A Phase II Randomized Prospective Trial of Docetaxel/Prednisone Versus Docetaxel/Prednisone and Enzalutamide in Castration-Resistant Prostate Cancer (CRPC) Patients Progressing on Enzalutamide

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University of Chicago

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APPROVAL OF PROTOCOL

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Sponsor Investigator/

Principal Investigator Signature: _____

Print: _____

Date: _____

Principal Statistician Signature: _____

Print: _____

Date: _____

PCCTC Signature: _____

Print: _____

Date: _____

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing University of Chicago with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

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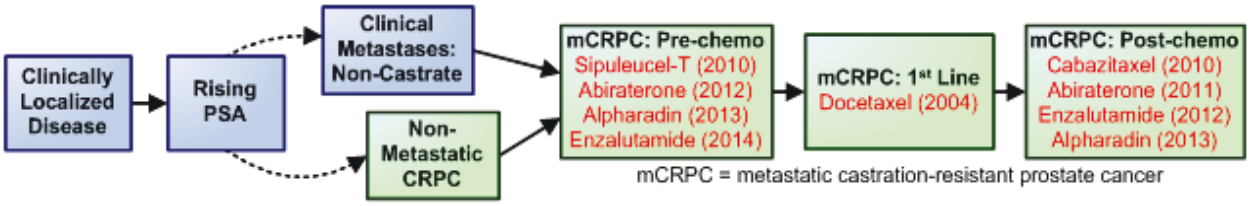
1. INTRODUCTION

1.1 Disease Background

Prostate cancer is the second leading cause of cancer deaths in men. According to American Cancer Society estimates in 2014, as many as 233,000 American men will be diagnosed with prostate cancer, and nearly 29,480 will die of the disease.[1] Yet, localized prostate carcinoma is often curable, and even metastatic disease frequently responds to treatment.

The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Fig. 1). These clinical states involve the complex interplay of a network of signaling molecules that collectively promote net cell proliferation relative to cell death. Based on the extent of disease, hormonal status, and absence or presence of detectable metastases on an imaging study, the states are localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the noncastrate or castrate state.

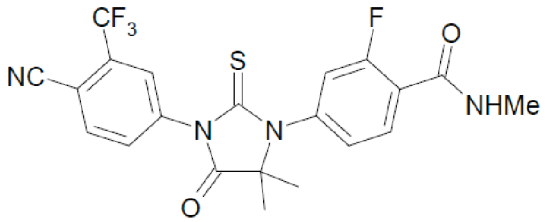
Figure 1 Clinical states of prostate cancer



1.2 Treatment Background

1.2.1 Description and mechanism of action

Enzalutamide (MDV3100) is an androgen receptor (AR) signaling inhibitor that targets several steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA, even in the setting of AR overexpression and in prostate cancer cells resistant to antiandrogens.



Astellas Pharma Global Development, Inc. (Astellas) and Medivation, Inc. (Medivation) are developing enzalutamide for the treatment of cancer. Enzalutamide was approved in the United States on 31 August 2012 under the trade name XTANDI® for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have previously received docetaxel. Enzalutamide has subsequently been approved in more than 35 countries. Clinical development is ongoing for other indications. Enzalutamide, which is formulated with Labrasol® (caprylocaproyl macrogolglycerides) and filled into soft gelatin capsules containing 40 mg of the active pharmaceutical ingredient, is provided as an orally available immediate-release dosage form.

Preclinical studies

Nonclinical pharmacology data demonstrate that enzalutamide is an AR signaling inhibitor that blocks multiple steps in the AR signaling pathway. Enzalutamide competitively inhibits androgen-induced receptor activation, inhibits nuclear translocation of AR and inhibits the association of the AR with chromatin. These inhibitory effects occur even in the setting of AR overexpression and in prostate cancer cells that are resistant to antiandrogens. By inhibiting AR signaling, enzalutamide elicits several downstream effects, which include reduced expression of AR dependent genes, decreased growth of prostate cancer cells, induction of cancer cell death and tumor regression. Enzalutamide lacks agonist activities such as those that may limit the sustained efficacy of current antiandrogens.

Enzalutamide is well absorbed after oral administration to mice, rats, rabbits, monkeys and dogs. Tissue distribution data in rats after oral administration of 14C-enzalutamide showed rapid and extensive distribution to all tissues. Enzalutamide is eliminated slowly from plasma with a long t1/2 across species; plasma clearance is low, and corresponds to ≤ 5% of liver plasma flow in rats and dogs.

The major metabolites in human plasma, the carboxylic acid metabolite and N-desmethyl enzalutamide, have been found in mouse, rat, rabbit, dog and monkey plasma. The carboxylic acid metabolite is considered an inactive metabolite based on primary pharmacodynamic studies. In addition, the carboxylic acid metabolite did not bind to the GABA-gated chloride channel in vitro and had low penetration into rat and mouse brains. In contrast, the primary and secondary pharmacodynamics profiles of N-desmethyl enzalutamide are essentially the same as those of enzalutamide. Like enzalutamide, N-desmethyl enzalutamide is thought to contribute to the safety and efficacy profiles of enzalutamide in patients. Like enzalutamide, N-desmethyl enzalutamide inhibits the GABA-gated chloride channel and also partitions readily to the brain; therefore, it is possible that N-desmethyl enzalutamide may also be associated with convulsions.

Quantitative structure activity relationship (QSAR) analysis of the carboxylic acid metabolite and N-desmethyl enzalutamide using DEREK software did not show any structural alerts that are different from enzalutamide. N-desmethyl enzalutamide is structurally similar to enzalutamide, and the toxicological profile of N-desmethyl

enzalutamide appears to be very similar to enzalutamide based on the dose-range-finding studies with N-desmethyl enzalutamide in mice.

The main findings in repeat-dose oral studies in mice, rats, and dogs were histopathological and organ weight changes in reproductive and hormone-sensitive tissues, consistent with the pharmacological activity of enzalutamide and similar to those reported for other antiandrogens.

Clinical studies
The efficacy of enzalutamide in patients with metastatic prostate cancer who progressed on androgen deprivation therapy has been demonstrated in two randomized controlled phase 3 studies including MDV3100-03 in asymptomatic or mildly symptomatic patients and CRPC2 in patients with more advanced disease who previously received docetaxel. Both studies showed a statistically significant advantage of enzalutamide treatment over placebo across multiple clinically relevant endpoints such as overall survival, rPFS, time to first skeletal-related event, time to PSA progression, PSA response rate, best overall soft tissue response, and quality of life as measured by the FACT-P. Notably, Study MDV3100-03 showed a significant benefit of enzalutamide in time to initiation of cytotoxic chemotherapy. Additional efficacy data from open-label Studies S-3100-1-01, CRPC-MDA-1, and 9785-CL-0111 in patients with metastatic CRPC provided supportive data on PSA response rate, time to PSA progression, and/or best overall soft tissue response, although the magnitude of these treatment effects varied based on the characteristics of the enrolled populations. In general, the treatment effect across these endpoints was larger in patients with metastatic CRPC who had not yet received chemotherapy compared with patients who previously received docetaxel, but the benefit was consistently demonstrated across endpoints within a patient population.

In both phase 3 studies of patients with metastatic CRPC, the benefit of enzalutamide treatment on overall survival as measured by the estimated hazard ratio was observed across all prespecified subgroups. The statistically significant benefit on overall survival was also observed despite substantially higher and earlier use in the placebo groups compared with the enzalutamide groups of subsequent therapies that have demonstrated a survival benefit in patients with prostate cancer. These findings limit the ability to observe the isolated treatment effect of enzalutamide on this endpoint. This is especially true for MDV3100-03, based on the wider availability during this study of subsequent therapies demonstrated to prolong survival in patients with metastatic CRPC.

In Study MDV3100-03, rPFS was a coprimary endpoint and was rigorously evaluated through use of blinded central reviewers as well as through a variety of sensitivity analyses of this endpoint. The magnitude of the relative treatment benefit (unstratified hazard ratio 0.186 [95% CI: 0.149, 0.231]) was coupled with a statistically greater best overall radiographic soft tissue response of 58.8% in the enzalutamide group versus 5.0% in the placebo group (difference of 53.9% [95% CI: 48.53, 59.17%]). Another clinically important finding in this patient population with earlier-stage disease included a 17.2 month delay in the median time to initiation of cytotoxic chemotherapy, which also delays treatment-associated morbidities. The decrease in risk of a skeletal-related event and PSA progression, and improvement

in radiographic response in enzalutamide-treated patients provide additional evidence of clinical benefit. Furthermore, the benefit on time to degradation of FACT-P scores suggests that treatment with enzalutamide may prolong quality of life.

In summary, the efficacy results in MDV3100-03 provide evidence of the benefit of enzalutamide treatment in asymptomatic or mildly symptomatic patients with metastatic prostate cancer who progressed on androgen deprivation therapy, which is consistent with the benefit observed with enzalutamide treatment in patients with metastatic CRPC who previously received docetaxel. The magnitude of the treatment benefit across a range of clinically relevant endpoints demonstrates that treatment with enzalutamide not only prolongs life in these patients, but delays the onset of disease-related and treatment-related morbidities that can negatively impact quality of life.

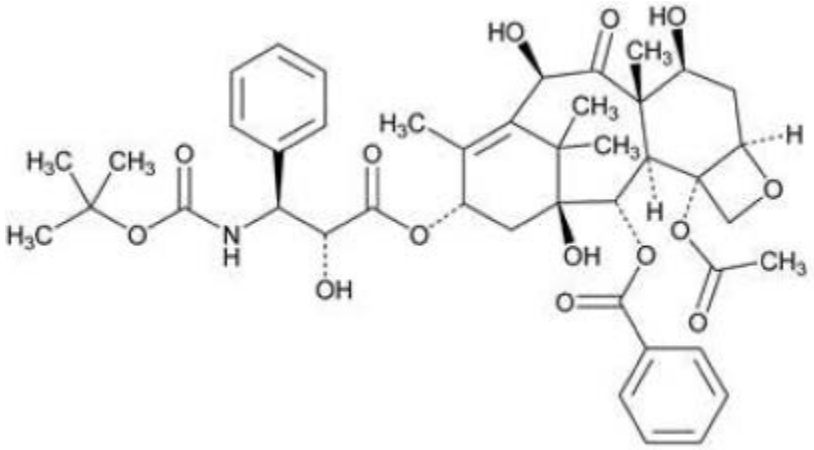
The benefit of enzalutamide for men with prostate cancer is consistently observed across studies of differing patient populations and across the majority of efficacy endpoints assessed.

Combination studies

Few studies combined docetaxel and enzalutamide. Fleming et al established safety of this combination. As CYP34A, an active enzyme that plays a critical role in docetaxel clearance, is induced by enzalutamide, understanding how these two agents are combined was essential. To that end, the study presented by Fleming et al at ASCO-2013 evaluated the safety and pharmacokinetics of docetaxel when co-administered with enzalutamide in CRPC patients. Enrolled patients received docetaxel at 75 mg/m^2 every 3 weeks. Enzalutamide was started at 160 mg daily at 24 hours after cycles 1 and 2 of docetaxel to enable within-subject comparisons of docetaxel plus/minus enzalutamide. Twenty-two patients were enrolled at the time of that report. Safety was established at these standard dose levels and biochemical responses were observed.

1.2.2 Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of C43H53NO14, and a molecular weight of 807.88. It is highly lipophilic and practically insoluble in water.

Mechanism of action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

1.3 Rationale

Mechanisms by which prostate cancer becomes castration-resistant continue to be investigated. The androgen receptor (AR)-dependent pathway is critical in the evolution of CRPC and has led to the development of several therapeutic agents targeting the AR. Enzalutamide, a potent AR inhibitor that induces apoptosis, is currently approved for CRPC patients who have failed standard cytotoxic docetaxel chemotherapy. This approval was based on a pivotal phase III clinical trial that demonstrated improvement in overall survival (OS) in patients treated with enzalutamide versus placebo. Further, another phase III prospective clinical trial has recently been completed in chemotherapy-naïve CRPC patients with preliminary data showing improvement in OS in this setting as well. As more agents become available in the chemotherapy-naïve space, it is anticipated that the use of cytotoxic chemotherapy will be delayed further but it will remain an integral part of managing patients with CRPC.

Whether patients who progress on enzalutamide and require chemotherapy would benefit from continuing enzalutamide remains unknown. While suppressing the AR pathway is appealing in this setting, it is unclear whether this is needed in progressing patients transitioning to standard docetaxel chemotherapy.

Accordingly, we propose a prospective phase II clinical trial where patients who are receiving enzalutamide in the pre-chemotherapy space are randomized upon objective

(radiographic and/or clinical per working group criteria) progression to docetaxel/prednisone alone or the same combination plus enzalutamide.

Pivotal studies that have led to docetaxel's approval in CRPC showed that median time to objective disease progression was 6.3 months (Petrylak et al, NEJM, 2004). However, patients treated on these studies were not exposed to contemporary AR-targeting agents such as enzalutamide. While not known, patients receiving docetaxel after enzalutamide failures could potentially have faster time to progression (TTP) than the 6.3 months previously reported.

Our primary aim is to evaluate whether continuing enzalutamide in combination with docetaxel in patients who failed or progressed while on enzalutamide would increase PFS by 4 months (HR 0.60). Our secondary end points are evaluating PSA responses, percent of patients alive at 1 and 2 years, measuring the decline in circulating tumor cells (CTCs), and assessing quality of life (QOL) in treated patients using validated scales. Further, we will study the existence of androgen receptor splice variant in patients and assess whether adding docetaxel chemotherapy overcomes such mutation.

Patients on the docetaxel/prednisone/enzalutamide arm are allowed to continue on enzalutamide monotherapy (maintenance) after 10 cycles of docetaxel are completed provided no evidence of objective disease progression is observed.

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare time to progression in the standard treatment arm (Docetaxel/Prednisone alone) and experimental treatment arm (Docetaxel/Prednisone plus Enzalutamide)

2.2 Secondary Objectives

- Overall Survival (OS) at both 1 year and 2 years from treatment start
- PSA response in the standard treatment arm and experimental treatment arm

2.3 Correlative/Exploratory/Tertiary Objectives

- Quality of life (QOL)
- Circulating Tumor Cells (CTCs)
- Analysis of androgen receptor splice variant

3. PATIENT SELECTION

3.1 Inclusion Criteria

To be included in this study, patients should meet all of the following criteria:

- Willing and able to provide written informed consent and HIPAA authorization for the release of personal health information.

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

- Males 18 years of age and above
- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features
- Having documented disease progression on enzalutamide within eight weeks of randomization defined **by 1 or more of the following criteria:**
    - PSA progression according to PCWG2 criteria with 3 consecutive rising PSA measurements, all collected at least 1 week apart
    - Radiographic progression in soft tissue or bone by modified RECIST 1.1 for subjects with measurable disease; or
    - Bone disease progression defined by 2 or more new lesions on 2 consecutive bone scans in the absence of falling PSA
- Patients who have not had a bilateral orchiectomy must have a plan to maintain effective GnRG-analogue therapy for the duration of the trial
- Serum testosterone level < 50 ng/dL at Screening visit
- ECOG PS: 0-1
- Throughout the study, male patients and their female partners of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) starting at screening and continuing throughout the study period and for 3 months after final study drug administration. Two acceptable methods of birth control thus include the following:
    - Condom (barrier method of contraception even if having sex with a pregnant woman)
    - One of the following is required:
        - Established use of oral, injected, or implanted hormonal method of contraception by the female partner
        - Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female partner
        - Additional barrier method: Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository by the female partner
        - Tubal litigation in the female partner
        - Vasectomy or other procedure resulting in infertility (eg, bilateral orchiectomy) for >6 months
- Patients must have adequate organ and marrow function as defined below
    - Leukocytes $\geq 3{,}000/mm^3$
    - absolute neutrophil count $\geq 1{,}500/mm^3$
    - platelets $\geq 100{,}000/mm^3$

- total bilirubin within normal institutional limits (or <2X the upper limit of normal in those with Gilbert's disease)
- AST(SGOT)/ALT(SGPT) ≤1.5 X institutional upper limit of normal
- creatinine within normal institutional limits

  OR

- creatinine clearance* ≥45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

- Estimated life expectancy of ≥ 6 months
- Able to swallow the study drug as prescribed and comply with study requirements

3.2 Exclusion Criteria

- Prior treatment with docetaxel-based chemotherapy. Chemotherapy given in the castration-sensitive setting is permissible if stopped at least 6 months prior to initial enzalutamide treatment.
- Prior treatment with abiraterone acetate
- Prior treatment with cabazitaxelSevere concurrent disease, infection, or co-morbidity that, in the judgment of the Investigator, would make the patient inappropriate for enrollment
- Ongoing investigational treatment
- Medical conditions such as uncontrolled hypertension, uncontrolled diabetes mellitus, cardiac disease that would, in the opinion of the investigator, make this protocol unreasonably hazardous
- Major surgery within 4 weeks of treatment start
- Use of an investigational therapeutic agent with 4 weeks of treatment start.
- History of seizure or any condition that may predispose to seizure.
- History of loss of consciousness or transient ischemic attack within 12 months of treatment start
- Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease) within 3 months of treatment start
- Grade > 2 treatment-related toxicity from prior therapy
- History of hypersensitivity to polysorbate 80
- Any known allergy to the compounds under investigation
- Any other condition which, in the opinion of the Investigator, would preclude participation in this trial

4. ENROLLMENT PLAN AND SUBJECT REGISTRATION

4.1 Enrollment Plan

4.1.1 Participating Study Centers
This study is anticipated to be conducted in 5 sites.

4.1.2 Recruitment
Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study.

4.2 Registration Procedure

After eligibility screening and confirmation that a subject is eligible, subjects who are selected to participate will be registered through PCCTC Caisis EDC, the PCCTC's Clinical Data Management System (CDMS). To complete the registration process, the study site must email the signed completed study-specific eligibility checklist, the signed informed consent, and registration information to PCCTC, LLC at pcctc@mskcc.org. A record of subjects who fail to meet eligibility criteria (i.e., screen failures) will be maintained. Once the enrollment packet is received and reviewed at PCCTC, LLC, the subject will be enrolled in PCCTC Caisis EDC. Subject registration must be complete before beginning any treatment or study activities. A complete, signed study consent and HIPAA authorization are required for registration.

4.3 Randomization

Eligible subjects who are progressing on enzalutamide will be randomized in a 1:1 fashion to receive docetaxel and prednisone alone or to the same combination plus enzalutamide. Randomization will be generated by PCCTC Caisis EDC.

5. TREATMENT/INTERVENTION PLAN

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Table 1.

Table 1 Study Calendar

Please note, each cycle is 3 weeks (21 Days). Subjects receiving maintenance enzalutamide (Cycles 11+) will return for assessments monthly

	Screening/ Baseline	Cycle 1/ Day 1	C2/ D1	C3/ D1	C4/ D1	C5/ D1	C6/ D1	C7/ D1	C8/ D1	C9/ D1	C10/D 1	C11+/ D1[1]	EOT	Follow-Up[2]
Informed Consent	X													
Physical Exam	X						X						X	
Medical history & demographics	X													
ECOG PS	X						X						X	
CBC w/ differential[3]	X						X						X	
CMP[4]	X						X						X	
PSA	X				X			X			X	X	X	
Testosterone	X				X			X			X	X	X	
LDH	X				X			X			X	X	X	
Radionuclide Bone Scan	X				X			X			X	X[5]	X	
CT-Scans C/A/P or MRI	X				X			X			X	X[5]	X	
CT-Head or MRI (as indicated)	X													
12-lead EKG	X													
Concomitant Meds	X						X						X	
AE assessment							X						X	
QoL assessment[6]	X				X			X			X		X	
Survival Status														X
Circulating Tumor Cells (CTCs)[7]	X				X[7]			X[7]			X[7]		X[7]	
Analysis of androgen receptor splice variant [7]	X				X[7]			X[7]			X[7]		X[7]	
Docetaxel[8]							X							
Prednisone							X							
Enzalutamide[9]							X							

1. Subjects randomized to the experimental treatment arm (docetaxel/prednisone + enzalutamide) may continue on enzalutamide as a maintenance approach following 10 cycles of docetaxel and will return every 4 weeks for routine assessments until progression
2. Subjects that have discontinued treatment will enter follow-up during which survival status will be confirmed every 12 weeks until death or 24 months post treatment.
3. CBC with differential: white blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), red cell distribution width (RDW), platelet count (UNVPLT), neutrophils (NEUTP).
4. Comprehensive Metabolic Panel includes calcium (CA), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI).
5. Subjects on maintenance enzalutamide therapy will have imaging assessments performed every 6 months following cycle 10.
6. Qol will be assessed using the M. D. Anderson Symptom Inventory (MDASI). Please see appendix D
7. CTCs and androgen receptor splice variant collection will be repeated every 3 cycles starting at C4/D1 and during progression
8. Subjects will receive docetaxel on Day 1 of each 21-day cycle
9. Only for subjects on the docetaxel/prednisone plus enzalutamide arm

5.1 Screening / Baseline Assessment (Day -28 to Day -1)

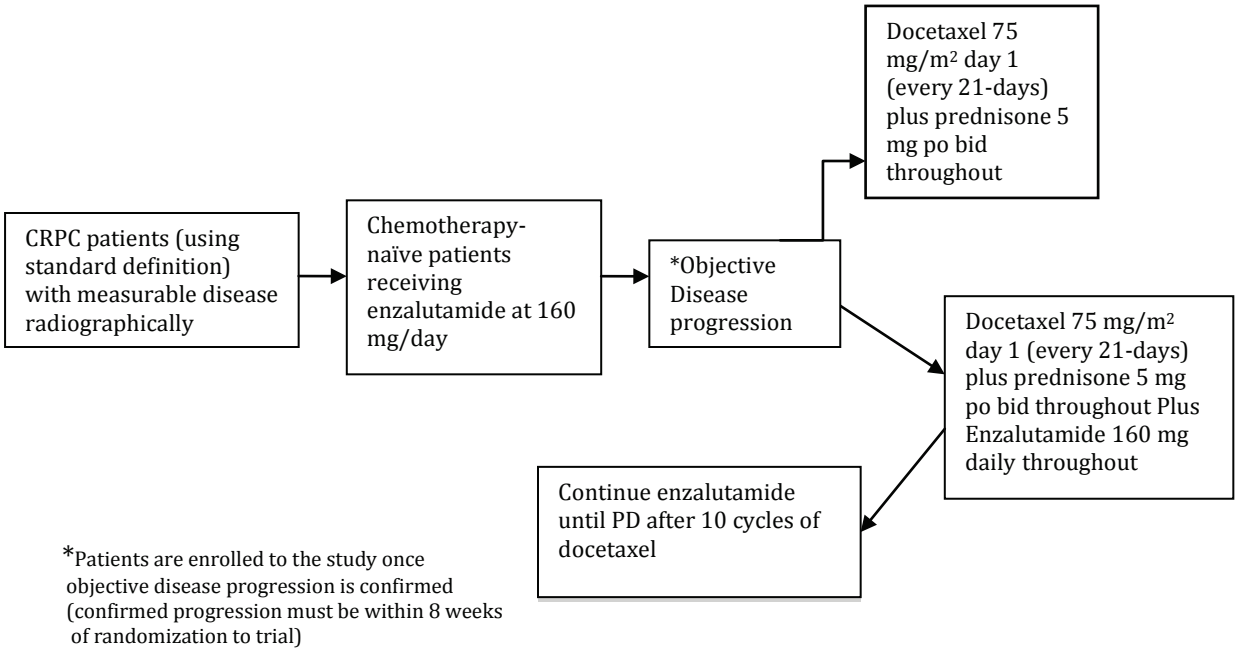
Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a Notice of Privacy Practice research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

During the screening period, subject eligibility will be determined according to the inclusion and exclusion criteria (**Sections 3.1 Inclusion Criteria & 3.2 Exclusion Criteria**). The following assessments will be performed during this time:

- obtain informed consent and research authorization
- record demographics (including age) and medical history (including prior treatment for prostate carcinoma)
- obtain histologic and radiologic confirmation of disease
- details and dates of the primary therapy (e.g., pathologic stage, dose and type of radiation therapy)
- details and dates of prior hormonal and nonhormonal therapies
- presence or absence of disease in the primary site
- conduct physical exam (vital signs, weight, etc)
- assess ECOG performance status (Appendix A)
- discuss concurrent medications (see Enzalutamide Package Insert for a listing of medications with the potential for drug interactions)
- perform laboratory tests (CBC, comprehensive metabolic panel, PSA, LDH, testosterone (TEST))
- additional PSA measurements that can be used to estimate PSA doubling times (PSA-DTs)
- imaging
    - EKG
    - chest by plain radiograph or computerized tomography (CT)
    - abdomen/pelvis by CT or magnetic resonance imaging (MRI)
    - head CT or MRI as indicated
    - radionuclide bone scan
- Quality of Life assessment
- CTCs
- Analysis of androgen receptor splice variant

5.2 Treatment/Intervention Period (Day 1 (-3 days) to Day 21 of each cycle)

Subjects will be seen before each cycle of therapy (up to 3 days before each cycle) for toxicity assessment and evaluation. Subjects will receive docetaxel either alone or with enzalutamide up to 10 cycles of therapy. In both intervention arms, subjects will receive prednisone at 5 mg po bid throughout therapy but steroids could be omitted if deemed appropriate by the treating physician. Treatment randomization is as described in the schema below.



The following assessments will be performed during this time:

- conduct physical exam (vital signs, weight, etc)
- assess ECOG performance status (Appendix A)
- perform laboratory tests (CBC, comprehensive metabolic panel)
- discuss concurrent medications (see Enzalutamide Package Insert for a listing of medications with the potential for drug interactions)
- toxicity assessment
- imaging (response assessment using imaging studies will take place before cycles 4, 7, and 10)
    - chest by plain radiograph or computerized tomography (CT)
    - abdomen/pelvis by CT or magnetic resonance imaging (MRI)
    - radionuclide bone scan
- Quality of Life assessment every 3 cycles starting at C4/D1
- PSA, LDH, testosterone, CTCs every 3 cycles starting at C4/D1

Subjects randomized to the experimental arm (docetaxel/prednisone plus enzalutamide) may continue on enzalutamide as a maintenance approach following 10 cycles of docetaxel. Subjects will be asked to return every 4 weeks for the following assessments:

- conduct physical exam (vital signs, weight, etc)
- assess ECOG performance status (Appendix A)
- discuss concurrent medications (see Enzalutamide Package Insert for a listing of medications with the potential for drug interactions)
- toxicity assessment
- Perform laboratory tests (CBC, comprehensive metabolic panel, PSA, LDH, testosterone (TEST))
- imaging (response assessment using imaging studies will take place every 6 months)
    - chest by plain radiograph or computerized tomography (CT)
    - abdomen/pelvis by CT or magnetic resonance imaging (MRI)
    - radionuclide bone scan

5.3 End of Treatment (30 days of discontinuing treatment)

A subject may be discontinued from study treatment at any time if the patient or the Investigator feels that it is not in the patient's best interest to continue on study. Please see section **5.8 Removing Subjects from the Protocol** for a list of possible reasons for early discontinuation.

Subjects withdrawn from the study because of AEs will be followed until the adverse event has either resolved or stabilized.

The following assessments will be performed during this time:

- conduct physical exam (vital signs, weight, etc)
- perform laboratory tests (CBC, comprehensive metabolic panel, PSA, LDH, testosterone (TEST))
- assess ECOG performance status (Appendix A)
- discuss concurrent medications (see Enzalutamide Package Insert for a listing of medications with the potential for drug interactions)
- toxicity assessment
- imaging
    - chest by plain radiograph or computerized tomography (CT)
    - abdomen/pelvis by CT or magnetic resonance imaging (MRI)
    - radionuclide bone scan
- Quality of Life assessment
- CTCs

- Analysis of androgen receptor splice variant

5.4 Follow-up (Every 12 weeks (±7 days) following treatment discontinuation)

Subjects will be followed for 24 months after removal from treatment or until death. During this time, survival status will be confirmed every 12 weeks.

5.5 Safety assessments

Medical History

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study

ECOG Performance Status

Performance status will be assessed using ECOG performance status criteria. See Appendix A.

Vital Signs

Vital signs include body temperature, blood pressure, respiratory rate, pulse, weight and height. Height will be performed at screening only.

Physical Exam

The physical exam will include a full review of the body systems.

Electrocardiogram (ECG)

Twelve-lead ECGs should be obtained after the patient has been resting for 5-10 minutes prior to each time point indicated. All ECGs should be recorded with the patient in the same physical position.

Adverse Event Monitoring

Subjects will be closely monitored throughout the study for adverse events. Adverse events and other symptoms will be graded according to NCI CTCAE v4.0.

Laboratory Test Assessments

- CBC with differential: white blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), red cell distribution width (RDW), platelet count (UNVPLT), neutrophils (NEUTP).
- Comprehensive Metabolic Panel includes calcium (CA), creatinine (CREAT), alkaline phosphatase (ALK), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBILI).
- Serum *PSA (PSA)*
- Lactate dehydrogenase (LDH)
- Testosterone (TEST)

Tumor Assessment and Bone Scan
Radiographic disease assessment will be obtained every 3 cycles during active treatment (starting at Cycle 4).

5.6 Dose Modifications

5.6.1 Docetaxel

Docetaxel should not be given to patients with bilirubin levels above the ULN, with AST and/or ALT> 1.5-fold ULN, or with alkaline phosphate >2.5-fold ULN.

Neutropenia (<2000 neutrophils/mm3) occurs in virtually all patients who receive 60 mg/m2 to 100 mg/m2 of docetaxel and grade 4 neutropenia (<500 cells/mm3) occurs in approximately 85% of patients who receive 100 mg/m2 and approximately 75% of patients who receive 60 mg/m2 of docetaxel. Febrile neutropenia occurs in approximately 12% of patients who receive 100 mg/m2, but is uncommon in patients who receive 60 mg/m2 of docetaxel. The following treatment emergent adverse reactions occurred at higher rates (≥10%) in patients 65 years or older compared to younger patients: anemia (71% vs 59%), infection (37% vs 24%), nail changes (34% vs 23%), anorexia (21% vs 10%), and weight loss (15% vs 5%), respectively.

Patients who experience either febrile neutropenia, neutrophils <500 cells/mm3 for more than 1 week, severe or cumulative cutaneous reactions, or moderate neurosensory signs and/or symptoms during docetaxel therapy should have the dosage of docetaxel reduced from 75 to 60 mg/m2. If the patient continues to experience these reactions at 60 mg/m2, the treatment should be discontinued. Any other Grade 3 or 4 possibly-related nonhematologic toxicity may be considered dose limiting at the discretion of the Investigator.

- Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80
- Docetaxel should not be used in patients with neutrophil counts <1500 cells/mm3
- Hypersensitivity reactions may occur within a few minutes following initiation of a docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of docetaxel.

5.6.2 Enzalutamide

Evidence of seizure will be considered a DLT warranting cessation of enzalutamide. If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg).

5.7 Concomitant Medications and Supportive Care

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented on the CRF.

The principal investigator should be alerted if the patient is taking any agent included in the list of medications with the potential for drug-drug interactions found in the Enzalutamide Package Insert.

The following medications are prohibited within 4 weeks of Study Day 1, unless otherwise indicated below:

- Androgens
- Potent CYP3A4/5 and CYP2C8 inhibitors or inducers
- Use of an investigational agent, unless prior approval by the Investigator for a shorter washout period, provided the patient has adequately recovered from any ongoing adverse events.

Hormonal treatment for treating complications of GnRH analogue treatment is allowed.

The doses of the following medication classes should be maintained during the Screening Period and while actively treated with study drug:

- Biphosphonates or other approved bone targeting agents for the treatment of metastatic prostate cancer
- GnRH analogues

The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Pain therapy per standard of care and institutional guidelines
- Radiation therapy including external beam radiotherapy or systemic radionuclides (e.g., Samarium or Strontium)
- Palliative surgical procedures to treat skeletal related events

Androgen deprivation therapy (either bilateral orchiectomy or GnRH analogue hormone agonist/antagonist) must be continued during the trial. If androgen deprivation therapy is discontinued, the patient must be withdrawn from study treatment.

5.8 Removing Subjects from Study Treatment

In the absence of treatment delays because of adverse events, treatment will continue for a maximum of 10 cycles of docetaxel or until one of the following criteria applies:

- subject decides to withdraw from the study
- disease progression
- symptomatic disease progression at any time
- objective clinical disease progression
- intercurrent illness that prevents further administration of treatment

- unacceptable adverse event(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the subject to be retreated
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study uninterruptable, unnecessary withdrawal of subjects should be avoided. When a subject discontinues treatment early, the investigator should make every effort to contact the subject and to follow the patient for study endpoints. If the patient withdraws entirely from the trial and refuses further follow-up, a final evaluation should be performed. The reason(s) for withdrawal should be recorded.

Patients on the docetaxel/prednisone/enzalutamide arm are allowed to continue on enzalutamide monotherapy (maintenance) after 10 cycles of docetaxel are completed provided no evidence of objective disease progression was observed. Patients on the docetaxel/prednisone/enzalutamide arm who discontinue docetaxel for treatment-related side effects prior to completion of 10 cycles may continue with enzalutamide maintenance therapy.

6. THERAPEUTIC/DIAGNOSTIC AGENT(S)/MODALITY(-IES)

6.1 Enzalutamide

6.1.1 Description of Treatments

Enzalutamide is provided as liquid-filled soft gelatin capsule for oral administration. Each capsule contains 40 mg of enzalutamide. The inactive ingredients are caprylocaproyl polyoxylglycerides (Caprylocaproyl macrogolglycerides [European Pharmacopoeia]),butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide and black iron oxide.

6.1.2 Pharmacokinetics

The pharmacokinetics and metabolism of enzalutamide have been evaluated in more than 2500 patients with prostate cancer and in more than 200 volunteers, including healthy male subjects and subjects with mild or moderate hepatic impairment. Individual daily doses have ranged from 30 to 600 mg. Pharmacokinetic studies of enzalutamide in women have not been completed.

Tissue distribution data in rats after oral administration of 14C-enzalutamide showed rapid and extensive distribution to all tissues. Data in rodents suggest that enzalutamide and N-desmethyl enzalutamide readily partition into the brain. In vitro protein binding of enzalutamide in human plasma is 97% to 98% and is comparable across species. The extent of plasma protein binding is constant over a wide range of concentrations (0.05 to 25 μg/mL). Albumin is the major binding protein for enzalutamide in human plasma; other human plasma proteins to which enzalutamide binds (in order of decreasing importance) are high density lipoprotein, low density lipoprotein, α1-glycoprotein and γ-globulin. In vitro protein

binding of N-desmethyl enzalutamide in human plasma was 95%, comparable across species and constant over a wide range of concentrations (0.5 to 25 μg/mL).

Oral absorption of enzalutamide, whether administered as single or multiple doses, is rapid and independent of dose. Peak concentrations of enzalutamide are generally achieved 1 to 2 hours postdose in both patients and healthy subjects. The rapid attainment of Cmax is consistent with rapid dissolution of the capsule and release of solubilized enzalutamide into the gut lumen. Enzalutamide is well absorbed (estimated bioavailability based on mass balance data ≥ 84.2%); an expected finding for a low extraction ratio drug that displays high permeability and that is not a substrate for P-gp or BCRP. A high-fat meal reduces the rate of enzalutamide absorption but the extent of absorption is unaffected. Enzalutamide has been administered without regard to meals in clinical trials in patients, including the pivotal phase 3 Studies MDV3100-03 and CRPC2.

A single dose of 160 mg (100 μCi) 14C-enzalutamide was administered orally to healthy subjects to assess mass balance and to obtain metabolic profiles (Study 9785-CL-0001). A total of 7 phase I metabolites were identified in plasma, urine and feces by comparison with reference standards and liquid chromatography with multiple stage mass spectrometry methods (Study 9785-ME-0020). These metabolites were formed via demethylation, oxidation and hydrolysis reactions. No phase II conjugation products were observed. The major metabolites in humans were an inactive carboxylic acid metabolite and an active Ndesmethyl metabolite of enzalutamide (N-desmethyl enzalutamide). Biotransformation pathways in animals and humans were similar. As 14C recovery was generally 100% during sample extraction procedures, there do not appear to be reactive metabolites in humans.

The carboxylic acid metabolite and N-desmethyl enzalutamide are formed slowly. After a single 160 mg dose of enzalutamide in healthy subjects, peak plasma concentrations of the carboxylic acid metabolite are typically achieved 4 to 6 days postdose and peak plasma concentrations of N-desmethyl enzalutamide are typically achieved 5.5 to 6 days postdose. At steady state, the active metabolite N-desmethyl enzalutamide circulates at approximately the same plasma concentration as enzalutamide; whereas, plasma concentrations of the inactive carboxylic acid metabolite are approximately 25% lower than enzalutamide (Study 9785-CL-0001).

In vitro studies show that enzalutamide is metabolized by CYP2C8 and CYP3A4/5, both of which play a role in the formation of N-desmethyl enzalutamide (Study 9785-ME-0001). A clinical DDI study in healthy volunteers (Study 9785-CL-0006) revealed that CYP2C8 plays an important role in the metabolism of enzalutamide and the formation of N-desmethyl enzalutamide.

6.1.3 Dosage Selected, Preparation, and Schedule of Administration

Enzalutamide will be administered at the standard dose of 160 mg orally. Patients will continue on that dose unless toxicities that require dose reductions are observed. Docetaxel will be given at the standard dose of 75 mg/m^2 intravenously every 21-days. Prednisone will be given at 5 mg orally twice daily. Prednisone may be tapered or omitted per investigators discretion. In the experimental arm, and after 10 cycles of docetaxel, patients are allowed to continue on enzalutamide

monotherapy at 160 mg daily as a maintenance approach. Patients on the enzalutamide arm will be asked to keep a drug diary. Premedications and precautions for both agents (docetaxel and enzalutamide) are as specified above. Treatment will be delivered as an outpatient.

6.1.3.1 Supply, storage requirements, and special handling

<u>*Supply and packaging*</u>
Capsules are packaged as a 1-month supply in bottles with child-resistant caps or 4- to 5-week supply in blister packs.

<u>*Storage requirements*</u>
Store at room temperature (≤ 25°C). For more information please follow the storage instructions provided on the drug product label.

6.1.4 Supportive Care Medications

Medications taken within 7 days before the Screening visit and up to the first dose of study medication will be documented on the appropriate case report form (CRF) as a prior medication. Medications taken after the first dose of study medication up to the Study Completion visit will be documented on the appropriate CRF as concomitant medication. All concomitant medication(s) must be reported on the appropriate CRF. Prior and concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications. If an intermittent or as needed use of any medication during the study is due to an adverse event, then the adverse event must also be recorded on the PCCTC SAE Report form.

6.1.5 Prohibited before enrollment and during administration of study treatment

Patients should have not received any investigational therapeutic agent for 28-days before being randomized. If radiotherapy was given, a 2-week washout period must elapse before randomization.

6.1.6 Potential for drug-drug interactions

The potential for enzalutamide to affect the pharmacokinetics of other drugs was assessed through a series of in vitro experiments. Based on in vitro findings, an in vivo phenotypic cocktail DDI trial was performed in patients with CRPC (Study 9785-CL-0007). In this study, a single oral dose of the CYP probe substrate cocktail (for CYP2C8, CYP2C9, CYP2C19 and CYP3A4) was administered before and concomitantly with enzalutamide (following at least 55 days of dosing at 160 mg daily). At steady state, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Enzalutamide did not cause clinically meaningful changes in exposure to the CYP2C8 substrate.

In a DDI trial in patients with metastatic CRPC, intravenously administered docetaxel (CYP3A4 substrate) was given before and concomitantly with enzalutamide (after at least 21 days of dosing at 160 mg daily). The results showed that enzalutamide did not cause a clinically meaningful change in exposure to the intravenously administered CYP3A4 substrate.

An in vitro study to assess the potential for DDIs with enzalutamide via displacement from protein binding sites in human plasma showed that

enzalutamide does not displace the binding of other highly bound drugs (warfarin, ibuprofen, and salicylic acid; Study 9785-ME-0017).

6.2 Docetaxel

6.2.1 Description of Treatments

Docetaxel is a white to almost-white powder with an empirical formula of C43H53NO14, and a molecular weight of 807.88. It is highly lipophilic and practically insoluble in water. Docetaxel Injection is a clear, colorless to pale yellow solution. Docetaxel Injection is sterile, non-pyrogenic, and is available in multiple dose vials, supplied as 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.

Each mL of Docetaxel Injection contains 10 mg docetaxel, 275.9 mg alcohol 96% (v/v), 4 mg citric acid, 648 mg polyethylene glycol 300, and 80 mg polysorbate 80.

6.2.2 *Pharmacokinetics*

Absorption

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m2 to 115 mg/m2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m2 to 115 mg/m2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m2.

Distribution

The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

Elimination

A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Effect of age
A population pharmacokinetic analysis was carried out after docetaxel treatment of 535 patients dosed at 100 mg/m2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of gender
The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic impairment
The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with Docetaxel Injection. Patients with severe hepatic impairment have not been studied.

Effect of race
Mean total body clearance for Japanese patients dosed at the range of 10 mg/m2 to 90 mg/m2 was similar to that of European/American populations dosed at 100 mg/m2, suggesting no significant difference in the elimination of docetaxel in the two populations.

6.2.3 Dosage Selected, Preparation, and Schedule of Administration

How supplied
Docetaxel Injection is supplied in a multiple dose vial as a sterile, pyrogen-free solution. Docetaxel Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution. The following strengths are available:

Strength	NDC Number	Volume
20 mg/2 mL	66758-050-01	Carton of 1 x 2 mL Multiple Dose Vial
80 mg/8 mL	66758-050-02	Carton of 1 x 8 mL Multiple Dose Vial
160 mg/16 mL	66758-050-03	Carton of 1 x 16 mL Multiple Dose Vial

Storage
Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.
After initial puncture, Docetaxel Injection multiple dose vials are stable for 28 days when stored between 2°C to 8°C and at room temperature, with or without protection from light.

Docetaxel is approved for the treatment of breast cancer, gastric cancer, lung cancer, head and neck cancer, and prostate cancer. In prostate cancer, the drug is currently

approved in the CRPC state at a dose of 75 mg/m^2 given every 3 weeks along with prednisone given at 5 mg twice daily.

Docetaxel Injection is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel Injection solutions. The use of gloves is recommended.
If Docetaxel Injection or diluted solution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Docetaxel Injection or diluted solution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the Docetaxel Injection with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel Injection dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Docetaxel Injection requires dilution prior to administration. Please follow the preparation instructions provided below.

Preparation and administration
Docetaxel Injection (10 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Dilution for infusion

1. Aseptically withdraw the required amount of Docetaxel Injection solution (10 mg docetaxel/mL) with a calibrated syringe and inject (as a single injection) into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL. If a dose greater than 200 mg of Docetaxel Injection is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel Injection is not exceeded.
2. Thoroughly mix the infusion bag or bottle manually by gentle inversion and rotation in a controlled manner and avoid foaming. Shaking or vigorous agitation should be avoided during preparation and transportation to the patient for administration.
3. As with all parenteral products, Docetaxel Injection should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel Injection vial or diluted solution is not clear or appears to have precipitation, these should be discarded. The Docetaxel Injection diluted solution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature below 25°C (77°F) and lighting conditions.

Overdosage
There is no known antidote for Docetaxel Injection overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone

marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m2 and the other received 200 mg/m2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

Toxic deaths
Breast Cancer. Docetaxel administered at 100 mg/m2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer. Docetaxel administered at a dose of 100 mg/m2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry

Hepatic impairment
Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection

Hematologic effects
Perform frequent peripheral blood cell counts on all patients receiving Docetaxel Injection. Patients should not be retreated with subsequent cycles of Docetaxel Injection until neutrophils recover to a level >1500 cells/mm3 and platelets recover to a level > 100,000 cells/mm3.

A 25% reduction in the dose of Docetaxel Injection is recommended during subsequent cycles following severe neutropenia (<500 cells/mm3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel Injection cycle

Neutropenia (<2000 neutrophils/mm3) occurs in virtually all patients given 60 mg/m2 to 100 mg/m2 of docetaxel and grade 4 neutropenia (<500 cells/mm3) occurs in 85% of patients given 100 mg/m2 and 75% of patients given 60 mg/m2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel Injection should not be administered to patients with

neutrophils <1500 cells/mm3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m2 but was very uncommon in patients given 60 mg/m2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection

Hypersensitivity reactions
Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel Injection infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with Docetaxel Injection.

Hypersensitivity reactions may occur within a few minutes following initiation of a Docetaxel Injection infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of Docetaxel Injection

Fluid retention
Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each Docetaxel Injection administration to reduce the incidence and severity of fluid retention. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m2. Nine of 92 patients (9.8%) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of docetaxel to resolution (range: 0 to 42+ weeks). Patients developing

peripheral edema may be treated with standard measures, e.g., salt restriction, oral diuretic(s).

Acute myeloid leukemia
Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (TAX316) AML occurred in 3 of 744 patients who received docetaxel, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up.

Cutaneous reactions
Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued docetaxel due to skin toxicity.

Neurologic reactions
Severe neurosensory symptoms (e.g. paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued.. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Asthenia
Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

7. SAFETY EVALUATION

7.1 Definitions

7.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

An adverse event will be recorded and followed from treatment administration to 30 days post treatment or resolution.

7.1.2 Expected Adverse Events

Expected adverse events are those that have been previously identified as resulting from administration of the agent. An adverse event can be considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

7.1.3 Unexpected Adverse Events

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product) (ICH E2A).

Contact the Principal Investigator to confirm unexpected adverse events when necessary.

7.1.4 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ICH E2A).

The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event.

7.1.5 Serious Adverse Event (SAE)

An SAE/ADR as defined in the Code of Federal Regulations (21CFR312.32) is any event that:

- results in death
- is life-threatening
- results in inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect
- is medically significant in the opinion of the investigator

Events that are **not** considered serious adverse events include:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

7.1.6 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose, progressive disease will be considered an SAE.

7.1.7 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening "if, in the view of the Principal Investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (FDA 21 CFR 312.32).

7.1.8 Hospitalization (or prolongation of hospitalization)

Hospitalization encompasses any inpatient admission (even for less than 24 hours) resulting from a precipitating, treatment-emergent adverse event. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

7.1.9 Persistent or Significant disability/incapacity

Any AE that results in persistent or significant incapacity or substantial disruption of the patient's ability to conduct normal life functions.

7.1.10 Congenital anomaly

If the female partner of a male patient becomes pregnant during the course of the study, the treating physician must be notified immediately. All confirmed pregnancies must be immediately reported to the lead site and PCCTC, LLC. All pregnancies will be followed until resolution (i.e., voluntary or spontaneous termination or birth) and assessed for congenital anomalies and birth defects.

7.2 Recording and Grading of Adverse Events

7.2.1 Recording

All observed or volunteered adverse events, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be recorded.

A clinically significant change in a physical examination finding or an abnormal test result should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study

- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the investigator

An abnormal test result that is subsequently determined to be in error does not require recording as an adverse event, even if it originally met one or more of the above criteria.

7.2.2 Grading severity

All adverse events will be graded based on the NCI CTCAE version 4.0.

7.2.3 Attributing causality

After assigning a grade to an adverse event, the investigator must evaluate all AEs for possible causal relationship to docetaxel/prednisone and enzalutamide administration. Causality attribution will be decided using the criteria outlined in Table 2.

Table 2 Relationship of Adverse Event to Study Drug

Relationship	Description
Unrelated	AE is clearly not related
Unlikely	AE is doubtfully related
Possible	AE may be related
Probable	AE is likely related
Definite	AE is clearly related

7.3 Reporting Serious Adverse Events

7.3.1 Reporting serious adverse events

- All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to Principal Investigator, UC CCC and PCCTC, LLC within 24 hours of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:
  - protocol # and title
  - study identification number, sex, age at event
  - date the event occurred
  - description of the SAE
  - causal relationship to the study drug

The PCCTC SAE Report Form (Appendix G) will be used for reporting each SAE and should be submitted to PCCTC, LLC within 5 business days. The PCCTC, LLC will facilitate all SAE report form submissions to UC CCC.

Severity, causality, action taken, concomitant medications, outcome, etc should be reported to the PCCTC, LLC as soon as possible.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

SAE Contact Information for PCCTC:

Prostate Cancer Clinical Trials Consortium
Phone: 646-888-0434/646-422-4383
Email: pcctc@mskcc.org

SAE Contact Information for UC CCC:

UC CCC Cancer Clinical Trials Office Quality Assurance
Email: qaccto@bsd.uchicago.edu

UC CCC Phase II CRA General
Phone: 773-834-3095
Fax: 773-702-4889
Email: phaseiiCRA@medicine.bsd.uchicago.edu

Within 24 hours of awareness of a serious adverse event, whether or not related to the study drug, the PCCTC, on behalf of the Principal Investigator, will complete and submit a PCCTC SAE Report Form (Appendix G) to FDA, containing all required information (reference 21 CFR 312.32). The PCCTC will submit a copy of this PCCTC SAE Report form to Astellas by either e-mail or fax, within the same timeframe. If submission of this SAE to FDA or Astellas or is not possible within 24 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The SAE documentation, including the PCCTC SAE Report Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

8. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

8.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment (<21 days). For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

- Measurement of clinical lesions

Superficial clinical lesions such as skin nodules, biopsy-proven skin rashes that are consistent with prostate cancer, and palpable lymph nodes are considered measurable. For skin lesions, documentation with a photograph and measurement of the lesion using a ruler is required.

- Conventional CT/ MRI
- Bone scan

- Tumor markers: Tumor markers alone cannot be used to assess response or progression. We use the PCWG2 definition for biochemical responses.

8.1.1 Primary endpoint

The primary endpoint will be progression-free survival (PFS), defined as the time from randomization to disease progression.

8.1.2 Secondary endpoints

Secondary endpoints are overall survival (OS), defined as the time from randomization to death from any cause, and PSA response rates, as defined in PCWG2. Exploratory outcome variables will include quality of life (QOL) and circulating tumor cells (CTCs). QOL will be measured at baseline and every 4 cycles. In addition, we will analyze androgen receptor splice variant on all patients.

8.2 Therapeutic Response

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[4] and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG2).[5]

Patients will need to be reevaluated for biochemical and radiographic response as dictated in the study schema/table above and according to the guidelines below.

8.2.1 PSA

Perform PSA testing at a minimum of 1-week intervals with the threshold PSA level at 2.0 ng/mL. To report PSA-based outcomes, PCWG2 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. Because the rate of rise has shown prognostic significance, estimate a pretreatment PSA doubling time (PSA-DT) if at least 3 values are available, but do not delay either treatment or enrollment onto the trial simply to estimate PSA-DT. Because declines in serum PSA, if they occur, may not do so for several weeks, PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making.[5]

8.2.2 Measurable disease

According to RECIST, measurable disease is defined as at least 1 lesion > 20 mm in its longest diameter as measured with conventional techniques (i.e., CT [nonspiral or nonhelical], MRI, physical exam) or > 10 mm as measured with spiral CT scan. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters).

8.2.3 Nonmeasurable disease

Following RECIST, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) and any of the following:

- bone lesions
- ascites
- pleural or pericardial effusion

- lymphangitis cutis or pulmonis
- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

  Note: If only a single, asymptomatic bone lesion is present at baseline, and will be irradiated, the metastatic nature of this lesion must be confirmed by x-ray, CT, or MRI.

8.2.4 Target (nodal and visceral) lesions

Following RECIST, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 5 lesions per organ and 10 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). The sum of the longest diameter (LD) of all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Because small lymph nodes are difficult to measure accurately and may not be malignant, the greatest diameter of a lymph node must measure at least 2 cm by spiral CT to be considered a target lesion.[5]

8.2.5 Bone lesions

When the bone scan is the sole indicator of progression, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with a prior scan used for trial entry.[5] In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities (e.g., MRI or fine-cut CT). If many new areas of uptake are observed, confirmation is generally not necessary.

8.2.6 Nontarget lesions

All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (5) or total of all involved organs (10), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

8.2.7 New lesions

The appearance of up to 10 new measurable lesions should be recorded. Each new lesion should be reassessed using the same imaging modality at each time point. If measurable, the LD of each new lesion should be recorded in the CRF and the sum

LD of new and old lesions should be calculated. See Table 5 for a description of the determination of progression based on the presence of new lesions.

> ***Note***: The appearance of a new lesion does not by itself satisfy the criteria for confirmed progressive disease. Rather, the tumor burden imposed by the new lesions must be evaluated within the context of the total tumor burden (i.e., preexisting plus new lesions). Confirming progression in target lesions, nontarget (i.e., other than bone) lesions, and bone lesions requires 2 assessment time points. The first must occur at Week 12 (or later) and the second occurring at least 6 weeks after the first. Progression declared at the first time point remains unconfirmed unless assessments at the second time point demonstrate continuing or worsening progression, as described in Section8.4.

8.3 Response Criteria for Control/Relieve/Eliminate Endpoints

8.3.1. Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 3 apply.

Table 3 RECIST response criteria for target (soft-tissue) lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	the disappearance of clinical and radiological evidence of all target lesions and normalization of tumor marker levels
Partial response (PR)	a decrease from baseline ≥ 30% in the sum of the LD of all target lesions
Progressive disease (PD)	an increase ≥ 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions or the appearance of new lesions
Stable disease (SD)	neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum LD recorded since treatment started

Abbreviations: LD, longest diameter.

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

Changes in nodal and visceral sites should be recorded and reported separately, and lymph nodes in the pelvis must measure at least 2 cm in greatest diameter to be considered target lesions. Complete elimination of disease at a particular site should be recorded separately. Any favorable change should be confirmed using a second follow-up scan.

8.3.2 PSA

As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

8.3.3 Bone

Record post-treatment changes as either "no new lesions" or "new lesions."

In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. In the rare case where visible lesions disappear, this too should be confirmed.

8.3.4 Nontarget lesions

When assessing nontarget lesions, the definitions in Table 4 will apply.

Table 4 RECIST response criteria for nontarget lesions

Response	Evaluation of Nontarget Lesions
Complete response (CR)	the disappearance of all nontarget lesions and normalization of tumor marker levels
Incomplete response/ stable disease (SD)	the persistence of one or more nontarget lesions and/or maintenance of tumor marker levels above the normal limits
Progressive disease (PD)	the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

A clear progression of nontarget lesions only is exceptional. In such circumstances, the progression status, as assigned by the investigator, may be reviewed by a PCCTC panel.

8.3.5 Symptoms

Transient increases in pain may occur before improvement, and those occurring in the first 12 weeks should not affect the course of treatment in the absence of other compelling evidence of disease progression. Changes in symptoms should be confirmed as for other outcome measures. Monitor other domains that may help determine whether the disease is progressing, including worsening in global quality of life, developing urinary or bowel compromise, or needing to change anticancer therapy.

8.3.6 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until either disease progression or recurrence. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessment performed 4-6 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet SD criteria at a minimum interval of 3 weeks after SD was first documented. Table 5 can be used as an assessment tool.

Table 5 Assessing Overall Response

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

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Subjects with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Subjects who do not have tumor response assessment due to rapid progression or toxicity will be considered nonresponders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- death attributed to disease progression
- early discontinuation attributed to disease progression
- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

Note: If a subject receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response.

8.4 Confirmatory Measures/Duration of Response

8.4.1 Confirming time-to-event outcomes

Any post treatment change in disease status, be it favorable or unfavorable, should be confirmed using a second assessment at a later time point after a minimum of 3 weeks.

8.4.2 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

8.4.3 Progression-free survival

Progression-free survival (PFS) is defined as the time from randomization to disease progression. All assessments of the PFS endpoint (i.e., PSA, bone, and CT scans) are performed at the same time points. All assessments of disease should be collected at the same time interval (as per the study schema above). In addition to PSA, post treatment changes in measurable target lesions, radionuclide bone scans, and symptoms should be confirmed within 3 weeks minimum intervals.

Table 6 Prostate Cancer Clinical Trials Working Group Outcome Measures[5]

Variable	Control/Relieve/Eliminate Endpoints	Prevent/Delay Endpoints
PSA	Record the percent change from baseline (rise or fall) at 12 weeks and, separately, the maximal change (rise or fall) at any time using a waterfall plot	**Decline from baseline:** record time from start of therapy to first PSA increase that is ~25% and ~2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)† Recording the duration of PSA decline of little value **No decline from baseline:** PSA progression ~25% and ~2 ng/mL after 12 weeks
Soft-tissue lesions	Use RECIST with caveats: Only report changes in lymph nodes that were ~2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot	Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later Note that for some treatments, a lesion may increase in size before it decreases
Bone	Record outcome as either *new lesions* or *no new lesions* First scheduled reassessment: No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: No new lesions: continue therapy Additional new lesions: progression Subsequent scheduled reassessments: No new lesions: continue New lesions: progression	The appearance of ~2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows at least 2 or more additional new lesions The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy Ignore early changes (~12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression Confirm response or progression of pain or HRQOL endpoints ~3 weeks later	

Abbreviations: PSA, prostate-specific antigen; HRQOL, health-related quality of life. †Particularly important when anticipated effect on PSA is delayed or for biologic therapies.

9. DATA REPORTING AND REGULATORY REQUIREMENTS

9.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

9.1.1 Electronic Case Report Forms (eCRFs)

Standardized eCRFs and completion guidelines will be created by the PCCTC, LLC for the collection of all study data. Access and training for PCCTC Caisis EDC will be made available to participating sites upon local regulatory approval. The participating site PI is responsible for ensuring eCRFs are completed accurately and in a timely manner.

9.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record.

9.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study-related documents. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

9.2 Source Documentation Submission for Registration at Participating Sites

9.2.2 Data Submission Timelines

All data should be transmitted to PCCTC, LLC within 14 days of visit except for SAE submission (see section 7.3.1).

9.2.3 Data Review and Queries

PCCTC, LLC will review data and source documentation as it is submitted. Data will be monitored against source documentation as necessary and discrepancies will be sent as queries to the participating sites. In addition, PCCTC, LLC will review data for logic, consistency, and obvious anomalies. Queries will be sent by PCCTC, LLC to participating sites as needed.

Participating sites should respond to data queries within 14 days of receipt.

9.3 Study Monitoring and Quality Assurance

9.3.1 Data and Safety Monitoring

Consistent with NCI guidelines, this trial will be carefully monitored through both institutional and UCCCC-specific central processes and committees including, the Institutional Review Board (IRB), the UCCCC Clinical Research Advisory

Committee (CRAC), the Clinical Trials Review Committee (CTRC), the Scientific and Accrual Monitoring (SAM) Committee, and regular safety monitoring conferences.

Under the governance of the CRAC, initial scientific review is conducted by the CTRC and annual monitoring of trial progress by the SAM Committee. This is managed internally through safety monitoring conferences, a rigorous adverse event reporting system, and the UCCCC audit program.

CRAC ensures that all aspects of the clinical research process at the UCCCC are conducted according to prescribed standard operating procedures. CRAC meetings are held quarterly with additional meetings on an as-needed basis.

The Scientific and Accrual Monitoring (SAM) Committee meets monthly and is responsible for performing annual protocol reviews, including reviews of all amendments, to:

a) Evaluate scientific progress of the study, including accrual to date compared to projected accrual and any new scientific findings which might alter the significance or objectives of the original study; and

b) Ensure that the conduct of the study is in compliance with the approved DSM plans, including review of documentation that audits have been carried out per CTRC recommendations.

If the committee determines that the study is not progressing and should be terminated and/or closed to accrual, a recommendation is made to the CTRC, which reviews the data and makes the final determination. The PI can provide additional information and/or appeal to the CTRC.

The PCCTC, LLC will provide a listing of all reported AEs and SAEs occurring during the reporting period for this clinical trial for submission to the CRAC and SAM Committee as needed.

9.3.2 Data Auditing and Quality Assurance

In addition to review by safety conferences, CRAC and SAM; PCCTC, LLC will conduct regularly scheduled monitoring visits according to the Monitoring Plan (MP). 10% of all subjects, but at least 2 from each site will be 100% source data verified. This study is subject to audit after it has been open to accrual for 12 months or at the discretion of the UCCCC. If the study accrues >50 subjects annually, a minimum of 10 charts will undergo full review.

Registration reports will be generated by the PCCTC, LLC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

Each site participating in the accrual of participants to this protocol will be monitored by the PCCTC, LLC once shortly after initiation of subject recruitment at a

site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial, for protocol and regulatory compliance, data verification and source documentation. Monitoring may be accomplished in one of two ways: (1) sending source documents and research records for selected patients from participating sites to the PCCTC, LLC for review, or (2) on-site monitoring of selected patient records at participating sites.

The monitoring visit will include a review of source documentation to evaluate compliance for:

1. Regulatory/IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
2. Protocol defined treatment compliance
3. Subject records
    - Each subject is monitored to determine that there is a signed and dated consent form
    - Adherence to eligibility criteria
    - Baseline, on study and follow-up protocol testing
    - eCRF completion

At the end of each monitoring visit, an exit interview with the monitor, PI (if possible), and study staff will take place. During this time, all findings are reviewed and discussed, and any questions can be answered. Additionally, the PI and study staff will receive a copy of the monitoring report, which will include corrective action items.

A monitoring report is issued within 30 days and sent to the protocol PI. A copy is filed in the CCTO Audit Binder. The PI is given 30 days to respond in writing to the deficiencies identified. Responses are reviewed by the Scientific and Technical Directors of the CCTO, the Associate Director for Clinical Sciences, and the CRAC, if necessary.

All clinical work conducted under this protocol is subject to Good Clinical Practice (GCP) guidelines. This includes inspection of study-related records by the lead site, its designee, or health authority representatives at any time.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Analysis of the primary endpoint

The primary endpoint will be progression-free survival (PFS), defined as the time from randomization to disease progression. Progression will be evaluated using a combination of RECIST[4] and PCWG2[5] guidelines, as described in section 8.2 above. One hundred patients (50 per arm) will be randomized. This sample-size will provide 85% power to detect an increase in the median PFS from 6 months in the

standard arm to 10 months in the experimental (triple combination) group, or a hazard ratio (HR) of 0.6, using on a one-sided test at the alpha=0.10 significance level. This calculation assumes 2 years of accrual and 1 further year of follow-up. PFS will be estimated using the Kaplan-Meier[6] procedure and compared between the two treatment arms by logrank test. Confidence intervals for the median PFS times will be generated using the Brookmeyer-Crowley[7] method. Cox[8] proportional hazard models will also be fit to estimate the HR and to assess and adjust for the effects of baseline covariates. The proportional hazards assumption will be checked graphically using log(-log) survival plots[9] and Schoenfeld residuals[10]. Martingale residuals will be inspected to determine the best functional form for covariates entered into the Cox model.

10.1.2 Analysis of secondary and exploratory endpoints

Secondary endpoints are overall survival (OS) and PSA response rates. OS will be analyzed as described above for PFS. PSA response rates in the two groups will be compared via chi-square test. Exploratory outcome variables will include quality of life (QOL), circulating tumor cells (CTCs) and analysis of androgen receptor splice variant. QOL will be measured at baseline and every 4 cycles. Mixed effects regression models will be fit to compare QOL over time. Total symptom scores obtained across the M. D. Anderson Symptom Inventory (MDASI), as well as subscores derived from specific questions, will be analyzed. CTCs will be measured at baseline, every 3 cycles starting at C4D1 (C4D1, C7D1, C10D1, etc), and upon disease progression. Changes from baseline to 4 weeks will be compared using two-sample t-tests. The distribution of CTC cells at the time of disease progression will be summarized descriptively. The prognostic value of analyzing androgen receptor splice variant at baseline will be assessed by Cox regression analysis.

10.2 Analysis Populations

10.2.1 Evaluable population

All subjects who meet eligibility criteria will be included in the main analysis of the response rate, even if there are major protocol deviations (e.g., incorrect treatment schedule or drug administration). Each subject will be assigned to one of the following categories:

Table 7 Categories for Response to Treatment

Category	Response
1	Complete response
2	Partial response
3	Stable disease
4	Progressive disease
5	Early death from malignant disease
6	Early death from toxicity
7	Early death from other causes
9	Unknown (not assessable/insufficient data)

NOTE: By arbitrary convention, category 9 designates unknown status in a clinical database. Subjects in response

categories 4 to 9 will be considered to have treatment failure (disease progression).

Conclusions are to be based on the population of all eligible subjects. Subanalyses may be performed on various subsets of subjects, such as those with no major protocol deviations or those who continued in the study for the entire treatment period (i.e., did not withdraw prematurely). Subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy.

10.2.2 Safety population

All subjects enrolled in the study will be included in the safety analysis population and considered evaluable for toxicity and safety from the time of their first dose. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data (e.g., sex, race/ethnicity) and by descriptive statistics for continuous data (e.g., weight, vital signs, EKG readings, disease status).

10.3 Safety Analysis

10.3.1 Evaluation of adverse events

Treatment-emergent adverse events will be translated from investigator terms to MedDRA v6.0 terminology and summarized (number and percentage of subjects) for each treatment arm for all subjects who receive at least 1 cycle. Adverse event summaries will be organized by body system, frequency of occurrence, intensity (i.e., severity grade), and causality or attribution. Subjects who experience an adverse event more than once will be counted only once. The occurrence with the maximum severity will be used to calculate intensity. Comparison of rates between the two treatment arms will be performed using chi-square or Fisher's exact test.

10.3.2 Evaluation of serious adverse events and premature withdrawals

Adverse events deemed serious and those resulting in treatment withdrawal or death will be summarized separately.

10.3.3 Evaluation of laboratory parameters and assays

Selected clinical laboratory parameters will be summarized for each treatment arm and clinically significant changes from baseline will be discussed.

10.3.4 Extent of exposure

Treatment exposure will be summarized for all subjects, including dose administration, number of cycles, dose modifications or delays, and duration of therapy.

10.4 Statistical Procedures (see above)

Summary statistics include the number of observations, mean, standard deviation, median, minimum, and maximum values. A *P* value of 0.05 will be used to declare statistical significance.

10.4.1 Sample size calculation

The sample-size of 100 patients (50 per treatment group) will provide 85% power to detect an increase in the median PFS from 6 months in the standard arm to 10 months in the experimental (triple combination) group, corresponding to a HR of

0.6, using on a one-sided test at the alpha=0.10 significance level. This calculation assumes 2 years of accrual and 1 further year of follow-up. The assumption of a 6 month median PFS for the docetaxel/prednisone arm is based on the findings reported by Petrylak et al. (2004), in which median time to progression for advanced, refractory prostate cancer patients receiving docetaxel plus estramustine was 6.3 months. While not known, patients receiving docetaxel after enzalutamide failure could potentially have faster time to progression; if so, this would serve to increase the number of events and enhance statistical power.

11. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

11.1 Roles and Responsibilities

11.1.1 Sponsor Investigator

The Sponsor Investigator is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all participating sites

11.1.2 PCCTC, LLC

The PCCTC, LLC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the PCCTC, LLC.
- Reviewing Serious Adverse Events (SAEs)
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating monitoring and audits by securing selected source documents and research records from participating sites for review, or by monitoring at participating sites.

11.1.3 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, the guidelines of Good Clinical Practice (GCP), and applicable Standard Operating Procedures (SOPs).Registering all patients

with the PCCTC, LLC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC, LLC
- Collecting and submitting data according to the schedule specified by the protocol
- Responding to queries in a timely manner

11.2 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

11.3 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Amendments to the protocol may be made only with consent of the Sponsor Investigator and are subject to IRB approval before instituting.

11.4 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an adverse event occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date an informed consent form that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the lead site and to the PCCTC, LLC, and a copy will be sent home with each patient.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol

- the right of the patient to accept or refuse treatment and to withdraw from participation in this study
- Text regarding the consortium and the coordinating center should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., "Prostate Cancer Clinical Trial Consortium")

11.5 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the principal investigator and approved by the IRB.

11.6 Terminating or Modifying the Study

Adverse event and laboratory data from this trial will be assessed by the Principal Investigator on an ongoing basis. At least quarterly, data from the clinical database will be reviewed. The results of this review will be shared with all investigators either in writing or as part of a teleconference. SAEs will be reviewed as they are reported to the lead site, and the Principal Investigator will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site or the Principal Investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are on the experimental arm will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

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Appendix A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to continue all predisease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office 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.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.
4	100% bedridden. Completely disabled, cannot carry on any self-care, totally confined to bed or chair.
5	Dead

Appendix B: Medications with the Potential for Drug-Drug Interactions
Please see the Enzalutamide Package Insert for medications with the potential for drug-drug interactions

Appendix C: Laboratory Manual

Please see the Laboratory & Correlative Studies Manual

Appendix D: M.D. Anderson Symptom Inventory

Date: _____

Participant Initials: _____

Participant Number: _____

Institution: _____

Hospital Chart #: _____

M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

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

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
2. Your **fatigue (tiredness)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
3. Your **nausea** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
4. Your **disturbed sleep** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
5. Your feelings of being **distressed (upset)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
6. Your **shortness of breath** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
7. Your problem with **remembering things** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
8. Your problem with **lack of appetite** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
9. Your feeling **drowsy (sleepy)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
10. Your having a **dry mouth** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Date: _____

Participant Initials: _____

Participant Number: _____

Institution: _____

Hospital Chart #: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
11. Your feeling **sad** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
12. Your **vomiting** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
13. Your **numbness or tingling** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Part II. How have your symptoms interfered with your life?

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

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
14. **General activity?**	O	O	O	O	O	O	O	O	O	O	O
15. **Mood?**	O	O	O	O	O	O	O	O	O	O	O
16. **Work (including work around the house)?**	O	O	O	O	O	O	O	O	O	O	O
17. **Relations with other people?**	O	O	O	O	O	O	O	O	O	O	O
18. **Walking?**	O	O	O	O	O	O	O	O	O	O	O
19. **Enjoyment of life?**	O	O	O	O	O	O	O	O	O	O	O

Appendix E: Glossary of Abbreviations and Acronyms

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
bid	bis in die (twice a day)
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
Cm	centimeter
Cmax	maximum plasma concentration
CMP	Comprehensive Metabolic Panel
CR	complete response
CRAC	Clinical Research Advisory Committee
CREAT	creatinine
CRF	case report form
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTRC	Clinical Trials Review Committee
DLT	dose-limiting toxicity
DSM	data and safety monitoring
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EKG	electrocardiogram
FACT-P	Functional Assessment of Cancer Therapy-Prostate scale
FDA	Food and Drug Administration
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug

IRB	Institutional Review Board
IV	intravenous
LD	longest diameter
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
N	number of subjects or observations
NCI	National Cancer Institute
NIH	National Institutes of Health
OS	overall survival
PCCTC	Prostate Cancer Clinical Trials Consortium
PD	progressive disease
PFS	progression-free survival
PI	principal investigator
PO	per os (by mouth)
PR	partial response
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
QOL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAM	Scientific and Accrual Monitoring
SD	stable disease
SOP	Standard Operating Procedures
TEST	testosterone
TTP	time to progression
UCCC	The University of Chicago Comprehensive Cancer Center
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

Appendix F. Pill Diary

A Phase II Randomized Prospective Trial of Docetaxel/Prednisone Versus Docetaxel/Prednisone and Enzalutamide in Castration-Resistant Prostate Cancer (CRPC) Patients Progressing on Enzalutamide

PCCTC 13-126

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT (Docetaxel/Prednisone plus Enzalutamide Arm only).

Instructions:

- Medications to be taken:
  - Enzalutamide: # Tablets to be taken daily: 4 tablets (40mg each, 160mg total)
  - Prednisone: # Tablets to be taken daily: 2 tablets (5mg each, 10mg total)
- Please record the date, time and number of pills taken each day (see example row). Please note reason if (1) dose was not taken or (2) full dose was not taken (indicate the actual amount taken)

Please return all unused study medication to your research nurse.

Day	Date	Time that Enzalutamide was taken	Number of 40 mg Pills of Enzalutamide taken	If dose not taken or if full dose not taken for Enzalutamide, provide reason	Number of 5 mg pills of prednisone taken
Ex	**1/1/2011**	**9:00 AM**	**4**	**N/A**	**2**
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

11					
12					
13					
14					
15					
16					
17					
18					
19					
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21					
22					
23					
24					
25					
26					
27					
28					

Patient Signature: _____Date: _____

MD/RN Signature: _____Date: _____

Comments:_____
_____
_____

Appendix G: PCCTC SAE Report form

The Prostate Cancer Clinical Trials Consortium

SERIOUS ADVERSE EVENT REPORTING FORM

*Event # Click here to enter text.

*Protocol Title: **A Phase II Randomized Prospective Trial of Docetaxel/Prednisone Versus Docetaxel/Prednisone and Enzalutamide in Castration-Resistant Prostate Cancer (CRPC) Patients Progressing on Enzalutamide**

*PCCTC Protocol # **c13-126**

*Site Protocol # Click here to enter text.

*Site Name: Click here to enter text.

*Date of Report: Click here to enter a date.

*Reported By: Click here to enter text.

☐ Initial Report ☐ Follow-up Report

*Date of Original Report: Click here to enter a date.

SUBJECT INFORMATION

*Subject Identifier (Study ID) Click here to enter text.

*Age at Time of Event: Click here to enter text.

*Sex ☒ Male

Weight: Click here to enter text. ☐ lb ☐ kg

SERIOUS ADVERSE EVENT

*CTCAE Term: Click here to enter text.

*Start Date: Click here to enter a date.

*End Date: Click here to enter a date. OR ☐ ongoing

*Grade: Click here to enter text.

*Type (check all that apply)

☐ Death Click here to enter a date.

☐ Disability or Permanent Damage

☐ Life-threatening

☐ Congenital Anomaly/Birth Defect

☐ Hospitalization

☐ Other Medically Important Condition

*Event Description

*Outcome

☐ Recovered/Resolved ☐ Not Recovered/Not Resolved ☐ Fatal

☐ Recovering/Resolving ☐ Recovered/Resolved sequelae ☐ Unknown

RELEVANT TESTS/LABORATORY DATA

Date mm/dd/yyyy	**Test**	**Result**	**Unit**	**Notes**
Click here to enter a date.				
Click here to enter a date.				
Click here to enter a date.				

OTHER RELEVANT HISTORY

Disease/surgical procedure/etc.	**Start Date** mm/dd/yyyy	**Continuing Y/N/U**	**End Date** mm/dd/yyyy	**Comments**
	Click here to enter a date.		Click here to enter a date.	
	Click here to enter a date.		Click here to enter a date.	
	Click here to enter a date.		Click here to enter a date.	

SUSPECT PRODUCT(S)

*Name	Relationship to Study Treatment	Action Taken	Dose	Frequency	Route	Start Date mm/dd/yyyy	Last Date Prior to SAE mm/dd/yyyy
	☐Unrelated ☐Unlikely ☐Possibly ☐Probably ☐Definite	☐Drug withdrawn ☐Dose reduced ☐Dose Increased ☐Dose not changed ☐Unknown ☐Not applicable				Click here to enter a date.	Click here to enter a date.
	☐Unrelated ☐Unlikely ☐Possibly ☐Probably ☐Definite	☐Drug withdrawn ☐Dose reduced ☐Dose Increased ☐Dose not changed ☐Unknown ☐Not applicable				Click here to enter a date.	Click here to enter a date.
	☐Unrelated ☐Unlikely ☐Possibly ☐Probably ☐Definite	☐Drug withdrawn ☐Dose reduced ☐Dose Increased ☐Dose not changed ☐Unknown ☐Not applicable				Click here to enter a date.	Click here to enter a date.

CHALLENGE/RECHALLENGE OF SUSPECT PRODUCT(S)

*Name	Did the Adverse Event abate after discontinuation of the suspect drug? (Dechallenge)	Did the Adverse Event re-occur after the suspect drug was re-introduced? (Rechallenge)
	☐Yes ☐No ☐Not applicable	☐Yes ☐No ☐Not applicable
	☐Yes ☐No ☐Not applicable	☐Yes ☐No ☐Not applicable
	☐Yes ☐No ☐Not applicable	☐Yes ☐No ☐Not applicable

CONCOMITTANT MEDICAL PRODUCT(S)

Name	Start Date mm/dd/yyyy	Last Date Prior to SAE mm/dd/yyyy
	Click here to enter a date.	Click here to enter a date.
	Click here to enter a date.	Click here to enter a date.
	Click here to enter a date.	Click here to enter a date.

INVESTIGATOR NAME AND SIGNATURE

*Investigator Name Click here to enter text.

*Investigator Signature _____

***Date Signed** Click here to enter a date.
mm/dd/yy