CITY OF HOPE NATIONAL MEDICAL CENTER
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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: **A Randomized, Phase II, Assessing Axitinib as Pre-Surgical Therapy in Patients with High Risk Prostate Cancer.**

CITY OF HOPE PROTOCOL NUMBER/VERSION: **IRB # 10151** **VERSION: 07**

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

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COH Amendment 06 at Continuation	Title Page Dated 01/25/2017	Version: 06
COH Amendment 07 at Continuation	Title Page Dated 12/18/2017	Version: 07

SITE: Prostate
STAGE (If applicable): II
MODALITY: Oral Medication
TYPE:

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PARTICIPATING INSTITUTION: City of Hope National Medical Center

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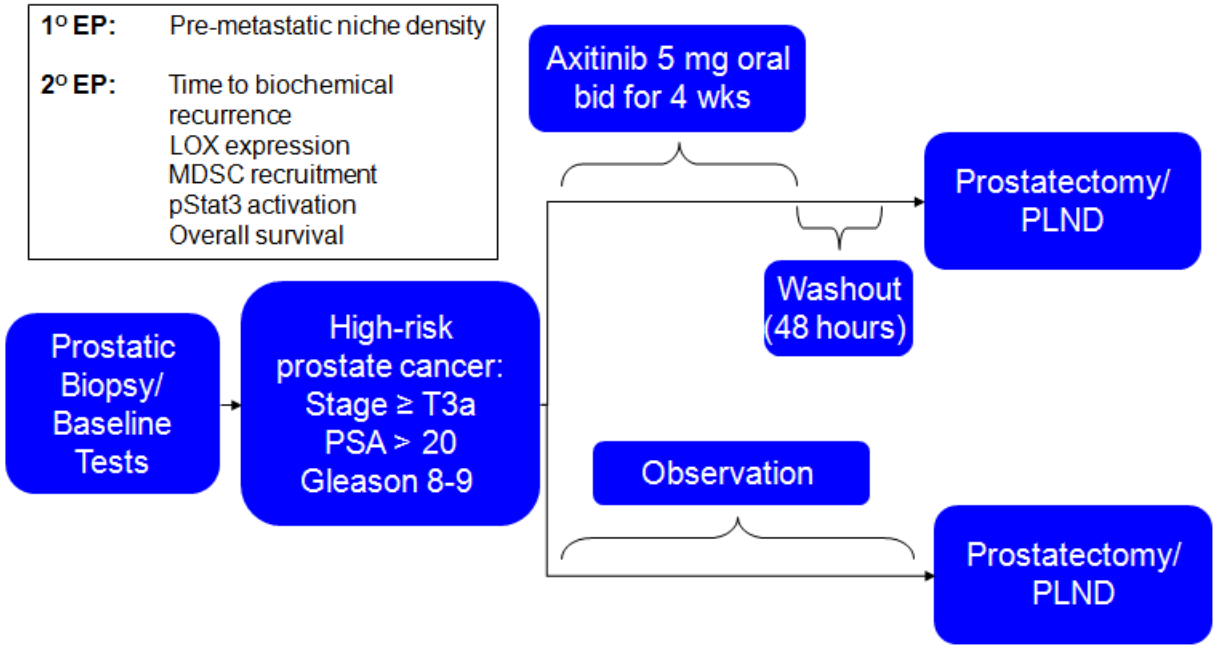
Experimental Design Schema

Open-label, randomized phase II design as represented in the following schema:



* See inclusion/exclusion criteria for full details.

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Protocol Synopsis

Protocol Title:
A RANDOMIZED, PHASE II STUDY ASSESSING AXITINIB AS PRE-SURGICAL THERAPY IN PATIENTS WITH HIGH RISK PROSTATE CANCER
Brief Protocol Title for the Lay Public (if applicable):
A RANDOMIZED, PHASE II STUDY ASSESSING AXITINIB AS PRE-SURGICAL THERAPY IN PATIENTS WITH HIGH RISK PROSTATE CANCER
Study Phase:
Randomized phase II
Participating Sites:
City of Hope Comprehensive Cancer Center
Rationale for this Study:
The „seed-and-soil" hypothesis was proposed by Paget in 1889, and suggests that the biological characteristics of certain tissues may foster invasion and growth of metastases.[1] Identification of these susceptible areas, termed pre-metastatic niches, has numerous potential clinical applications. For instance, patients with more abundant niches may have increased metastatic potential – niche prevalence could therefore serve as a personalized supplement to current prognostic models.[2] Alternatively, the pre-metastatic niche could act as a target of anticancer therapy, preventing metastases from developing. Treatment of patients with high-risk prostate cancer with axitinib will decrease the extent of pre-metastatic niche formation. Consequently, patients may experience improved clinical outcome (delayed biochemical recurrence and prolonged time to metastatic recurrence/overall survival (OS)).
Primary Objective:
To determine if axinitinb modulates pre-metastatic niche density in patients with high-risk prostate cancer
Secondary Objective(s):
• To determine if therapy with axitinib prolongs time to biochemical recurrence • To determine if pSTAT3 in tumor tissue is associated with biochemical recurrence • To determine if MDSC recruitment in tumor tissue is associated with biochemical recurrence • To determine if lysyl oxidase (LOX) expression in tumor tissue is associated with biochemical recurrence • To evaluate time to metastatic recurrence • To evaluate the rates of urinary incontinence (grade ≥ 3) and erectile dysfunction (grade ≥ 3) associated with preoperative axitinib therapy (as defined by CTCAE 4.0 criteria) • To evaluate changes in blood-based biomarkers (pSTAT3 and selected angiogenic factors) from baseline to the time of prostatectomy
Study Design:
Open-label, randomized phase II study
Primary Endpoint and Secondary Endpoints:
<u>Primary:</u> • Pre-metastatic niche density

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Secondary:

- Toxicity, time to biochemical recurrence, time to metastatic recurrence,, rate of urinary incontinence, rate of erectile dysfunction

Sample Size:

44

Estimated Duration of the Study

24 months

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

- Histologically confirmed diagnosis of prostate cancer
- High-risk prostate cancer as defined by 1 of the 3 following criteria: (1) baseline PSA > 20, (2) clinical stage ≥ T3a, and (3) Gleason score 8-9.
- Subjects must be appropriate candidates for prostatectomy and pelvic lymph node dissection by a multidisciplinary team and must provide informed consent to these procedures prior to initiating study treatment
- Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up. Procedures conducted as part of the subject‟s routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.
- Adequate organ function as defined by the following criteria:
  - absolute neutrophil count (ANC) ≥1500 cells/mm3;
  - platelets ≥100,000 cells/mm3.
  - Hemoglobin ≥9.0 g/dL.
  - AST and ALT ≤2.5 x upper limit of normal (ULN);
  - Total bilirubin ≤1.5 x ULN;
  - Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥60 mL/min (see Appendix A);
  - Urinary protein <2+ by urine analysis (UA). If dipstick is ≥2+ then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours.
- Male patients, age ≥18 years.
- ECOG performance status of 0 or 1.
- Life expectancy of ≥12 weeks.
- No prior systemic therapy for prostate cancer
- No evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken within 1 hour. The baseline systolic blood pressure readings must be ≤140 mm Hg, and the baseline diastolic blood pressure readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.
- Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.

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Exclusion Criteria:

- Prior systemic therapy for prostate cancer (including but not limited to endocrine therapy; i.e., LHRH analogues, antiandrogens, etc.)
- Evidence of metastatic disease
- Prior radiation therapy for prostate cancer
- Known history of allergic reactions to axitinib or other VEGF-TKIs
- Presence of serious or uncontrolled infection
- Major surgery <4 weeks of starting the study treatment.
- Gastrointestinal abnormalities including:
  - inability to take oral medication;
  - requirement for intravenous alimentation;
  - prior surgical procedures affecting absorption including total gastric resection;
  - treatment for active peptic ulcer disease in the past 6 months;
  - active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
  - malabsorption syndromes.
- Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine).
- Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St. John‟s wort).
- Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.
- Active seizure disorder
- A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.
- Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.
- Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
- History of a malignancy (other than prostate cancer) except those treated with curative intent for skin cancer (other than melanoma), in situ breast or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 2 years.
- Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.
- 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

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judgment of the investigator would make the patient inappropriate for entry into this study.
Investigational Product Dosage and Administration:
Axitinib 5 mg 1 tab oral bid
Clinical Observations and Tests to be Performed:

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Assessments within 2 Weeks of the First Dose (unless otherwise indicated)

- Demography: date of birth, race and gender.
- Medical history:
  - Prostate cancer-specific history including: date of diagnosis, current stage of cancer, prior systemic treatment for prostate cancer (an exclusion criterion); and history of other malignancies
  - Prior surgery and/or radiotherapy (date, organ/anatomic region(s) of surgery and/or radiotherapy must be documented), other significant medical and surgical histories within the past 6 months.
- Baseline bone scan for tumor assessment (within 8 weeks prior to first dose)
- Baseline CT scan of the abdomen and pelvis (within 8 weeks prior to first dose)
- Physical examinations: height (only recorded at baseline) and body weight and current medical conditions.
- Vital signs: body temperature, blood pressure and heart rate. **Note:** If a subject presents with poorly controlled hypertension, defined as SBP ≥140mmHg or DBP ≥90mmHg, antihypertensive medication(s) should be initiated or adjusted with a goal to control the blood pressure to <140/90 mmHg.
- Clinical laboratory assessments, as listed in the study calendar.
- Verification of an operative date for prostatectomy/pelvic lymph node dissection that allows for the 28 day therapeutic period as well as a 48 hour washout period prior to surgery. Prostatectomy may be performed via any accepted methodology (open, laparoscopic, robotic-assisted, etc.). Notably, standard wait times for prostatectomy at City of Hope vary between 5-6 weeks from the time of biopsy confirmation of prostate cancer. Thus, it is not anticipated that the current protocol will delay standard of care therapies on the control or experimental arms.

Pre-dose Assessments on Day 1

- Physical examination: to identify any changes in the subject‟s mental and medical conditions since baseline assessment that would make him/her ineligible for the study.
- Blood pressure measurements: subjects must have a blood pressure reading of <140/90mmHg to be eligible. If anti-hypertensives were initiated and/or dosing has been adjusted during the Baseline Period, the blood pressure must be re-assessed on two occasions consecutively that are within 1 hour. The mean SBP/DBP values from both blood pressure assessments must be <140/90mmHg in order for a subject to be eligible. ECOG PS: Any changes since baseline assessment should be recorded in the eCRF.
- Record all the medication(s) received within 2 weeks prior to the first dose of study medication and indicate if the medication is continuing.
- Obtain archived tumor tissue samples (derived from prostatic biopsy) for biomarker assessments.

Assessments while on Study

- Physical examination: to identify any changes in the subject‟s mental and medical conditions since baseline assessment that would make him/her ineligible for the study. This will occur at day 15 and day 28 of protocol-based therapy for patients randomized to the Axitinib arm only. Patients will then be evaluated in the clinic with a physical examination and examination for pertinent toxicities one month following prostatectomy (constituting a standard post-operative assessment), and then every 3 months, until evidence of disease progression, death, or initiation of a subsequent line of prostate cancer therapy.

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- ECOG PS.
- PSA will be performed per the study calendar, section 10.0, from randomization until the development of metastatic recurrence.
- Blood will be sequestered for correlative studies (see section 10.1) at baseline and at the time of prostatectomy, as well as the post-prostatectomy follow-up visit 4 weeks following the procedure. A total of 20 mL of blood will be collected at each of these visits; 10 mL will be collected in a CPT tube for PBMC isolation and assessment, while 10 mL will be collected for assessment of selected plasma angiogenic factors. Within 4 hours of collection, this blood will be transported to the lab of Dr. Marcin Kortylewski (Beckman Research Institute, Room 3220).
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Post-Study Assessments

- Any patient who is discontinued from study treatment for any reason other than progressive disease (PD) will continue to have PSA measurements every 24 weeks (+/- 2 weeks) until the patient starts another anticancer therapy. The investigator or his/ designee will continue collecting information on the initiation of anticancer therapies until the date of data cutoff for the final analysis. All new anticancer therapy therapies after the last dose of treatment will be recorded on the appropriate CRF.

Clinical Laboratory Assessments

The City of Hope main laboratory is to be used to perform all clinical laboratory assessments. Laboratory tests should be performed as indicated in the Study Calendar, section 10.0. All laboratories prior to week 9 may be performed/collected within +/- 3 days of the dates specified in the study calendar. From week 9 onwards, all laboratories may be performed/collected within +/- 7 days of the dates specified in the study calendar. Assessments may be performed more frequently if clinically indicated.

All laboratory tests with values that become clinically abnormal while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated at the PI‟s discretion until the values return to normal or baseline.

Results for all unscheduled clinical laboratory assessments (i.e., hematology, TSH/T_4, coagulation parameters) should be recorded on an unscheduled laboratory form in the eCRF.

Hematology and Clinical Chemistry

Hematology and clinical chemistry laboratory parameters that should be reported include white blood cell count, hemoglobin, hematocrit, platelet count, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, and blood glucose. Assays for hematology and clinical chemistry should be performed at baseline, at 2, 4 and 8 weeks, , and then every 12 weeks thereafter. Hepatic assays should be performed at baseline, 2, 4, and 8 weeks, followed by every 12 weeks thereafter.

Liver Function Tests

When a separate liver function test (LFT) panel is conducted, this panel should include the following: ALT, AST, alkaline phosphatase, GGT, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 x upper limit of normal (ULN). Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to ensure subject safety.

Evaluation of Proteinuria

Proteinuria will be evaluated using the urine protein to creatinine ratio (UPC; see Appendix B). UPC will be determined at times specified in the Study Calendar.

Coagulation Tests

Coagulation tests should be performed as specified in the Study Calendar and also in response to an AE/SAE as clinically indicated. Coagulation tests include activated partial thromboplastin time (aPTT),prothrombin time (PT) and international normalized ratio (INR).

Lipid Tests

Lipid tests include cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. These tests should be performed as specified in the Study Calendar. Additional testing may be performed if clinically indicated. In such a case, the subject should be in a fasting state.

Thyroid Function Tests

Thyroid function tests to assess thyroid stimulating hormone (TSH) and thyroxine (free T_4) should be performed as specified in the Study Calendar. Unscheduled thyroid function tests (TSH and free T_4) may be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

Statistical Considerations:

The primary endpoint of this study is pre-metastatic niche density, as defined by the average number of VEGFR1 clusters in 8 distinct 40x microscopic fields. We will use a two sample student‟s T-test to compare the primary endpoint of pre-metastatic niche density in the regional lymph nodes of patients treated with axitinib, as compared to the pre-metastatic niche density in the lymph nodes of patients enrolled on the control arm. With a sample of 22 patients per group, we will have 80% power to determine significance across groups if the average niche density is 3.13 in patients in the control arm, and at most 2.19 in patients treated with axitinib (a one-sided t-test with type I error = 10% calculated using nQuery Advisor 6.01).

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Table of Contents

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Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease

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1.0 Goals and Objectives (Scientific Aims)

1.1 Primary Objectives

1.1.1 To determine if axinitinb modulates pre-metastatic niche density in patients with high-risk prostate cancer

1.2 Secondary Objectives

1.2.1 To determine if pre-metastatic niche density in regional LNs is associated with PFS

1.2.2 To determine if therapy with axitinib prolongs time to biochemical recurrence

1.2.3 To determine if pSTAT3 in tumor tissue is associated with biochemical recurrence

1.2.4 To determine if myeloid derived suppressor cell (MDSC) recruitment in tumor tissue is associated with biochemical recurrence

1.2.5 To determine if lysyl oxidase (LOX) expression in tumor tissue is associated with biochemical recurrence

1.2.6 To evaluate time to metastatic recurrence

1.2.7 To determine the rate of erectile dysfunction and urinary incontinence (grade ≥ 3 for both) in the setting of preoperative axitinib therapy

1.2.8 To evaluate changes in blood-based biomarkers (pSTAT3 and selected angiogenic factors) from baseline to the time of prostatectomy

2.0 Background

2.1 Defining prognosis in prostate cancer.

Prostate cancer represents the most common malignancy in males, with an estimated 192,280 cases diagnosed in 2009.[3] The incidence of prostate cancer rose sharply between 1990 and 1995, likely attributable to an increase in widespread adoption of PSA screening. PSA screening has also resulted in a drastic stage migration in prostate cancer, with far fewer patients presenting with *de novo* metastatic disease.[4] While these data are encouraging, the increasing proportion of patients with localized disease underscores the need to develop accurate predictive tools to determine the risk of metastatic progression. Clinical guidelines, such as those published by the NCCN, employ risk stratification tools combining stage, grade and PSA to determine the risk of biochemical recurrence after definitive local therapy.[5] These tools have been validated in several series and provide a superior basis for treatment recommendations compared to clinical stage alone.[6,7] However, no currently available risk stratification schema has perfect accuracy, and furthermore, only a limited number can predict outcomes outside of biochemical recurrence, such as the risk of metastases and cancer-specific death.[8,9] Appropriate identification of patients at higher likelihood for such outcomes may provide an opportunity for therapeutic interventions to mitigate this risk.

2.2 Personalizing prognostic models in prostate cancer: The pre-metastatic niche.

The „seed-and-soil" hypothesis was proposed by Paget in 1889, and suggests that the biological characteristics of certain tissues may foster invasion and growth of metastases.[1] Identification of these susceptible areas, termed pre-metastatic niches, has numerous potential clinical applications. For instance, patients with more abundant niches may have increased metastatic potential – niche prevalence

could therefore serve as a personalized supplement to current prognostic models.[2] Alternatively, the pre-metastatic niche could act as a target of anticancer therapy, preventing metastases from developing. A necessary precursor to clinical use of the pre-metastatic niche is accurate molecular characterization of this entity. The seminal studies defining the composition of the pre-metastatic niche are described herein.

2.3 VEGFR1$^+$ Bone Marrow Derived Cells (BMDCs) initiate the pre-metastatic niche.

Kaplan *et al* assessed mice injected with either LLC or B16 melanoma cells. While LLC cells have a predilection for pulmonary spread, B16 melanoma cells metastasize in a more widely disseminated fashion. At day 14 after tumor inoculation, it was observed that deposition and clustering of VEGFR1$^+$ BMDCs occurred in terminal bronchioles prior to arrival of tumor cells. By day 23, tumor micrometastases were visible. Sites of BMDC clustering appeared to be tumor specific; while LLC cells deposited only in the lungs and liver, B16 cells deposited in a range of tissues, such as the lung, liver, testis and spleen. VEGFR1$^+$ BMDCs recruited to pre-metastatic niche sites had increased expression of the fibronectin receptor VLA-4 (integrin $\alpha_4\beta_1$), implicating the role of fibronectin in BMDC clustering.

2.4 Hypoxia-induced LOX recruits BMDCs to the pre-metastatic niche.

LOX is an enzyme that crosslinks elastin and collagen in the ECM.[10] Conditions of hypoxia lead to increased expression of LOX, and increased LOX expression has been linked to an increased risk of metastasis across a spectrum of malignancies.[11] As a result of the latter, the role of LOX has been examined in formation of the pre-metastatic niche. Erler *et al* assessed mice orthotopically implanted with MDA-MB-231 human breast cancer cells (wild type, WT) or MDA-MB-231 cells expressing a *LOX*-targeting shRNA.[12] Decreased expression of LOX in MDA-MB-231 cells led to decreased numbers of pulmonary metastatic lesions. Subsequent kinetic studies demonstrated that LOX expression enhanced recruitment of BMDCs to future sites of metastasis. Thus, LOX appears to have a critical role in pre-metastatic niche formation.

2.5 MDSC recruitment may represent an early event in pre-metastatic niche formation.

Amongst the VEGFR1$^+$ BMDCs that populate the pre-metastatic niche, a proportion are MDSCs, characterized by a Gr-1$^+$/MAC1$^+$ immunophenotype.[2] Recent evidence suggests that MDSCs play a critical role in inhibition of the antitumor immune response.[13] The recruitment of MDSCs to tumor sites appears to be driven by Stat3, and work done in Dr Hua Yu's laboratory at our institution suggests that Stat3 may further activate tumor angiogenesis, promoting a functional tumor micro-environment.[14] Thus, abrogation of Stat3-mediated MDSC recruitment to the pre-metastatic niche may reduce metastatic potential. As discussed in the subsequent section, therapy with a VEGF-TKI could potentially inhibit these Stat3-mediated effects.

2.6 Preliminary Data: VEGF-TKI therapy decreases MDSC accumulation in tumor tissue.

We have previously reported a series of experiments in Renca-tumor bearing mice suggesting an antitumor effect of sunitinib that is Stat3 dependent.[15] Specifically, our studies demonstrate a reduction in Stat3 activation in MDSCs with sunitinib therapy. This reduction correlated with a decrease in expression of Stat3-mediated pro-angiogenic factors, such as VEGF and CXCL2 (the latter inhibits endothelial progenitor cell recruitment).[16] Furthermore, treatment with sunitinib decreased recruitment of MDSCs to tumor tissue.

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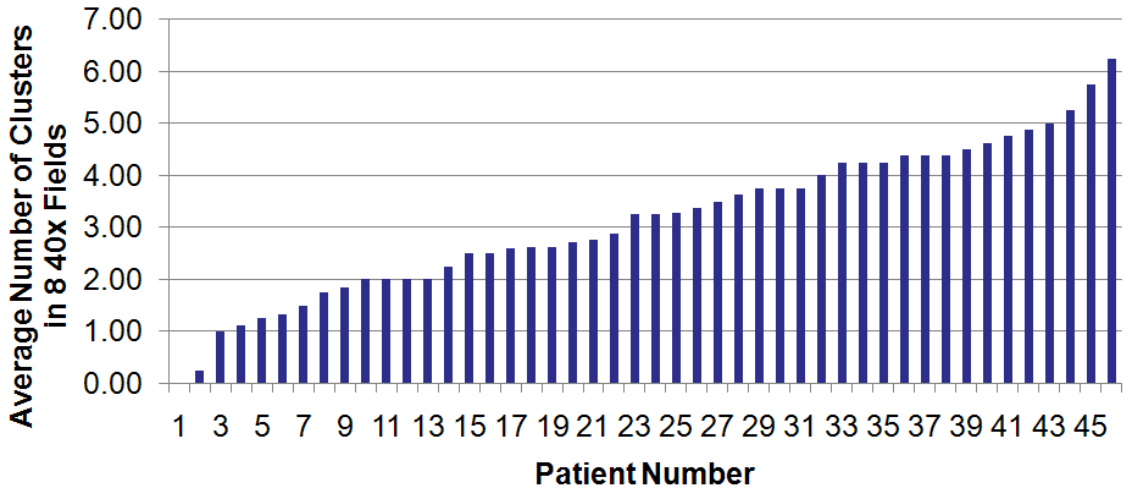
2.7 Preliminary Data: The pre-metastatic niche is detectable in high-risk prostate cancer.

To determine the role of the pre-metastatic niche in prostate cancer, we embarked on a separate retrospective study, specifically examining the predictive role of the niche in the benign lymph nodes of men with high risk prostate cancer. In COH IRB 09213, the City of Hope Prostate Cancer Database (COH Database) was used to identify 46 patients with high-risk PCa (baseline PSA > 20, pT3a-4 disease, or biopsy Gleason 8-10) who had undergone radical prostatectomy and pelvic lymph node dissection (PLND). The COH PCR prospectively collects clinical data associated with patients undergoing prostatectomy at the institution, and warehouses available clinical specimens. Benign tissue specimens (paraffin-embedded) derived from PLND were acquired for each patient, and were stained for VEGFR1 expression. VEGFR1+ cell clusters were counted within 8 distinct 40x fields, and the cluster count was averaged. The average cluster count was 3.13 (standard deviation, 1.43), and ranged from 0-6.25 (see Figure 1). VEGFR1+ clustering in PLND specimens was a significant predictor of biochemical recurrence on multivariate Cox proportional hazards analysis, and outperformed other variables including established prognostic factors such as age, extracapsular spread, seminal vesicle invasion, and the aforementioned high-risk features. Patients with increased VEGFR1+ clustering pelvic lymph node tissue had a shorter interval to biochemical recurrence (HR 0.18, P<0.10). These preliminary results indicate that increased VEGFR1+ cell clustering in benign nodal tissue may predict poorer clinical outcome in patients with high-risk PCa. Our dataset is consistent with a recent report from Fujita *et al* (*Cancer Sci* 2009; 100(6):1047-50), which also suggested that VEGFR1 staining in pelvic lymph nodes predicted the risk of biochemical recurrence after radical prostatectomy in a more heterogeneous group. Together with our dataset, there is emerging rationale for examining VEGFR1 as a key component of the pre-metastatic niche.

Figure 1. Distribution of VEGFR1 clustering in the pelvic lymph nodes of 46 patients with lymph node negative prostate cancer who have been treated with definitive surgical intervention. The number of clusters visualized in 8 40x fields was averaged.



2.8 Preliminary Data: VEGF-TKIs have demonstrable efficacy in the setting of prostate cancer, and have been employed in neoadjuvant trials.

Data has emerged for the agent sunitinib in the setting of metastatic, hormone refractory prostate cancer. In one phase II study, patients who had received no prior cytotoxic therapy (Group A) or prior docetaxel therapy (Group B), (n=17 in each group), were treated with daily sunitinib.[18] One patient in each group

had a documented PSA response. Furthermore, 7 and 8 patients had a stable PSA at 12 weeks in groups A and B, respectively. Interestingly, radiographic responses were observed in the absence of PSA responses. A separate phase II study assessed sunitinib specifically in the setting of docetaxel failure, and elicited similar response rates.[19] Preclinical studies have suggested potential synergy between sunitinib and docetaxel; this combined regimen is being further explored.[20,21] At least two studies have assessed sunitinib prior to prostatectomy.[22,23] An experience reported by the M.D. Anderson Cancer Center exploring three cycles of sunitinib (37.5 mg oral daily) prior to surgery enrolled a total of 44 patients.[23] Thus far, in 30 patients that have completed surgery, 1 CR has been reported. However, 3 patients were characterized as treatment failures (defined by unresectable pelvic nodal disease, confirmed post-operative PSA $\geq$ 0.2 ng/mL, or administration of post-operative radiation or ADT. Thus, while sunitinib appears to be relatively safe in the neoadjuvant setting (no grade 4 toxicities or toxicity-related discontinuations were observed), there may be rationale to explore more potent agents in this setting, such as axitinib.

2.9 Rationale for axitinib therapy.

Axitinib has been chosen because of its higher affinity for VEGFR1 compared to sunitinib (IC_{50} = 1 nM versus 23 nM).[24] Given the role of VEGFR1+ cells in establishing the pre-metastatic niche, axitinib will presumably have a more potent effect on niche formation. Axitinib is currently under investigation in several solid malignancies.[25,26] The area of most pronounced development is in the domain of mRCC. In a study including 62 patients who had received prior sorafenib therapy, an ORR of 22.6% and median duration of response of 17.5 months were recorded.[27] In a separate study including patients who had failed prior cytokine therapy, an even more impressive ORR of 44.6% was recorded.[28] A phase III study of axitinib as second-line therapy in mRCC is ongoing, comparing the agent to sorafenib.[29] The extensive prior use of axitinib in other solid tumors suggests the safety of monotherapy.

2.10 Axitinib

Axitinib is an oral, potent and selective inhibitor of VEGF (vascular endothelial growth factor) receptors 1, 2, and 3. It is being evaluated for use in solid tumors. VEGF receptors are critical components of the processes leading to the branching, extension, and survival of endothelial cells which form new blood vessels during angiogenesis, an absolute necessity for tumor growth beyond microscopic size. In nonclinical tumor mouse models, twice-daily (BID) oral administration of axitinib demonstrated consistent and significant anti-tumor efficacy (marked inhibitory effect on local and distant tumor metastasis and prolonged animal survival). In multiple animal models, combination of axitinib with various standard chemotherapies (eg, docetaxel or carboplatin) and other antiangiogenic agents (eg, bevacizumab) demonstrated improved benefit compared with single-agent chemotherapeutic/ antiangiogenic agents.

The nonclinical safety profile of axitinib has been well characterized through the conduct of single-dose and repeat-dose toxicity studies of up to 39 weeks in duration, and safety pharmacology, genetic toxicity, reproductive and developmental toxicity, and phototoxicity studies. The primary target organ toxicities were observed in the gastrointestinal,hematopoietic, musculoskeletal, and reproductive systems. Additionally, hemodynamic effects (elevated blood pressure, reduced heart rate) were identified from repeat-dosing in conscious, telemetered animals. Axitinib was not identified as a mutagen or clastogen,but considered an aneugen at AUC exposure that exceeds that at the recommended human dose (RHD) of 5 mg BID. While axitinib has relevant UV absorbance with the potential to distribute to sun-exposed tissues, no phototoxicity potential was identified from in vitro testing in 3T3 fibroblasts. Many of the findings identified from non-clinical safety testing are consistent with the anticipated pharmacological

response to a VEGFR inhibitor, including the blood pressure changes and effects on ovarian follicles and the growth plate of actively growing animals, which are reliant on angiogenesis for development.

Fertility and developmental effects were also observed, consistent with the effects identified from toxicity studies on reproductive organs and role of angiogenesis in the development of a fetus. In mice, rats, dogs, monkeys, and humans, axitinib appeared to undergo some cytochrome P450 (CYP)-mediated metabolism. In vitro studies demonstrated that axitinib was predominantly metabolized by CYP3A4 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. CYP inhibition and induction studies suggest the potential for clinical interactions with substrates of CYP2C8 and CYP1A2. Axitinib and its metabolites were widely distributed into tissues in mice, but were not accumulated or retained for long periods in most tissues. The plasma protein binding was 97%, 98%, and 99% in the mouse, dog, and human, respectively.

In humans, the median recovery of [^{14}C]axitinib radioactivity in feces was 37.0% and in urine was 22.7% (total recovery = 59.7%) of the total orally administered dose (5 mg). In plasma, the glucuronide was the predominant metabolite and accounted for approximately 50% of the circulating radioactivity. The sulfoxide and unchanged parent drug accounted for approximately 20% of the circulating radioactivity. In feces, the parent drug represented the single most predominant radioactive component (12% of the dose). As of 03 June 2009, 35 studies evaluating the safety, efficacy, and PK of axitinib have been completed or are ongoing. These studies include 11 Phase 1 studies in healthy subjects and 24 studies in subjects with cancer including 1 continued access protocol. Data are available for 24 of these studies.

A study in healthy volunteers (Protocol A4061007) indicated that the mean absolute oral bioavailability of the drug was 58%. Interaction studies in healthy volunteers with ketoconazole (CYP3A4 inhibitor) and rifampin (CYP3A inducer) produced a 2-fold increase and 79% reduction in axitinib plasma exposures, respectively (Protocols A4061004 and A4061026). Axitinib has two major (non-pharmacologically active) circulating plasma metabolites, a glucuronide product and a sulfoxide product (Protocol A4061003). In subjects with moderate hepatic impairment (Child Pugh B), there was a ~2-fold increase in axitinib AUC0-∞ and a 1.3-fold increase in axitinib Cmax compared to subjects with normal hepatic function (Protocol A4061036). No difference in axitinib plasma pharmacokinetics was observed between Caucasian and first-generation Japanese volunteers (n=20 each) (Protocol A4061026). Phase 1 studies in combination with chemotherapeutic/anticancer agents in cancer patients have indicated plasma pharmacokinetics of docetaxel, paclitaxel, carboplatin, capecitabine, gemcitabine, cisplatin, pemetrexed, oxaliplatin, 5-FU, bevacizumab and irinotecan (including SN-38) were similar in the absence and presence of axitinib. Likewise, axitinib plasma profiles and pharmacokinetic parameters were similar in the presence and absence of these coadministered chemotherapeutic/anticancer agents (Protocols A4061019 and A4061020). In all ongoing studies, the starting dose is 5 mg BID axitinib and the dose is titrated up to 7 mg BID and then to a maximum of 10 mg BID in patients tolerating axitinib.

Currently, those subjects who could tolerate axitinib with no adverse events related to axitinib above CTCAE Grade 2 for consecutive 2 week periods are permitted to increase their dose step-wise to 7 mg BID and then to 10 mg BID, unless their BP is >150/90 mm Hg or the subject is receiving antihypertensive medication. All ongoing studies allow axitinib dose reductions to as low as 2 mg BID for > Grade 2 treatment-related adverse events.

Overall, the adverse events reported for axitinib in clinical studies are considered manageable, generally reversible and expected for this class of agents (described in detail herein).

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Histologically confirmed diagnosis of prostate cancer

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3.1.2 High-risk prostate cancer as defined by 1 of the 3 following criteria: (1) baseline PSA > 20, (2) clinical stage ≥ T3a, and (3) Gleason score 8-9.

3.1.3 Subjects must be appropriate candidates for prostatectomy and pelvic lymph node dissection, as deemed by a multidisciplinary team. Subjects must provide informed consent to these procedures prior to initiating study treatment

3.1.4 Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up. Procedures conducted as part of the subject‟s routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

3.1.5 Adequate organ function as defined by the following criteria:

3.1.5.1 absolute neutrophil count (ANC) ≥1500 cells/mm3;

3.1.5.2 platelets ≥100,000 cells/mm3.

3.1.5.3 Hemoglobin ≥9.0 g/dL.

3.1.5.4 AST and ALT ≤2.5 x upper limit of normal (ULN);

3.1.5.5 Total bilirubin ≤1.5 x ULN;

3.1.5.6 Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥60 mL/min;

3.1.5.7 Urinary protein <2+ by urine analysis (UA). If UA is ≥2+ for protein then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours.

3.1.6 Male patients, age ≥18 years.

3.1.7 ECOG performance status of 0 or 1.

3.1.8 Life expectancy of ≥12 weeks.

3.1.9 No prior systemic therapy for prostate cancer

3.1.10 No evidence of preexisting uncontrolled hypertension as documented by 2 consecutive blood pressure readings taken within 1 hour. The baseline systolic blood pressure readings must be ≤140 mm Hg, and the baseline diastolic blood pressure readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.

3.1.11 Within 2 weeks of consent (and prior to initiating systemic therapy with axitinib if randomized to that arm), patients should visit with a radiation oncologist to discuss the option of radiation therapy (potentially with concomitant androgen deprivation therapy) for high-risk disease. If the patient has met with a radiation oncologist within 3 months of study enrollment to discuss the possibility of radiation therapy for localized prostate cancer, then this will suffice. Patients do have the right to refuse this consultation; if this is the case, it must be documented by the treating physician in the medical record.

Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.

3.2 Exclusion Criteria

3.2.1 Prior systemic therapy for prostate cancer (including but not limited to endocrine therapy; i.e., LHRH analogues, antiandrogens, etc.)

3.2.2 Evidence of metastatic disease

3.2.3 Prior radiation therapy for prostate cancer

3.2.4 Known history of allergic reactions to axitinib or other VEGF-TKIs
3.2.5 Presence of serious or uncontrolled infection
3.2.6 Major surgery <4 weeks of starting the study treatment.
3.2.7 Gastrointestinal abnormalities including:
  3.2.7.1 inability to take oral medication;
  3.2.7.2 requirement for intravenous alimentation;
  3.2.7.3 prior surgical procedures affecting absorption including total gastric resection;
  3.2.7.4 treatment for active peptic ulcer disease in the past 6 months;
  3.2.7.5 active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
  3.2.7.6 malabsorption syndromes.
3.2.8 Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine). (Note: This is not a comprehensive list. For a comprehensive list of CYP3A4 inhibitors, please refer to the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx; patients who are using these agents will be excluded.)
3.2.9 Current use or anticipated need for treatment with drugs that are known potent CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St. John‟s wort). (Note: This is not a comprehensive list. For a comprehensive list of CYP1A2 and CYP3A4 inducers, please refer to the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx; patients who are using these agents will be excluded.)
3.2.10 Requirement of anticoagulant therapy with oral vitamin K antagonists. Therapeutic use of low molecular weight heparin is allowed.
3.2.11 Active seizure disorder
3.2.12 A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.
3.2.13 Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.
3.2.14 Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
3.2.15 History of a malignancy (other than prostate cancer) except those treated with curative intent for skin cancer (other than melanoma), in situ breast or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 2 years.
3.2.16 Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.
3.2.17 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 patient inappropriate for entry into this study.

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3.3 Inclusion of Minorities

The study is open to all participants regardless of ethnicity. Efforts will be made to extend the accrual to a representative population, but in this trial which will accrue approximately 44 patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore racial and ethnic aspects of clinical research on the other. If differences in outcome that correlate to racial or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4.0 Screening and Registration Procedures

4.1 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the patient‟s research chart and medical record. Studies or procedures that were performed for clinical indications (not exclusively to determine study eligibility) and within the screening window may be used for baseline values even if the studies were done before informed consent was obtained. If a patient is randomized, but ultimately does not meet the eligibility criteria for the study, he will be considered a "screen failure" and will not participate in the study. A list of screen failures and the reason for which they are considered a screen failure will be maintained.

4.1.1 Assessments within 8 weeks of the first dose

4.1.1.1 *4.1.1.1* Baseline bone scan for tumor assessment

4.1.1.2 Baseline CT or MRI scan of the abdomen and pelvis

4.1.2 Assessments within 2 weeks of the first dose

4.1.2.1 Demography: date of birth, race and gender.

4.1.2.2 Medical history:

4.1.2.2.1 Prostate cancer-specific history including: date of diagnosis, current stage of cancer, prior systemic treatment for prostate cancer (an exclusion criterion); and history of other malignancies

4.1.2.2.2 Prior surgery and/or radiotherapy (date, organ/anatomic region(s) of surgery and/or radiotherapy must be documented), other significant medical and surgical histories within the past 6 months.

4.1.2.3

4.1.2.4

4.1.2.5 Physical examinations: height (only recorded at baseline) and body weight and current medical conditions.

4.1.2.6 Vital signs: body temperature, blood pressure and heart rate. **Note:** If a subject presents with poorly controlled hypertension, defined as SBP ≥140mmHg or DBP ≥90mmHg, antihypertensive medication(s) should be initiated or adjusted with a goal to control the blood pressure to <140/90 mmHg.

4.1.2.7 ECOG PS

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4.1.2.8 Clinical laboratory assessments, as listed on the study calendar.

4.1.2.9 Verification of an operative date for prostatectomy/pelvic lymph node dissection that allows for the 28 day therapeutic period as well as a 48 hour washout period prior to surgery. Prostatectomy may be performed via any accepted methodology (open, laparoscopic, robotic-assisted, etc.). Notably, standard wait times for prostatectomy at City of Hope vary between 5-6 weeks from the time of biopsy confirmation of prostate cancer. Thus, it is not anticipated that the current protocol will delay standard of care therapies on the control or experimental arms.

4.1.2.10 Randomization to either surgery alone or preoperative axitinib therapy, to be performed by the designated study biostatistician

4.1.3 Pre-dose Assessments on Day 1 for patients randomized to axitinib (Note: Day 1 for patients randomized to axitinib treatment is considered the first day of axitinib therapy, whereas Day 1 for patients randomized to observation will represent the date of surgical intervention. Thus, the observation period reflects the time elapsed between the date of consent and the date of surgery.)

4.1.3.1 Physical examination: to identify any changes in the subject‟s mental and medical conditions since baseline assessment that would make him/her ineligible for the study.

4.1.3.2 Blood pressure measurements: subjects must have a blood pressure reading of <140/90mmHg to be eligible. If anti-hypertensives were initiated and/or dosing has been adjusted during the Baseline Period, the blood pressure must be re-assessed on two occasions consecutively that are separated by a minimum of 1 hour. The mean SBP/DBP values from both blood pressure assessments must be <140/90mmHg in order for a subject to be eligible. These two assessments must also be the most recent ones prior to treatment (the blood pressure values from the later assessment will be used as the subject‟s baseline blood pressure values).

4.1.3.3 ECOG PS.

4.1.3.4 Record all the medication(s) received within 2 weeks prior to the first dose of study medication and indicate if the medication is continuing.

4.1.3.5 Obtain archived tumor tissue samples for biomarker assessments.

5.0 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient and a signed informed consent will be obtained.

5.1 Registration Requirements/Process

To register a patient, the treating physician should contact the protocol nurse or the responsible Clinical Research Associate (CRA) in Clinical Trial Office (CTO) to complete the eligibility/registration form. The protocol nurse or CRA will contact the Data Coordinating Center at the City of Hope (626-256-4673, ext. 64267 or e-mail dcc@coh.org), EMAIL a copy of the completed eligibility checklist, required pre-study tests (per protocol – and may include laboratory, CT and pathology reports), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form to dcc@coh.org.

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Registration Process The patient registration process will be handled by the Department of Clinical Research Information Support (CRIS) Data Coordinating Center (DCC) at City of Hope. The steps below are to be taken when registering a **patient:**

- The research staff must assure they have the most current and updated version of the protocol and informed consent prior to enrolling a patient. If a question arises, please contact the Data Coordinating Center at 626-256-4673 extension 64267 or via email at dcc@coh.org.
- The study staff must assure that all prestudy laboratory tests, scans and x-rays have been completed prior to registration according to the study calendar
- The study staff must assure that the patient has signed an approved informed consent prior to registration/randomization, including the Experimental Subject Bill of Rights and appropriate HIPAA authorization.
- The study staff must confirm that the patient meets all inclusion and exclusion eligibility criteria for the protocol. The eligibility checklist (provided by the COH DCC) must be completed in its entirety.
- Patients must be registered prior to initiation of treatment but no more than 5 working days prior to planned start of treatment. A patient failing to meet all protocol requirements may not be registered.
- Once a patient is eligible, all the pre-study requirements have been fulfilled, and the informed consent obtained, the research nurse or the data manager (study coordinator) will inform the COH Data Coordinating Center at (626) 256-4673, extension 64267; email dcc@coh.org and FAX (fax number 626 256-8794) a copy of the patient"s signed informed consent, , completed eligibility checklist and corresponding source documentation confirming eligibility (including pathology reports, lab reports, x-ray reports, etc.).

The City of Hope Data Coordinating Center will:

- Review all materials/source documentation to ensure the patient is eligible.
- Ensure the consent form is valid and is signed correctly by all parties. If additional information is needed or should there be any questions, the Data Coordinating Center will immediately contact the participating institution and registration will not occur until all issues are resolved.
- If there are questions regarding exceptions to the eligibility criteria, please contact he study Principal Investigator, as well as the COH DCC. Documentation of IRB approval of exception will need to be submitted as well as the COH DCC.
- The patient will be registered and randomized centrally at City of Hope.
- Confirmation of Registration/Randomization will be emailed/faxed to the study staff noting the patient"s study number as well as assigning the randomization arm within 24 hours post receipt of a complete eligibility packet.
- The COH DCC will call the research nurse or data manager (study coordinator) and verbally confirm the registration (if needed).

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- If the patient does not receive protocol therapy following registration, the patient‟s registration on the study may be cancelled. The COH DCC should be notified of cancellations as soon as possible.
- The COH DCC will log into the Electronic Data Capture (EDC) system and enter the patient‟s study number.

5.2 Randomization

Randomization will be performed by the Department of Biostatistics

6.0 Treatment Program

6.1 Treatment Overview

Treatment will be administered in an outpatient setting.

6.1.1 Schedule

In patients on the experimental arm, axitinib should be taken at a dose of 5 mg oral bid, with 28 days of therapy constituting 1 cycle.

The date of initiation of axitinib therapy will be contingent upon the date selected for prostatectomy and pelvic lymph node dissection, with 28 days of planned therapy to conclude 48 hours prior to surgical intervention.

In patients on the control arm, no systemic therapy will be instituted. Rather, prostatectomy and pelvic lymph node dissection will be carried out within 5-6 weeks after biopsy confirmation of prostate cancer.

6.1.2 Criteria for Starting Subsequent Cycles

Only one cycle of axitinib (28 days of therapy) will be instituted in the current protocol.

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6.2 Laboratory Studies

A local laboratory is to be used to perform all clinical laboratory assessments. Laboratory tests should be performed as indicated in the Time and Events Table(s). All laboratories prior to week 9 may be performed/collected within +/- 3 days of the dates specified in the study calendar. From week 9 onwards, all laboratories may be performed/collected within +/- 7 days of the dates specified in the study calendar. Assessments may be performed more frequently if clinically indicated.

All laboratory tests with values that become clinically abnormal while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline.

Results for all unscheduled clinical laboratory assessments (i.e., haematology, TSH/T_4, coagulation parameters) should be recorded on an unscheduled laboratory form in the eCRF.

Hematology and Clinical Chemistry

Hematology and clinical chemistry laboratory parameters that should be reported include white blood cell count, hemoglobin, hematocrit, platelet count, sodium, potassium, chloride, carbon dioxide, BUN, creatinine, and blood glucose. Assays for hematology and clinical chemistry should be performed according to the study calendar. Estimated creatinine clearance should be calculated using the Cockroft and Gault method.

Liver Function Tests

When a separate liver function test (LFT) panel is conducted, this panel should include the following: ALT, AST, alkaline phosphatase,, and total bilirubin. A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 x upper limit of normal (ULN). Liver chemistry threshold stopping criteria and dose modification guidelines have been designed to ensure subject safety.

Evaluation of Proteinuria To be eligible for the current protocol, urinary protein must be <2+ by standard urine analysis (UA). If UA is ≥2+ for protein then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours.Proteinuria will be evaluated using the urine protein to creatinine ratio (UPC; see Appendix B). .

Coagulation Tests

Coagulation tests should be performed as specified in the Time and Events Table and also in response to an AE/SAE as clinically indicated. Coagulation tests include activated partial thromboplastin time (aPTT),prothrombin time (PT) and international normalized ratio (INR).

Lipid Tests

Lipid tests include cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. These tests should be performed as specified in the Time and Events Table. Additional testing may be performed if clinically indicated. In such a case, the subject should be in a fasting state.

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Thyroid Function Tests

Thyroid function tests to assess thyroid stimulating hormone (TSH) and thyroxine (free T_4) should be performed as specified in the Study Calendar. Unscheduled thyroid function tests (TSH and free T_4) may be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

6.3 Studies Obtained During the Trial

Physical examination: to identify any changes in the subject‟s mental and medical conditions since baseline assessment that would make him ineligible for the study. This will occur as per the study calendar. Patients will then be evaluated in the clinic with a physical examination and examination for pertinent toxicities one month following prostatectomy (constituting a standard post-operative assessment), and then every 3 months, until evidence of disease progression, death, or initiation of a subsequent line of prostate cancer therapy.

ECOG PS: Per study calendar, section 10.0.

PSA will be performed per the study calendar, section 10.0, from randomization until the development of metastatic recurrence.

Blood will be sequestered for correlative studies (see section 10.1) at baseline and at the time of prostatectomy, as well as the post-prostatectomy follow-up visit 4 weeks following the procedure. A total of 20 mL of blood will be collected at each of these visits; 10 mL will be collected in a CPT tube for PBMC isolation and assessment, while 10 mL will be collected for assessment of selected plasma angiogenic factors. Within 4 hours of collection, this blood will be transported to the lab of Dr. Marcin Kortylewski (Beckman Research Institute, Room 3220).

6.4 Post-Study Assessments

Any patient who is discontinued from study treatment for any reason other than progressive disease (PD) will continue to have PSA measurements every 24 weeks (+/- 2 weeks) until the patient starts another anticancer therapy. The investigator or his/her designee will continue collecting information on the initiation of anticancer therapies until the date of data cutoff for the final analysis. All new anticancer therapy therapies after the last dose of treatment will be recorded on the appropriate CRF.

6.5 Criteria for Removal from Study

Treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
- Treatment delays of > 1 week due to adverse events.

Treatment may be interrupted for up to 1 week and missed doses should be omitted. However, patients will be replaced if they do not receive at least 75% of the planned treatment with axtinib in the first cycle of therapy, amounting to 21 days of treatment out of the planned 28 days of therapy.

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6.6 Supportive Care and Other Concomitant Therapy

6.6.1 Investigational Therapy

No other investigational treatment may be given while the patient is on study.

6.6.2 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

6.6.3 Concomitant Medications

Palliative and supportive care for disease-related symptoms, including pain medications, is permitted. Patients may receive loperamide or other medications for treatment or prophylaxis of potential diarrhea. Specific guidelines for managing diarrhea are noted in Appendix C. Anti-inflammatory or narcotic analgesics may be offered as needed. Patients with fever or infection may undergo diagnostic tests and treated with antibiotics as appropriate and may receive therapeutic colony-stimulating factors as appropriate. Erythropoietic agents such as epoetin or darbepoetin may be used at the discretion of the treating physician. Packed red blood cell and platelet transfusions should be administered as clinically indicated. Low-dose oral steroids (defined as $\leq$5 mg per day prednisone or equivalent), short course of oral steroids (defined as < 5 consecutive days or topical or inhaled steroids at any dose may be taken during the study.

Patients who need to be on anticoagulant therapy during treatment with axitinib should be treated with low molecular weight heparin as the preferred therapy. The administration of coumadin or other coumarin derivatives is not allowed due to the possibility of inhibition of CYP1A2-mediated metabolism of coumadin by axitiniband resultant effects on coagulation parameters.

In vitro studies with human liver microenzymes and recombinant CYP enzymes indicated that axitinib metabolism was primarily mediated by the drug-metabolizing enzyme CYP3A, and to a lesser extent by CYP1A2. Additionally, the drug also undergoes N-glucuronidation in liver microsomes of some species. Clinically, there is likelihood that axitinib plasma concentrations may be increased in the presence of co-administered potent inhibitors of the CYP3A and glucuronosyltransferase enzymes. In a healthy volunteer study, ketoconazole, a potent CYP3A inhibitor, produced a 2-fold increase in plasma exposure and a 1.5-fold increase in peak plasma concentration of axitinib. Therefore a potential exists for drug-drug interactions with CYP3A inhibitors such as grapefruit juice, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, telithromycin, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine. Treatment is prohibited in patients receiving axitinib in combination with these and other potent CYP3A inhibitors until appropriate clinical drug interaction studies are performed.

Axitinib metabolism may be induced in patients taking CYP3A4 or CYP1A2 inducers (carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, amobarbital, phenytoin, primidone, rifabutin, rifampin, nevirapine, and St John‟s wort) and this may reduce axitinib plasma concentrations. Patients who require concomitant treatment with potent CYP3A4 or CYP1A2 inducers are not eligible for the study. Since CYP1A2 is also known to be induced in chronic smokers, there is likelihood that axitinib plasma concentrations may be reduced in these individuals. (Note: these patients are not excluded from enrolment, however.)

The ability of axitinib to increase concentrations of coadministered drugs was also investigated in studies with human liver microsomes. At expected therapeutic plasma concentrations (0.01 to 1.0 μg/mL),

axitinib appears most likely to inhibit the drug metabolizing enzymes CYP1A2 and CYP2C8, 2 enzymes not frequently observed as predominant drug metabolizing enzymes. Theophylline, and tacrine are among the few drugs whose plasma concentrations are likely to be increased by axitinib.

Axitinib is highly bound to proteins in human plasma (99.5% bound at concentrations between 0.2 to 20 μg/mL). Therefore, drug interactions with other agents that are also highly bound to plasma proteins are a possibility.

Patients who need to be on chronic antacid therapy with histamine H_2 antagonists (eg, cimetidine [Tagamet®], famotidine [Pepcid®], nizatidine [Axid®], ranitidine [Zantac®]), proton-pump inhibitors (eg, lansoprazole [Prevacid®], rabeprazole [Aciphex®], pantoprazole [Protonix®], and esomeprazole [Nexium®]), or locally acting antacids (eg, Maalox®, Milk of Magnesia®, Amphojel®) should stagger the timing of their axitinib and antacid dosing. Patients should avoid use of antacids for 2 hours before through 2 hours after taking axitinib tablets. Note, however, that patients taking the proton-pump inhibitor omeprazole (Prilosec®) are not eligible for this study and that patients should not use omeprazole while taking axitinib tablets because omeprazole is a CYP1A2 inducer.

Axitinib is not likely to have drug-drug interactions with commonly used antihypertensive agents belonging to the class of ACE inhibitors including angiotensin II receptor antagonists (enalapril, captopril, losartan, vasartan), beta-blockers (atenolol, metoprolol, labetalol), or diuretics (hydrochlorothiazide, furosemide). Within the class of calcium channel blockers, verapamil, and to a lesser extent nifedipine, nicardipine, and diltiazem have a potential for increasing plasma AG-013736 plasma concentrations, due to CYP3A inhibition and should not be used as first choice in antihypertensive treatment. Other calcium channel blockers (amlodipine, bepridil, felodipine) are less likely to raise axitinib plasma levels.

The above information is based on preclinical data from studies using human and animal metabolizing enzyme systems.

All concomitant medications and blood products, as well as interventions (eg, analgesic use or paracentesis) received by patients from the first dose of axitinib until the end of study visit should be recorded on the CRF. Furthermore, all concomitant medications being used at the time of study entry should be reviewed by the prescribing MD and protocol nurse to ensure eligibility and exclusion criteria for the study are not violated. All changes to concomitant medications during the course of therapy will additionally be reviewed by the prescribing MD and protocol nurse, as well, to ensure that prohibited medications are avoided.

6.6.4 Other Treatments Allowed on Study

Surgery (outside of the mandated prostatectomy and pelvic lymph node dissection), androgen deprivation therapy and radiation therapy are not permitted prior to the time of prostatectomy and pelvic lymph node dissection. However, after prostatectomy, these modalities may be used as clinically indicated. Use of these modalities will be recorded in the data capture form.

7.0 Dose Delays/Modifications for Adverse Events

This section contains recommendations for the management of adverse events except hypertension and proteinuria which are discussed in subsequent sections. The following table is provided as a reference for guiding dose reductions. Notably, given the short course of therapy rendered in this study (28 days), dose reductions below 2 mg BID are not permitted.

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DOSE MODIFICATION SCHEMA FOR AXITINIB- RELATED ADVERSE EVENTS			
Dose Level	**Dose**	**Dispensed as**	
0 (Starting dose)	5 mg bid	1 x 5 mg tablet bid	
-1	3 mg bid		3 x 1 mg tablet bid
-2	2 mg bid		2 x 1 mg tablet bid

Patients developing an axitinib-related CTCAE Grade 1 or 2 adverse events may have their dose continued at the same dose level.

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Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments until disease progression or start of new treatment, and for survival thereafter.

The criterion for dose modification for study-drug-related adverse events (from previously on-going trials across the axitinib development program) is summarized in the table below:

CRITERIA FOR DOSE MODIFICATION FOR AXITINIB- RELATED ADVERSE EVENTS OTHER THAN HYPERTENSION	
Related Adverse Events	**INTERVENTION**
Grade 1	Continue at same dose level
Grade 2	Continue at same dose level
Grade 3 nonhematologic treatment-related toxicity*	Decrease dose to one lower dose level.
Grade 4 nonhematologic treatment-related toxicity or Grade 4 hematologic toxicity**	Interrupt dosing; re-start at one lower dose level as soon as improvement to CTCAE Grade ≤2. Dose reductions below 2 mg BID are not permitted.

* Patients who develop Grade 3 nonhematologic toxicities that are controlled with symptomatic medications or Grade 3 asymptomatic biochemistry laboratory abnormalities may be continued at the same dose level at the discretion of the investigator.
** Patients who develop Grade 4 lymphopenia or Grade 4 asymptomatic biochemistry laboratory abnormality may continue study treatment without interruption.

Guidelines for dose reductions for specific adverse events are provided in the following sections.

7.1 Axitinib Dose Reduction for Hypertension

In sponsored studies, patients treated with axitinib were issued blood pressure cuffs for home monitoring and instructed to measure their blood pressure (BP) twice daily, prior to taking each dose. All blood pressure measurements were recorded in a diary and brought to the nurse or study coordinator at each clinic visit. Patients were instructed by the study staff to contact their physician immediately for guidance if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance). See below for dose modifications for hypertension.

New or additional antihypertensive therapy (See Section 6.6.3, Concomitant Medication(s) for guidance) should be started if 2 BP readings, preferably taken in the clinic and separated by at least 1 hour, show the following: 2 systolic BP readings greater than 150 or 2 dBP readings greater than 100 mm Hg. Alternately, the dose of existing antihypertensive medication(s) may be increased. If the patient is already on maximal antihypertensive treatment, the axitinib dose should be reduced by 1 dose level.

Patients who have 2 systolic BP readings, separated by at least 1 hour, greater than 160 mm Hg, or 2 dBP readings, separated by at least 1 hour, greater than 105 mm Hg, should have treatment with axitinib held. (Note: if axitinib is held, patients receiving antihypertensive medications should monitor closely for hypotension and restart axitinib at one lower dose level as soon as BP is <150/100 mm Hg. Plasma half-life of axitinib is 2 – 4 hours and BP usually decreases within 1-2 days following dose interruption.) Treatment with axitinib should be restarted at 1 lower dose level as soon as the systolic blood pressure reduces to less than 150 mm Hg and the dBP reduces to less than 100 mm Hg.

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Patients who develop recurrent systolic hypertension (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg) or recurrent diastolic BP >100 mm Hg following previous axitinib dose reduction should undergo another dose reduction by one dose level.

Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments until disease progression or start of new treatment, and for survival thereafter. Guidance on dose interruption and reduction for hypertension is summarized in the table below.

HYPERTENSION MANAGEMENT PLAN FOR AXITINIB			
Degree of Blood Pressure Elevation			**Management**
Systolic Pressure		Diastolic Pressure	
2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain dose of axitinib. If on maximal antihypertensive treatment, reduce axitinib to one lower dose level.
2 BP readings separated by at least 1 hour show systolic pressure >160 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	Interrupt dosing*; adjust antihypertensive medication; as soon as BP is less than 150/100 mm Hg, restart axitinib at one lower dose level.
Recurrent hypertension following previous dose reduction (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg)	OR	Recurrent dBP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	Repeat axitinib dose reduction by one lower dose level. Dose reductions below 2 mg BID are not permitted.

* If axitinib is held, patients receiving antihypertensive medications should monitor closely for hypotension. Plasma half-life of axitinib is 2 – 4 hours and BP usually decreases within 1-2 days following dose interruption.

7.2 Axitinib Dose Interruption for Surgery or Surgical Procedures

If a major surgery or an interventional procedure (eg, endoscopy) is required, treatment with axitinib must be interrupted at least 24 hours before the procedure and the patient blood pressure should be monitored closely for hypotension. Patients may resume axitinib seven days after minor surgery and 2-3 weeks after major surgery, assuming wound has completely healed and no wound healing complications (eg, delayed healing, wound infection or fistula).

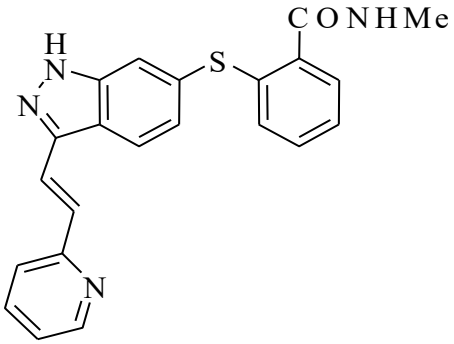
8.0 Agent Information

8.1 Axitinib (AG013736)

NSC#:

8.1.1 Structure and Molecular Weight:

C22H18N4OS (MW 386.47)



8.1.2 Supplier

Pfizer Oncology

8.1.3 Formulation

Axitinib is supplied as a series of aqueous film-coated tablets containing 5 mg or 1 mg of the freebase. Refer to the axitinib IB for information regarding the physical and chemical properties of axitinib and a list of excipients.

8.1.4 Storage

The intact bottles should be stored at controlled room temperature [20°C-25°C (68°F-77°F)]. Excursions are permitted between 15°C and 30°C.

8.1.5 Stability

Stability studies are ongoing.

8.1.6 Administration

Axitinib should be taken orally without food at least one hour before or two hours after a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. If a dose is missed, the subject should take the dose as soon as possible, but not if there are less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking axitinib another dose is not permitted on that day. The subject should resume taking axitinib at the next scheduled dose. If vomiting persists, the subject should be instructed to notify the investigator.

8.1.7 Human Toxicities

Table 1 summarizes the treatment-emergent adverse events in (≥10%) cancer subjects who received single-agent axitinib regardless of whether the event was reported as related to axitinib treatment or other cause. The combined results are summarized for the following studies: Phase 1 studies in subjects with various solid tumors (Protocols A4061022 and A4061044), thyroid cancer (Protocols A4061014 and A4061027), melanoma (Protocol A4061015), NSCLC (Protocol A4061011), and RCC (Protocols A4061012, A4061023 and A4061035). Study A4061032 has not been included since it is an ongoing Phase 3 study. Study A4061013 was excluded since it involved subjects with hematological malignancies and the first-in-human (FIH) Phase 1 study A4060010 was excluded since a number of patients received starting doses above the recommended starting dose of 5 mg BID. Overall, the adverse events reported in

axitinib clinical studies are considered manageable, generally reversible and expected for this class of agents. For single-agent axitinib, the most common adverse events reported from 364 cancer subjects regardless of causality included fatigue (227 subjects, 62.4%), diarrhea (197 subjects, 54.1%), hypertension (173 subjects, 47.5%), anorexia (150 subjects, 41.2%), nausea (139 subjects, 38.2%), dysphonia (129 subjects, 35.4%), headache (104 subjects, 28.6%), palmar-plantar erythrodysaesthesia syndrome (104 subjects, 28.6%), weight decreased (100 subjects, 27.5%), cough (89 subjects, 24.5%), dyspnoea (88 subjects, 24.2%), constipation (86 subjects, 23.6%), arthralgia (83 subjects, 22.8%), vomiting (77 subjects, 21.2%), stomatitis (76 subjects 20.9%), and pain in extremity (73 subjects, 20.1%). Additionally, proteinuria was reported as an adverse event in 72 subjects (19.8%). Grade 3+ events occurred most frequently for hypertension (68 subjects, 18.7%) and fatigue (52 subjects, 14.3%).

Table 1. Treatment-Emergent, All-Causality Adverse Events Summarized by Descending Frequency Occurring in at Least 10% of Subjects with Solid Tumors Receiving Single Agent AG 013736*

MedDRA Preferred Term	Solid Tumor Single-Agent (N =364) All Grades n (%)		Grade 3+ n (%)	
Fatigue	227	(62.4)	52	(14.3)
Diarrhea	197	(54.1)	27	(7.4)
Hypertension	173	(47.5)	68	(18.7)
Anorexia	150	(41.2)	11	(3.0)
Nausea	139	(38.2)	6	(1.6)
Dysphonia	129	(35.4)	0	(0.0)
Headache	104	(28.6)	8	(2.2)
Palmar-plantar erythrodysaesthesia syndrome	104	(28.6)	25	(6.9)
Weight decreased	100	(27.5)	12	(3.3)
Cough	89	(24.5)	5	(1.4)
Dyspnoea	88	(24.2)	30	(8.2)
Constipation	86	(23.6)	2	(0.5)
Arthralgia	83	(22.8)	9	(2.5)
Vomiting	77	(21.2)	6	(1.6)
Stomatitis	76	(20.9)	7	(1.9)
Pain in extremity	73	(20.1)	11	(3.0)
Proteinuria	72	(19.8)	15	(4.1)
Dyspepsia	62	(17.0)	1	(0.3)
Mucosal inflammation	62	(17.0)	2	(0.5)
Abdominal pain	59	(16.2)	15	(4.1)
Rash	58	(15.9)	1	(0.3)
Back pain	57	(15.7)	6	(1.6)
Dizziness	49	(13.5)	1	(0.3)
Dry skin	49	(13.5)	1	(0.3)
Epistaxis	48	(13.2)	0	(0.0)

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Insomnia	48	(13.2)	0	(0.0)
Oedema peripheral	47	(12.9)	0	(0.0)
Pyrexia	47	(12.9)	0	(0.0)
Dysgeusia	46	(12.6)	0	(0.0)
Oropharyngeal pain	41	(11.3)	0	(0.0)
Chest pain	40	(11.0)	5	(1.4)
Hypothyroidism	40	(11.0)	0	(0.0)
Dry mouth	38	(10.4)	0	(0.0)
Myalgia	38	(10.4)	4	(1.1)
Abdominal pain upper	37	(10.2)	4	(1.1)
Nasopharyngitis	37	(10.2)	0	(0.0)

Data in table represents combined safety data from individual studies including protocols A4061011, A4061012, A4061014, A4061015, A4061022, A4061023, A4061027, A4061035, and A4061044

Laboratory test results, summarized by maximum grade for subjects with solid tumors who received single-agent axitinib are presented in Table 2. Grade 3 hyponatremia was reported in 16 subjects (4.6%), elevations in SGOT in 11 subjects (3.2%), hyperglycemia in 13 subjects (3.8%) and proteinuria in 11 subjects (3.3%). Grade 4 creatinine increases were reported in 4 subjects (1.2%). Grade 3 or 4 lymphopenia was reported in 42 subjects (12.2%), and neutropenia in 15 subjects (4.4%).

Table 2. Laboratory Test Results Reported for Subjects with Solid TumorsvReceiving Single-Agent AG 013736

		n (%)[a] at Maximum Grade				
Group/Parameter[b]	**N**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Chemistry						
Total Bilirubin	347	44 (12.7)	21 (6.1)	2 (0.6)	2 (0.6)	69 (19.9)
Hypoalbuminemia	343	117 (34.1)	39 (11.4)	6 (1.7)	0 (0.0)	162 (47.2)
SGOT[c]	347	113 (32.6)	20 (5.8)	11 (3.2)	0 (0.0)	144 (41.5)
SGPT[d]	345	88 (25.5)	32 (9.3)	7 (2.0)	0 (0.0)	127 (36.8)
Alkaline Phosphatase	339	108 (31.9)	26 (7.7)	6 (1.8)	0 (0.0)	140 (41.3)
Creatinine	347	103 (29.7)	25 (7.2)	0 (0.0)	4 (1.2)	132 (38.0)
Hypernatremia	347	21 (6.1)	1 (0.3)	0 (0.0)	0 (0.0)	22 (6.3)
Hyponatremia	347	108 (31.1)	0 (0.0)	16 (4.6)	0 (0.0)	124 (35.7)
Hyperkalemia	347	74 (21.3)	24 (6.9)	9 (2.6)	0 (0.0)	107 (30.8)
Hypokalemia	347	46 (13.3)	0 (0.0)	4 (1.2)	0 (0.0)	50 (14.4)
Bicarbonate	261	67 (25.7)	9 (3.4)	1 (0.4)	1 (0.4)	78 (29.9)
Hypercalcemia	171	23 (13.5)	1 (0.6)	1 (0.6)	1 (0.6)	26 (15.2)
Hypocalcemia	171	29 (17.0)	11 (6.4)	1 (0.6)	2 (1.2)	43 (25.1)
Hyperglycemia	344	158 (45.9)	56 (16.3)	13 (3.8)	0 (0.0)	227 (66.0)
Hypoglycemia	344	47 (13.7)	10 (2.9)	2 (0.6)	1 (0.3)	60 (17.4)
Hematology						
Hemoglobin	347	134 (38.6)	30 (8.6)	0 (0.0)	3 (0.9)	167 (48.1)
Platelets	346	68 (19.7)	4 (1.2)	1 (0.3)	2 (0.6)	75 (21.7)
White Blood Cells	347	52 (15.0)	12 (3.5)	0 (0.0)	1 (0.3)	65 (18.7)
Neutrophils (Abs)	344	32 (9.3)	10 (2.9)	3 (0.9)	12 (3.5)	57 (16.6)

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Lymphocytes (Abs)	345	65 (18.8)	60 (17.4)	29 (8.4)	13 (3.8)	167 (48.4)
Urinalysis						
Urine Protein	337	63 (18.7)	72 (21.4)	11 (3.3)	0 (0.0)	146 (43.3)

Data in table represents combined laboratory data from individual studies including Protocols A4061011, A4061012, A4061014, A4061015, A4061022, A4061023, A4061027, A4061035, and A4061044
[a] Number of subjects at their maximum after-dosing grade
[b] Only laboratory values which fall within CTCAE grading criteria are included
[c] SGOT = Aspartate aminotransferase
[d] SGPT = Alanine aminotransferase

For purposes of the informed consent, toxicities (all grades) noted to occur in > 35% of the study population in the aforementioned single-agent trials of axitinib are denoted "Most Common". Toxicities (all grades) occurring in < 35% of the study population are denoted as "Less Common".

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

8.2 Agent Ordering

A drug supply request form will be supplied to the Investigational Drug Pharmacy.

9.0 Correlative/Special Studies

9.1 Laboratory Correlative Studies

Analysis of pre-metastatic niche density will take place through previously reported techniques. Briefly, a total of 12 4 μm sections of benign lymph node tissue (derived from paraffin-embedded sections) will be stained with monoclonal antibodies directed at VEGFR1 (ImClone Systems). VEGFR1 clustering will be counted within 8 distinct 40x fields, and the cluster count will be averaged.

Analysis of pSTAT3 and related mediators will be conducted through previously reported techniques. Briefly, 4 mm sections of tumor tissue (derived from paraffin-embedded sections) will be stained with monoclonal antibodies directed at IL-6R (Calbiochem) and pSTAT3 (Santa Cruz Biotechnology). Using both IPLAB and Adobe Photoshop 7.0, random x100 objective fields will be analyzed by selected a standardized color range for immunohistochemical staining. After boundary delineation, the area under the pixilation histogram will be calculated, and the total staining area will be compared to the area of total tissue.

Of note, the laboratory investigator (Dr. Kortylewski, Dr. Yu, or associates) will be blinded to the patient randomization. A total of 12 unstained slides derived from tumor and 12 unstained slides derived from normal lymph node tissue will be requested. These slides will be marked with a unique patient identifier number (UPIN) designated by the pathology core facility. Only the study PI and biostatistician will have access to the data to correlate UPIN with patient identification; this data will be housed in a password-protected electronic database.

Blood (a total of 20 mL) will be obtained at baseline, at the time of prostatectomy and at a follow-up visit 4 weeks following the procedure for correlative studies to examine levels of pSTAT3 in PMBCs and selected angiogenic markers. A total of 10 mL will be collected in a CPT tube (for PBMC isolation), and a separate aliquot of 10 mL will be collected in an EDTA tube (for assessment of angiogenic markers) at

the specified times of collection. Blood will be delivered to the lab of Dr. Marcin Kortylewski (Beckman Research Institute, Room 3220) within four hours of collection.

For isolation of PBMCs, 10ml of the whole blood in the CPT tube will be sent to the laboratory of Dr. Marcin Kortylewski (in the Beckman Research Institute Building, Room 3111) within 4 hours of collection to avoid degradation of the phosphomoieties (i.e., pSTAT3) assessed in this protocol. If a sample is not delivered to the laboratory within a 4 hour time frame, the sample will be discarded. CPT tubes will be centrifuged at 1800 x g (approximately 2800 rpm on a Sorvall RT6000 centrifuge) for 20 minutes at room temperature. After centrifugation, plasma in the CPT tubes will be gently pipetted against the gel plug to dislodge cells stuck to the top of the gel. The cell suspension will be transferred to a 50 mL conical polypropylene tube. cRPMI will be added to a total of 40 mL. A 10 μL aliquot of cell suspension for counting will be removed. The 50 mL tubes will then be centrifuged at 250 x g for seven minutes at room temperature. When centrifugation is complete, the supernatant will be aspirated. PMBCs will be either cryopreserved or used fresh.

Analysis of pSTAT3 in PBMCs will be conducted through previously reported techniques (Chalmin F, Ladoire S, Mignot G, et al. Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. J Clin Invest 2010;120:457-71.). PBMCs will be immersed in a mixture of PBS, 2% FCS and 0.1% (wt/vol) sodium azide with Fc III/IIR-specific antibody to block nonspecific binding and stained the cells with different combinations of fluorochrome-coupled antibodies to CD11c, I-Ab (MHC class II), CD86, CD11b, Gr1, CD49b, CD3, CD25 or Lag-3, or with annexin V (BD Biosciences). We collected fluorescence data on FACSCalibur (Beckton Dickinson) and analyzed them using FlowJo software (Tree Star). This method has been previously published by Chalmin et al.

For assessment of angiogenic markers, 10 mL of blood will be centrifuged (1500 rpm for 5 minutes) to separate plasma. Plasma concentration of VEGF-A, PDGF-AB and soluble VEGFR-2 were determined by enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions from appropriate kits to quantitate these entities (R & D Systems). These methods have been previously reported by Kontovinis et al (Kontovinis L, Papazisis K, Touplikioti P, Andreadis C, Mouratidou D, Kortsaris A. Sunitinib treatment for patients with clear-cell metastatic renal cell carcinoma: clinical outcomes and plasma angiogenesis markers. BMC Cancer 2009;9:82.)

10.0 Study Calendar

10.1 Study calendar for patients randomized to axitinib therapy

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 9	Wk 21	Wk 33	Wk 45	Wk 57
Axitinib 5 mg oral bid[a]		X	X	X	X						
Prostatectomy/PLND						X					
Informed Consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------									
Physical exam	X	X		X			X	X	X	X	X
Vital signs	X	X	X[e]	X	X[e]		X	X	X	X	X
Height	X										
Weight	X	X		X			X	X	X	X	X
Performance Status	X	X		X			X	X	X	X	X
CBC w/diff, plts*	X	X		X			X	X	X	X	X
Serum chemistry[b*]	X	X		X			X	X	X	X	X
Lipid panel (with LDL)*	X										
Thyroid function tests (TSH, fT4)*	X										
PT, PTT, INR*	X										
PSA*	X	X		X			X	X	X	X	X
Correlative blood (Section 9.1)	X					X	X				
Adverse event evaluation		X									
Bone scan (section 4.1.1)	X	Radiologic evaluations beyond the baseline evaluation shou performed in the setting of two consecutive PSA ris									
CT/MRI (section 4.1.1)	X	Radiologic evaluations beyond the baseline evaluation shou performed in the setting of two consecutive PSA ris									
UA[f*]	X	X				X					
Collection of tumor specimens (Section 9.1)						X					

a: Excepting adjustments for toxicity. b: Albumin, alkaline phosphatase, total bilirubin (direct bilirubin should be obtai
level is >1.5x ULN), bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total prot
SGPT[ALT], GGT, sodium. c: After week 81, on study, continue assessments noted at weeks 9, 21, and 33 every 12 w
biochemical recurrence. d: Off-study evaluation. e: Patients will be supplied with a blood pressure cuff. At the specifie
2 and week 4 of axitinib therapy), the study nurse will call the patients to obtain blood pressure data and report any abn
treating clinician. The treating clinician will dictate a progress note incorporating these data using the template in Appe
≥2+ for protein then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per
clinic visits and laboratories prior to week 9 may be performed/collected within +/- 3 days of the dates specified in the
From week 9 onwards, all clinic visits and laboratories may be performed/collected within +/- 7 days of the dates speci

calendar. Pre-study labs may coincide with day 1 labs if performed within +/- 3 days.

10.2 Study calendar for patients randomized to observation

	Pre-Study	Wk 1	Wk 5	Wk 9	Wk 21	Wk 33	Wk 45	Wk 57	Wk 69	Off Stud
Axitinib 5 mg oral bid[a]										
Prostatectomy/PLND		X								
Informed Consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X									
Physical exam[e]	X		X	X	X	X	X	X	X	X
Vital signs	X		X	X	X	X	X	X	X	X
Height	X									
Weight	X		X	X	X	X	X	X	X	X
Performance Status	X		X	X	X	X	X	X	X	X
CBC w/diff, plts*	X		X	X	X	X	X	X	X	X
Serum chemistry[b*]	X		X	X	X	X	X	X	X	X
Lipid panel (with LDL)*	X									
Thyroid function tests (TSH, fT4)*	X									
PT, PTT, INR*	X									
PSA*	X		X	X	X	X	X	X	X	X
Correlative blood (Section 9.1)	X	X	X							
Adverse event evaluation								X		
Bone scan (section 4.1.1)	X									
CT/MRI(section 4.1.1)	X									
UA[f*]	X									X
Collection of tumor specimens (Section 9.1)		X								

a: Excepting adjustments for toxicity. b: Albumin, alkaline phosphatase, total bilirubin (direct bilirubin should be obtained level is >1.5x ULN), bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGPT[ALT], GGT, sodium. c: After week 81, on study, continue assessments noted at weeks 9, 21, and 33 every 12 weeks biochemical recurrence. d: Off-study evaluation. e: Patients will be supplied with a blood pressure cuff. At the specified in 2 and week 4 of axitinib therapy), the study nurse will call the patients to obtain blood pressure data and report any abnorm treating clinician. The treating clinician will dictate a progress note incorporating these data using the template in Append is ≥2+ for protein then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 2 clinic visits and laboratories prior to week 9 may be performed/collected within +/- 3 days of the dates specified in the stud From week 9 onwards, all clinic visits and laboratories may be performed/collected within +/- 7 days of the dates specified calendar. Pre-study labs may coincide with day 1 labs if performed within +/- 3 days.

11.0 Evaluation Criteria/Measurement of Effect

11.1 Assessment of the pre-metastatic niche

Normal lymph node tissue will be assessed for pre-metastatic niche density, characterized as the average number of VEGFR1-positive clusters in 8 distinct 40x microscopic fields. This assessment will be performed through previously defined techniques.

11.2 Time to Biochemical Recurrence

Time to biochemical recurrence will be defined as the number of days elapsed between prostatectomy and the first recording of a PSA value ≥ 0.2.

11.3 Time to Metastatic Recurrence

Time to metastatic recurrence will be defined as the number of days elapsed between prostatectomy and the first bone scan or CT scan with findings consistent with metastatic prostate cancer.

11.4 Overall survival

Overall survival will be defined as the number of days elapsed between prostatectomy and date of death.

11.5 Erectile Dysfunction

Erectile dysfunction will be defined by CTCAE 4.0, and we will assess the rate of grade ≥ 3 toxicity.

11.6 Urinary Incontinence

Urinary incontinence will be defined by CTCAE 4.0 criteria, and we will assess the rate of grade ≥ 3 toxicity.

12.0 Data Reporting/Protocol Deviations

12.1 Data Reporting

12.1.1 Confidentiality of Records

The original data collection forms will be stored at the originating institution in a secure location. When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act.

12.1.2 Patient Consent Form

At the time of registration, the original signed and dated patient‟s Informed Consent with the Experimental Subject‟s Bill of Rights (for the medical record). All Institutional, NCI, Federal, and State of California regulations concerning the Informed Consent form will be fulfilled. }

12.1.3 Data Collection Forms and Submission Schedule

All data will be collected in a timely manner using protocol defined electronic data capture (EDC) case report forms. Data will be accessible to study biostatisticians from the City of Hope Department of Biostatistics and stored in a secure location.

12.1.3.1 *Eligibility Checklist*

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by a participating investigator prior to registering the patient.

12.1.3.2*Prior Therapy and On-Study Forms*

Within two weeks of registration, the clinical research associate will submit pre-study data collection forms.

12.2 Protocol Deviations

The clinical research associate at COH will also submit copies to the Protocol Management Team and the COH Data and Safety Management Board.

12.2.1 Deviation Policy

In accordance with the COH Policy on Clinical Research Protocol Deviation, there will be a "no deviations" rule for this protocol. However, for subject safety or unforeseen scheduling problems, planned deviations from this protocol will be permitted in accordance with COH IRB policies and if applicable, FDA approval.

12.2.2 Reporting of Unplanned Deviations

All unplanned deviations will be reported to the COH DSMB.

12.2.3 Resolving Disputes

If there is a dispute among the persons involved in the provision of research treatment, in regard to whether a treatment deviates from the protocol, the facts of the case will be reported to the DSMB which will be serve as the arbiter of whether a deviation exists.

13.0 Data and Safety Monitoring Plan

DATA AND SAFETY MONITORING

13.1 **Definition of Risk Level**

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx involving a COH-held IND.

13.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA/protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMC. Protocol specific data collection will include the following items: Adverse event reporting and quarterly safety assessment of axitinib. Reporting of data and safety to the DSMC will occur at least quarterly using the PMT report.

13.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

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Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator‟s brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

- *Serious Adverse Event (SAE)* ***[21 CFR 312.32] is defined as*** **any expected or unexpected adverse event** ***that results in any of the following outcomes:***
    - Death
    - Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred);
    - Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization;
    - A persistent or significant disability/incapacity;
    - A congenital anomaly/birth defect
    - Secondary Malignancy, or
    - Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject‟s health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

13.4 **Reporting of Unanticipated Problems and Adverse Events**

Unanticipated Problems: Unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

- *Serious Adverse Events* - ***All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 1 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).***

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 1 below).

Table 1: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required*
Unlikely, Unrelated	No reporting required*	No reporting required*
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	5 calendar days	5 calendar days
	Grade 1 and 2 AND resulting in hospitalization #	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

*Such events are not required to be reported to the DSMC. These events should be included with the SAE/AE summary provided to the DSMC in the PMT reports and to the IRB in the Annual Continuation reports.

Hospitalization = Unplanned admission equal to or greater than 24 hours

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

ADDITIONAL REPORTING REQUIRMENTS

SAEs meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting which can found at:http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];
- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]

- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

14.0 Statistical Considerations

14.1 Study Design

14.1.1 The study is an open label, randomized phase II assessment of axitinib as pre-surgical therapy in high risk prostate cancer. In particular, a permuted block randomization scheme will be carried out to achieve treatment/control balance. To avoid selection bias, the blocking scheme will be masked to the principal investigator. The number of blocks will be determined by stratifying high risk patients according to PSA levels (≥ 20 or not) and Gleason scores (>=8 or not). For each block, we will randomly choose one arrangement from all possible realizations*Primary Endpoints:* The primary endpoint of this study is pre-metastatic niche density, as defined by the average number of VEGFR1 clusters in 8 distinct 40x microscopic fields. We will use a two sample student‟s T-test to compare the primary endpoint of pre-metastatic niche density in the regional lymph nodes of patients treated with axitinib, as compared to the pre-metastatic niche density in the lymph nodes of patients enrolled on the control arm. With a sample of 22 patients per group, we will have 80% power to determine significance across groups if the average niche density is 3.13 in patients in the control arm, and at most 2.19 in patients treated with axitinib, with a common standard deviation 1.43 using a one-sided t-test assuming a type I error = 10% (Calculated using nQuery Advisor 6.01) Taking this into consideration, 30 patients per group will be recruited according to an empirical replacement rate of 27%. The intention-to-treat analysis will be the primary analysis conducted to obtain unbiased comparisons between the treatment and control. In addition, some as-treated subgroup analysis would also be investigated if necessary.*Secondary Endpoints:* Toxicity, time to biochemical recurrence, time to metastatic recurrence. With respect to secondary endpoints, Cox regression will be used (with the log-rank test) to compare time to biochemical recurrence (PSA ≥ 0.2), TTP and OS in patients treated with axitinib to patients treated with surgery alone. The Chi-square test will be used to compare the pStat3, LOX expression and MDSC density in patients treated with axitinib to patients treated with surgery alone. Descriptive statistics will be used to compare serum levels of VEGF-A, sVEGFR2, PDGF-AB and pSTAT3 at various timepoints during therapy.

14.1.2 *Stopping Rules. T*oxicity will be monitored on an ongoing basis. If the number of unacceptable toxicities exceeds 1 in the first 3 patients, or exceeds 2 in the first 6 patients or more than 25% thereafter, the study will hold accrual for an amendment regarding treatment modifications or study termination. Toxicity will be graded and recorded for each patient in this population according to CTCAE 4.0. Also, a delay in surgery exceeding 7 days as a consequence of axitinib-related toxicity will be considered an unacceptable toxicity.

14.2 Sample Size Accrual Rate

The previously noted sample size of 60 patients is anticipated to accrue over the course of 60 months.

15.0 Human Subject Issues

15.1 Institutional Review Board

In accordance with federal regulations, an Institutional Review Board (IRB) that complies with regulations at 45 CFR 46 and 21 CFR 50, 56 must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

15.2 Recruitment of Subjects

Patients with high-risk prostate cancer will be recruited from patients undergoing evaluation and treatment at City of Hope Cancer Center for this diagnosis.

15.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

15.4 Study location and Performance Sites

This study will be performed at COH.

15.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI).

15.6 Financial Obligations and Compensation

If there is a serious medical complication of the research, treatment will be available at City of Hope, but there will be no compensation to the subject for this injury.

15.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will advise the research subjects about their rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without jeopardizing, include as applicable, their future care or their employment at City of Hope or any relationship they have with City of Hope.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. Following this procedure, the research team will review the results of eligibility testing and determine if the research subject is a candidate for study enrollment.

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