + | 81 (B1)      | = 81 (C1)    |
| <b>Racial Category</b>                        |                   |   |              |              |
| American Indian or Alaskan Native             | 0                 | + |              | =            |
| Asian   | 0                 | + | 4            | = 4          |
| Black or African American                     | 0                 | + | 35           | = 35         |
| Native Hawaiian or other Pacific Islander     | 0                 | + |              | =            |
| White   | 0                 | + | 42           | = 42         |
| <b>Racial Category: Total of all subjects</b> | 0 (A2)            | + | 81 (B2)      | = 81 (C2)    |

(A1 = A2)

(B1 = B2)

(C1 = C2)

### 13.3 ANALYSIS OF SECONDARY ENDPOINTS

Secondary objectives include: assessment of pharmacokinetics of each agents during combination therapy; evaluation of antitumor activities of combination therapy via measurable disease as determined by Response Evaluation Criteria in Solid Tumors (RECIST); assessment of changes in molecular biomarkers in the pathways of receptor tyrosine kinases and angiogenesis, as well as the biomarkers for bone metabolism.

## 14 HUMAN SUBJECTS PROTECTIONS

### 14.1 RATIONALE FOR SUBJECT SELECTION

Subjects treated on this study, will be individuals with metastatic prostate cancer, which has recurred (or persisted) after appropriate standard treatment. Individuals of any race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

### **14.1.1 NHLBI IRB Multi-Institutional Guidelines**

#### **14.1.1.1 IRB Approvals**

The PI will provide the NHLBI IRB and Central Registration Office with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NHLBI IRB.

#### **14.1.1.2 Amendments and Consents**

The CCR PI will provide the NHLBI IRB with copies of all amendments, consents and approvals from each participating institution.

### **14.2 PARTICIPATION OF CHILDREN**

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have prostate cancer, and because of unknown toxicities of cabozantinib in combination with docetaxel and prednisone in the pediatric patient.

### **14.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT**

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section 14.4), all subjects  $\geq$  age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

### **14.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS**

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor and improvement in their bony lesions, which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis.

### **14.5 RISKS/BENEFITS ANALYSIS**

For patients with castrate-resistant prostate cancer, median survival is in the range of 12-18 months. Potential risks include the possible occurrence of any of a range of side effects listed in section 7. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

## **14.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION**

The principal investigator or a designee will obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness will be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness's signature on the form will attest that the information in the consent form was accurately explained and understood.

If new safety information results in significant changes in the risk/ benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, be given a copy of the revised form, and be asked give their consent to continue in the study.

It will be documented in the medical record that informed consent has been obtained.

### ***14.6.1 Telephone Re-Consent Procedure***

Reconsent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. A copy of the informed consent document will be kept in the subject's research record.

### ***14.6.2 Informed Consent of Non-English Speaking Subjects***

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We will request prospective IRB approval of the use of the short form for up to a maximum of 5 participants in a given language and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form. Should we reach the threshold of 5, we will notify the IRB of the need for an additional use of the Short Form and that we will have that consent document translated into the given inherent language.

## **15 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

The Principal Investigator (Protocol Chair) holds the primary responsibility for publication of the study results; provided that the PI 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 PI's institution (National Cancer Institute) and Exelixis, Inc. in the Clinical Trial Agreement related to this study. The results will be made public within 24 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.

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**17 APPENDICES**

**17.1 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.  |

## 17.2 APPENDIX B: PATIENT INFORMATION ON POSSIBLE DRUG INTERACTIONS

### Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient \_\_\_\_\_ is enrolled on a clinical trial using the experimental **cabozantinib**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

*Cabozantinib* interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet.** These are the things that you and they need to know:

Cabozantinib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is **CYP3A4**. This enzyme breaks down cabozantinib, gradually reducing the level of the active drug in your system.
- Other medicines may affect the activity of the enzyme. Cabozantinib must be used very carefully with these medicines, or you may need to switch to alternate medications.
  - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**."
- Your prescribers should look at this web site <http://medicine.iupui.edu/clinpharm/ddis/> or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:

- If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John’s wort while you are taking cabozantinib
- If you take medications used to treat indigestion, you should avoid using drugs such as cimetidine, ranitidine, famotidine, nizatidine omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, and rabeprazole. Instead, you should take antacids for the initial treatment of indigestion. If antacids are not adequate, please contact a member of the research team before taking any other medications.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor’s name is **Dr. William Dahut** and he can be contacted at **301 435 8183**.

|  |  |
|--|--|
| <p style="text-align: center;"><b>INFORMATION ON POSSIBLE DRUG INTERACTIONS</b></p> <p>You are enrolled on a clinical trial using the experimental agent <b>XL184 (cabozantinib)</b>. This clinical trial is sponsored by the NCI. <b>XL184 (cabozantinib)</b> interacts with drugs that are processed by your liver. Because of this, it is very important to:</p> <ul style="list-style-type: none"> <li>➤ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.</li> <li>➤ Tell all of your prescribers (doctor, physicians’ assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.</li> <li>➤ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.</li> </ul> | <p style="text-align: center;"><b>INFORMATION ON POSSIBLE DRUG INTERACTIONS</b></p> <p>You are enrolled on a clinical trial using the experimental agent <b>XL184 (cabozantinib)</b>. This clinical trial is sponsored by the NCI. <b>XL184 (cabozantinib)</b> interacts with drugs that are processed by your liver. Because of this, it is very important to:</p> <ul style="list-style-type: none"> <li>➤ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.</li> <li>➤ Tell all of your prescribers (doctor, physicians’ assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.</li> <li>➤ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.</li> </ul> |
|--|--|

### 17.3 APPENDIX C: GUIDELINES FOR PROPHYLAXIS AND TREATMENT FOR HYPERSENSITIVITY REACTIONS (HSR) ASSOCIATED WITH DOCETAXEL

| Initial Regimen  | HSR Interventions Step 1  | HSR Interventions Step 2   | HSR Interventions Step 3   |
|--|---|--|--|
| For ALL patients who have not experienced an HSR associated with Docetaxel   | For pts with a H/O a single HSR episode   | For pts who experience a HSR after implementing Step 1 interventions   | For pts with severe or repeated HSR episodes after implementing Steps 1 & 2 interventions  |
| <p>PREMEDICATION WITH:</p> <p><b>Dexamethasone</b> 8 mg PO for 3 doses at 12 h, 3 h, &amp; 1 h before starting docetaxel</p> <p style="text-align: center;"><i>OR</i></p> <p><b>Dexamethasone</b> 8 mg IV 30 – 60 min before docetaxel for patients who miss <math>\geq 1</math> oral dexamethasone doses</p> <ul style="list-style-type: none"> <li>Reference: study protocol, Section 5.3.2</li> </ul> | <p>PREMEDICATION WITH:</p> <p><b>Dexamethasone</b> 8 mg PO for 2 doses at 12 h &amp; 3 h before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Dexamethasone</b> 8 mg IV 30 – 60 min before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Diphenhydramine</b> 50 mg IV push 15 – 30 min before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Ranitidine</b> 50 mg IV infusion 30 min before starting docetaxel</p> | <p>PREMEDICATION WITH:</p> <p><b>Dexamethasone</b> 8 – 20 mg PO for 2 doses between 24 – 36 h and at 12 hours before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Dexamethasone</b> 20 mg IV 30 – 60 min before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Diphenhydramine</b> 50 – 150 mg IV push 15 – 30 min before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Ranitidine</b> 50 mg IV infusion 15 – 30 min before starting docetaxel</p> | <p>PREMEDICATION WITH:</p> <p><b>Dexamethasone</b> 8 – 20 mg PO for 2 doses between 24 – 36 h and at 12 hours before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Dexamethasone</b> 20 mg IV 30 – 60 min before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Diphenhydramine</b> 50 – 150 mg IV push 15 – 30 min before starting docetaxel</p> <p style="text-align: center;">+</p> <p><b>Ranitidine</b> 50 mg IV infusion 15 – 30 min before starting docetaxel</p> |
| <b>Docetaxel</b> 75 mg/m <sup>2</sup> * IV over 60 minutes†  | <b>Docetaxel</b> 75 mg/m <sup>2</sup> * IV over 1 – 2 hours†  | <p><b>Docetaxel</b> 75 mg/m<sup>2</sup>* IV over 4 hours</p> <ul style="list-style-type: none"> <li>Given in two portions‡, as: Docetaxel 37.5 mg/m<sup>2</sup> IV over 2 hours, q.2 h for 2 doses</li> </ul>  | <p><b>Docetaxel</b> 75 mg/m<sup>2</sup>* IV</p> <ul style="list-style-type: none"> <li>Given in three portions‡, as follows:                             <ol style="list-style-type: none"> <li>Docetaxel 5 mg in 10 mL IV via syringe pump over 60 min, followed immediately afterward by:</li> <li>Docetaxel 25 mg in 50 mL IV over 60 min, followed immediately afterward</li> </ol> </li> </ul>  |

| Initial Regimen   | HSR Interventions<br>Step 1             | HSR Interventions<br>Step 2  | HSR Interventions<br>Step 3   |
|---|---|--|---|
| For ALL patients who have not experienced an HSR associated with Docetaxel  | For pts with a H/O a single HSR episode | For pts who experience a HSR after implementing Step 1 interventions | For pts with severe or repeated HSR episodes after implementing Steps 1 & 2 interventions |
|   |   |  | by:<br>3. Docetaxel 75 mg/m <sup>2</sup> (minus 30 mg) IV over 120 min                    |
| <p><b>PRN Orders:</b></p> <p><b>Hydrocortisone</b> 100 mg IV push q.15 min for 2 doses, PRN docetaxel reaction</p> <p>+</p> <p><b>Diphenhydramine</b> 50 mg IV push q.15 min for 2 doses, PRN docetaxel reaction</p> <p>+</p> <p><b>Ranitidine</b> 50 mg IV, PRN docetaxel reaction</p> <p>+</p> <p><b>Hydromorphone</b> 1 mg IV push q.15 min for 4 doses, PRN pain with docetaxel reaction</p> <p>+</p> <p><b>Aluminum Hydroxide</b> 200 mg + <b>Magnesium Hydroxide</b> 200 mg + <b>Simethicone</b> 20 mg chewable tablet<br/>                     1 – 2 tablets q.3 hours, PRN epigastric discomfort (drug name in CRIS is cross-referenced with “Mylanta”)</p> |   |  |   |

\* Initial (unmodified) docetaxel dosage is identified. Consult the study protocol or a medically responsible investigator to determine whether docetaxel dose/dosage modification is indicated.

† For each docetaxel product, drug delivery will be attempted over the administration period indicated, but rate titration is permitted. If rate titration is needed to accommodate patient tolerance, the following escalation scheme is recommended:

|                               |                          |
|-------------------------------|--------------------------|
| <b>Initial Rate:</b>          | 25 mL/h for 5 minutes    |
| <b>Rate Escalation Steps:</b> |                          |
| 1 <sup>st</sup>               | 50 mL/h for 5 minutes    |
| 2 <sup>nd</sup>               | 100 mL/h for 5 minutes   |
| 3 <sup>rd</sup>               | 200 mL/h for 5 minutes   |
| 4 <sup>th</sup>               | 250 mL/h until completed |

‡ Docetaxel stability is concentration dependent. All docetaxel products diluted within the range 0.3 – 0.74 mg/mL are labeled to expire 4 hours after preparation was completed.

**CRIS Chemotherapy/Biotherapy Treatment Note**

| For patients WITHOUT a prior H/O HSR   | For Step 1 HSR Interventions  | For Step 2 HSR Interventions  | For Step 3 HSR Interventions   |
|--|---|---|--|
| Docetaxel _____ mg/m <sup>2</sup><br>(calculated dose = _____ mg) IV over 60 min   | Docetaxel _____ mg/m <sup>2</sup><br>(calculated dose = _____ mg) IV over 1 – 2 hours | Docetaxel _____ mg/m <sup>2</sup> (calculated TOTAL dose = _____ mg) continuous IV infusion over 2 hours, every 2 hours for 2 doses | Docetaxel _____ mg/m <sup>2</sup> (calculated TOTAL dose = _____ mg) given in 3 portions, as follows:<br><br>#1 of 3: Docetaxel 5 mg IV over 60 minutes<br><br>#2 of 3: Docetaxel 25 mg IV over 60 minutes<br><br>#3 of 3: Docetaxel _____ mg (calculated TOTAL dose minus 30 mg from products #1 & #2, above) IV over 2 hours |
| Because patient, _____, has a history of hypersensitivity reaction with docetaxel administration, they will receive pre-medication and docetaxel according to Step # _____ of the guidelines for Prophylaxis and Treatment for Hypersensitivity Reactions (HSR) Associated with Docetaxel.   |   |   |  |
| In the event of a hypersensitivity reaction associated with docetaxel administration: <ol style="list-style-type: none"> <li>1. Immediately STOP docetaxel administration.</li> <li>2. Rapidly administer PRN doses of hydrocortisone &amp; diphenhydramine.</li> <li>3. Assess patient to determine whether additional PRN meds are indicated.</li> <li>4. Reinitiate docetaxel after hypersensitivity signs and symptoms have completely resolved.</li> <li>5. In the event of a hypersensitivity reaction, contact:<br/><br/>                             Dr. _____ at 102-_____.<br/>                             Anna Couvillon at 102-10744.                         </li> </ol> |   |   |  |



**TAKE HOME Dexamethasone Orders for the Next Treatment Cycle**

| <b>For patients WITHOUT a prior H/O HSR</b>  | <b>For Step 1 HSR Interventions</b>  | <b>For Step 2 HSR Interventions</b> | <b>For Step 3 HSR Interventions</b>   |
|--|--|-------------------------------------|---|
| <b>Dexamethasone</b> 8 mg PO for 3 doses at 12 h, 3 h, & 1 h before starting docetaxel | <b>Dexamethasone</b> 8 mg PO for 2 doses at 12 h & 3 h before starting docetaxel |                                     | <b>Dexamethasone</b> 8 – 20 mg PO for 2 doses between 24 – 36 h and at 12 hours before starting docetaxel |

**17.4 APPENDIX D: CCR PATIENT SELF-ADMINISTERED STUDY AGENT COMPLIANCE LOG**

This form is to be updated at every study contact where patient receives or returns study drug. This form may be used for multiple self-administered study agents. This form is to be used in conjunction with a note in CRIS about study drug self-administration and case report form and will be maintained in the research record. If patient is bringing back their study drug and you will not be returning that to the pharmacy, rather, the patient will be taking it back home with them, please use the form entitled ‘CCR Patient Self-Administered Study Agent Interim Compliance Form’.

|  |                               |
|--|-------------------------------|
| CC Protocol Number: _____              | Principal Investigator: _____ |
| Protocol Title: _____                  |                               |
| Patient’s Medical Record Number: _____ | Patient’s Name: _____         |
| Patient Study ID: _____                | Cycle Number _____            |

| Date Dispensed                   | Amount Dispensed | Dose Form<br><i>(e.g., tablets, pills, bottles, capsules, vials)</i> | Date Returned                    | Actual Amount Returned | Expected Amount Taken | Expected Amount Returned | Reason for difference between actual and expected amount returned, if applicable | Site Staff Initials |
|----------------------------------|------------------|--|----------------------------------|------------------------|-----------------------|--------------------------|--|---------------------|
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |

| Date Dispensed                   | Amount Dispensed | Dose Form<br><i>(e.g., tablets, pills, bottles, capsules, vials)</i> | Date Returned                    | Actual Amount Returned | Expected Amount Taken | Expected Amount Returned | Reason for difference between actual and expected amount returned, if applicable | Site Staff Initials |
|----------------------------------|------------------|--|----------------------------------|------------------------|-----------------------|--------------------------|--|---------------------|
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |
| ____/____/20____<br>(mm/dd/yyyy) |                  |  | ____/____/20____<br>(mm/dd/yyyy) |                        |                       |                          |  |                     |

## **17.5 APPENDIX E: CTEP MULTICENTER GUIDELINES**

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

### Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

### Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

**17.6 APPENDIX F: CCR PROBLEM REPORT FORM**

|  |  |      |
|--|--|------|
| <b>CC Protocol #:</b>  | <b>Protocol Title:</b>   |      |
|  | <b>Report version: (select one)</b><br>___ Initial Report<br>___ Revised Report<br>___ Follow-up |      |
| <b>Site Principal Investigator:</b>  |  |      |
| <b>Date of problem:</b>  | <b>Location of problem: (e.g., patient's home, doctor's office)</b>                              |      |
| <b>Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc...)</b>   |  |      |
| <b>Brief Description of Subject (if applicable)</b><br><i>(Do NOT include personal identifiers)</i>  | Sex: ___ Male ___ Female   | Age: |
|  | ___ Not applicable (more than subject is involved)   |      |
| <b>Diagnosis under study:</b>  |  |      |
| <b>Name the problem: (select all that apply)</b>   |  |      |
| <input type="checkbox"/> Adverse drug reaction<br><input type="checkbox"/> Abnormal lab value<br><input type="checkbox"/> Death<br><input type="checkbox"/> Cardiac Arrest/ code<br><input type="checkbox"/> Anaphylaxis<br><input type="checkbox"/> Sepsis/Infection<br><input type="checkbox"/> Blood product reaction |  |      |

- Unanticipated surgery/procedure
- Change in status (e.g. increased level of care required)
- Allergy (non-medication)
- Fall
- Injury/Accident (not fall)
- Specimen collection issue
- Informed consent issue
- Ineligible for enrollment
- Breach of PII
- Tests/procedures not performed on schedule
- Other, brief 1-2 word description: \_\_\_\_\_

**Detailed Description of the problem:** *(Include any relevant treatment, outcomes or pertinent history):*

**\*Is this problem unexpected?** *(see the definition of unexpected in the protocol)* \_\_YES \_\_NO **Please explain:**

**\*Is this problem related or possibly related to participation in the research?** \_\_YES \_\_NO **Please explain:**

**\*Does the problem suggest the research places subjects or others at a greater risk of harm than was previously known or recognized?** \_\_YES \_\_NO **Please explain:**

**Is this problem?** *(select all that apply)*

- An Unanticipated Problem\* that is:     Serious     Not Serious
- A Protocol Deviation that is:             Serious     Not Serious
- Non-compliance

*\*Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*

|  |              |
|--|--------------|
| <b>Is the problem also (select one) [ ] AE [ ] Non-AE</b>  |              |
| <b>Have similar problems occurred on this protocol at your site? __YES __NO</b><br><b>If "Yes", how many? _____ Please describe:</b>   |              |
| <b>Describe what steps you have already taken as a result of this problem:</b>   |              |
| <b>In addition to the NHLBI IRB, this problem is also being reported to: (select all that apply)</b><br>[ ] Local IRB<br>[ ] Study Sponsor<br>[ ] Manufacturer : _____<br>[ ] Institutional Biosafety Committee<br>[ ] Data Safety Monitoring Board<br>[ ] Other: _____<br>[ ] None of the above, not applicable |              |
| <b>INVESTIGATOR'S SIGNATURE:</b>   | <b>DATE:</b> |