A PHASE II, OPEN-LABEL RANDOMIZED STUDY OF IMMEDIATE PROSTATECTOMY VS. CABOZANTINIB FOLLOWED BY PROSTATECTOMY IN MEN WITH HIGH-RISK PROSTATE CANCER (SPARC)

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TBD

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase II, open-label randomized study of immediate prostatectomy vs. cabozantinib followed by prostatectomy in men with high-risk prostate cancer.
Study Description:	Subjects will be assigned (Safety Lead-In Cohort) or randomized to either: (1) cabozantinib 40 mg PO daily for 4 weeks, followed by a 2 week drug washout period before prostatectomy (n = 20), or (2) immediate prostatectomy (n = 10). The Safety Lead-In Cohort will consist of 6 subjects receiving cabozantinib prior to prostatectomy. The randomized portion will consist of the remaining cabozantinib prior to prostatectomy subjects (n=14) and immediate prostatectomy subjects (n=10).
Primary Objective:	To compare pathologic apoptotic indices (cleaved caspase-3) in prostatectomy specimens from patients who undergo immediate prostatectomy (controls) versus those treated with cabozantinib followed by prostatectomy.
Secondary Objective:	To conduct immune phenotypic profiling on the peripheral blood and tumor microenvironment in prostatectomy specimens from patients who undergo immediate prostatectomy versus those treated with cabozantinib prior to prostatectomy.
Exploratory Objectives:	1. To estimate the pathologic complete response rate (pCR) and ≤pathologic T2 (≤pT2) rate in each arm. 2. To evaluate relapse-free survival in each arm. 3. To compare apoptosis (TUNEL), proliferation (Ki-67), and microvessel density (CD31) indices in prostatectomy specimens from patients who undergo immediate prostatectomy versus those treated with cabozantinib prior to prostatectomy. 4. To measure expression levels of c-MET, VEGF, and HGF, as well as activation status of c-MET in prostate tissue. 5. To describe changes in plasticity signaling markers associated with prostate tumors, including vimentin, AR, SNAIL, AXL, and N-cadherin with cabozantinib exposure. 6. To evaluate PTEN and p53 genomic and protein expression status in tumor tissue 7. To demonstrate that cabozantinib is safe and tolerable in patients undergoing radical prostatectomy. 8. To demonstrate that surgery is safe and feasible in patients undergoing treatment with cabozantinib. 9. To collect plasma angiome samples (multiplex ELISA) for analysis and correlation with primary and key secondary endpoints. 10. To describe gene expression patterns (in particular those associated with apoptosis, androgen receptor signaling, c-MET activation, and a c-MET-specific endocytosis panel) correlated with cabozantinib administration using RNA sequencing.

	11. To explore changes in serum and intratumoral androgen concentrations related to cabozantinib treatment. 12. To collect cell-free DNA (cfDNA) for analysis and correlation with primary and key secondary endpoints.
Endpoints:	Primary: Apoptotic index by cleaved caspase-3 Secondary: Description of immune biomarkers, including: • Immune phenotyping of paired peripheral blood and tumor tissue: Myeloid-derived suppressor cells (MDSCs), neutrophils, M1 macrophages, and M2 macrophages in tumor tissue • Immunohistochemical (IHC) analysis of CD8+, programmed death ligand-1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), interleukin-1 receptor antagonist (IL-1RA) and B7H3 in tumor tissue • Neutrophil chemotactic factors (CXCL12 and HMGB1) and MDSC-promoting cytokines (CCL5, CCL12, CD40) in tumor tissue Exploratory: 1. Rates of pCR and ≤pT2 2. Relapse-free survival rate at 3 years 3. Quantification of TUNEL, Ki-67, and CD31 staining 4. Quantification of c-MET, VEGF, HGF, and activated c-MET in prostatectomy tissue 5. Correlation of vimentin, AR, SNAIL, AXL, and N-cadherin with cabozantinib exposure 6. Measurement of PTEN and p53 genomic and protein expression status in tumor tissue 7. Adverse events by CTCAE v5.0, dose intensity of cabozantinib 8. Blood loss at prostatectomy and duration of hospital stay 9. Angiome biomarkers 10. Gene expression patterns using RNA sequencing 11. Serum and intratumoral androgen concentrations 12. Alterations in cfDNA
Study Population:	Eligible patients will have histologic evidence of adenocarcinoma of the prostate and be deemed candidates for curative radical prostatectomy. They will have intermediate-or high-risk, clinically localized disease and have not received prior treatment for prostate cancer.
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	This is a multicenter study of 30 evaluable subjects. Duke is the lead site for this trial. Subjects who do not receive 21 out of 28 days of planned study drug administration and proceed to radical prostatectomy within 14 (+3) days of their last dose of study drug (Arm A only) or do not proceed to radical prostatectomy (Arm B only) will be replaced. There will be a second site selected TBD.
Description of Study Intervention:	Patients will be assigned (Safety Lead-In Cohort) or randomized to either: (1) cabozantinib 40 mg PO daily for 4 weeks, followed by a 2 week drug

	washout period before prostatectomy (n = 20), or (2) immediate prostatectomy within 12 weeks of registration (n = 10). The Safety Lead-In Cohort will consist of 6 subjects receiving cabozantinib prior to prostatectomy. The randomized portion will consist of the remaining cabozantinib prior to prostatectomy subjects (n=14) and immediate prostatectomy subjects (n=10).
Study Duration:	We estimate an accrual period of 1 year, with last patient last visit at 22 months and final report at 25 months.
Participant Duration:	Screening Phase: Six weeks (42 days) Treatment Phase (including prostatectomy) • Arm A (cabozantinib): up to 85 days • Arm B (immediate prostatectomy): 1 day Follow-up Phase: 3 years post-prostatectomy for relapse-free survival

1.2 SCHEMA

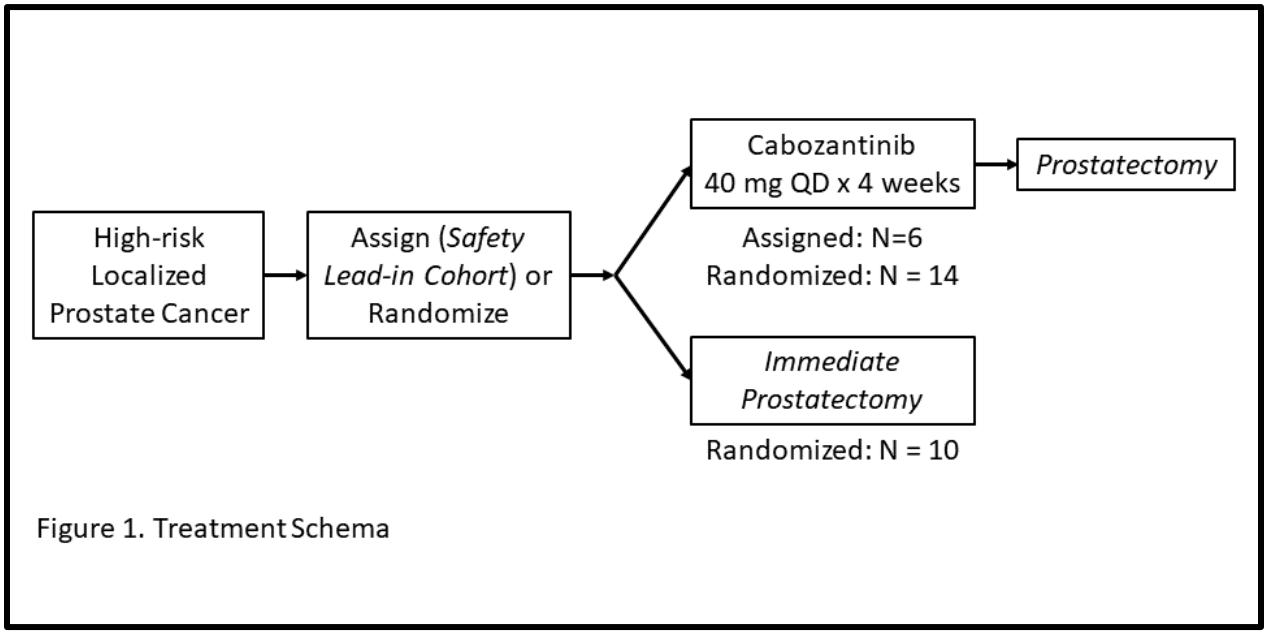

Figure 1. Treatment Schema

2 INTRODUCTION

2.1 INTRODUCTORY STATEMENT

Prostate cancer is the most common cancer and second leading cause of cancer death in men, with approximately 165,00 new cases and 29,000 deaths in 2018 [1]. Radiotherapy and radical prostatectomy have been the gold standards for primary treatment of localized disease. Androgen deprivation therapy (ADT; lowering of serum testosterone to <50 ng/dl) is used for localized prostate cancer in combination with radiotherapy, biochemically recurrent (M0) prostate cancer after primary therapy (both with and

without radiotherapy), and for metastatic castration-sensitive prostate cancer (mCSPC). In contrast, neoadjuvant ADT has not shown benefit over prostatectomy alone and adjuvant ADT post-prostatectomy is controversial. After prostate cancer recurrence ADT is typically continued intermittently or continuously life-long [2]. Both docetaxel and abiraterone acetate plus prednisone have recently demonstrated benefits when added to ADT for mCSPC [3]. Enzalutamide and apalutamide have both been approved for M0 castration resistant prostate cancer (CRPC) [4]. Five therapies, including an immunotherapy, two androgen receptor signaling inhibitors, two cytotoxic chemotherapies, and a radiopharmaceutical, are approved for metastatic (M1) CRPC: sipuleucel-T, abiraterone plus prednisone, enzalutamide, docetaxel, cabazitaxel, and radium-223 [5].

Aside from sipuleucel-T, which improves overall survival without inducing measureable tumor regression, there are no immunotherapies approved for prostate cancer. Immune checkpoint inhibitors (ICIs) have demonstrated substantial benefits and have been approved in multiple other solid tumors; however, they have not shown benefit in prostate cancer: a large phase II study of the PD-1 inhibitor pembrolizumab demonstrated an overall response rate of just 5% [6] and two phase III studies of the CTLA-4 inhibitor ipilimumab failed to meet their primary endpoint of improving overall survival [7,8]. However, in both studies there were other signs of antitumor activity in a specific subset. The prevailing conventional wisdom is that prostate cancer is generally a "cold" tumor and so, for ICIs to demonstrate benefit, either subsets of "hot" tumors must be selected or ICIs must be combined with other therapies that render the tumor more "hot" by affecting different parts of the cancer immunity cycle. Preclinically, cabozantinib has been shown to target myeloid-derived suppressor cells (MDSCs) and synergize with ICIs (cocktail of anti-PD-1 and anti-CTLA4 antibodies) in a CRPC model [9]. Cabozantinib has also been demonstrated to eradicate tumors in a PTEN/p53-deficient murine prostate cancer model through activation of neutrophil-mediated antitumor innate immunity [10]. Cabozantinib has demonstrated single agent activity in prostate cancer in a phase II study [11]. Cabozantinib was also tested in a phase III randomized (2:1) trial in men with progressive mCRPC after docetaxel and abiraterone plus prednisone and/or enzalutamide (N=1,028). Although cabozantinib failed significantly improve overall survival, its activity was demonstrated as measured by bone scan response, radiographic progression free survival, symptomatic skeletal related events, circulating tumor cell conversions, and bone biomarkers [12]. Thus, since neither cabozantinib nor ICIs have improved overall survival alone, cabozantinib may fill an unmet need in prostate cancer by synergizing with ICIs.

Cabozantinib (Cabometyx) is approved for treatment of patients with advanced renal cell carcinoma (RCC) and patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib[13]. Cabozantinib (Cometriq) is approved for treatment of patients with progressive, metastatic medullary thyroid cancer (MTC)[14]. Cabometyx is supplied as a tablet and Cometriq is supplied as a capsule; the two are not equivalent. The most commonly reported (≥ 25%) adverse reactions with cabozantinib (Cabometyx) in RCC studies are: diarrhea, fatigue, nausea, decreased appetite, hypertension, palmar-plantar erythrodysesthesia (PPE), weight decreased, vomiting, dysgeusia, and stomatitis[15]. In the COMET-1 study in heavily pre-treated mCRPC patients, the most common (≥ 25%) adverse events with cabozantinib were decreased appetite, nausea, diarrhea, fatigue, vomiting, asthenia, decreased weight, constipation, anemia, PPE syndrome, hypertension, dysphonia, and

dysgeusia [12]. SAEs were reported by 62% of patients in the cabozantinib arm. The following SAEs occurred at an incidence of at least 2% higher with cabozantinib compared with prednisone (comparator): pulmonary embolism (6.2% v 0.9%), vomiting (4.1% v 1.8%), fatigue (2.9% v 0.9%), and dehydration (2.9% v 0.3%). Study drug discontinuations because of AEs were reported for 33% of patients in the cabozantinib group. AEs leading to dose reductions or interruptions were reported for 88% of patients in the cabozantinib group, and AEs that led to dose reductions were reported for 67% of patients. Grade 5 AEs occurring within 30 days of the last study drug dose were reported in 15% of patients in the cabozantinib group and were most commonly considered disease related. The authors concluded that the safety data from the COMET-1 trial were consistent with those observed in earlier trials of cabozantinib in mCRPC, with no new or unexpected AEs observed.

2.2 STUDY RATIONALE

The COMET-1 study of cabozantinib in heavily pre-treated metastatic castration-resistant prostate cancer (mCRPC) patients did not meet its primary endpoint of improved overall survival compared with prednisone; however, cabozantinib did demonstrate activity in improving bone scan response, radiographic progression-free survival, symptomatic skeletal events, circulating tumor cell conversions, and bone biomarkers.[12] Furthermore, in subgroup analysis the point estimate of the unstratified hazard ratio for death for those with *visceral* metastases favored cabozantinib (HR=0.77; 95% CI: 0.54 to 1.09). Improved benefit of cabozantinib in visceral disease subgroups has also been demonstrated in two randomized trials in metastatic renal cell carcinoma.[16,17] While much of the development of cabozantinib in prostate cancer focused on its effects in bone,[18-20] we hypothesize that understanding its effects in soft tissue may contribute novel insights and shed light on a possible path forward for further development of cabozantinib in prostate cancer.

Neoadjuvant or pre-surgical studies permit *in vivo* assessment of response and mechanism of action after a short window of treatment.[21] We have demonstrated the safety and feasibility of using the VEGFR TKI sunitinib in the neoadjuvant or pre-prostatectomy setting.[22] Compared with soft tissue and bone biopsies, such an approach has the advantage of providing more plentiful amounts of whole-tumor and stromal tissue for analysis. Cabozantinib may function in prostate cancer partly through modulation of critical stromal interactions within the tumor microenvironment.

Study of the effects of cabozantinib in early stage prostate cancer, specifically in soft tissue prostatectomy specimens, may complement the knowledge gained from ongoing and completed studies in advanced disease. Other groups are currently studying cabozantinib in advanced prostate cancer (mCRPC), with the goals of: (1) determining the lowest effective dose of cabozantinib and correlating bone scan changes with MR imaging (Matthew R. Smith, MD, PhD, et al.); (2) developing cabozantinib biomarkers from bone and soft tissue biopsies and comparing 11C-acetate and 18F-fluoride PET/CT to monitor cabozantinib treatment response (Beatrice Knudsen and Evan Yu, PCF Creativity Award; Philip Febbo, Tia Higano et al., PCF Challenge award); and (3) investigating bone – tumor interactions and the development of resistance (Leland Chung et al., PCF Challenge award).

Understanding the effects of cabozantinib in soft tissue prostatectomy specimens may also confirm important *in vitro* and *in vivo* observations in prostate cancer models, providing rationale for novel combinations with cabozantinib. For example, emerging data in a chimeric mouse model of mCRPC suggest that cabozantinib may inactivate myeloid derived suppressor cells (MDSCs) and synergize with immune checkpoint blockade (specifically, anti-CTLA4 + anti-PD-1) to overcome *de novo* resistance.[9] Mechanistically, this stemmed from upregulation of interleukin-1 receptor antagonist and suppression of MDSC-promoting cytokines secreted by prostate cancer cells. A separate study in a pTEN/p53-deficient murine model of advanced prostate cancer has demonstrated that cabozantinib induces tumor clearance by triggering a neutrophil-mediated anti-cancer innate immune response.[10] Cabozantinib also affects M1 macrophage polarization mouse models of prostate cancer.[23] Finally, an *in vivo* and *in vitro* study suggested synergy between cabozantinib and the androgen receptor (AR) signaling inhibitor enzalutamide in CRPC.[24] Data like these must be confirmed in prospective clinical trials in humans with prostate cancer.

The HGF/cMET pathway appears to be generally immunosuppressive. MET is expressed by immature CD14+ monocytes which can acquire an immunosuppressive phenotype when exposed to HGF secreted by tumor stromal and/or and mesenchymal stem cells. Neutralization of HGF secretion by mesenchymal stem cells reverses this suppression of effector T-cell proliferation and triggers a shift to a TH1-activated T-cell phenotype.[25,26] Also, HGF secreted by tumor cells and by mesenchymal stem cells can result in the expansion of MDSCs (harboring cMET). This effect is likely mediated, at least in part, by phosphorylation of STAT3 (part of the HGF/cMET signal transduction pathway).[25] APC, such as dendritic cells, also express cMET which can be activated by HGF subsequently suppressing APC function, including both antigen presenting capacity and antigen-dependent T-cell responses both in vitro and in vivo.[27,28] cMET on tumor cells is associated with VEGF-A production which also has immunosuppressive properties.

In order to provide rationale for combination of cabozantinib with novel immunotherapies and AR-targeted therapies, a hypothesis-generating study of the effects of cabozantinib in soft tissue is clearly warranted. Therefore, with the goal of determining the soft tissue, stromal, cellular, immunologic, molecular and genetic effects of cabozantinib in patients with clinically localized prostate cancer, we propose the following prospective, randomized, open-label, phase II trial of cabozantinib in subjects with untreated, high risk prostate cancer prior to undergoing radical prostatectomy.

2.3 HYPOTHESES

We hypothesize that in those treated with cabozantinib followed by prostatectomy compared with immediate prostatectomy:

1. Apoptotic index (cleaved caspase-3) will be 2-fold higher in prostate cancer tissues following cabozantinib as compared with men proceeding to immediate radical prostatectomy.
2. Infiltration of neutrophils and release of neutrophil chemotactic factors (CXCL12 and HMGB1) will be 2-fold higher in prostate cancer tissues following cabozantinib as compared with men proceeding to immediate radical prostatectomy.

3. Interleukin-1 receptor antagonist will be upregulated and MDSC-promoting cytokines will be suppressed in prostate cancer tissues following cabozantinib as compared with men proceeding to immediate radical prostatectomy.
4. The M1 macrophage population will be decreased without affecting the M2 macrophage population in prostate cancer tissues following cabozantinib as compared with men proceeding to immediate radical prostatectomy.
5. Pathologic complete responses (pCRs) will be observed in the minority population of men harboring the TP53 mutant / PTEN null localized prostate cancer and will be associated with myeloid immune cell activation in the prostate and peripheral blood.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare pathologic apoptotic indices in prostatectomy specimens from patients who undergo immediate prostatectomy versus those treated with cabozantinib followed by prostatectomy.	Apoptotic index by cleaved caspase-3	To evaluate the activity of cabozantinib in prostate tumors by understanding its ability to cause cell death.
Secondary		
To conduct immune phenotypic profiling on the peripheral blood and tumor microenvironment in prostatectomy specimens from patients who undergo immediate prostatectomy versus those treated with cabozantinib prior to prostatectomy.	Description of immune biomarkers, including: • Immune phenotyping of paired peripheral blood and tumor tissue: Myeloid-derived suppressor cells (MDSCs), neutrophils, M1 macrophages, and M2 macrophages in tumor tissue • Immunohistochemical (IHC) analysis of CD8+, programmed death ligand-1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), interleukin-1 receptor antagonist (IL-1RA) and B7H3 in tumor tissue • Neutrophil chemotactic factors (CXCL12 and HMGB1) and MDSC-promoting	To confirm pre-clinical observations,[9,10,23] understand the effects of cabozantinib on the immune microenvironment, and evaluate the rationale for combination of cabozantinib with immune checkpoint inhibitor (ICI) therapy.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	cytokines (CCL5, CCL12, CD40) in tumor tissue	
Exploratory		
1. To estimate the pathologic complete response rate (pCR) and ≤pathologic T2 (≤pT2) rate in each arm.	1. Rates of pCR and ≤pT2	1. To understand the efficacy of cabozantinib as measured by key clinical pathologic endpoints.
2. To evaluate relapse-free survival in each arm.	2. Relapse-free survival rate at 3 years	2. To understand the efficacy of cabozantinib as measured by a key clinical endpoint.
3. To compare apoptosis (TUNEL), proliferation (Ki-67), and microvessel density (CD31) indices in prostatectomy specimens from patients who undergo immediate prostatectomy versus those treated with cabozantinib prior to prostatectomy.	3. Quantification of TUNEL, Ki-67, and CD31 staining	3. To describe the effects of cabozantinib on tumor tissue as measured by other standard pathologic parameters.
4. To measure expression levels of c-MET, VEGF, and HGF, as well as activation status of c-MET in prostate tissue.	4. Quantification of c-MET, VEGF, HGF, and activated c-MET in prostatectomy tissue	4. To evaluate effects on the c-MET/HGF axis.
5. To describe changes in plasticity signaling markers associated with prostate tumors, including vimentin, AR, SNAIL, AXL, and N-cadherin, with cabozantinib exposure	5. Correlation of changes in vimentin, AR, SNAIL, AXL, and N-cadherin with cabozantinib exposure	5. To describe effects on markers of epithelial-mesenchymal transitions (EMT).
6. To evaluate PTEN and p53 genomic and protein expression status in tumor tissue	6. Measurement of PTEN and p53 genomic and protein expression status in tumor tissue	6. To evaluate whether cabozantinib may be more active in a subset of pTEN/p53-deficient tumors.10
7. To demonstrate that cabozantinib is safe and tolerable in patients	7. Adverse events by CTCAE v5.0, dose intensity of cabozantinib.	7. To demonstrate that cabozantinib is safe and tolerable in patients

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
undergoing radical prostatectomy.		undergoing radical prostatectomy.
8. To demonstrate that surgery is safe and feasible in patients undergoing treatment with cabozantinib.	8. Blood loss at prostatectomy and duration of hospital stay.	8. To demonstrate that surgery is safe and feasible in patients undergoing treatment with cabozantinib.
9. To collect plasma angiome samples (multiplex ELISA) for analysis and correlation with primary and key secondary endpoints.	9. Angiome biomarkers.	9. To collect samples for possible later analysis and correlation with key endpoints
10. To describe gene expression patterns (in particular those associated with apoptosis, androgen receptor signaling, c-MET activation, and a c-MET-specific endocytosis panel) correlated with cabozantinib administration using RNA sequencing analysis.	10. Gene expression patterns.	10. To collect samples for possible later analysis and correlation with key endpoints.
11. To explore changes in serum and intratumoral androgen concentrations related to cabozantinib treatment.	11. Serum and intratumoral androgen concentrations.	11. To collect samples for possible later analysis and correlation with key endpoints.12
12. To collect cell-free DNA (cfDNA) for analysis and correlation with primary and key secondary endpoints.	12. Alterations in cfDNA	12. To collect samples for possible later analysis and correlation with key endpoints.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, randomized, open-label, phase II trial of cabozantinib in subjects with untreated, high risk prostate cancer undergoing radical prostatectomy. This multicenter study will enroll 30 subjects. Duke is the lead site for this trial. There will be a second site selected TBD. Patients will be

assigned or randomized to either: (A) cabozantinib 40 mg PO daily for 4 weeks, followed by a 2 week drug washout period before prostatectomy (n = 20), or (B) immediate prostatectomy (n = 10). The Safety Lead-In Cohort will consist of 6 subjects receiving cabozantinib prior to prostatectomy. The randomized portion will consist of the remaining cabozantinib prior to prostatectomy subjects (n=14) and immediate prostatectomy subjects (n=10).

The first 6 subjects assigned to cabozantinib treatment will constitute the *Safety Lead-In Cohort*, which will be only accrued at Duke. Of these subjects, the first 3 subjects will be enrolled sequentially (that is, after each prior subject completes the day 57-85 safety visit). This will constitute the *Safety Lead-In Cohort Part A.* After 3 cabozantinib treatment patients are accrued sequentially (Part A), the remaining 3 cabozantinib treatment subjects will be accrued non-sequentially, constituting the *Safety Lead-In Cohort Part B*.

If there are ≥2 dose-limiting toxicities (DLTs) in the first 6 subjects receiving cabozantinib, the trial will be stopped for safety purposes (*first stopping rule*). DLTs are defined as CTCAE v5 grade ≥2 wound dehiscence or wound complication, any grade fistula, grade ≥2 hemorrhage of any type, grade ≥3 infections [except urinary tract infections (UTIs) which are expected in this population], any AE that leads to permanent discontinuation of cabozantinib, or other grade ≥3 cabozantinib-related perioperative complications. The DLT period is defined as day 1 of drug through day 57 of the protocol (inclusive). The seventh subject randomized to cabozantinib may not be enrolled until the sixth subject completes the day 57-85 safety visit ***and*** the Duke principal investigator agrees that the stopping rule should not be put into effect.

After six subjects have received cabozantinib and completed the 57-85 day safety visit without triggering a stopping rule, subjects may be accrued at ex-Duke site(s). A *second stopping rule* will be triggered if there are ≥3 DLTs in the first 12 subjects treated with cabozantinib. In the event that a stopping rule is triggered, thorough review of the cabozantinib-treated patients' files will be performed and the Duke principal investigator will consider whether the trial can be redesigned or should be permanently discontinued.

4.2 CORRELATIVE STUDIES

Please see the lab manual for further details of these analyses.

Apoptosis

Cleaved Caspase-3. Caspase-3 is a central downstream executor of both the intrinsic and extrinsic apoptosis pathways, and is responsible for the proteolytic cleavage of key effector molecules such as nuclear poly (ADP-ribose) polymerase (PARP).[29] Cleavage of the zymogen form of caspase-3 to its active p17 and p12 fragments by caspase 8,9,10, or 12 is essential for downstream induction of apoptosis. The primary endpoint is comparison of apoptosis in prostatectomy specimens in cabozantinib-treated patients versus controls.

Comprehensive Immune Profiling

We will focus on comprehensive immune profiling of available samples representing the cabozantinib-treated and untreated tumor microenvironment (TE) as well as baseline and longitudinal PBMC samples in cabozantinib-treated and untreated patients in an attempt to identify both: (1) baseline signatures that predict which patients might benefit from cabozantinib, as well as (2) pharmacodynamic signatures that could provide mechanistic insights regarding therapeutic responses. The TE (tissue) will be analyzed in the laboratory of Dr. Jiaoti Huang (Duke Chair of Pathology). The profiling platform to be used to analyze the peripheral blood (PBMC) samples will be highly standardized, polychromatic flow cytometry assays that have been developed by the Duke Immune Profiling Core (DIPC; Director: Kent Weinhold, PhD) specifically for monitoring immune signatures in the context of immune checkpoint blockade trials.

Pathologic Response

Complete pathologic response (pCR) is defined as complete resolution of all cancerous glands in the prostatectomy specimen. Patients treated with cabozantinib who have pCR will be defined as *extraordinary responders*. Tissue from these patients' prostate biopsy will be collected for analysis and correlation with key correlative endpoints.

Relapse-free Survival

After completion of the treatment period (if applicable), prostatectomy, and safety follow up period (if applicable), patients will be followed for relapse-free survival, so that this rate may be estimated at 3 years (landmarked from the prostatectomy). *Relapse* is defined as biochemical recurrence (AUA guidelines), radiographic evidence of metastasis (in the opinion of the investigator), new treatment for prostate cancer or death. According to AUA guidelines, a biochemical recurrence is defined as a serum PSA ≥0.2 ng/mL, which is confirmed by a second determination with a PSA ≥0.2 ng/mL.

Apoptosis

TUNEL. Apoptotic index will be assessed in tissue biopsies and prostatectomy specimens from all patients using the TdT nick-end labeling technique.

Proliferation

Ki-67. Proliferation index (PI) will be assessed in tissue biopsies and prostatectomy specimens from all patients.

Angiogenesis

CD31. We will perform immunohistochemistry staining for CD31, an angiogenesis marker, in tissue biopsies and prostatectomy specimens from all patients on formalin-fixed tissue sections that are consecutive to those stained for apoptosis and proliferation.

HGF-c-MET Axis

c-MET. Tumor specimens will be evaluated for c-MET, HGF, and phospho-c-MET expression as a measure of pharmacodynamic response to cabozantinib treatment.

HGF/phospho-c-MET double stain. HGF is the ligand of the c-MET receptor and controls its activity through paracrine activation. HGF is secreted by prostate stromal cells and by inflammatory cells in the prostate stroma. HGF is also secreted by vascular smooth muscle cells. Stroma will be evaluated for expression of HGF as a measure of pharmacodynamic response to cabozantinib treatment.

Plasma Angiome

Blood for use in the plasma angiome multiplex ELISA will be collected as described previously.[30] Samples will be stored for possible future processing in the Phase I Biomarker Laboratory at Duke (Director: Andrew Nixon, PhD), Molecular Reference Laboratory for the Alliance Oncology Cooperative Group, a national clinical trial research group sponsored by the National Cancer Institute.

Gene Expression Analysis

The Affymetrix® U133A 2.0 Microarray, or similar, will be used for all analyses. Microarray hybridization and scanning will be performed as previously described.[31] A k-nn (nearest neighbor) analysis will be performed to identify genes that have their expression most closely associated with cabozantinib administration. Random permutation testing will be used to determine if the number of genes identified as having expression differences associated with cabozantinib administration is greater than would be expected by chance alone. Additional analyses can be performed to determine if particular patterns of gene expression are associated with response to cabozantinib. This analysis can initially be performed using pathologic response to cabozantinib as a dichotomous variable based on pre-established criteria. In this analysis, genes are identified in the control and cabozantinib-treated prostatectomy specimens that are most closely associated with response to cabozantinib using k-nn, similar to the analysis above. Using a similar dichotomous variable analysis, expression patterns will be correlated with VEGF and c-MET, HGF, and phospho-c-MET levels. Finally, we will test genes associated with apoptosis, androgen receptor signaling, c-MET activation,[32,33] and a c-MET-specific endocytosis panel[34,35] for correlation with response to cabozantinib. These studies will be performed and analyzed by Dr. Jennifer Freedman at the Duke Cancer Institute, Assistant Professor of Medicine and Research Scientist in the Genitourinary Oncology Laboratory. Dr. Freedman completed a postdoctoral fellowship in the Duke Institute for Genome Sciences and Policy (IGSP) and has experience analyzing gene expression and pathway signatures in human solid tumors.

Mesenchymal Markers

An exploratory endpoint of this study will be to describe changes in mesenchymal markers associated with cabozantinib treatment. We hypothesize that patients treated with cabozantinib will have evidence of mesenchymal markers to a lower degree than controls, indicative of a mesenchymal-epithelial transition (MET).

Intratumoral Androgens

The importance of ongoing steroidogenesis within prostate tumors, despite anorchid serum androgen levels, is now appreciated.[36] Two recently reported studies of androgen suppression in the neoadjuvant-to-prostatectomy setting demonstrated that the androgen receptor (AR) axis is still active despite near

total ablation of tissue dihydrotestosterone (DHT) levels and impressive rates of pCR and near-pCR.[37,38] Given the apparent inverse relationship between the AR and c-MET,[39] we hypothesize that patients treated with cabozantinib will have increased intratumoral androgen concentrations relative to the prostatectomy specimens of controls. In prostatectomy specimens, tissue androgen and androgen precursor levels (i.e. testosterone, DHT, DHEA, etc.) will be store for possible analysis by mass spectrometry (MS) using methods previously described.[40] The same androgen levels in serum will also be measured at baseline and prior to prostatectomy.

Cell-free DNA (cfDNA)

We will collect double-spun platelet poor plasma EDTA samples for circulating cfDNA analysis. Samples will be stored at -80°C for later analysis in a non-CLIA format.

4.3 DOSE

The first 6 subjects will constitute the *Safety Lead-In Cohort* and be assigned to cabozantinib 40 mg PO daily for 4 weeks, followed by a 2 week drug washout period before prostatectomy. The remaining subjects will be randomized to either: (1) cabozantinib 40 mg PO daily for 4 weeks, followed by a 2 week drug washout period before prostatectomy (n = 14), or (2) immediate prostatectomy (n = 10). The dose of cabozantinib is based on information from both the dose escalation and phase II randomized discontinuation trials in mCRPC patients.[41] This dose escalation trial by Smith et al. indicated that the impressive bone scan changes are demonstrated at the 40 mg dose with better tolerability that reported at the 100 mg dose. Because of this and the relatively high number of dose reductions and grade 3 adverse events on the phase III trial (COMET-1),[12] we believe that the 40 mg dose may have a more favorable risk-benefit ratio in the population of men with localized prostate cancer. The minimum two week washout period is based on both cabozantinib' s terminal half-life of approximately 120 hours (cabozantinib [XL-184] IB, Version 9.0) and extrapolation from neoadjuvant trials of anti-angiogenic agents in renal cell carcinoma.[42,43]

4.4 PROSTATECTOMY

Subjects will undergo a radical prostatectomy as part of their routine medical care at Day 43 (Arm A, cabozantinib) or Day 1 (Arm B, immediate prostatectomy). The surgeon must plan to use robotic or laparoscopic techniques with a low risk for conversion to open prostatectomy, in the opinion of the treating surgeon.

4.5 DEFINITION OF EVALUABLE SUBJECTS

Arm A subjects must complete 21 out of 28 days of planned cabozantinib dosing and proceed to prostatectomy within 14 (+3) days of their last dose of cabozantinib in order to be evaluable for this study's endpoints. Arm B subjects must receive a prostatectomy in order to be evaluable. Subjects who are not evaluable will be replaced.

5 TARGET POPULATION

5.1 INCLUSION CRITERIA

1. Male, age ≥ 18 years old.
2. Karnofsky Performance Status (KPS) of ≥ 70.
3. Histologic evidence of adenocarcinoma of the prostate who are deemed candidates for curative radical prostatectomy.
4. Planned robotic or laparoscopic prostatectomy technique.
5. Low risk for conversion to open prostatectomy, in the opinion of the treating surgeon.
6. Intermediate-high or high risk, clinically localized disease by the following criteria:
   - Prostate cancer in at least 2 cores with a Gleason score ≥ 7 (4+3 or 3+4) in at least 1 of those cores.
   - No definite evidence of metastasis, in the opinion of the investigator.
7. Adequate organ function as defined by the following criteria within 14 days prior to first dose of study treatment:
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3 x local laboratory upper limit of normal (ULN)
   - Total serum bilirubin ≤1.5 x ULN, (for subjects with Gilbert's disease ≤ 3 × ULN)
   - Absolute neutrophil count (ANC) ≥1500/L without granulocyte colony-stimulating factor support.
   - White blood cell count ≥ 2500/mm^3
   - Serum albumin ≥ 2.8 g/dl
   - Platelets ≥100,000/mm^3
   - Hemoglobin ≥9.0 g/dL
   - Serum calcium ≤12.0 mg/dL
   - Serum creatinine ≤ 2.0 x ULN or calculated creatinine clearance ≥ 30mL/min.
   - Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol).
8. Written Authorization for Use and Release of Health and Research Study Information (HIPAA authorization per institutional requirements)
9. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the trial.
10. Willing/able to adhere to the prohibitions and restrictions specified in this protocol.
11. Agrees to use a condom (even men with vasectomies) and another effective method of birth control if subject is having sex with a woman who is pregnant or a woman of childbearing potential while on study drug and for 4 months following the last dose of study drug.

5.2 EXCLUSION CRITERIA

Subjects cannot have the following:

1. Prior treatment for prostate cancer.
2. Major surgery or radiation therapy within 4 weeks of Day 1 on study.
3. Planned radiation therapy until at least 4 weeks after prostatectomy.

4. NCI CTCAE v5.0 grade 3 hemorrhage within 4 weeks of Day 1 on study.
5. Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test ≥ 1.3 × the laboratory ULN within 14 days before Day 1 on study (Arm A subjects only) or within 14 days of the completion of screening (Arm B subjects only)
6. Concomitant anticoagulation with oral anticoagulants (e.g., warfarin, direct thrombin and Factor Xa inhibitors) or platelet inhibitors (e.g., clopidogrel). However, low-dose aspirin for cardio protection is allowed (per local applicable guidelines).
7. History of or known metastatic prostate cancer.
8. QT_{cf} interval > 500 msec on baseline EKG.
9. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders:
        i. Symptomatic congestive heart failure (CHF) New York Heart Association Class 3 or 4, unstable angina pectoris, ongoing cardiac dysrhythmias of NCI CTCAE grade ≥2. coronary/peripheral artery bypass graft (CABG), within 6 months prior to screening.
        ii. Stroke (including transient ischemic attack [TIA]), cerebrovascular accident (CVA), myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism (PE)) within 6 months prior to screening.
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
        i. Evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose.

        Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose.
    c. Clinically significant hematuria, hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks before first dose.
    d. Serious non-healing wound/ulcer/bone fracture.
    e. Other clinically significant disorders that would preclude safe study participation.
10. Hypertension that cannot be controlled by medications (>140/90 mm Hg despite optimal medical therapy).
11. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.
12. Concurrent treatment on another clinical trial. Supportive care trials or non-treatment trials, e.g. QOL, are allowed.
13. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may

interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.
14. Inability to swallow tablets.
15. Diagnosis of another malignancy within 2 years before first dose of study treatment, except for superficial skin cancers, or localized, low grade tumors deemed cured and not treated with systemic therapy.

6 STUDY ASSESSMENTS

The first 6 subjects assigned to cabozantinib treatment will constitute the *Safety Lead-In cohort*, which will be only accrued at Duke. Of these subjects, the first 3 subjects will be enrolled sequentially (after each prior subject completes the day 57-85 safety visit). This will constitute the *Safety Lead-In Cohort Part A*. After 3 cabozantinib treatment patients are accrued sequentially, the remaining 3 cabozantinib treatment subjects will be accrued non-sequentially, constituting the *Safety Lead-In Cohort Part B*.

If there are ≥2 dose-limiting toxicities (DLTs) in the first 6 subjects receiving cabozantinib, the trial will be stopped for safety purposes (*first stopping rule*). DLTs are defined as CTCAE v5 grade ≥2 wound dehiscence or wound complication, any grade fistula, grade ≥2 hemorrhage of any type, grade ≥3 infections [except urinary tract infections (UTIs) which are expected in this population], any AE that leads to permanent discontinuation of cabozantinib, or other grade ≥3 cabozantinib-related perioperative complications. The DLT period is defined as day 1 of drug through day 57 of the protocol (inclusive). The seventh subject receiving cabozantinib may not be enrolled until the sixth subject completes the day 57-85 safety visit ***and*** the Duke principal investigator agrees that the stopping rule should not be put into effect. From the seventh subject on, subjects may be accrued at ex-Duke site(s). A second stopping rule will be triggered if there are ≥3 DLTs in the first 12 subjects treated with cabozantinib. In the event that a stopping rule is triggered, thorough review of the cabozantinib-treated patients' files will be performed and the Duke principal investigator will consider whether the trial can be redesigned or should be permanently discontinued.

Subjects assigned or randomized to receive cabozantinib will receive 28 days of study drug. The washout time between the last dose of cabozantinib and surgery will be 14 days (window: +3 days). Reasons for early discontinuation of cabozantinib may include evidence of disease progression, unacceptable toxicity associated with cabozantinib, withdrawal of consent, or other reasons that may impact on the subject's ability to undergo prostatectomy.

Subjects will be monitored closely for toxicity, and the cabozantinib dose may be adjusted from the 40 mg dose level to 20 mg daily according to individual patient tolerance. Patients will be assessed for adverse events every 2 weeks for the 4 weeks during cabozantinib treatment and at approximately 3 weeks and 4-6 weeks following the final day of cabozantinib administration.

Plasma and serum correlative studies will generally be drawn at baseline, day 29, and day 57-85 in the cabozantinib arm and baseline in the immediate prostatectomy arm. Tissue will be collected for analysis at prostatectomy on both arms.

See **Figures 2** and **3** below for full details of study assessments.

6.1 SCHEDULE OF EVENTS (SOE)

Figure 2: **SCHEDULE OF EVENTS**

Arm A: Cabozantinib

Assessment	Screening	Day						Relapse-free Follow up
	D -42 to -1	1 (+/- 3 days)	15 (+/- 3 days)	29 (+/- 3 days)	43 (+ 3 days)	50 (+/- 3 days)[1]	57-85 Safety Follow Up Visit	3 year follow up (from prostatectomy) [2]
Informed consent	X							
Medical history and demographics	X							
Interval history[3]		X	X	X		X	X	
Concomitant medicines	X	X	X	X		X	X	
Physical exam and vital signs[4]	X	X[5]	X	X		X	X	
Karnofsky Performance Status (KPS)	X	X[5]	X	X		X	X	
ECG	X							
Randomization[6]	X							
Toxicity assessment		X	X	X		X	X	
Dispensing of cabozantinib[7]		X						
Prostatectomy[8]					X			
Phone call or chart review[9]								X
Laboratory assessments								
CBC with differential[10]	X[11]	X	X	X		X	X	
Serum chemistries (CMP) [10]	X[11]	X	X	X		X	X	
Coagulation factors[10]	X[11]	X						
PSA[10]	X	X		X			X	
Testosterone[10]	X			X			X	
Thyroid function testing[10]		X		X			X[12]	
Urine Protein Creatinine Ratio[10]	X[11]	X	X	X		X	X	
Correlative/Research studies								
Plasma/serum cfDNA, immune, androgen, and angiome correlates[13]	X			X			X	
Retrieval of archival prostate biopsy tissue[14]							X	

1. In conjunction with the usual post-operative visit to remove the patient's foley catheter.
2. Follow up will occur every 3 months (+/- 1 month). Follow up may be obtained by a phone call, clinic visit or chart review.
3. Interval history consists of the following:
    a. Medical history collected as clinically indicated during standard of care clinic visits, which may include disease related symptoms (i.e. pain, changes in urination) and drug related side effects (i.e. bleeding, diarrhea, fatigue, etc.).
    b. Select imaging to rule out metastatic disease will be done as clinically indicated. Subjects will not routinely receive bone scan, CT, or MRI imaging unless there is clinical concern for possible metastatic disease.
    c. Interval history during the safety follow-up visit to include review of hospital course while patient underwent prostatectomy.
4. Vital signs must be performed at screening, day 1, day 15, day 29, day 50, and day 57-85 visit by a medical professional. Blood pressure, temperature, pulse, respiratory rate, height (at screening only) and weight will be collected.
5. Day 1 physical exam and KPS do not have to be repeated if screening physical exam and KPS were performed within 7 days prior to Day 1 visit. Vitals signs must be completed on Day 1 regardless of when they were collected during screening.
6. Randomization may take place any time before or on day 1, after the patient is confirmed to be eligible.
7. Cabozantinib will be administered at 40 mg daily for 28 days. A pill diary will be provided to the subject. Study drug will be dispensed directly from the clinic. Unused drug will be returned to the clinic.
8. Prostatectomy will occur 2 weeks (14 + 3 days) after the last dose of cabozantinib. Tissue will be procured for pathologic, molecular, and immunologic assessments.
9. Relapse free survival follow up may be captured over the telephone, clinic visit or chart review every 3 months +/- 1 month.
10. Laboratory assessments at the times indicated include:

    Complete blood count (CBC) with differential
    Serum chemistries (CMP): Sodium, Potassium, Chloride, Bicarbonate, blood urea nitrogen (BUN), Creatinine, Glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and LDH.
    Coagulation Factors: PT/INR or PTT will be drawn at baseline only.
    PSA
    Testosterone
    Thyroid function testing: Will include TSH and T4.
    Urine Protein Creatinine Ratio: UPCR=(Urine protein mg/dl)/ (urine creatinine mg/dl) = numerically equivalent to gm protein excreted in urine over 24 hours.
    Notes: Screening labs (except testosterone) must be completed within 7 days of day 1, or they must be repeated on day 1.
11. CBC with differential, CMP, coagulation factors and urine protein creatinine ratio must be completed within 14 days of Day 1 if subject is assigned or randomized to Arm A: Cabozantinib.
12. Thyroid function tests (TFTs) will be repeated at the safety follow up visit in those who require clinical intervention due to alteration in TFTs at an earlier time point.
13. Immune and androgen correlates will only be collected at baseline and on Day 29.
14. For extraordinary responders (i.e. pCRs) we will obtain archival tissue from their pre-prostatectomy prostate biopsy if available.

FIGURE 3: SCHEDULE OF EVENTS

Arm B: Immediate Prostatectomy

Assessment	Screening	Day	Relapse free Follow up
	D-42 to -1	1[1]	3 year follow up (from prostatectomy)
Informed Consent	X		
Medical History and Demographics	X		
Interval history[2]		X	
Concomitant Medicines	X		
Physical Exam[3]	X		
Karnofsky Performance Status (KPS)	X		
ECG	X		
Randomization[4]	X		
Prostatectomy[5]		X	
Phone call or chart review[6]			X
Laboratory assessments			
CBC with differential[7,8]	X		
Serum chemistries (CMP) [7,8]	X		
Coagulation factors[7,8]	X		
PSA[7]	X		
Testosterone[7]	X		
Urine Protein Creatinine Ratio[7, 8]	X		
Correlative/Research studies			
Plasma/serum cfDNA, immune, androgen and angiome correlates	X		

1 For this arm, "Day 1" is defined as the day on which the prostatectomy is performed. While the end of screening is labelled as Day -1 and the prostatectomy as Day 1, these days are not intended to be consecutive. It is expected that there will be intervening days in order to allow scheduling of the prostatectomy.

2 Interval history consists of the following:
   a. Medical history collected as clinically indicated during standard of care clinic visits, which may include disease related symptoms (i.e. pain, changes in urination) and drug related side effects (i.e. bleeding, diarrhea, fatigue, etc.).
   b. Select imaging to rule out metastatic disease will be done as clinically indicated. Subjects will not routinely receive bone scan, CT, or MRI imaging unless there is clinical concern for possible metastatic disease.

3 Vital signs must be performed at screening visit by a medical professional. Blood pressure, temperature, pulse, respiratory rate, height and weight will be collected.
4 Randomization may take place any time before or on day 1, after the patient is confirmed to be eligible.
5 With tissue procurement for pathologic, molecular, and immunologic assessments.
6 Relapse free survival follow up may be captured over the telephone, clinic visit or chart review every 3 months +/- 1 month.
7 Laboratory assessments at the times indicated include:

Complete blood count (CBC) with differential
Serum chemistries (CMP): Sodium, Potassium, Chloride, Bicarbonate, blood urea nitrogen (BUN), Creatinine, Glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and LDH.
Coagulation Factors: PT/INR or PTT.
PSA
Testosterone
Urine Protein Creatinine Ratio: UPCR=(Urine protein mg/dl)/ (urine creatinine mg/dl) = numerically equivalent to gm protein excreted in urine over 24 hours.

8 CBC with differential, CMP, coagulation factors and urine protein creatinine ratio must be completed within 14 days of the completion of screening if the subject randomized to Arm B: Immediate Prostatectomy.

6.2 INFORMED CONSENT

Authorized study personnel should fully explain the scope of the study to each subject before obtaining informed consent. Subjects should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy.

When obtaining informed consent, study personnel should:

First: Confirm that the subject is a potential candidate for study participation.

Next: Obtain dated and signed informed consent.

Finally: Confirm that the subject is eligible as defined in Section 5.0 (Inclusion/Exclusion Criteria). A record of subjects who fail to meet entry criteria (i.e., screening failures) will be maintained.

For subjects consented at the lead site ONLY, registration in the Duke clinical trial subject registry (i.e. Oncore) must be completed within 1 business day of the subject providing informed consent.

6.3 SCREENING- BOTH ARMS

The screening examination will take place within 42 days of initiation of therapy or surgery. An informed consent form must be signed by the subject before any study-specific screening procedure takes place.

Subject data to be collected at the Screening Examination includes:

- Informed consent process utilizing a signed and dated IRB-approved ICF
- Confirmation of inclusion/exclusion criteria

- Medical history including concomitant illnesses and oncologic history. Oncologic history must include specific documentation of prostate cancer histologic diagnosis.
- Prior and concomitant medications and non-pharmacologic treatments taken within 4 weeks of screening will be recorded.
- ECG
- Sample collection for the following laboratory evaluations (all standard-of-care except PT/INR and PTT):
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, LDH.
    - Urine protein creatinine ratio
    - Testosterone and PSA levels.
    - Prothrombin time (PT)/INR or partial thromboplastin time (PTT) test.
- Correlative samples will be drawn at screening. See lab manual for details.
- Physical examination to be conducted and height (cm), weight (kg), and vital signs (including temperature [°C], blood pressure [mmHg], heart rate [beats per minute], respiratory rate [breaths per minute]. Height will be collected at screening only.
- Karnofsky Performance Status (KPS)

Once the subject completes the screening examinations and is determined to be eligible, he will be assigned or randomized to arm A or arm B and enrolled.

Arm A

- Cabozantinib will be administered orally at 40 mg daily for 28 days
- 14 day + 3 days washout prior to prostatectomy
- Prostatectomy

Arm B

- Immediate prostatectomy

6.4 SUBJECT REGISTRATION AND ENROLLMENT

After signing informed consent, subjects will be registered with the lead site (Duke) and with their study site/institution. A record of subjects who fail to meet entry criteria (i.e., screen failures) will be maintained.

6.5 LEAD SITE REGISTRATION AND ENROLLMENT

Subject registration for all subjects signing informed consent will be completed by Duke University Medical Center Genitourinary Oncology Group. Following consent, documents will be submitted for review and registration of subject. Consented subjects will be assigned a unique study ID at registration.

Subjects will be enrolled only after all pre-treatment screening evaluations are completed, all eligibility criteria are met and the lead site reviews the Eligibility Checklist. Once the subject has signed consent and been found to meet all eligibility criteria with the approval from the lead site, the subject will be randomized, except for the Safety Lead-In Cohort subjects which will be assigned. Treatment must not commence until the subject has received approval from the lead site.

6.6 INSTITUTIONAL REGISTRATION

Subject registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, subjects will be asked to sign and date an Institutional Review Board (IRB)-approved consent form. Subjects must be registered with their local site/institution and with the lead site before beginning any treatment or study activities.

6.7 TREATMENT PERIOD

6.8 DAY 1 - ARM A ONLY

The following must be performed on Day 1 prior to dose of cabozantinib:

- Interval history
- Physical examination including major body systems. The Day 1 physical examination does not need to be performed if the screening physical examination was performed within 7 days of the Day 1 visit.
- Karnofsky Performance Status (KPS), body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate). The Day 1 KPS evaluation does not need to be performed if the screening KPS evaluation was performed within 7 days of the Day 1 visit.
- Assessment of concomitant medications, toxicities and treatments
- Dispense study drug to the patient
- Sample collection for the following laboratory evaluations if not done for screening with 7 days:
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, LDH.
    - Urine protein creatinine ratio
    - PSA level
    - Thyroid function testing: TSH and T4.

6.9 DAY 15 - ARM A ONLY

The following must be performed on Day 15:

- Interval history
- Physical examination including major body systems.

- Karnofsky Performance Status (KPS), body weight, and vital signs (temperature, blood pressure, heart rate, respiratory rate)
- Sample collection for the following laboratory evaluations:
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, LDH.
    - Urine protein creatinine ratio
- Assessment of concomitant medications, toxicities and treatments

6.10 DAY 29 - ARM A ONLY

The following procedures must be performed on Day 29:

- Interval history
- Physical examination including major body systems
- Karnofsky Performance Status (KPS), body weight, and vital signs
- Sample collection for the following laboratory evaluations:
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, LDH.
    - Urine protein creatinine ratio
    - PSA level
    - Testosterone level
    - Thyroid function testing: TSH and T4.
- Assessment of concomitant medications, toxicities and treatments
- Plasma/serum biomarker studies

6.11 DAY 43 - ARM A ONLY

The following procedures must be performed on Day 43:

- Prostatectomy
- Tissue procurement at the time of surgery for pathologic and research assessments.

6.12 DAY 50 - ARM A ONLY

The following procedures must be performed on Day 50:

- Interval history
- Physical examination including major body systems
- Karnofsky Performance Status (KPS), body weight, and vital signs

- Sample collection for the following laboratory evaluations:
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, LDH.
    - Urine protein creatinine ratio
- Assessment of concomitant medications, toxicities and treatments

6.13 SAFETY FOLLOW UP VISIT - ARM A ONLY

At the post-surgery follow-up visit, the following procedures should be performed:

- Interval history (to include review of hospital course while patient underwent prostatectomy)
- Assessment of any adverse events and tumor-related signs and symptoms
- Physical examination including major body systems
- Karnofsky Performance Status (KPS), body weight, and vital signs and other tests as necessary to follow unresolved or evaluate new adverse events
- Sample collection for the following laboratory evaluations:
    - Complete blood count (CBC) with differential: WBC count with differential, platelet count, hemoglobin, and hematocrit.
    - Serum chemistries: Sodium, potassium, chloride, blood urea nitrogen (BUN) or urea, creatinine, glucose, carbon dioxide (CO_2) or bicarbonate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, alkaline phosphatase, LDH.
    - Urine protein creatinine ratio
    - PSA level
    - Testosterone level
    - Thyroid function testing: TSH and T4. Thyroid function tests (TFTs) will be performed only for subjects who require clinical intervention due to alteration in TFTs at an earlier time point.
- Assessment of concomitant medications, toxicities and treatments
- Plasma/serum biomarker studies
- For extraordinary responders we will obtain archival tissue from their prostate biopsy pre prostatectomy

6.14 DAY 1 - ARM B ONLY

The following procedures must be performed on Day 1:

- Prostatectomy
- Tissue procurement at the time of surgery for pathologic and research assessments

6.15 RELAPSE FREE SURVIVAL FOLLOW UP PERIOD

Arm A and Arm B subjects will be followed for relapse free survival for 3 years from date of prostatectomy. Follow up will occur every 3 months (+/- 1 month). Follow up may be obtained by a phone call, clinic visit or chart review.

6.16 END OF STUDY

Reasons to discontinue the subject prior to 3 years include: biochemical progression, disease progression, new treatment for prostate cancer, withdrawal, or death. This determination may require obtaining outside records and interpretation by the investigator.

7 STUDY INTERVENTION

7.1 COMPOSITION, FORMULATION, AND STORAGE

At study sites, all study medication will be stored as described in the appropriate prescribing information and inventoried in accordance with applicable state and federal regulations.

7.2 INVESTIGATIONAL TREATMENT: CABOZANTINIB

Cabozantinib tablets are supplied as film-coated tablets containing cabozantinib malate equivalent to 20 mg and contain microcrystalline cellulose, lactose anhydrous, hydoxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate and Opadry® yellow. The 20-mg tablets are round. Doses of 40 mg will comprise two 20-mg tablets. The components of the tablets are listed in **Table 7-1**.

Table 7-1: Cabozantinib Tablet Components and Composition

Ingredient	Function	% w/w[a]
Cabozantinib Drug Substance (25% drug load as free base)	Active Ingredient	31.68
Microcrystalline Cellulose (Avicel® PH-102)	Filler	38.85
Lactose Anhydrous (60M)	Filler	19.42
Hydroxypropyl Cellulose (EXF)	Binder	3.00
Croscarmellose Sodium (Ac-Di-Sol®)	Disintegrant	6.00
Colloidal Silicon Dioxide	Glidant	0.30
Magnesium Stearate	Lubricant	0.75
Opadry® yellow film coating which includes HPMC 2910/hypromellose 6 cp, titanium dioxide, triacetin, and iron oxide yellow	Film Coating	4.00

[a] weight fraction, expressed in percentage; HPMC, hydroxypropyl methylcellulose

7.3 CABOZANTINIB ADMINISTRATION

Subjects will receive cabozantinib orally at a (starting) dose of 40 mg once daily. Study drug will be provided by Exelixis. Study drug should at all times be kept in the original packaging. Study drug will be

dispensed directly in clinic and returned at the end of 28 days. Cabozantinib will be supplied as 20 mg tablets in bottles of 30 tablets. Subjects will be given two bottles for their 28 day dosing. Doses of 40 mg will comprise two 20 mg tablets. A pill diary will be provided to keep accurate information on drug administration and any notes that the subject adds to the diary.

Cabozantinib must be taken on an empty stomach. Subjects must be instructed not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. Subjects should be instructed to take their cabozantinib dose at approximately the same time every day. If a subject misses a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. The missed dose should not be made up if it is within 12 hours of the next scheduled dose.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges and their products should be avoided by subjects taking cabozantinib.

In all subjects, dose reductions and delays to manage toxicity are allowed under the guidelines in Table 7.3

7.4 CABOZANTINIB DOSE MODIFICATIONS, INTERRUPTIONS, AND DISCONTINUATION

The following should be taken into consideration in decisions regarding dose modifications (reductions or interruption):

- As a general approach all AEs should be managed with supportive care at the earliest signs of toxicity considered related to the study treatment. Should this be ineffective, dose interruptions and/or reductions should be considered to prevent worsening of toxicity.

- The assigned starting dose for cabozantinib is 40 mg/day. One dose reduction level of cabozantinib to 20 mg/day is permitted (see Table 7-2).

- Dose modification criteria for cabozantinib are shown in Table 7-3. Dose interruptions and/or reductions should be implemented for unacceptable toxicity. Doses may be modified at any time while a subject is on treatment.

- Dose reductions or interruptions may also occur in the setting of lower grade toxicity than defined in Table 7-3, if the investigator feels it is in the interest of a subject's safety and will optimize drug tolerability.

- Interruption of cabozantinib treatment for cabozantinib-related AEs may occur at any time per investigator discretion. If treatment is interrupted due to related AEs for more than 1 week, cabozantinib should be discontinued unless there is unequivocal evidence that the subject is benefitting. In this situation, a subject may be able to restart therapy with a dose reduction upon resolution of the toxicity per the discretion of the investigator.

Guidelines for the management of specific AEs are provided in Section 7.4.2.

Table 7-2: Dose Reductions of Cabozantinib

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
40-mg cabozantinib oral qd	20-mg cabozantinib oral qd	No dose reduction permitted

Cabozantinib will be discontinued if a daily dose of 20-mg cabozantinib (minimum dose) is not tolerated

Table 7-3: Dose Modifications of Cabozantinib for Treatment-Related AEs

CTCAE v.5.0 Grade	Recommended Guidelines for Management[a]
Grade 1 AEs	Add supportive care as indicated. Continue cabozantinib treatment at the current dose level if AE is manageable and tolerable.
Grade 2 AEs which are tolerable and are easily managed	Continue cabozantinib treatment at the current dose level with supportive care.
Grade 2 AEs which are **intolerable** and **cannot be adequately managed**	At the discretion of the investigator, cabozantinib should be dose reduced or interrupted. Note: It is recommended that dose holds be as brief as possible.
Grade 3 AEs (except clinically non-relevant laboratory abnormalities)	Cabozantinib should be interrupted unless the toxicity can be easily managed with a dose reduction and optimal medical care. Note: It is recommended that dose holds be as brief as possible.
Grade 4 AEs (except clinically non-relevant laboratory abnormalities)	Subjects should have cabozantinib interrupted immediately. Discontinue cabozantinib unless the following criteria are met: • Subject is deriving clear clinical benefit as determined by the investigator • Toxicity can be managed with a dose reduction following recovery to Grade 1 (or baseline) and optimal medical care

Note: The dose delay and modification criteria for specific medical conditions are provided in Section 7.4.2 For re-treatment criteria of study treatment after a dose hold see Section 7.4.1.

[a]Study treatment dose adjustment is only needed if the toxicity was deemed related to cabozantinib treatment or had an unclear relationship to cabozantinib treatment.

7.4.1 CABOZANTINIB DOSE REINSTITUTION AND REESCALATION

If the subject recovers from his or her toxicities to CTCAE v.5.0 Grade ≤ 1 or to the baseline value (or lower) and the toxicity was unrelated to study treatment, then study treatment may be restarted with no change in dose.

If the subject recovers from his or her toxicities to Grade ≤ 1 or to the baseline value (or lower) the toxicity was deemed possibly related to study treatment, then study treatment may be restarted at a reduced dose (see Table 7-2 for the schedule of dose reductions).

Subjects receiving a daily dose of 20 mg may be restarted at the same dose if deemed safe at the discretion of the investigator. Subjects unable to tolerate a daily dose of 20 mg should discontinue study treatment.

Re-escalation to the previous dose, (but not higher than 40 mg/day) may be allowed at the discretion of the investigator for AEs which have resolved or recovered to Grade 1 (or baseline value) and deemed tolerable and easily managed by optimized supportive treatment. Dose re escalation is not allowed for a drug-related dose reduction triggered by Grade 4 hematologic toxicities or by Grade 4 AEs affecting major organs (e.g., central nervous system, cardiac, hepatic, renal).

7.4.2 GUIDELINES FOR MANAGEMENT OF POTENTIAL ADVERSE EVENTS

Subjects on Arm A receiving cabozantinib will be monitored for AEs from the time of taking the first dose of study drug through their last follow-up visit (30 days after the date of the last dose of cabozantinib treatment). Subjects will be instructed to notify their physician immediately at the onset of any AE. Seriousness, severity grade, and relationship to study treatment of AEs will be determined by the investigator. AE severity will be graded by the investigator in accordance with CTCAE v.5.0.

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption for cabozantinib.

7.4.2.1 CABOZANTINIB

The most frequent AEs experienced by ≥ 20% of subjects treated with cabozantinib in descending order of frequency were diarrhea, fatigue, decreased appetite, nausea, weight decreased, PPES, vomiting, constipation, hypertension, dysgeusia, dysphonia, asthenia, and dyspnea. For a full description of the safety profile of cabozantinib, refer to the Cabozantinib Investigator's Brochure.

Other medically important but less frequent AEs including arterial thrombotic AEs (e.g., transient ischemic attack [TIA], and myocardial infarction [MI]) and venous thrombotic AEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism), severe hemorrhagic events, proteinuria, wound healing complications, gastrointestinal (GI) perforation, abscesses including intra-abdominal and pelvic abscess, GI and non-GI fistula formation, osteonecrosis, and reversible posterior leukoencephalopathy syndrome (RPLS).

Adverse events associated with laboratory abnormalities experienced by ≥ 5% of subjects treated with cabozantinib in descending order of frequency were anemia, AST increased, ALT increased, hypothyroidism, hypokalemia, hypomagnesemia, thrombocytopenia, hypocalcemia, hypophosphatemia, lactate dehydrogenase (LDH) increased, lipase increased, neutropenia, hyponatremia, ALP increased, leukopenia, and hyperglycemia.

Adverse events may occur within the first few weeks in the course of treatment with cabozantinib, as cabozantinib is expected to reach steady state exposure at approximately 2 weeks following first dose. Events that generally have an early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, PPES, abdominal pain, mucosal inflammation, constipation, diarrhea, and vomiting. Adverse events should be managed with supportive care at the earliest signs of toxicity. Dose reductions and treatment interruptions should be considered. Dose reductions are recommended for events that, if persistent, could become serious or intolerable (Section 7.3).

Cabozantinib should be discontinued for the following AEs: visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic events, nephrotic syndrome, hypertensive emergency, persistent uncontrolled hypertension despite optimal medical management, and RPLS.

7.4.2.2 GASTROINTESTINAL DISORDERS

Gastrointestinal perforation, GI fistula, and intra-abdominal and pelvic abscess: After starting treatment with cabozantinib, subjects should be monitored for early signs of GI perforation such as abdominal pain, nausea, emesis, constipation, and fever especially if known risk factors for developing GI perforation or fistula (Turnage and Badgwell 2016) are present. Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

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. Guidelines for the evaluation and management of diarrhea are shown in **Table 7-4**. Administration of antidiarrheal/antimotility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, cabozantinib should be temporarily interrupted or dose reduced. When the diarrhea is controlled, retreatment with cabozantinib may be acceptable per investigator decision. In addition, general supportive measures should be implemented such as continuous oral isotonic hydration, correction of fluid and electrolyte abnormalities, small frequent meals, and stopping lactose-containing products, high-fat meals, and alcohol.

Recurrent or prolonged diarrhea can be associated with anal or perianal skin erosions which increase the risk for anal abscesses, fistulas, or proctitis. Good personal hygiene should be emphasized. Regular examinations of the perianal region should be performed whenever diarrhea has occurred during treatment with cabozantinib. Infections of the perianal region should be treated per local guidelines.

Table 7-4: Management of Diarrhea Associated with Cabozantinib

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue with study treatment and consider dose reduction • Initiate treatment with an antidiarrheal agent (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]) • Dietary modifications (e.g., small lactose-free meals, bananas and rice) • Intake of isotonic fluids (1-1.5 L/day) • Re-assess after 24 hours: o Diarrhea resolving to baseline bowel habits: gradually add solid foods and discontinue or decrease antidiarrheal treatment after 12 h diarrhea-free interval o Diarrhea not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Ask subject to attend clinic • Rule out infection (e.g., stool sample for culture) o Administer antibiotics as needed (e.g., if fever or Grade 3-4 neutropenia persists > 24 h) • Administer fluids (1-1.5 L/day orally or IV, as appropriate) for hydration or to correct electrolyte abnormalities • For Grade 3-4 or complicated lower grade diarrhea consider hospitalization and IV hydration • Re-assess after 24 h o Diarrhea resolving to baseline bowel habits or Grade ≤ 1: consider restarting study treatment at reduced dose o Diarrhea not resolving: Start and or continue antidiarrheal treatment (e.g., loperamide 4 mg followed by 2 mg after each episode of diarrhea [maximum: 16 mg loperamide per day]). Consider starting second line antidiarrheal or referral to gastroenterologist

Nausea and vomiting: Antiemetic agents are recommended as clinically appropriate for treatment or prophylaxis of nausea and vomiting, along with supportive care. Dehydration and electrolyte abnormalities may be associated with vomiting and monitoring for and correction of fluid and electrolyte disturbances should be implemented. Antiemetic medications should be assessed for potential drug interactions (refer to Section 8.2 for further details).

Dehydration: Dehydration events have been identified with comparable incidence and occurring in a shorter time to onset in the prostate cancer studies than previously experienced with cabozantinib in other tumor types. 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.

7.4.2.3 NON-GASTROINTESTINAL FISTULA

Complications from radiation therapy especially of the thoracic cavity including mediastinum have been identified as a possible predisposing risk factor for non-GI fistula formation in subjects undergoing treatment with VEGF pathway inhibitors.

Discontinue cabozantinib and initiate appropriate management in subjects who have been diagnosed with a non-GI fistula.

7.4.2.4 HEMORRHAGE

Hemorrhagic events, including serious and sometimes fatal events, have been reported with cabozantinib. Subjects should be monitored for bleeding events with serial complete blood counts and physical examination while on study. The risk of hemorrhage in cabozantinib-treated subjects with brain metastases has not been thoroughly analyzed. Subjects enrolled with treated and stable brain metastases should be monitored with a high index of suspicion if symptoms that could be due to a CNS hemorrhage occur.

Cabozantinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis (≥ 2.5 mL of red blood).

7.4.2.5 THROMBOEMBOLIC EVENTS

Thromboembolic events are frequent in cancer subjects due to procoagulant changes induced by the malignancy or anticancer therapy. DVT and pulmonary embolism have been observed in clinical studies with cabozantinib, including fatal events. Subjects who develop a pulmonary embolism and/or DVT should have study treatment interrupted until therapeutic anticoagulation is established. Treatment with cabozantinib may be resumed in subjects with pulmonary embolism or DVT if it is determined that the event is uncomplicated and that the subject is deriving clinical benefit from cabozantinib treatment and that anticoagulation does not place them at a significant risk that outweighs the benefit of resuming treatment per discretion of the investigator and according to individual protocols. Low molecular weight heparins are the preferred management for thrombotic events; oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines) are not allowed.

Arterial thrombotic events (e.g., TIA, MI) have been observed in studies with cabozantinib. Further treatment with cabozantinib should be discontinued in subjects who develop an acute MI, cerebral infarction, or any other clinically significant arterial thromboembolic complication.

7.4.2.6 HYPERTENSION

Table 7-5 provides treatment guidelines for hypertension deemed related to cabozantinib. Blood pressure should be monitored in a constant position visit to visit, either sitting or supine in a relaxed setting. Decisions to reduce or interrupt 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.

Cabozantinib should be discontinued in subjects with hypertensive emergency.

Table 7-5: Management of Hypertension Associated with Cabozantinib

Criteria for Dose Modifications	Treatment/Cabozantinib Dose Modification
Subjects NOT receiving optimized anti-hypertensive therapy	
> 150 mm Hg (systolic)[a] and < 160 mm Hg OR > 100 mm Hg (diastolic) and < 110 mm Hg	• Optimize antihypertensive medications by adding new or additional antihypertensive medications and/or increase dose of existing medications. • Reduce cabozantinib treatment by one dose level if optimal antihypertensive therapy (usually to include 3 agents) does not result in BP <150 mm Hg systolic or <100 mm Hg diastolic • If subject is symptomatic interrupt cabozantinib treatment
≥ 160 mm Hg (systolic) OR ≥ 110 mm Hg (diastolic)	• Reduce cabozantinib by one dose level[b] or interrupt cabozantinib treatment per investigator discretion • Add new or additional anti-hypertensive medications and/or increase dose of existing medications and monitor subject closely for hypotension. If optimized antihypertensive therapy (usually to include 3 agents) does not result in BP < 150 mm Hg systolic or < 100 mm Hg diastolic, cabozantinib treatment should be dose reduced further or interrupted • Cabozantinib treatment should be dose interrupted if upper limits of systolic BP (≥ 160 mm Hg) are sustained and not adequately manageable or if systolic BP is > 180 mm Hg or diastolic BP > 110 mm Hg, or if subject is symptomatic • Re-start cabozantinib treatment at the most tolerable dose and re-escalate only if BP falls to and is sustained at < 150 mm Hg systolic and < 100 mm Hg diastolic
Hypertensive emergency[c]	• Discontinue cabozantinib treatment

BP, blood pressure.

[a] The investigator may decide to initiate or adjust antihypertensive treatment at a lower threshold than systolic BP >150 or diastolic BP >100 based on their clinical judgment and assessment of the individual subject.

[b] Permitted dose levels are defined by individual protocols.

[c] Hypertensive emergency is defined as uncontrolled elevated BP with clinical evidence of progressive or impending end-organ damage (e.g., myocardial infarction/ischemia, intracranial hemorrhage, cerebral ischemia, pulmonary edema, encephalopathy, kidney damage).

7.4.2.7 STOMATITIS AND MUCOSITIS

Preventive measures may include a comprehensive oral examination to identify and treat any potential risk for 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 and non-irritating cleansing, and oral rinses (e.g., with a weak solution of salt and baking soda) should be maintained. Lips should be kept moisturized with lip balm. The use of lipstick, lip-gloss, and Vaseline should be avoided.

Local treatment should be instituted at the earliest onset of symptoms. Obtain bacterial/viral culture if oral infection is suspected and treat infection as clinically indicated.

7.4.2.8 SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Wound healing and surgery: Cabozantinib has the potential to cause wound healing complications and wound dehiscence which may even occur long after a wound has been considered healed. Therefore, surgical and traumatic wounds must not only be completely healed prior to starting cabozantinib treatment but must also be monitored for wound dehiscence, wound infection and other signs of impaired wound healing while the subject is being treated with cabozantinib. If dehiscence occurs, cabozantinib treatment should not be restarted until complete healing has taken place.

Palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand-foot syndrome), skin rash (including blister, erythematous rash, macular rash, skin exfoliation, dermatitis acneiform, and papular rash), pruritus, dry skin, erythema, pigmentary changes, and alopecia have been reported with cabozantinib. All subjects on study should be advised on prophylactic measures including the use of emollients, removal of calluses, avoidance of exposure of hands and feet to hot water leading to vasodilatation, protection of pressure-sensitive areas of hands and feet, and use of cotton gloves and socks to prevent injury and keep the palms and soles dry.

Early manifestations include tingling, numbness, mild hyperkeratosis, and 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. Analgesics may be required for pain control.

Aggressive management of symptoms is recommended, including early dermatology referral. Treatment recommendations in response to PPES are summarized in **Table 7-6**.

Table 7-6: Management of Hand-Foot Syndrome (PPES) Associated with Cabozantinib

CTCAE v.5.0 Grade	Action To Be Taken
Grade 1	Cabozantinib treatment may be continued at the current dose if PPES is clinically insignificant and tolerable. Otherwise, cabozantinib should be reduced to the next lower dose level.[a] Start urea 20% cream twice daily AND clobetasol 0.05% cream once daily. Reassess at least weekly; if PPES worsens at any time or does not improve after 2 weeks, proceed to the intervention guidelines for Grade 2.
Grade 2	Cabozantinib treatment may be continued if PPES is tolerated. Cabozantinib should be dose reduced or interrupted if PPES is intolerable. Continue urea 20% cream twice daily AND high potency steroid cream (e.g., clobetasol 0.05%) once daily and add analgesics (e.g., NSAIDs/gamma-aminobutyric acid agonists) for pain control if needed. Reassess at least weekly; if PPES worsens or affects self-care, proceed to the intervention guidelines for Grade 3.
Grade 3	Interrupt cabozantinib treatment until severity decreases to Grade 1 or 0. Continue treatment of skin reaction with high potency steroid cream (e.g., clobetasol 0.05%) twice daily AND analgesics. Resume study drug at a reduced dose if PPES recovers to Grade ≤ 1. Discontinue subject from study treatment if PPES does not improve within 6 weeks.

CTCAE, Common Terminology Criteria for Adverse Events; NSAID, non-steroidal anti-inflammatory drug; PPES, palmar plantar erythrodysesthesia syndrome.

[a] Permitted dose levels are defined by individual protocols.

7.4.2.9 OSTEONECROSIS

Osteonecrosis has been reported in subjects treated with cabozantinib. Additional risk factors include use of bisphosphonates and denosumab, chemotherapy and anti-angiogenic drugs, use of corticosteroids, local radiotherapy, and dental or orofacial surgery procedures.

Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of osteonecrosis.

Advise subjects regarding oral hygiene practice and to quickly report symptoms to investigator. Caution should be used in subjects receiving bisphosphonates.

Invasive dental procedures should be avoided. In cases where dental procedures are unavoidable, treatment with cabozantinib should be interrupted for at least 4 weeks prior to the procedure and resumed after complete wound healing has occurred. Bone healing may often require a protracted time.

Cabozantinib will be permanently be discontinued in subjects who develop osteonecrosis of the jaw.

7.4.2.10 PROTEINURIA

Proteinuria has been reported with cabozantinib. Proteinuria should be monitored by measuring UPCR. **Table 7-7** provides treatment guidelines for proteinuria deemed related to cabozantinib.

Cabozantinib should be discontinued in subjects who develop nephrotic syndrome (proteinuria > 3.5 grams per day in combination with low blood protein levels, high cholesterol levels, high triglyceride levels, and edema).

Table 7-7: Management of Proteinuria Associated with Cabozantinib

Severity of Proteinuria (UPCR)	Management of Proteinuria
≤ 1 mg/mg (≤ 113.1 mg/mmol)	• No change in cabozantinib treatment or monitoring
> 1 and < 3.5 mg/mg (> 113.1 and < 395.9 mg/mmol)	• Consider confirming with a 24-h protein assessment within 7 days • No change in cabozantinib treatment required if UPCR ≤ 2 mg/mg or urine protein ≤ 2 g/24 h on 24-h urine collection. • Dose reduce or interrupt cabozantinib treatment if UPCR > 2 mg/mg on repeat UPCR testing or urine protein > 2 g/24 h on 24-h urine collection. Continue cabozantinib on a reduced dose if UPCR decreases to < 2 mg/mg. Consider interrupting cabozantinib treatment if UPCR remains > 2 mg/mg despite a dose reduction until UPCR decreases to < 2 mg/mg. Restart cabozantinib treatment at a reduced dose after a dose interruption. • Repeat UPCR within 7 days and once per week. If UPCR < 1 mg/mg on 2 consecutive readings, UPCR monitoring can revert to protocol-specific times. (Second reading is confirmatory and can be done within 1 week of first reading.) If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
≥ 3.5 mg/mg (≥ 395.9 mg/mmol)	• Interrupt cabozantinib treatment pending repeat UPCR within 7 days and/or 24-h urine protein. • If ≥ 3.5 mg/mg on repeat UPCR, continue to interrupt cabozantinib treatment and check UPCR every 7 days. If UPCR decreases to < 2 mg/mg, restart cabozantinib treatment at a reduced dose and monitoring of urine protein/creatinine should continue weekly until the UPCR decreases to < 1 mg/mg. If UPCR remains > 1 mg/mg and < 2 mg/mg for 1 month or is determined to be stable (< 20% change) for 1 month, check urine protein/creatinine per protocol or as clinically indicated.
Nephrotic syndrome	• Discontinue cabozantinib treatment

RCC, renal cell carcinoma; UC, urothelial carcinoma; UPCR, urine protein/creatinine ratio.

7.4.2.11 NERVOUS SYSTEM DISORDERS

Cabozantinib appears to represent minimal risk of adverse neurological effects based on nonclinical Good Laboratory Practice (GLP)-compliant toxicology studies. Dysphonia, dysgeusia, headache, dizziness, confusional state, convulsion, depression, memory impairment, hypoesthesia, peripheral neuropathy, insomnia, ataxia, and encephalopathy have been observed in clinical studies with cabozantinib. The development of any new or progressive, unexplained neurological symptoms should be assessed for underlying causes.

RPLS has been reported. RPLS should be considered in any subject presenting with seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in subjects with RPLS.

7.4.2.12 HEPATOCELLULAR TOXICITY

Elevation of aminotransferases (ALT and AST): Evaluation of subjects with elevated transaminases or bilirubin should be individualized and guided by the presence of specific risk factors such as liver conditions (e.g., liver cirrhosis, metastases to the liver, thrombosis of portal or hepatic vein, hepatocellular carcinoma, hepatitis), concomitant hepatotoxic medication, alcohol consumption, and cancer related causes.

Cabozantinib should be interrupted for related CTCAE Grade 3 or higher hepatic injury (transaminase increase to > 5 × ULN) and when transaminase increases are accompanied by progressive elevations of total bilirubin, and/or elevations of coagulation tests (e.g., International Normalized Ratio [INR]). More frequent monitoring of transaminases should be considered and cabozantinib should be interrupted until the etiology of the abnormalities is determined and these abnormalities are corrected or stabilize at clinically acceptable levels. Cabozantinib should be discontinued if hepatic dysfunction is not reversed despite interruption of study treatment. Elevations of aminotransferases when hepatic metastases are present may not require dose modifications if there are no progressive changes in the aminotransferases (less than a doubling) and if there are no progressive elevations in serum bilirubin concentration or coagulation factors. Elevations >3 × ULN of ALT or AST concurrent with >2 × ULN total bilirubin without other explanation (such as initial findings of cholestasis and obstructive disease, viral hepatitis, pre-existing or acute liver disease, or another drug capable of causing the observed injury) can indicate drug-induced liver injury (DILI). Study drug should be permanently discontinued in cases determined to be DILI according to Hy's Law review.

7.4.2.13 INFECTIONS AND INFESTATIONS

Infections are commonly observed in cancer subjects. Predisposing risk factor include a decreased immune status (e.g., after myelosuppressive anticancer therapies, splenectomy), destructive growth of the underlying malignancy including bone marrow infiltration with suppression of normal hematopoiesis, as well as the presence of IV devices.

Infections and abscesses should be treated with appropriate local care and systemic therapy. Cabozantinib should be interrupted until adequate healing has taken place.

7.4.2.14 BLOOD AND LYMPHATIC SYSTEM DISORDERS

Hematological toxicities (i.e., neutropenia and thrombocytopenia) and associated complications have been observed after administration of cabozantinib and may be managed with dose interruptions

and/or dose reductions. Subjects with hematologic toxicities may require additional or more frequent laboratory tests according to institutional guidelines.

Dose reductions or dose interruptions for hematological toxicities are not mandated but can be applied as clinically indicated. Supportive care for thrombocytopenia or anemia, such as transfusions, may be managed according to institutional guidelines. The use of colony-stimulating growth factors should be considered. Febrile neutropenia or evidence of infection associated with neutropenia must be assessed immediately and treated appropriately and in a timely manner according to institutional guidelines.

7.4.2.15 FATIGUE

Common causes of fatigue, such as anemia, deconditioning, emotional distress (depression and/or anxiety), poor nutrition, dehydration, sleep disturbance, and hypothyroidism should be ruled out and treated according to standard of care. Pharmacological management should be considered after disease specific morbidities have been excluded when not prohibited.

7.4.2.16 WEIGHT LOSS

Anorexia and weight loss should be managed according to local standard of care including nutritional support. Pharmacologic therapy should be considered for appetite enhancement when not prohibited by a particular protocol.

7.4.2.17 CORRECTED QT PROLONGATION

The effect of orally administered cabozantinib 140 mg qd on QTc interval was evaluated in a placebo-controlled study in subjects with MTC. A mean increase in QTcF of 10-15 ms was observed after 4 weeks after initiating cabozantinib treatment. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated subjects in this study had a QTcF > 500 ms. Review of the larger safety database (~5000 subjects exposed to cabozantinib in clinical trials and in post-marketing experience) confirmed the absence of safety concerns associated with QT prolongation. There were no events of torsades de pointes reported.

Concomitant treatment with strong cytochrome P450 (CYP) 3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be avoided.

If at any time on study there is an increase in QTcF to an absolute value > 500 ms, two additional ECGs must be performed with intervals not less than 3 min apart within 30 min after the initial ECG.

If the average QTcF from the three ECGs is > 500 ms, the following actions must be taken:

- Interrupt cabozantinib treatment
- Hospitalize symptomatic subjects (e.g., with palpitations, dizziness, syncope, orthostatic hypotension, a significant ventricular arrhythmia on ECG) for a thorough cardiology evaluation and management
- Consider cardiology consultation for asymptomatic subjects for evaluation and management
- Check electrolytes, especially magnesium, potassium and calcium; correct abnormalities as clinically indicated

- Check concomitant medications for any medication that may have contributed to QT prolongation, and if possible, discontinue these medications (http://www.qtdrugs.org)
- Repeat ECG triplicates hourly until the average QTcF is ≤ 500 msec, or otherwise determined by consultation with a cardiologist or appropriate expert.

Subjects with QTc prolongation and symptoms must be monitored closely until the QTc elevation and symptoms have resolved. Cabozantinib treatment may be restarted at a reduced dose level if all of the following conditions are met:

- Symptoms are determined to be unrelated to the QT interval prolongation
- The QTcF value > 500 ms is not confirmed
- Cabozantinib treatment has been interrupted through a minimum of 1 week following the return of the QTcF to ≤ 500 ms.
- QT prolongation can be unequivocally associated with an event other than cabozantinib administration and is treatable/has been resolved

Following reinitiation of study treatment, ECGs must be repeated weekly for 2 weeks, then every 2 weeks for 1 month, then according to the protocol-defined time points.

Cabozantinib treatment must be permanently discontinued if either of the following applies:

- Cardiac evaluation confirms that symptoms are the consequence of QT interval prolongation
- Recurrence of QTcF prolongation after reinitiation of study treatment at a reduced dose

7.4.2.18 ELECTROLYTE DISORDERS

Serum electrolyte disorders including hyponatremia, hypokalemia, hypomagnesemia, and hypophosphatemia have been reported during treatment with cabozantinib, and serum electrolyte levels should be monitored frequently while receiving cabozantinib. Clinically relevant electrolyte disorders should be managed according to the dose modification guidelines as outlined in Section 7.3 or as clinically indicated. Standard clinical practice guidelines should be used for management of electrolyte disorders and may include oral or intravenous replacement.

7.4.2.19 ENDOCRINE DISORDERS

Treatment-emergent elevation of thyroid-stimulating hormone (TSH) has been observed with cabozantinib treatment. Currently available data are insufficient to determine the mechanism of thyroid function test alterations and its clinical relevance. Management of thyroid dysfunction (e.g., symptomatic hypothyroidism) should follow accepted clinical practice guidelines.

7.4.2.20 ANGIOEDEMA

Angioedema should be managed according to standard practice. The subject should be observed until symptoms resolve, with particular attention to maintaining an open airway.

8 CONCOMITANT THERAPY

8.1 ALLOWED, PROHIBITED AND RESTRICTED THERAPIES

Allowed Therapy

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g., ASCO or ESMO guidelines).

- Bisphosphonates can be used to control bone loss or hypocalcemia if the benefit outweighs the risk per the investigator's discretion.

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates (Section 7.4.2.9). Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.

- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.

- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:

  - *Therapeutic doses of LMWH* after first dose of study treatment are allowed if clinically indicated (e.g., for the treatment of deep venous thrombosis), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 7.4.2.5.

  - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (e.g., due to kidney dysfunction).

  - For restrictions on oral anticoagulants see below.

Potential drug interactions with cabozantinib are summarized in Section 8.2.

Prohibited or Restricted Therapy

The following therapies are prohibited during the 28 day treatment with cabozantinib on ARM A:

- Any investigational agent or investigational medical device.

- Oral anticoagulants (e.g., warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).

- Any nonprotocol systemic anticancer treatment (e.g., chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).

The following therapies should be avoided during the 28 day treatment with cabozantinib on ARM A.

- Please review medications taken by the subject with your pharmacist/physician as this is not an all inclusive list of medications that may interact with cabozantinib.

- Erythropoietic stimulating agents (e.g., epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).

- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects who receive cabozantinib until they have permanently discontinued cabozantinib treatment (refer to *http://www.qtdrugs.org* for a list of drugs which have the potential to prolong the QTc interval).

- Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

- 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.

- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (e.g., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided.

Additional information on potential drug interactions with cabozantinib is provided in Section 8.2.

8.2 POTENTIAL DRUG INTERACTIONS WITH CABOZANTINIB

Cytochrome P450: 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 area under the plasma concentration-vs-time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared to CYP2C8 (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 and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical

pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% 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., boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. 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 refer to the drug interaction tables at the following websites for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

Http://medicine.iupui.edu/clinpharm/ddis/table.aspx

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm).

Protein Binding: Cabozantinib is highly bound (≥ 99.7%) 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).

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but it does appear to have the potential to inhibit the P-glycoprotein transport activity. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-glycoprotein. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (i.e., PPIs, H_2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

Additional details regarding potential drug interactions with cabozantinib can be found in the investigator brochure.

Cabozantinib was shown to be a substrate of drug transporter MRP2 in an in vitro assay. Administration of MRP2 inhibitors to subjects may result in increases in cabozantinib plasma concentrations.

8.3 STUDY TREATMENT ACCOUNTABILITY

The investigator or designee will maintain accurate records of receipt of all study treatment including dates of receipt. In addition, accurate records will be kept regarding the date, lot number, 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 study treatment will be reconciled and destroyed according to applicable state, federal, and local regulations.

9 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

9.1 DISCONTINUATION OF STUDY INTERVENTION

At any time, the study may be terminated by the study sponsor, the sponsoring institution, or by Exelixis. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the investigator(s) shall cease enrolling subjects into the study, and shall discontinue conduct of the study as soon as is medically practicable.

10 SAFETY

10.1 ADVERSE EVENTS AND LABORATORY ABNORMALITIES

10.1.1 ADVERSE EVENTS (AES)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event can arise from any use of the drug (e.g. off-label use, use in combination with another drug) and with any route of administration, formulation, or dose,

including an overdose. This definition also includes AEs associated with medication errors and uses of the investigational product outside what is in the protocol, including misuse and abuse. Pre-existing medical conditions that worsen during the study should be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in this protocol. All untoward events that occur from the first dose of study drug through 30 days after the decision to discontinue study treatment (or the date the subject is deemed to be a screen failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits and includes the new onset of or increase in pain during this period.

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade, and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the current version of the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE).

10.1.2 SERIOUS ADVERSE EVENTS (SAES)

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

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

- Result in death;
- Is life-threatening (i.e., in the opinion of the investigator, the AE places the subject at risk of death; it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
    - Note: While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows: elective or previously scheduled surgeries or procedures for pre-existing conditions that have not worsened after initiation of treatment (e.g., a previously scheduled ventral hernia repair); pre-specified study hospitalizations for observation; or events that result in hospital stays of fewer than 24 hours and that do not require admission (e.g., an ER visit for hematuria that results in a diagnosis of cystitis and discharge home on oral antibiotics). SAEs must, however, be reported for any surgical complication resulting in prolongation of the hospitalization.
- Results in persistent or significant disability or incapacity:
    - Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.

- Is a congenital anomaly or birth defect;
- Is an important medical event (IME):
    - Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed. Examples of IMEs include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

10.1.3 RELATIOSHIP TO STUDY TREATMENT

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

- Not Related: A not-related AE is defined as an AE that is not associated with the study treatment and is attributable to another cause or there is no evidence to support a causal relationship;
- Related: A related AE is defined as an AE where a causal relationship between the event and the study treatment is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment. Possibly and probably related AEs should be documented as related.

10.1.4 SERIOUS ADVERSE EVENT REPORTING

As soon as an investigator becomes aware of an AE that meets the definition of ‘serious,’ this must be documented on an SAE Report Form and include the following: (i) all SAEs that occur after starting cabozantinib and through 30 days after the decision to discontinue study treatment and (ii) any SAEs assessed as related to study treatment or study procedures (for patients on the cabozantinib arm), from the time of informed consent, even if the SAE occurs more than 30 days after the decision to discontinue study treatment. The prostatectomy is considered a standard of care procedure, not a study procedure. SAEs solely related to the prostatectomy will not be collected.

All SAEs that are assessed by the PI as **related** to drug or study procedure and all pregnancy/lactation reports regardless of outcome must be sent to the Duke Safety Desk within one (1) business day of the PI’s knowledge of the event. The Duke Safety Desk will report to Exelixis within one (1) business day of the receipt of the report. The reports must be sent to drugsafety@exelixis.com or fax 650-837-7392.

- The PI will perform adequate due diligence with regard to obtaining follow-up information on incomplete reports. All follow-up information must be sent to Exelixis within one (1) business

day of the PI's receipt of the new information. Upon Exelixis request, the PI will query for follow-up information.

10.1.5 REGULATORY REPORTING

The Investigator will assess the expectedness of each related SAE. The current cabozantinib Reference Safety Information (Appendix K of the most recent approved Investigator Brochure) will be used as the reference document for assessing the expectedness of the event with regard to cabozantinib. All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to all appropriate regulatory authorities and Ethics Committees by the investigator as required by 21 CFR 312.32 or by Directive 2011/20/EC:

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) or a CIOMS-1 form;
- Exelixis reserves the right to upgrade the Investigator assessment of an SAE based on Exelixis assessment.
- Institutions and PIs shall promptly provide all information requested by Exelixis regarding all adverse events occurring during the conduct of the study.
- The PI is responsible for complying with all regulatory authority reporting requirements for the study that are applicable to the sponsor of a clinical trial. The PI shall provide a copy of all responses to regulatory agency requests, periodic reports, and final study reports to Exelixis within one (1) business day of the submission.
- Exelixis will provide relevant product safety updates and notifications, as necessary. In the case of multi-center studies, it is the responsibility of the sponsoring PI/Institution to disseminate these updates to participating PIs.

10.2 OTHER SAFETY CONSIDERATIONS

10.2.1 LABORATORY DATA

All laboratory data required by this protocol and any other clinical investigations should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the investigator should be reported as an AE or SAE as appropriate.

10.2.2 PREGNANCY/LACTATION EXPOSURE

Pregnancy in partner, although not an SAE, should be reported to Exelixis. The partner will be asked to sign a pregnant partner form allowing collection of her information and the offspring. The outcome of a pregnancy (for the partner of a subject) and the medical condition of any resultant offspring must be reported to Exelixis, if the pregnant partner agrees. Any birth defect or congenital anomaly must be

reported as an SAE, and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

10.2.3 MEDICATION ERRORS/OVERDOSE

Any overdose, or study drug administration error that results in an AE, even if it does not meet the definition of serious, requires reporting within one (1) business day to Exelixis.

10.2.4 FOLLOW-UP OF ADVERSE EVENTS

Any related SAEs or any AEs assessed as related that led to treatment discontinuation, including clinically significant abnormal laboratory values that meet these criteria, ongoing 30 days after the decision to discontinue study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur more than 30 days after the decision to discontinue study treatment. The status of all other continuing AEs will be documented as of 30 days after the decision to discontinue study treatment.

10.3 SAFETY MONITORING

Safety data will be monitored by the PI, urology co-PI and statistician by regular reviews. This monitoring is separate, but complementary to the stopping rules.

A safety assessment will at the following time points:

- The first 6 subjects receiving cabozantinib treatment have completed the day 57-85 safety visit.
- The first 12 subjects receiving cabozantinib treatment have completed the day 57-85 safety visit.
- The first 18 subjects receiving cabozantinib treatment have completed the day 57-85 safety visit.

The statistician or their designee will compile a report of all AEs documented on study, including any SAEs and DLTs. The PI and urology co-PI will review the report and determine if the safety data warrant a change to the study. Enrollment will not be suspended for the safety assessments.

11 STATISTICAL CONSIDERATIONS

11.1 STATISTICAL METHODS

Safety Lead-In and Stopping Rules. The first 6 subjects assigned to cabozantinib treatment will constitute the *Safety Lead-In cohort*, which will be only accrued at Duke. Of these 6 subjects receiving cabozantinib, the first 3 subjects will be enrolled sequentially (after each prior subject completes the day 57-85 safety visit). After this, the remaining 3 subjects receiving cabozantinib may be enrolled non-sequentially in the cohort. If there are ≥2 dose-limiting toxicities (DLTs) in the first 6 subjects, the trial will be stopped for safety purposes (*first stopping rule*). DLTs are defined as CTCAE v5 grade ≥2 wound dehiscence or wound complication, any grade fistula, grade ≥2 hemorrhage of any type, grade ≥3 infections [except urinary tract infections (UTIs) which are expected in this population], any AE that leads to permanent discontinuation of cabozantinib, or other grade ≥3 cabozantinib-related

perioperative complications. The DLT period is defined as day 1 of drug through day 57 of the protocol (inclusive). The seventh subject randomized to cabozantinib may not be enrolled until the sixth subject completes the day 57-85 safety visit ***and*** the Duke principal investigator agrees that the stopping rule should not be put into effect. From the seventh subject on, subjects may be accrued at ex-Duke site(s). A *second stopping rule* will be triggered if there are ≥3 DLTs in the first 12 subjects treated with cabozantinib. In the event that a stopping rule is triggered, thorough review of the cabozantinib-treated patients' files will be performed and the Duke principal investigator will consider whether the trial can be redesigned or should be permanently discontinued.

Sample Size Justification. The primary endpoint of this randomized phase II study is the apoptotic index by cleaved caspase-3 in prostatectomy specimens following 4 weeks of treatment with cabozantinib compared with prostatectomy specimens of untreated patients. The target sample size of convenience is 30 patients where the randomization allocation ratio will be 2:1 cabozantinib-to-control. The randomization will not be stratified on any variable. The null hypothesis is that the mean apoptotic indices are equal between the two groups. The percent of tumor cells positive for cleaved caspase 3 staining for each patient will be evaluated for the primary objective. The 6 subjects assigned during the Safety Lead-In Cohort are included in the 30 patient sample size and 2:1 randomization allocation ratio.

Based on data from a prior, unpublished pre-prostatectomy study of sunitinib, we expect the controls to have minimal staining (i.e., ≤5%). In the proposed study we will enroll 10 controls and 20 cabozantinib-treated patients to demonstrate increased staining (i.e., >5%). A two sample t-test will be used to compare group means. With 10 and 20 evaluable patients in the control and cabozantinib-treated groups, respectively, the test will provide 70% power to detect a mean (for positive tumor cells percentage) difference of one-fold standard deviation based on a two-sided type I error of 0.05; or 96% power to detect an one-and-half fold standard deviation difference. Assuming a 10% unevaluable rate, we will enroll up to 33 patients total to have 30 evaluable patients.

Data Analysis. Box plots and statistical summaries of apoptotic (cleaved caspase-3, TUNEL), proliferation (Ki-67), and MVD (CD31) indices will be presented. In addition, the t-test will be used to compare the two arms on apoptotic index, proliferation and MVD indices. Further, the Chi-square test will be used to compare the two treatment arms on pathologic complete response rate (pCR) and pathologic T2 (pT2) rate. The angiome, gene expression, cell-free DNA and mesenchymal markers analyses will be reported descriptively as the trial's limited sample size will not permit definitive analyses for these exploratory objectives. The t-test will be used to compare the two arms' serum and tissue androgen and androgen precursor levels.

12 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and crosscheck of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator.

13 STUDY COMMITTEES

13.1 MONITORING

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, the Duke Office of Audit, Risk and Compliance, a sponsor, an investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring

13.2 SAFETY OVERSIGHT COMMITTEE

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator Phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-

investigator. The SOC in concert with the DCI Monitoring Team oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

13.3 DATA MANAGEMENT AND PROCESSING

13.3.1 STUDY DOCUMENTATION

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

13.3.2 CASE REPORT FORMS (CRFS)

The electronic CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system. All users of this system will complete user training, as required or appropriate per regulations.

13.3.3 DATA MANAGEMENT PROCEDURES AND DATA VERIFICATION

Users of the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data manager and project manager will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

13.3.4 STUDY CLOSURE

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 LOCAL REGULATIONS

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" (GCP) ICH E6 Tripartite Guideline (January 1997). The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations, subpart D, Part 312, "Responsibilities of Sponsors and Investigators" Part 50, "Protection of Human Subjects" and Part 56, "Institutional Review Boards."

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.2 INFORMED CONSENT

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or designee must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

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

14.3 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

This study is being conducted under a United States Investigational New Drug application or other Clinical Trial Application, as appropriate. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB/EC. This board must operate in accordance with current local, regional, and federal regulations. The investigator will send a letter or certificate of IRB/EC approval to Exelixis (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

14.4 PROTOCOL AMENDMENTS

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

The CPC will be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

14.5 RECORDS RETENTION

The Principal Investigator will maintain study-related records for a period of at least six years after study completion per Duke policy.

14.6 CONFLICT OF INTEREST

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

14.7 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the investigator. Protocol modifications or amendments must be reviewed and approved by Exelixis prior to implementation.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (e.g., change in monitor or change of telephone number).

14.8 CONDITIONS FOR TERMINATING THE STUDY

At any time, the study may be terminated by the study sponsor, the sponsoring institution, or by Exelixis. Should this be necessary, Exelixis and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Exelixis and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the investigator(s) shall cease enrolling subjects into the study, and shall discontinue conduct of the study as soon as is medically practicable.

14.9 STUDY DOCUMENTATION AND RECORD-KEEPING

14.9.1 INVESTIGATOR'S FILES AND RETENTION OF DOCUMENTS

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

An electronic case report form (CRF) will be the primary data collection document for the study. Only the key personnel delegated on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system.

14.9.2 SOURCE DOCUMENTS AND BACKGROUND DATA

Upon request, the investigator will supply its licensees and collaborators with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

14.9.3 AUDITS AND INSPECTIONS

The investigator should understand that source documents for this study must be made available, after appropriate notification, to qualified personnel from the Exelixis Quality Assurance Unit (or designee) or to health authority inspectors. The verification of the CRF data must be by direct inspection of source documents.

14.9.4 CASE REPORT FORMS

For enrolled subjects, all and only data from the procedures and assessments specified in this protocol and required by the CRFs should be entered on the appropriate CRF. Data from some procedures required by the protocol, such as physical examinations and laboratory results, will be recorded only on the source documents and will not be transcribed to CRFs. Additional procedures and assessments may

be performed as part of the investigator's institution or medical practice standard of care and may not be required for CRF entry.

For each subject enrolled, the CRF (paper or electronic) must be completed and signed by the PI or authorized delegate from the study staff.

All paper forms should be typed or filled out using indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his or her authorized delegate.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs and in all required reports.

14.10 DATA AND SAFETY MONITORING THE STUDY

Data and Safety Monitoring will be performed in accordance with the external site Data and Safety Monitoring Plan, provided under separate cover.

14.11 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated web-access secure database, which is housed in an encrypted and password-protected server behind the Duke firewall. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per institutional policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.12 PUBLICATIONS 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 Exelixis with a copy of any proposed publication or release: (a) for abstracts, slide presentations or posters, at least five (5) business day prior to submission (in the case of abstracts) or first public presentation (in the case of slide presentations and posters); and (b) at least thirty (30) days in advance of first submission and each subsequent submission in the case of

manuscripts and also comply with any provisions regarding publication that are agreed to between the PI's institution (e.g., institution name.) and Exelixis, Inc. in the Clinical Trial Agreement related to this study.

15 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOE	Schedule of Events
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

16 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7-30.

2. Tosco L, Briganti A, D'Amico A V, et al. Systematic Review of Systemic Therapies and Therapeutic Combinations with Local Treatments for High-risk Localized Prostate Cancer. *Eur Urol.* 2019;75(1):44-60.

3. Hahn AW, Higano CS, Taplin ME, Ryan CJ, Agarwal N. Metastatic Castration-Sensitive Prostate Cancer: Optimizing Patient Selection and Treatment. *Am Soc Clin Oncol Educ Book.* 2018(38):363-371.

4. Loriot Y, Supiot S, Beauval JB, et al. Management of non-metastatic castrate-resistant prostate cancer: A systematic review. *Cancer Treat Rev.* 2018;70:223-231.

5. Nuhn P, De Bono JS, Fizazi K, et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology. *Eur Urol.* 2019;75(1):88-99.

6. De Bono JS, Goh JC, Ojamaa K, et al. KEYNOTE-199: Pembrolizumab (pembro) for docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol.* 2018;36(15).

7. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2014;15(7):700-712.

8. Beer TM, Kwon ED, Drake CG, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. *J Clin Oncol.* 2017;35(1):40-47.

9. Lu X, Horner JW, Paul E, et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. *Nature.* 2017;543(7647):728-732.

10. Patnaik A, Swanson KD, Csizmadia E, et al. Cabozantinib Eradicates Advanced Murine Prostate Cancer by Activating Antitumor Innate Immunity. *Cancer Discov.* 2017;7(7):750-765.

11. Smith MR, Sweeney CJ, Corn PG, et al. Cabozantinib in chemotherapy-pretreated metastatic castration-resistant prostate cancer: results of a phase II nonrandomized expansion study. *J Clin Oncol.* 2014;32(30):3391-3399.

12. Smith M, De Bono J, Sternberg C, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. *J Clin Oncol.* 2016;34(25):3005-3013.

13. CABOMETYX Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208692s003lbl.pdf*. Published 01/2019. Accessed 10/28/19.

14. COMETRIQ Prescribing Information. *https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203756s005lbl.pdf*. Published 01/2018. Accessed 10/28/19.

15. *https://cabometyx.com/downloads/CABOMETYXUSPI.pdf*. Published 12/2017. Accessed 11/26/2018

16. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *J Clin Oncol.* 2017;35(6):591-597.

17. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015;373(19):1814-1823.

18. Nguyen HM, Ruppender N, Zhang X, et al. Cabozantinib inhibits growth of androgen-sensitive and castration-resistant prostate cancer and affects bone remodeling. *PLoS One.* 2013;8(10):e78881.

19. Dai J, Zhang H, Karatsinides A, et al. Cabozantinib inhibits prostate cancer growth and prevents tumor-induced bone lesions. *Clin Cancer Res.* 2014;20(3):617-630.

20. Varkaris A, Corn PG, Parikh NU, et al. Integrating Murine and Clinical Trials with Cabozantinib to Understand Roles of MET and VEGFR2 as Targets for Growth Inhibition of Prostate Cancer. *Clin Cancer Res.* 2016;22(1):107-121.

21. Sonpavde G, Palapattu GS. Neoadjuvant therapy preceding prostatectomy for prostate cancer: rationale and current trials. *Expert Rev Anticancer Ther.* 2010;10(3):439-450.

22. George DJ, Halabi S, Zurita AJ, et al. Investigator-initiated pilot study of sunitinib malate in patients with newly diagnosed prostate cancer prior to prostatectomy: A trial of the DoD/PCF Prostate Cancer Clinical Trials Consortium. *Journal of Clinical Oncology.* 2011;29(15_suppl):4664-4664.

23. Tripathi M, Nandana S, Billet S, et al. Modulation of cabozantinib efficacy by the prostate tumor microenvironment. *Oncotarget.* 2017;8(50):87891-87902.

24. Qiao Y, Feng FY, Wang Y, et al. Mechanistic Support for Combined MET and AR Blockade in Castration-Resistant Prostate Cancer. *Neoplasia.* 2016;18(1):1-9.

25. Yen BL, Yen ML, Hsu PJ, et al. Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-met and STAT3. *Stem Cell Reports.* 2013;1(2):139-151.

26. Chen PM, Liu KJ, Hsu PJ, et al. Induction of immunomodulatory monocytes by human mesenchymal stem cell-derived hepatocyte growth factor through ERK1/2. *J Leukoc Biol.* 2014;96(2):295-303.

27. Okunishi K, Dohi M, Nakagome K, et al. A novel role of hepatocyte growth factor as an immune regulator through suppressing dendritic cell function. *J Immunol.* 2005;175(7):4745-4753.

28. Benkhoucha M, Santiago-Raber ML, Schneiter G, et al. Hepatocyte growth factor inhibits CNS autoimmunity by inducing tolerogenic dendritic cells and CD25+Foxp3+ regulatory T cells. *Proc Natl Acad Sci U S A.* 2010;107(14):6424-6429.

29. Igney FH, Krammer PH. Immune escape of tumors: apoptosis resistance and tumor counterattack. *J Leukoc Biol.* 2002;71(6):907-920.

30. Liu Y, Starr MD, Bulusu A, et al. Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab. *Cancer medicine.* 2013;2(2):234-242.

31. Singh D, Febbo PG, Ross K, et al. Gene expression correlates of clinical prostate cancer behavior. *Cancer Cell.* 2002;1(2):203-209.

32. Kaposi-Novak P, Lee JS, Gomez-Quiroz L, Coulouarn C, Factor VM, Thorgeirsson SS. Met-regulated expression signature defines a subset of human hepatocellular carcinomas with poor prognosis and aggressive phenotype. *J Clin Invest.* 2006;116(6):1582-1595.

33. Ponzo MG, Lesurf R, Petkiewicz S, et al. Met induces mammary tumors with diverse histologies and is associated with poor outcome and human basal breast cancer. *Proc Natl Acad Sci U S A.* 2009;106(31):12903-12908.

34. Parachoniak CA, Luo Y, Abella JV, Keen JH, Park M. GGA3 Functions as a Switch to Promote Met Receptor Recycling, Essential for Sustained ERK and Cell Migration. *Dev Cell.* 2011;20(6):751-763.

35. Joffre C, Barrow R, Menard L, Calleja V, Hart IR, Kermorgant S. A direct role for Met endocytosis in tumorigenesis. *Nat Cell Biol.* 2011;13(7):827-837.

36. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res.* 2008;68(11):4447-4454.

37. Mostaghel EA, Nelson P, Lange PH, et al. Neoadjuvant androgen pathway suppression prior to prostatectomy. *J Clin Oncol.* 2012;30(suppl):abstr 4520.

38. Taplin M-E, Montgomery RB, Logothetis C, et al. Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): Results of a randomized phase II study. *J Clin Oncol.* 2012;30(suppl):abstr 4521.

39. Verras M, Lee J, Xue H, Li TH, Wang Y, Sun Z. The androgen receptor negatively regulates the expression of c-Met: implications for a novel mechanism of prostate cancer progression. *Cancer Res.* 2007;67(3):967-975.

40. Page ST, Kalhorn TF, Bremner WJ, Anawalt BD, Matsumoto AM, Amory JK. Intratesticular androgens and spermatogenesis during severe gonadotropin suppression induced by male hormonal contraceptive treatment. *J Androl.* 2007;28(5):734-741.

41. Lee RJ, Saylor PJ, Michaelson MD, et al. A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases. *Clin Cancer Res.* 2013;19(11):3088-3094.

42. Rini BI, Garcia J, Elson P, et al. The effect of sunitinib on primary renal cell carcinoma and facilitation of subsequent surgery. *J Urol.* 2012;187(5):1548-1554.

43. Cowey CL, Amin C, Pruthi RS, et al. Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. *J Clin Oncol.* 2010;28(9):1502-1507.

17 APPENDICES

17.1 APPENDIX A: ECOG AND KARNOFSKY PERFORMANCE SCALE CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**%**	**Description**
0	Normal activity. Fully active, able to continue all predisease 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	80	Normal activity with effort, some signs or symptoms of disease

	activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	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 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 > 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