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Title: Phase 2 Combination Trial of Tivozanib and Enzalutamide in Men with Advanced Prostate Cancer

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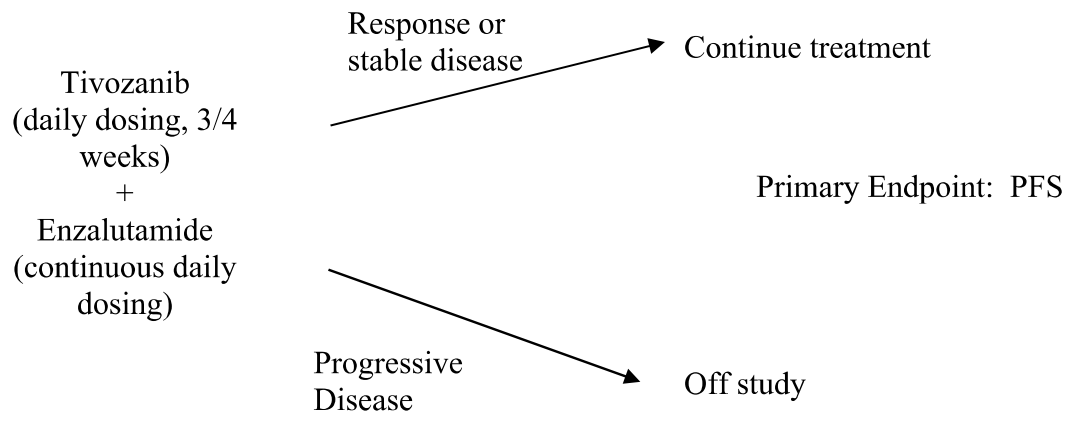
Agent(s):
Tivozanib – Aveo, Astellas
Enzalutamide – Astellas, Medivation

SCHEMA


Tivozanib
(daily dosing, 3/4 weeks)
+
Enzalutamide
(continuous daily dosing)
Response or stable disease
Continue treatment
Primary Endpoint: PFS
Progressive Disease
Off study

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1. OBJECTIVES

The objective of this study is to determine whether combination therapy with tivozanib and enzalutamide is an effective and well tolerated regimen in men with advanced prostate cancer.

1.1 Study Design

We plan to conduct a single arm, open label, combination study with tivozanib and enzalutamide (enz) in men with metastatic castration resistant prostate cancer (mCRPC). All men will receive standard dosing of each drug, with tivozanib administered at 1.5 mg once daily for 3 weeks followed by a one-week break, and enzalutamide taken continuously at 160 mg once daily. Both will be orally administered. A single dose reduction of tivozanib will be permitted, if necessary, to 1.0 mg daily. Patients will continue on treatment until they experience objective or clinical disease progression, or unacceptable toxicity.

Because this combination has not been previously tested, a safety run-in will be conducted at the outset of the trial. While waiting for the first 3 patients to complete one month of treatment, no more than 10 total patients may be enrolled. These patients will be analyzed for safety and toxicity. If any treatment-related, expected or unexpected grade 3 or higher adverse events occur during the first month of treatment in the first 3 patients, or if the rate is >30% among the first 10 patients during the first month of treatment, further accrual will be halted for reconsideration of the appropriateness of the dosing schedules.

1.2 Primary Objectives

The primary objective of the study will be to demonstrate an improvement in progression free survival in men with mCRPC treated with tivozanib and enzalutamide.

1.3 Secondary Objectives

Secondary objectives will be to demonstrate an acceptable tolerability profile of tivozanib and enz, to estimate overall survival and time to PSA progression, to evaluate PSA and objective response and to explore an angiogenesis signature that may predict benefit from VEGFR-targeted therapy in advanced prostate cancer.

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Tivozanib

2.1.1.1 Tivozanib Background

Tivozanib hydrochloride (also known as AV-951; previously known as KRN951) has the chemical name (*N*-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea hydrochloride monohydrate). Tivozanib hydrochloride is a novel and potent pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with potent

activity against all 3 VEGF receptors (VEGFR-1, -2, and -3). Tivozanib hydrochloride inhibits phosphorylation of VEGF receptors-1, -2 and -3 at picomolar concentrations (IC_{50} of 0.21, 0.16 and 0.24 nM respectively), and inhibits c-Kit and PDGFR at 10-times higher concentrations (IC_{50} of 1.63 and 1.72 nM respectively). In nonclinical models and studies performed in humans, tivozanib hydrochloride has shown strong anti-angiogenesis and antitumor activity. VEGF is a potent induction factor, playing a central role in angiogenesis and vascular permeability of tumor tissues. By inhibiting VEGF-induced VEGFR activation, tivozanib hydrochloride inhibits angiogenesis and vascular permeability in tumor tissues, leading indirectly to inhibition of tumor growth.
Tivozanib hydrochloride has been studied in several clinical trials in multiple tumor types. A summary of tivozanib's hydrochloride pertinent efficacy results and safety data follow. Please refer to the tivozanib hydrochloride Investigator Brochure (IB) for descriptions of all available data.

2.1.1.2 Tivozanib Clinical Experience

In phase 1 clinical trials of tivo, different doses and schedules were studied, and PK properties were further defined. Based on these studies, the preferred dosing regimen for additional studies was identified as 3 weeks of once-daily dosing followed by a one-week break, at a starting dose of 1.5 mg daily.

In a Phase 2 study (AV-951-07-201) in 272 patients with metastatic renal cell carcinoma (RCC), there were 2 primary efficacy analyses: best tumor response rates throughout the 16-week open-label period and progression-free survival (PFS) rates at 12 weeks post-randomization. Throughout the 16-week, open-label period, the overall response rate (ORR) for all treated subjects was 24.6% by investigator assessment and 18% by independent radiology review (IRR) assessment. By both investigator assessment and IRR assessment, the disease control rate (DCR) for all treated subjects was 84.2% (229/272 subjects). At 12 weeks post-randomization, PFS rates were 57.4% for tivozanib hydrochloride subjects and 28.1% for placebo subjects (p=0.001). By IRR assessment, PFS rates were 49.2% for tivozanib hydrochloride subjects and 21.1% for placebo subjects (p=0.001)[1].

This promising clinical activity in patients with renal cell carcinoma ultimately led to a registrational, international phase 3 trial of tivozanib in metastatic RCC. The phase 3 trial of randomized patients in 1:1 fashion to treatment with either tivozanib or sorafenib, another small molecule receptor tyrosine kinase inhibitor previously approved for the treatment of mRCC[2]. The primary endpoint was PFS, and tivozanib significantly prolonged PFS compared with sorafenib, 11.9 versus 9.1 months, respectively[3]. The adverse event profile of tivozanib was favorable as well, with primarily on-target and easily managed adverse events such as hypertension. Tivozanib has not previously been studies in men with prostate cancer.

2.1.1.3 Tivozanib Safety Experience

Excluding the phase 3 trial, safety data are summarized below for 14 completed or ongoing clinical studies of tivozanib. Adverse events were generally manageable using standard medical therapy and/or discontinuation or reduction of study drug.

Related treatment emergent adverse events (TEAEs) that resulted in a fatal outcome occurred in 4 subjects and included post-procedural hemorrhage, cerebrovascular accident, pulmonary embolism, and hypertension.

Related TEAEs for combination therapy studies can be summarized as follows:

Combination therapy studies: Related TEAEs were reported in 65/81 subjects (80.2%). The most frequently related TEAEs (occurring in ≥10% of treated subjects) were fatique (50.6%), nausea (40.7%), diarrhea (35.8%), stomatitis (33.3%), vomiting (24.7%), decreased appetite (23.5%), hypertension (22.2%), peripheral sensor neuropathy (22.2%), epistaxis (19.8%), dysphonia (16.0%), thrombocytopenia (16.0%), alopecia (14.8%), headache (12.3%), neutropenia (12.3%), and blood triglycerides increased (11.1%).

RCC monotherapy studies: Treatment-emergent adverse events occurring in ≥ 10% of the total number of subjects in the 4 core RCC monotherapy studies (Studies AV 951-09-301, AV-951-07-201, AV-951-10-202, and AV-951-09-902) treated with tivozanib hydrochloride are presented by preferred term for subjects in the 4 core RCC monotherapy studies in the table below. The table also presents TEAEs for subjects treated with tivozanib hydrochloride in the Phase 3 Study AV 951-09-301/902. TEAEs were reported in 681 of the 785 subjects treated with tivozanib hydrochloride (86.8%). The most frequently reported TEAEs in tivozanib hydrochloride-treated subjects were hypertension, dysphonia, fatigue, and diarrhea. Hypertension, the most frequently occurring TEAE, is a recognized side effect of VEGF receptor inhibitors, the class of drug to which tivozanib hydrochloride belongs, and is likely related to the mechanism of action of these drugs. Across the 4 core RCC monotherapy studies, the incidence of hypertension was lowest in subjects in Study AV-951-09-902 (35 subjects, 23.5%), when tivozanib hydrochloride was given as a next-line VEGF receptor inhibitor after progression on sorafenib in Study AV-951-09-301. In subjects treated as randomized in Studies AV-951-07-301/902 (ie, subjects randomized in Study AV-951-07-301 and continuing with their randomized treatment after rollover into Study AV-951-09-902) , the overall incidence of AEs reported in the tivozanib hydrochloride group was 90.7% (235 subjects). The AE profile was similar between tivozanib hydrochloride and sorafenib-treated subjects, although the incidence of on-target toxicities (hypertension and dysphonia) was higher in tivozanib hydrochloride-treated subjects than in sorafenib-treated subjects. The incidence of off-target toxicities (palmar-plantar erythrodysesthesia, diarrhea, alopecia, and increased lipase) was lower in tivozanib hydrochloride-treated subjects than in sorafenib-treated subjects.

In this trial, 16 subjects experienced adverse events leading to death, and one of these AEs leading to death (hypertension) was considered probably related to study treatment. Three of the AEs were considered possibly related to study treatment (cerebrovascular, pulmonary embolism, post-procedural hemorrhage) and the remaining were unlikely related or unrelated to tivo.

Preferred Term	Total Tivozanib (N=785) n (%)	AV-951-09-301/902 Tivozanib (N=259) n (%)
Any Adverse Event	**681 (86.8)**	**235 (90.7)**
Hypertension	333 (42.4)	113 (43.6)
Dysphonia	176 (22.4)	55 (21.2)
Fatigue	173 (22.0)	50 (19.3)
Diarrhea	168 (21.4)	59 (22.8)
Asthenia	123 (15.7)	40 (15.4)
Dyspnea	111 (14.1)	29 (11.2)
Back pain	101 (12.9)	35 (13.5)
Nausea	99 (12.6)	31 (12.0)
Decreased appetite	89 (11.3)	27 (10.4)
Cough	85 (10.8)	20 (7.7)
Palmar-plantar erythrodysesthesia	82 (10.4)	36 (13.9)
Weight decreased	79 (10.1)	47 (18.1)

Pooled data from 4 core RCC monotherapy studies AV-951-07-201, AV-951-10-202, AV-951-09-902, and AV-951-09-301. From Tivozanib Hydrochloride Investigator Brochure, version 9.2, May 2012.

The incidence of hypertension and palmar-plantar erythrodysesthesia syndrome presented in this table include events of all grades. For the purposes of regulatory reporting, these events are considered expected at ≤ CTCAE Grade 3. Higher grades are considered unexpected.

In other monotherapy studies AV-951-10-112, KRN951/03-B01, and AV-951-08-105, TEAEs were reported in 106 of the 109 subjects (47/50 [94.0%], 42/42 [100%], and 17/17 [100%], respectively). In general, the most frequently reported TEAEs in tivozanib hydrochloride-treated subjects across these 3 studies were hypertension (range of 41.2% to 59.5%), fatigue (26.0% to 76.5%), diarrhea (10.0% to 54.8%), nausea (16.0% to 52.9%), and headache (20.0% to 38.1%). The lowest incidence of TEAEs was observed in Study AV-951-10-112, in which subjects were administered tivozanib hydrochloride for only 3 weeks. Despite differences in dosing duration, and other factors such as underlying disease, dosing schedule, and the small number of subjects in each study, the TEAE patterns are generally consistent with those seen in the 4 core monotherapy studies.

When tivozanib hydrochloride is administered in combination with 1 or more approved antineoplastic agents, the expectedness determination should take into account the labeling of each specific marketed drug taken in combination based upon reference documents which will be included or referenced in the clinical study protocol. The labeled events should, in general, be

considered expected for at least one of the drugs in the combination. The contribution of tivozanib to the severity or frequency of the events is currently unknown.

2.1.1.4 Tivozanib-related Hypertension

Given the frequency of observed hypertension with tivozanib hydrochloride, investigators should exercise caution in treating subjects with a history of severe hypertension or uncontrolled hypertension. Investigators should impress upon all subjects adherence to current anti-hypertensive regimens and the importance of reporting signs and symptoms of elevated blood pressure. In addition, all subjects treated with tivozanib hydrochloride must have their blood pressure controlled prior to starting tivozanib hydrochloride and are required to have periodic blood pressure monitoring during therapy. Three cases exemplify the clinical significance of this adverse drug reaction:

- **Phase 1 dose escalation study:** One subject erroneously took 10 mg once daily x 2 consecutive days (instead of 2 mg once daily) and this resulted in moderate to severe hypertension and an SAE of severe hypertensive retinopathy. The SAE was assessed as probably related to tivozanib hydrochloride and resolved upon discontinuation of study drug.
- **Rollover Study (Parent Protocol Solid Tumor ECG Study):** One SAE of hypertension resulted in a diagnosis of posterior reversible leuko-encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS). The subject was receiving 1.0 mg of tivozanib hydrochloride and had a past medical history of Grade 2 hypertension and non-compliance with her hypertensive regimen. The SAE was assessed as possibly related to tivoxanib hydrochloride and resolved upon discontinuation of study drug.
- **Phase 3 RCC monotherapy study:** One SAE of uncontrolled hypertension was reported in a subject who reportedly took an accidental overdose of tivozanib hydrochloride which resulted in death.

2.1.2 Enzalutamide

Enzalutamide (MDV3100) is a small molecule antagonist of the androgen receptor (AR) that was originally selected based on its activity *in vitro* against prostate cancer cells that overexpressed androgen receptor[4]. In addition to binding tightly to AR, enzalutamide blocks nuclear translocation and DNA binding activity of AR, and furthermore has no known agonist activity against AR in contrast to previous generations of AR antagonists.

The rapid clinical development of enzalutamide is a testimony both to its clear efficacy against prostate cancer as well as its favorable tolerability profile. Clinical activity was observed at many dose levels, and the maximum tolerated dose for sustained treatment was 240 mg daily[5]. The dose chosen for subsequent trials was 160 mg daily. A randomized phase 3 trial of placebo versus enzalutamide in men with mCRPC was halted after an interim analysis demonstrated a

robust improvement in overall survival from 13.6 months to 18.4 months (P<0.0001)[6]. Treatment was well tolerated overall, and the most common reported side effects were fatigue and diarrhea. Early preclinical and clinical studies with enzalutamide raised a concern for an increased rate of seizures, and in the phase 3 trial, seizures were observed in 5 patients receiving enzalutamide (0.6%). Full efficacy and toxicity information is available in the package insert (http://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf).Based on the results of the phase 3 trial, enzalutamide was approved by the US FDA for men with mCRPC previously treated with docetaxel chemotherapy.

Another phase 3 trial has studied the efficacy of enzalutamide in mCRPC patients who were chemotherapy naïve. This trial demonstrated a significant benefit in both primary endpoints, progression free and overall survival[7]. At 12 months, the rate of radiographic progression-free survival was 65% among enzalutamide-treated men, compared with only 14% among placebo-treated men. All secondary endpoints similarly showed significant benefit to enzalutamide in this patient population.

2.2 Study Disease

Novel treatments for advanced prostate cancer are urgently needed. Despite the optimism engendered by a series of new approved therapies in the past three years, death due to prostate cancer will occur in an estimated 28,170 men in the United States in 2012, compared with 28,660 in 2008[8,9]. Two classes of agents that have been studied in advanced prostate cancer are novel hormonal agents as discussed above, including the antiandrogen enzalutamide[6] and the lyase inhibitor abiraterone[7], and antiangiogenic agents such as bevacizumab[10] and sunitinib[11].

2.3 Rationale

Among the most exciting recent results in prostate cancer research has been the demonstration that enzalutamide improves overall survival in metastatic, castration resistant prostate cancer (mCRPC)[6]. Enzalutamide is a novel pure antagonist of androgen receptor (AR) that functions by binding with high affinity to AR, preventing AR translocation to the nucleus, and ultimately inducing apoptosis of tumor cells. In the pivotal phase 3 trial, median survival in men previously treated with chemotherapy for mCRPC increased from 13.6 months to 18.4 months with the addition of enzalutamide[6]. There were also significant improvements in progression free survival (PFS) and other efficacy endpoints, with a median PFS of 8.3 months. Treatment with enzalutamide was well tolerated, in line with generally held and validated beliefs that effective hormonal agents offer substantial improvements in risk/benefit profiles compared with cytotoxic chemotherapy. A phase 3 trial with enzalutamide in chemotherapy-naïve patients with mCRPC has been completed, with results not yet available. Novel hormonal agents such as enz, abiraterone and others are unequivocally central to the current treatment paradigm in mCRPC.

The role of antiangiogenic therapy in prostate cancer is less certain, and at this time remains investigational. Two recent phase 3 trials, with bevacizumab and sunitinib respectively, failed to demonstrate an overall survival benefit for men with mCRPC receiving antiangiogenic therapy[10,11]. However, each of these trials did show significant improvement in PFS. In the bevacizumab trial, men treated with docetaxel and prednisone (DP) had median PFS of 7.5

months, compared with 9.9 months in men treated with DP plus bevacizumab (P < 0.001). In the post-docetaxel sunitinib trial, men treated with prednisone alone had median PFS of 4.1 months, compared with 5.5 months in men treated with prednisone plus sunitinib (P < 0.001). It is not clear why the PFS benefits did not translate to overall survival benefits, but one plausible explanation may relate to tolerability. In the sunitinib trial, for example, more than 25% of men discontinued due to toxicity, likely blunting any signal for positive therapeutic impact. Additionally, both trials studied unselected populations of men with mCRPC, and conceivably there are particular subgroups of men who may benefit; predictive biomarkers of antiangiogenic response have not yet been validated in this patient population.

Tivozanib is a potent tyrosine kinase inhibitor (TKI) of VEGF receptors that has shown encouraging results in renal cell carcinoma[3]. Among the unique features of tivozanib are its marked selectivity for the VEGF receptors[12], as well as an outstanding tolerability profile that may be directly linked to this selectivity[1]. The tolerability of tivozanib suggests that combination therapy with other classes of antineoplastic agents may be more feasible than previous attempts with other TKIs. However, it is likely that combining tivozanib with cytotoxic agents will still result in exaggerated adverse effects, as has been observed with bevacizumab and other VEGF pathway inhibitors. Therefore, it is of particular interest to attempt combination therapy with other targeted agents, and in prostate cancer, specifically with AR-targeted agents. Given the non-overlapping toxicity profile of tivozanib and enz, there is an opportunity to merge additive or potentially synergistic benefits by combining them in an appropriate patient population.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have adenocarcinoma of the prostate that is metastatic or unresectable and for which standard curative options do not exist

3.1.2 Participants must have radiographic evidence of metastatic prostate cancer

3.1.3 Participants must have progressive disease despite ongoing androgen deprivation therapy (ADT) and castrate levels of testosterone, defined as castration resistant prostate cancer (CRPC)

3.1.4 Other than ongoing ADT, prior treatment with other hormonal agents such as antiandrogens or ketoconazole must have been stopped at least two weeks prior to enrollment

3.1.5 Participants may have received prior docetaxel-based chemotherapy for prostate cancer. Such chemotherapy must have been stopped at least three weeks prior to the first dosing in this study.

3.1.6 Male patients age ≥ 18. Because no dosing or adverse event data are currently available on the use of enzalutamide or tivozanib in participants <18 years of age, children are excluded from this study.

3.1.7 Life expectancy of greater than 12 weeks

3.1.8 ECOG performance status ≤2

3.1.9 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 50,000/mcL
- total bilirubin ≤ 1.5 × ULN (or ≤ 2.5 x ULN for subjects with asymptomatic Gilbert's syndrome)
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
- Creatinine ≤ 2x ULN
- Proteinuria < 3+ by urinalysis or urine dipstick

3.1.10 The effects of tivozanib and enzalutamide on the developing human fetus are unknown. For this reason, participating men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

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

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Prior treatment with enzalutamide, TOK-001, or ARN-509. Prior therapy with abiraterone or orteronel is permitted, but must have been stopped a minimum of two weeks prior to study entry. Prior and/or concurrent treatment with bone-targeted therapy such as bisphosphonates or denosumab is permitted.

3.2.2 Participants who have received more than two prior chemotherapy regimens for metastatic CRPC

3.2.3 Participants may not be receiving any other investigational anticancer agents

3.2.4 Participants with known brain metastases

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to tivozanib or enzalutamide

3.2.6 Radiotherapy or minor surgical procedure within 2 weeks, or major surgical procedure within 4 weeks prior to administration of first dose of study drug; inadequate recovery from prior surgical procedure

3.2.7 Any history of seizure or condition that may predispose to seizure

3.2.8 Significant cardiovascular disease, including

- Uncontrolled hypertension: systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg documented on 2 consecutive measurements taken at least 24 hours apart;
- Myocardial infarction, severe angina, or unstable angina within 6 months prior to administration of first dose of study drug;
- History of Class III or IV congestive heart failure, as defined by the New York Heart Association;
- History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation);
- Cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well-controlled with anti-arrhythmic medication; and/or
- Coronary or peripheral artery bypass graft within 6 months of screening

3.2.9 Non-healing wound, bone fracture or skin ulcer

3.2.10 Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to administration of first dose of study drug

3.2.11 Serious/active infection or infection requiring parenteral antibiotics

3.2.12 Significant thromboembolic or vascular disorders within 6 months prior to administration of first dose of study drug, including but not limited to:

- Deep vein thrombosis;
- Pulmonary embolism;
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)

- Peripheral arterial ischemia > Grade 2 (per National Cancer Institute [NCI] C*ommon Terminology Criteria for Adverse Events [CTCAE] Version 4.0*

3.2.13 Corrected QT interval (QTc) of > 480 msec using Bazett's formula

3.2.14 Currently active second primary malignancy, including hematologic malignancies, except for non-melanoma skin cancers, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Subjects are considered to have a currently active malignancy if they have completed anti-cancer therapy and have not been disease free for > 2 years.

3.2.15 History of genetic or acquired immune suppression disease such as human immunodeficiency virus (HIV); subjects on immune suppressive therapy for organ transplant.

3.2.16 Inability to swallow capsules, malabsorption syndrome or gastrointestinal disease that severely affects the absorption of study drugs, major resection of the stomach or small bowel, or gastric bypass procedure

3.2.17 Significant bleeding disorders within 6 months prior to administration of first dose of study drug, including but not limited to:

- Hematemesis, hematochezia, melena or other gastrointestinal bleeding ≥ Grade 2 (per CTCAE Version 4.0);
- Hemoptysis or other pulmonary bleeding ≥ Grade 2 (per CTCAE Version 4.0);
- Hematuria or other genitourinary bleeding ≥ Grade 2 (per CTCAE Version 4.0).

3.2.18 Psychiatric disorder or altered mental status precluding informed consent or protocol-related testing.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Women are not relevant for this study in prostate cancer. We will make every effort to include minorities and other underrepresented populations in this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

   Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification).

The treatment plan is outlined in the table below. Tivozanib will be taken orally once daily for 3 out of 4 weeks on a continuous basis. Enzalutamide will be taken orally once daily without any scheduled interruptions, on a continuous basis.

Treatment Description					
Agent	**Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Tivozanib	None	1.5 mg	PO once daily	Weeks 1-3	28 days
Enzalutamide	None	160 mg	PO once daily	Continuous	

Because this combination has not been previously tested, a safety run-in will be conducted at the outset of the trial. After the first 3 patients are enrolled, accrual will be held until all three patients complete the first 1 month of treatment. Additionally, after a total of 10 patients are enrolled, these patients will be analyzed for safety and toxicity by the DSMC. If any treatment-related, expected or unexpected grade 3 or higher adverse events occur during the first month of treatment in the first 3 patients, or if the rate is >30% among the first 10 patients during the first month of treatment, further accrual will be halted for reconsideration of the appropriateness of the dosing schedules.

5.1 Pre-treatment Criteria

All subjects must have the following within 21 days prior to start of protocol therapy:

- History and physical examination
- ECOG performance status
- Vital signs (including blood pressure, body temperature, heart rate and respiratory rate)
- Availability and review of prior medical records
- Concomitant medications
- Adverse event assessments
- Serum PSA
- Serum testosterone
- Complete blood count
- Serum chemistries
- Thyroid function test (TSH only)
- Coagulation studies
- Urinalysis (urine protein only)
- Electrocardiogram
- Chest x-ray

- Bone scan (repeat scans every 3 cycles up to Cycle 46 then repeat every 6 cycles)
- Abdomen/pelvic CT scan (repeat scans every 3 cycles up to Cycle 46 then repeat every 6 cycles)

Based on these studies, eligibility must be confirmed according to the guidelines in Section 3 above.

5.1.1 Day 1 of Cycle 1

The following data should be collected on Cycle 1 Day 1 (+/- 3 days):

- History and physical exam
- Concomitant medications
- Vital signs (including blood pressure, body temperature, heart rate and respiratory rate)
- ECOG performance status
- Complete blood count
- Serum chemistries
- Urinalysis (urine protein only)
- Adverse event assessments

5.1.2 Day 1 of Every 3rd Cycle

The following data should be collected on Day 1 (+/- 3 days) of every 3rd cycle (see Schedule of Events):

- History and physical examination
- ECOG performance status
- Vital signs (including blood pressure, body temperature, heart rate and respiratory rate)
- Complete blood count
- Serum chemistries
- Thyroid function test (TSH only; every odd number Cycle beyond Cycle 1 up to Cycle 46 and then every 3rd Cycle)
- Urinalysis (urine protein only)
- Serum PSA
- Concomitant medications
- Adverse event assessments
- Study drug diary

[Note: If ECOG performance status, physical examination, hematology, serum chemistry, coagulation studies, and urinalysis were measured/performed within 7 days prior to Cycle 1, Day 1, they need not be repeated at that visit.]

If any treatment-related grade $\geq$ 3 non-hematologic or grade $\geq$ 4 hematologic adverse events are observed, then treatment should be held until resolution of the event(s) to $\leq$ grade 2. The attribution of the events to either or both of the study drugs will be at the discretion of the treating physician, and only the responsible drug should be held. Doses that are held will not be

made up, and the cycle number and cycle day will continue chronologically regardless of whether treatment is held.

If either study drug is held for ≥ 4 weeks, regardless of cause, then the patient should be removed from study treatment.

5.1.3 Off Study Visit

The following data should be collected during the off study visit:

- History and physical exam
- Concomitant medications
- Vital signs (including blood pressure, body temperature, heart rate and respiratory rate)
- ECOG performance status
- Serum PSA
- Complete blood count
- Serum chemistries
- Urinalysis (protein only)
- Bone scan and abdominal/pelvic CT scans (performed if an assessment has not been performed within the prior 6 weeks)
- Adverse event assessments

5.2 Drug Administration and Formulation

5.2.1. Tivozanib

Patients will be treated with 1.5 mg/day of tivozanib, taken orally once daily for 3 weeks, followed by 1 week off tivozanib (1 cycle = 3 weeks on, 1 week off). One cycle is defined as 4 weeks. Cycles will be repeated every 4 weeks in the absence of disease progression or unacceptable toxicities.

Tivozanib should be taken at approximately the same time every day, preferably in the morning, with up to 200 mL of water. Tivozanib should be taken at least 1 hour before or 2 hours after ingesting any food or other medications. On days of a scheduled clinic visit, the dose of tivozanib should not be taken until after visit procedures are completed. If a dose is vomited or missed the dose should not be made up. Only one tivozanib capsule should be taken each day. Grapefruit and grapefruit juice should be avoided during the study.

In the event that tivozanib hydrochloride dosing is interrupted, the duration of cycle/treatment will not be extended; doses missed during the interruption will be captured as omitted rather than delayed.

5.2.2. Enzalutamide

Patients will be treated with 160 mg/day of enzalutamide, taken orally.

Enzalutamide has the chemical name 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4 (methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one. The drug substance has no chiral centers and no salt forms are available at ~ pH 2 to 10. It is essentially insoluble in water, but partially soluble in lipid-based solutions.

Study drug doses should be taken at approximately the same time each day. If dosing is missed on one day for any reason, including vomiting of the dose, the dose should not be repeated or made up. On days of a scheduled clinic visit, the dose of enzalutamide should not be taken until after visit procedures are completed. Dosing will be on a continuous basis unless drug-related adverse events are noted as described in Section 5.1.

Study drug should be stored in a secure location with limited access within the following temperature range: 59°F to 86°F (15°C to 30°C). Bottles should be labeled with the study protocol number, medication or kit number, contents, directions for use, expiration date, and storage directions. Patients will be instructed to store study drug at room temperature out of the reach of children. The drug substance is formulated in the surfactant Labrasol to create a self-emulsifying (or microemulsifying) dosage form. The product will be provided as gelatin capsules in bottles with child-resistant caps.

Patients will be asked to keep a drug diary to document their daily dosing. Study drug accountability will be performed at study visits every 12 weeks to document compliance. Any remaining capsules should be returned at the study visit that will occur every 12 weeks.

Enzalutamide can be taken without regard to other food or beverage intake, and may be taken before or after tivozanib.

5.3 General Concomitant Medication and Supportive Care Guidelines

The only permitted concurrent anticancer therapy during study treatment is ongoing GnRH agonist therapy (e.g. leuprolide, goserelin, etc.). Subjects should avoid agents known to be Cytochrome P450 (CYP3A4) inducers or inhibitors for the duration of study treatment. See Appendix B for a list of CYP3A4 inducers and inhibitors.

5.3.1. Hormonal agents

Ongoing GnRH agonist therapy is required, unless a patient has undergone surgical castration. Prior treatment with other hormonal agents, such as antiandrogens, ketoconazole, orteronel or abiraterone, must have been stopped a minimum of two weeks prior to study entry. No prior therapy with enzalutamide, TOK-001, or ARN-509 is permitted.

5.3.2. Other anticancer therapy

Concurrent treatment with chemotherapy, immunotherapy or other cancer-directed treatment is not permitted. Prior chemotherapy for metastatic CPRC must have finished at least three weeks prior to initiation of treatment on this study. Prior treatment with sipuleucel-T is permitted, and must have been completed a minimum of two weeks prior to study entry. Treatment with concurrent radiotherapy is not permitted, and prior radiation must have been completed a

minimum of two weeks prior to study entry. Similarly, treatment with radiopharmaceuticals, including alpharadin, must have been completed a minimum of two weeks prior to study entry.

5.3.3 Bone targeted therapy

Concurrent administration of denosumab, or bisphosphonates such as zoledronic acid, is permitted. If a patient is not being treated with any of these agents prior to study entry, he should not begin treatment while on study.

5.3.4. Supportive care medications

Use of growth factor support and antiemetics is permitted at the discretion of the treating physician. Steroids may be given at low-dose maintenance therapy (equivalent of prednisone ≤ 10 mg/day) or a short course (≤ 2 weeks) of higher dose therapy.

Low dose oral anticoagulation is allowed provided INR remains < 1.5 from this therapy. Treatment with full dose warfarin is not permitted. Full dose anticoagulation with unfractionated heparin or low molecular weight heparin is permitted.

5.3.5. Other prohibited medications

Subjects should avoid agents known to be Cytochrome P450 (CYP3A4) inducers or inhibitors for the duration of study treatment. See Appendix B for a list of CYP3A4 inducers and inhibitors.

In addition, the following drugs should be avoided throughout the study period because they are known to lower seizure threshold or prolong the QT interval:

- Aminophylline/theophylline
- Atypical antipsychotics (e.g., clozapine, olanzapine, risperidone, ziprasidone)
- Bupropion
- Class IA and III antiarrhythmics (e.g., amiodarone, bretylium, disopyramide, ibutilide, procainamide, quinidine, sotalol)
- Dolasetron
- Droperidol
- Gatafloxacin/moxifloxacin
- Insulin
- Lithium
- Macrolide antibiotics (e.g., erythromycin, clarithromycin)
- Pethidine
- Phenothiazine antipsychotics (e.g., chlorpromazine, mesoridazine, thioridazine)
- Pimozide
- Tricyclic and tetracyclic antidepressants(e.g., amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Venlafaxine

5.4 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up

Patients will be followed for survival information every 3 months until death, up to 2 years after discontinuing therapy, or patient is lost to follow-up. If a patient has withdrawn consent, no further follow up will occur.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant is removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

All men will be initially treated at starting doses of 1.5 mg/day of tivozanib and 160 mg/day of enzalutamide.

6.1 Anticipated Toxicities of Tivozanib

In the phase 3 trial of tivozanib in renal cell carcinoma, 66.9% of the 272 subjects treated with tivozanib experienced at least one treatment-related adverse event. The most common adverse events were: hypertension (44.9%), dysphonia (21.7%), asthenia/fatigue (18.4%), diarrhea (12.1%), dyspnea (5.9%), anorexia (4.8%), cough (4.8%), stomatitis (4.4%) and hand-foot syndrome (4.0%)[3].

In this trial, 16 subjects experienced adverse events leading to death, and one of these AEs leading to death (hypertension) was considered probably related to study treatment. Three of the AEs were considered possibly related to study treatment (cerebrovascular, pulmonary embolism, post-procedural hemorrhage) and the remaining were unlikely related or unrelated to tivo.

6.2 Tivozanib Dose Modification

Clinical judgment will be used to determine appropriate management of the subject experiencing any adverse event (AE). The suggested criteria for dose modification for tivozanib hydrochloride drug-related AEs (excluding hypertension) are summarized in the table below.

Tivozanib Hydrochloride Dose Modification Guidelines for Drug-Related Adverse Events

Drug-Related Adverse Events (excluding Hypertension[a])	Action Taken	Subsequent Dosing Modification
Grade 1	No dose interruption, or reduction required; adverse event management is at the discretion of the Investigator	None required; Dosing may continue at the same dose
Grade 2	No dose interruption, or reduction required; adverse event management is at the discretion of the Investigator	None required; Dosing may continue at the same dose
Grade 3	Interrupt dosing until toxicity resolves to baseline.	Dosing may resume at same dose or reduced dose at the discretion of the Investigator (see below for dose reduction guidelines).
Grade 4	Interrupt dosing until toxicity resolves to baseline.	Dosing may resume at same dose or reduced dose at the discretion of the investigator (see below for dose reduction guidelines).

[a] Hypertension must be treated as described in Section 6.2.1 prior to any dose modification

If a patient experiences unacceptable toxicity related to tivozanib at 1 mg/day, he should be removed from study. Once the dose of tivozanib is reduced, it should not be re-escalated throughout the study.

Subjects with clinically significant Grade 3/4 AEs that are assessed as possibly, probably or definitely study drug-related by the Investigator should have their dose interrupted to allow for resolution of toxicities to baseline. The exception is HTN, which must first be treated as described in Section 6.2.1 prior to any dose modification. Tivozanib may be held for up to 4 weeks. If any drug-related toxicity results in interruption of > 4 weeks, the subject should be discontinued from the study.

Dose escalation of tivozanib above 1.5 mg/day will not be allowed.

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to

experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.2.1. Management of Hypertension

Hypertension (HTN) that occurs during study treatment must be treated with anti-hypertensive drugs prior to any dose reduction. Recommended management of HTN for subjects receiving study drug is presented in Appendix C.

Persistent HTN is defined as 2 consecutive elevated blood pressure (BP) measurements preferably taken in the clinic and obtained at least 1 hour apart. It is recommended that 24-48 hours should elapse between the decision steps. For a listing of recommended DHP (dihydropyridine) calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, see Appendix C, Recommended Anti-hypertensive Medications. Note: If a subject has controlled HTN on an anti-hypertensive regimen at baseline and then develops a worsening of HTN requiring more intensive therapy then the previous regimen, this would be considered Grade 3 HTN.

6.3 Anticipated Toxicities of Enzalutamide

A comprehensive list of adverse events associated with enzalutamide can be found in the package insert for this product. This is generally a well tolerated agent, and in the placebo-controlled phase 3 trial in mCRPC, a similar number of AEs were observed in the enz-treated patients and in the placebo-treated patients. The most common adverse events were fatigue (34%), diarrhea (21%), hot flashes (20%), pain (14%) and headache (12%). Cardiac disorders and liver function abnormalities occurred at similar percentages in the enz-treated and placebo-treated patients. Seizures occurred in 5 patients in the enzalutamide group, and 0 patients in the placebo group.

6.4 Enzalutamide Dose Modification

Dose modification of enzalutamide will generally not be permitted. Patients who experience Grade 3 or greater toxicity related to enzalutamide that cannot be ameliorated by the use of adequate medical intervention should have treatment interrupted until the toxicity improves to Grade 2 or lower severity. A treatment break of up to 4 weeks is permitted. If a patient experiences unacceptable toxicity related to enzalutamide at 160 mg/day, he should be removed from study unless specific permission to restart at a reduced dose is granted by the PI.

Dose escalation of enzalutamide above 160 mg/day will not be allowed.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Tivozanib

7.1.1 Description

Tivozanib is a small molecule inhibitor of receptor tyrosine kinases, and has the chemical name (N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea hydrochloride monohydrate.

7.1.2 Form

Tivozanib hydrochloride is formulated for oral administration as a dark blue/bright yellow or bright yellow number 4 gelatin capsule depending on the capsule strength (see below). The following dosage strengths will be made available:

- 1.5 mg (bright yellow capsule)
- 1.0 mg (dark blue/bright yellow capsule)

The amount of study drug dispensed to the subject at the beginning of every 3rd dosing cycle will be sufficient to allow for a total of 9 weeks (63 days) during which tivozanib hydrochloride will be taken orally once daily for 3 out of 4 weeks. Dosing compliance will be monitored at each clinic visit.

7.1.3 Storage and Stability

Tivozanib hydrochloride drug product should be stored at room temperature (15°– 25°C) in a controlled access room that can be entered only by authorized pharmacy or investigative personnel.

Long-term stability studies conducted according to ICH guidelines support an expiration dating of 36 months for dose strengths ranging from 0.5 mg to 2.0 mg when stored at 15-25ºC with allowable excursions up to 30ºC. Tivozanib hydrochloride drug product is an investigational new drug. Accordingly, all drug handling and disposal procedures for orally administered investigational drugs should be performed by qualified personnel as documented by the American Hospital Formulary Service or other recognized formulary requirements.

Complete study drug information (including packaging, labeling, storage and disposition) is provided in the Tivozanib Hydrochloride Investigator's Brochure.

7.1.4 Availability

Tivozanib is an investigational product and will be supplied free-of-charge by the manufacturer.

7.1.5 Administration

Tivozanib should be taken at approximately the same time every day, preferably in the morning, with up to 200 mL of water. Tivozanib should be taken at least 1 hour before or 2 hours after ingesting any food or other medications. On days of a scheduled clinic visit, the dose of tivozanib should not be taken until after visit procedures are completed. If a dose is vomited or missed the dose should not be made up. Only one tivozanib capsule should be taken each day.

7.1.6 Accountability

Patients will be asked to keep a drug diary to document their daily dosing. Study drug accountability will be performed at scheduled study visits to document compliance. Any remaining capsules should be returned at the scheduled study visits.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.1.7 Destruction and Return

At the end of the study, unused supplies of tivozanib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 Enzalutamide

7.2.1 Description

Enzalutamide has the chemical name 3-(4-cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4 (methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one. The drug substance has no chiral centers and no salt forms are available at ~ pH 2 to 10. It is essentially insoluble in water, but partially soluble in lipid-based solutions.

7.2.2 Form

Enzalutamide will be supplied in 160 mg tablets. It is manufactured and supplied by Astellas (Chicago, IL) and Medivation (San Francisco, CA).

7.2.3 Storage and Stability

Study drug should be stored in a secure location with limited access within the following temperature range: 59°F to 86°F (15°C to 30°C). Bottles should be labeled with the study protocol number, medication or kit number, contents, directions for use, expiration date, and storage directions. Patients will be instructed to store study drug at room temperature out of the reach of children. The drug substance is formulated in the surfactant Labrasol to create a self-emulsifying (or microemulsifying) dosage form. The product will be provided as gelatin capsules in bottles with child-resistant caps.

7.2.4 Availability

Enzalutamide is a commercially available product, and is indicated for the treatment of men with mCRPC following failure of chemotherapy. For the purposes of this study, the product will be billed to patients' insurance.

7.2.5 Administration

Study drug doses should be taken at approximately the same time each day. If dosing is missed on one day for any reason, including vomiting of the dose, the dose should not be repeated or made up. On days of a scheduled clinic visit, the dose of enzalutamide should not be taken until after visit procedures are completed. Enzalutamide can be taken without regard to other food or beverage intake, and may be taken before or after tivozanib.

7.2.6 Accountability

Patients will be asked to keep a drug diary to document their daily dosing. Study drug accountability will be performed at scheduled study visits to document compliance. Any remaining capsules should be returned at the scheduled study visits.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.2.7 Destruction and Return

At the end of the study, unused supplies of enzalutamide should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. STUDY CALENDAR

Baseline evaluations are to be conducted within 3 weeks prior to start of protocol therapy. Subsequent evaluations should be carried out on Day 1 of subsequent cycles (+/- 3 days) every 12 weeks from Cycle 46 on. Radiographic evaluations including bone and abdominal/pelvic CT scans should be conducted at baseline and every 24 weeks from Cycle 46 on.

	Pre-Study	Cycle 1 Day 1[x]	Cycle 2 to Cycle 45, Day 1[x]	Day 1 Cycles ≥ 46, Every 12 Weeks[x]	Off Study[b]
Treatment Schedule:					
Tivozanib		X (days 1-21)	X (days 1-21)	X (days 1-21)	
Enzalutamide		X (Days 1-28)	X (days 1-28)	X (days 1-28)	
Informed consent	X				
Demographics	X				
Medical/Interval history	X	X	X	X	X
Concurrent meds	X	X	X	X	X
Physical exam	X	X	X	X	X
Vital signs/ BP	X	X	X	X	X
Performance status	X	X	X	X	X
Serum PSA	X		X	X	X
PT, PT/INR, and PTT	X				
CBC w/diff, plts	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X
Serum testosterone	X				
Thyroid Function (TSH only)	X		X (odd cycles)	X	
Urinalysis (urine protein only)	X	X	X	X	X
Chest xray	X		as clinically indicated		
Bone scan and abdominal/pelvis CT scans	X	Repeat scans every 24 weeks			X[c]
EKG	X				
Adverse Event Evaluation	X	X----------X			
Survival follow-up					X[d]

x: ± 3 days for treatment or assessment requirement
a: Sodium, potassium, chloride, BUN, creatinine, glucose, albumin, total protein , total bilirubin, alkaline phosphatase, SGOT [AST], SGPT [ALT]
b: Off-study evaluation should occur within 30 days after the last dose of study treatment
c: Post-treatment scans will be performed if an assessment has not been performed within the prior 6 weeks
d: Follow for survival information every 3 months until death, up to 2 years after discontinuing therapy, or patient lost to follow-up

9. MEASUREMENT OF EFFECT

The primary endpoint of the study is progression free survival (PFS). Secondary clinical endpoints will include safety, overall survival, time to PSA progression, PSA response rate and objective response rate.

The consensus guidelines of RECIST 1.1 and PCWG2 have been taken into consideration for the determination of radiographic disease progression {Eisenhauer, 2009 #274;Scher, 2008 #261}. Disease progression will consist of confirmed radiographic disease progression, death due to disease, or clinical disease progression. Radiographic disease progression is defined either by RECIST 1.1 for soft tissue disease, or by the appearance of two or more new bone lesions on bone scan (PCWG2).

Confirmation of progression by RECIST requires redemonstration of soft tissue progression by a scan of the same modality a minimum of 4 weeks later.

If the initial restaging bone scan showed progression by PCWG2 (two or more bone lesions), then confirmation of progression by PCWG2 on the next bone scan requires two or more new bone lesions compared to the first bone scan showing progression. Additionally, at least two of the new lesions from the first scan must still be present.

If progression by PCWG2 occurs not on the initial bone scan but on subsequent bone scans, then confirmation of progression requires either persistence or increase in number of lesions compared to the first bone scan showing progression.

9.1 Antitumor Effect– Solid Tumors

For the purposes of this study, participants will undergo radiographic reevaluation at baseline, every 24 weeks from Cycle 46 on, and at their off-study evaluation. In addition to a baseline scan, confirmatory scans may also be obtained 4-6 weeks following initial documentation of objective response. Response and progression will be evaluated using consensus guidelines of RECIST 1.1 and PCWG2[14,15].

9.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

9.1.2 Disease Parameters by RECIST 1.1

Measurable disease. Measurable disease is a lesion that can be accurately measured in at least one dimension with longest diameter >20 millimeters (mm)

using conventional techniques (CT, MRI, x-ray) or >10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, and cystic lesions are all considered non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT scan. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above.

9.1.3 Response Criteria

9.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

9.1.3.2 Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

9.1.4 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from registration to time of documented disease progression (radiographic or clinical) or death without documentation of disease progression. Patients who are alive and without evidence of progression will be censored at the date of last disease evaluation.

9.2 Other Response Parameters

9.2.1 Time to PSA Progression

PSA progression will be defined according to the consensus guidelines of PCWG2[15]. For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value 3 or more weeks later. For patients with no PSA decline at Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second consecutive value 3 or more weeks later.

9.2.2 Overall survival

The duration of overall survival will be calculated for all patients from the date of registration until the date of death due to any cause.

10.2.3 PSA Response

PSA responses will be evaluated according to the criteria defined by the PCWG2[15].

11.0 ADVERSE EVENTS

11.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without any judgment about causality. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

An adverse event is considered a **serious adverse event** (SAE) if it results in any of the following outcomes:

1) Results in death
2) Is a life-threatening (ie, its occurrence places the patient or subject at immediate risk of death)
3) Requires inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) Is a congenital anomaly/birth defect
6) Is an important medical event that may not result in death, be life threatening, or require

hospitalization but may be considered serious when, based upon medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7) Results in cancer

Suspected Adverse Event

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

Unexpected Adverse Events

An adverse event is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

11.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix D) will be utilized for AE reporting. If specific grading is not available in the CTCAE for a particular AE's severity/intensity, the Investigator is to revert to the general definitions of Grade 1 through 5 and use his/her best medical judgment. The 5 general grades are: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening or disabling, Grade 5 = death related to AE.

Attribution of the AE:

Investigators are required to assess whether there is a reasonable possibility that tivozanib hydrochloride caused or contributed to the adverse event. The following general guidance may be used.

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

11.3 Procedures for Reporting AEs and SAEs

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation (from time of written informed consent through 30 days after receiving the last dose of tivozanib hydrochloride) will be documented. All subjects receiving at least 1 dose of tivozanib hydrochloride, whether completing the treatment period or not, should be followed for

30 days after the last dose of tivozanib hydrochloride. New AEs and changes in ongoing AEs or those with an unknown outcome must be followed for 30 days after the last dose of tivozanib hydrochloride. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). The Investigator will determine the seriousness, intensity, and causality of an adverse event associated with the use of the study drug (ie, events where there is a reasonable possibility that the event may have been caused by the study drug).

All SAEs should be recorded on a Medwatch Form 3500A and sent to the ~~FDA~~, to AVEO Pharmacovigilance/Drug Safety, National Comprehensive Cancer Network (NCCN), and to the Principal Investigator/Study Coordination Center (if applicable).

SAE Reporting Contact Information
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

SAE Reporting Contact Information
Please submit SAE Reports to Parexel GPPG via email (AVEOsafety@parexel.com). If submission via email is not possible or delayed then submission via fax (NA +1-781-434-5957) is acceptable.

Pharmacovigilance/Drug Safety
AVEO Pharmaceuticals, Inc
One Broadway, 14th FloorCambridge, MA 02142
Fax: 1-781-434-5957
E-mail: AVEOsafety@parexel.com

SAE Reporting Contact Information
National Comprehensive Cancer Network (NCCN)
Fax: (215)358-7699
Email: orpreports@nccn.org

SAE Reporting Contact Information
Dr. Michaelson/Massachusetts General Hospital Cancer Center
Fax: 617-726-3440
Telephone: 617-726-1594
Email: dmichaelson1@partners.org

Medwatch 3500A Reporting Guidelines:

In addition to completing appropriate demographic and suspect medication information, the report should include the following information within the Event Description (Section 5) of the Medwatch Form 3500A (Appendix E):

- Treatment regimen (dosing, frequency, combination therapy)
- Protocol description (include number if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive diagnostic and laboratory results
- Investigator's assessment of the relationship of the SAE to each investigational product and suspect medication

Follow-up information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original Medwatch Form 3500A and submitting it as follow-up
- Adding supplementary summary information and submitting it as follow-up with the original Medwatch Form 3500A
- Summarizing new information and faxing it with a cover letter including subject identifiers (ie, DOB, initials, subject number), protocol description and number, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted

Occasionally, AVEO Pharmacovigilance/Drug Safety may contact the reporter for additional information, clarification, or current status of the subject for whom the adverse event was reported.

11.4 Safety Reporting Requirements for IND Holders

For Investigator Sponsored IND Studies there are additional reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 312.32. Sponsor-investigators of studies conducted under an IND must comply with the following safety reporting requirements:

1. Expedited IND Safety Reports

The Sponsor-Investigator is required to report all serious, unexpected and related adverse events directly to the FDA on a MEDWATCH Form 3500A (Appendix E) within 7 (if fatal or life-threatening) or 15 calendar days of first awareness, as described below.

AVEO Pharmacovigilance/Drug Safety and NCCN must be informed of ALL SAEs (final report) on a MEDWATCH Form 3500A within 15 days of first awareness, whether or not they are considered related to the investigational agent(s)/protocol intervention(s).

Reporting to the FDA

The Sponsor-Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected (21 CFR 312.32). Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report to the FDA.

The timeframe for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days after the investigator determines that the suspected adverse event or other information qualifies for reporting.

Any fatal or life-threatening serious, unexpected and related adverse event must be reported to FDA no later than 7 calendar days after initial awareness. Sponsor-Investigators should initially notify FDA by telephone or facsimile transmission. Other means of rapid communication (e.g., email) may also be used, if prior to transmission, the Project Manager in the FDA review division that has responsibility for review of the IND confirms that other means of rapid transmission are acceptable.

Any serious, unexpected and related adverse event that is not fatal or life-threatening must be reported to FDA no later than 15 calendar days after initial awareness.

Reporting to AVEO Pharmacovigilance/Drug Safety and NCCN
AVEO Pharmacovigilance/Drug Safety and NCCN must be informed of **ALL** SAE/suspected unexpected serious adverse reaction (SUSAR) final reports within 15 days of first awareness.

The Sponsor-Investigator must comply with any applicable requirements related to the reporting of SAEs involving his/her subjects to the IRB that approved the study.

2. IND Annual Reports

In accordance with the regulation 21 CFR 312.33, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR 312.33 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to AVEO. Copies of such reports should be submitted to AVEO via NCCN.

11.5 Procedures for Reporting Subject Death

Any death experienced by a subject after enrollment through 30 days of receiving the last dose of tivozanib hydrochloride, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug that is believed to be study drug-related must be promptly reported (within 24 hours of the investigator becoming aware of the event) by telephone, telefax, or e-mail transmission to AVEO Pharmacovigilance/Drug Safety and NCCN. Reports of all on-study deaths must also be communicated promptly to the FDA and the appropriate Institutional Review Board (IRB) and/or reported in accordance with local law and regulations.

11.6 Procedures for Reporting Study Drug Overdose

An overdose of tivozanib hydrochloride should be reported if the dose of tivozanib hydrochloride administered is greater than the assigned dose for the subject.

Should a subject experience an overdose during the course of the study (whether symptomatic or not, and regardless of seriousness), the Sponsor-Investigator or qualified designee must complete a Medwatch Form 3500A to report the overdose to AVEO Pharmacovigilance/Drug Safety and NCCN within 24 hours of first becoming aware of the overdose. Follow-up information on the outcome of the overdose should be forwarded to the AVEO Pharmacovigilance/Drug Safety and NCCN.

Any event associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is considered an AE and should be reported as such. If a SAE occurs in conjunction with the overdose, then the reporting time frame for a SAE should be followed.

11.7 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

All pregnancies, including pregnancies in female partners of male study participants, occurring from the date of ICF signature until 45 days following tivozanib hydrochloride administration must be documented. If it is confirmed that a study participant has become pregnant while participating in this trial, study drug administration will be discontinued immediately. Any pregnancy occurring during this study will be reported immediately to AVEO Pharmacovigilance/Drug Safety and NCCN.

The Sponsor-Investigator must actively follow-up, document and report the outcome of any pregnancy even if the subject has withdrawn from the study. The Sponsor-Investigator will then report follow-up information to AVEO Pharmacovigilance/Drug Safety and NCCN regarding the course of the pregnancy, including perinatal and neonatal outcome. Timelines vary according to the nature of the pregnancy outcome:

- For normal outcomes, AVEO Pharmacovigilance/Drug Safety should be notified within 45 days from birth/delivery.
- For abnormal outcomes, the fully completed Medwatch Form 3500A must be sent to AVEO Pharmacovigilance/Drug Safety according to the same procedures and timelines described for expedited AE reporting.

For questions related to safety reporting, contact: AVEO Pharmacovigilance/Drug Safety.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

The QACT will collect, manage, and monitor data for this study. The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol,

institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1. Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by the DF/HCC IRB.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2. Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3. Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

- Title 21 Part 11 – Electronic Records; Electronic Signatures
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
- Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4. Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5. Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14. STATISTICAL CONSIDERATIONS

14.1. Study Design/Endpoints

The phase 2 study will evaluate the efficacy of enzalutamide and tivozanib in patients with mCRPC. The primary endpoint will be progression free survival (PFS), defined as the time from registration to the earlier of progression (radiographic or clinical) or death and, if censored, the date of last disease evaluation. Based on phase 3 data, the median PFS with enzalutamide alone in chemotherapy naive mCRPC is 14 months. The hypothesis is that the addition of tivozanib will significantly enhance efficacy. An improvement of 60% to a median PFS of 22.4 months will be considered worthy of further study. Assuming exponential distribution, this implies a hazard ratio (HR) of 0.625 relative to historical control (hazard rate from 0.0495 to 0.0309). Using a one-sample exponential test, there will be 80% power to demonstrate a 60% improvement at a one-sided Type 1 error rate of 10% with enrollment of 38 patients and 20 PFS events.

Because this combination has not been previously tested, a safety run-in will be conducted at the outset of the trial. After the first 3 patients are enrolled, accrual will be held until all three patients complete the first 1 month of treatment. Additionally, after a total of 10 patients are enrolled, these patients will be analyzed for safety and toxicity by the DSMC. If any treatment-related, expected or unexpected grade 3 or higher adverse events occur during the first month of treatment in the first 3 patients, or if the rate is >30% among the first 10 patients during the first month of treatment, further accrual will be halted for reconsideration of the appropriateness of the dosing schedules.

The table below gives the probability of observing 1 or more toxicities among the first 3 patients or 3 or more among the first 10 patients given different true underlying toxicity rates.

True toxicity rate	1%	10%	20%	30%	40%	50%
Probability of Stopping Early ($\geq$ 1/3)	0.030	0.271	0.488	0.657	0.784	0.875
Probability of Stopping Early ($\geq$ 3/10)	<0.001	0.070	0.322	0.617	0.832	0.945

Thus, if the true underlying proportion of toxic events is 30% at the current dosing schedules, there is a greater than 60% chance of stopping early.

14.2. Sample Size/Accrual Rate

A total of 38 evaluable patients will be needed to meet the primary endpoint. Sample size will be inflated to 42 patients to account for unevaluable patients. Accrual duration is expected to be

21 months (accrual rate of 2 patients per month) with additional follow-up of 6 months required to reach full event information.

14.3. Analysis of Secondary Endpoints

Secondary clinical endpoints will include toxicity, overall survival, time to PSA progression, objective response rate and PSA response rate.

We will monitor toxicities experienced by all treated patients on the study. With 42 patients, the maximum width of a 90% CI for a given toxicity rate is 27%. The probability of observing at least one rare severe toxicity (true rate=5%) is 88%.

Objective and PSA response will be estimated as the number of responders divided by the total number of evaluable patients. Exact binomial confidence intervals will be calculated for the true response proportion.

Distribution of overall survival defined as the time from registration to death due to any cause will be estimated using Kaplan-Meier methods. PSA progression will be defined according to the recommendations of PCWG2[15].

14.4. Reporting and Exclusions

Any patients who withdraw consent prior to receiving a single dose of study drug will not be counted toward accrual, and will not be considered evaluable for toxicity or response.

Patients who withdraw consent from the study prior to reaching the first on-study disease assessment (after 2 cycles) will not be considered evaluable for response.

14.4.1 **Evaluation of toxicity.** Any participant who receives one or more doses of study drug will be evaluable for toxicity.

14.4.2 **Evaluation of response.** All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. However, patients who withdraw consent from the study prior to reaching the first on-study disease assessment (after 3 cycles) will not be considered evaluable for response. Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.

15. PUBLICATION PLAN

The Principal Investigator holds the primary responsibility for publication of the study results. The Principal Investigator will provide any such publication to NCCN, Aveo and Astellas for review at least sixty (60) days prior to submission and also comply with any provisions regarding publication as are agreed to between the Principal Investigator's institution (Dana Farber/Partners Cancer Care, Inc.) and NCCN in the Clinical Trial Agreement related to this

study. The results will be made public within 24 months of the end of data collection. However, if a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. Authorship for abstracts and manuscripts resulting from this study will be determined according to guidelines established by the International Committee of Medical Journal Editors.

16. REFERENCES

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3. Motzer R, Nosov DA, Eisen T, et al: Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a phase III randomized, open-label, multicenter trial. J Clin Oncol 30 (suppl; abstr 4501), 2012

4. Tran C, Ouk S, Clegg NJ, et al: Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 324:787-90, 2009

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model with clinical activity in a phase II study in renal cell carcinoma. J Clin Oncol 28:e13564a, 2011

14. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009

15. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-59, 2008

17. APPENDICES

Appendix A Performance Status Criteria

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

Appendix B Cytochrome P450 (CYP3A4) Inducers/Inhibitors

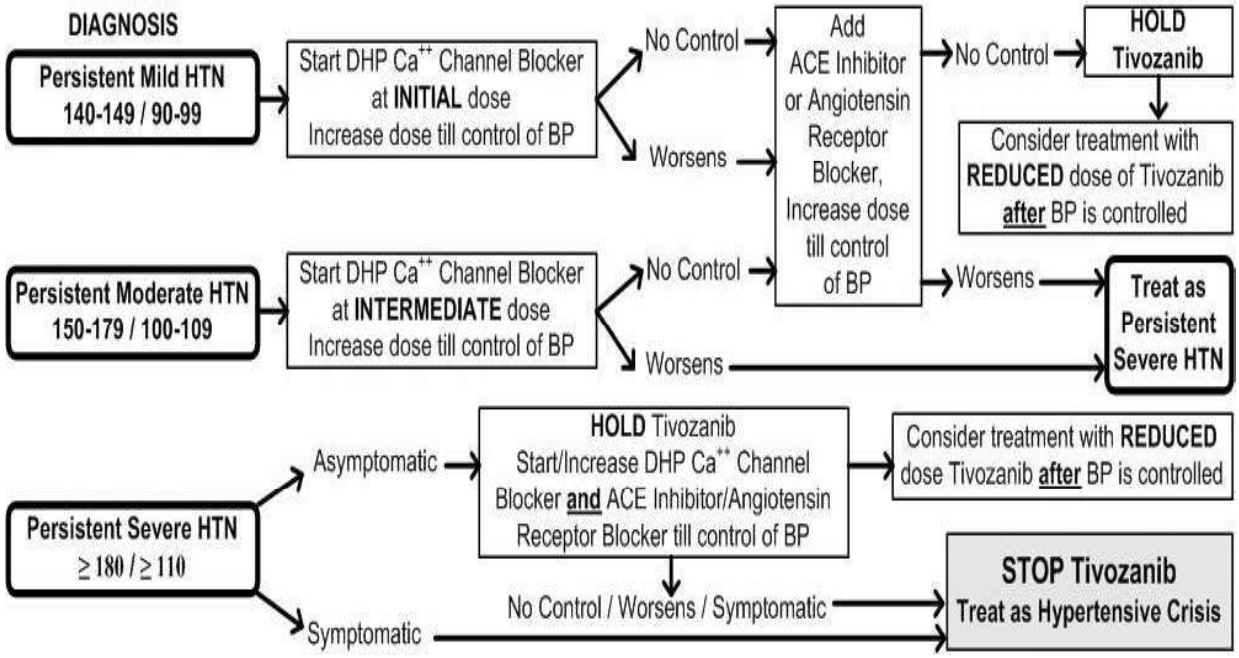
Cytochrome P450 (CYP3A4) Drug interaction table	
INHIBITORS	INDUCERS
Amiodarone	Aprepitant
Cimetidine	Barbiturates
Clarithromycin	Carbamazepine
Diltiazem	Glucocorticoids
Erythromycin	Phenobarbital
Fluvoxamine	Phenytoin
Fruit Juices or products grapefruit, Seville orange, star fruit, and pomegranate	Rifabutin*
Indinavir	Rifampin*
Itraconazole	St. John's Wort
Ketoconazole*	Troglitazone
Mibefradil	
Nefazodone*	
Nelfinavir*	
Ritonavir*	
Troleandomycin	
Verapamil	
NOT azithromycin	

* Asterisk denotes strong inhibition / induction.
Strong inhibition implies that it can cause a > 5-fold increase in the plasma AUC values or > 80% decrease in clearance of sensitive CYP substrates. Moderate inhibitor implies that is can cause a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance of sensitive CYP substrates. Distinction is not always categorical as interaction can vary according to conditions.

This table is a guide and additional inducers/inhibitors may be identified. Please refer to the source of this table for any updated information: http://medicine.iupui.edu/clinpharm/ddis/

Appendix C Recommended Management for Tivozanib-Related Hypertension

Figure 1 provides a guideline for treatment of hypertension (HTN); however, changes may be made at the discretion of the treating physician.



RECOMMENDED ANTI-HYPERTENSIVE MEDICATIONS

Agent	Initial Dose	Intermediate Dose	Maximum Dose
Dihydropyridine (DHP) Calcium Channel Blockers			
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd
Felodipine	2.5 mg po qd	5 mg po qd	10 mg po qd
Angiotensin Converting Enzyme (ACE) Inhibitors			
Captopril	12.5 mg po tid	25 mg po tid	50 mg po tid
Enalapril	5 mg po qd	10–20 mg po qd	40 mg po qd
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd
Lisinopril	5 mg po qd	10–20 mg po qd	40 mg po qd
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd
Perindopril	4 mg po qd	None	8 mg po qd
Quinapril	10 mg po qd	20 mg po qd	20 mg po qd
Angiotensin II Receptor Blockers			
Losartan	25 mg po qd	50 mg po qd	100 mg po qd
Candesartan	4 mg po qd	8–16 mg po qd	32 mg po qd
Ibresartan	75 mg po qd	150 mg po qd	300 mg po qd
Telmisartan	40 mg po qd	None	80 mg po qd
Valsartan	80 mg po qd	None	160 mg po qd

po = oral administration; qd = once daily; tid = three times daily
Adapted from Kollmannsberger C, et al, *CUAJ*. 2007;Vol 1 (Issue 2 Suppl):S41–54.

Appendix D CTCAE v.4.0

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix E Medwatch Form 3500A

http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf