TITLE: A phase I/II trial of enzalutamide plus the glucocorticoid receptor antagonist mifepristone for patients with metastatic castration resistant prostate cancer (CRPC)

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SUMMARY

Study design: This is a phase I/II, open label study of enzalutamide in combination with the glucocorticoid receptor (GR) antagonist mifepristone for patients with castration resistant prostate cancer (CRPC). The phase I portion will assess the safety of the two-drug combination along with pharmacokinetic (PK) impact of mifepristone on enzalutamide exposure. Dose escalations and de-escalations will be made based on PK and safety to arrive at the randomized phase II dose (RP2D). For the phase II portion, patients who are already on standard of care enzalutamide will be randomized to stay on enzalutamide alone or to change to enzalutamide plus mifepristone at the RP2D.

Primary objective: Phase I- To establish the safe and pharmacologically active doses of mifepristone and enzalutamide to use in combination. Phase II- to determine if mifepristone when added to enzalutamide delays time to PSA progression compared to enzalutamide alone.

Secondary objectives: (1) To evaluate the effect of mifepristone on endocrine biomarkers such as serum cortisol, thyrotropin. (2) To determine the effect of mifepristone on enzalutamide clearance and steady state enzalutamide exposure. (3) To determine if mifepristone affects PSA response rate when added to enzalutamide. (4) To determine if mifepristone extends time to radiographic and clinical progression, according to standard criteria, compared to enzalutamide alone. (5) To explore the role of circulating tumor cells, as a pharmacodynamic biomarker for mifepristone and enzalutamide in CRPC. (6) To evaluate the baseline and post progression AR and GR status within metastatic tumor biopsies.

Key eligibility criteria: Patients must have histologically confirmed prostate cancer with evidence of castration resistance defined as rising PSA or clinical/radiographic progression following androgen deprivation. For the phase II portion, patients must be currently on standard of care enzalutamide within the first 12 weeks for treatment of CRPC. Patients must have an ECOG performance status of 0-2 and have adequate bone marrow, liver and renal function.

Sample size: For the phase I portion of the study, there are several dose adjustment rules that make determination of sample size not possible, however, based on the design, it is estimated that 24 patients will enroll in the phase I study. The phase II portion of the study will randomize 42 patients/arm for a total of 84 patients in the phase II. Thus the total estimated accrual for the study is 108 patients.

Therapies and route of administration: Mifepristone and enzalutamide will both be administered daily via oral route.

Key study procedures:

- Imaging examinations including CT scan and bone scans
- Pharmacokinetic studies on peripheral blood
- Endocrine biomarker studies from peripheral blood
- Circulating tumor cell isolation and analysis from peripheral blood
- Optional tumor biopsy specimen

TABLE OF CONTENTS

Page

1.0 BACKGROUND

1.1 Castrate Resistant Prostate Cancer (CRPC)

Although most men are diagnosed with early stage, curable prostate cancer, unfortunately, prostate cancer (CaP) recurrence is seen in ~40% of patients over time[1]. Androgen deprivation therapy (ADT) remains the mainstay of treatment and induces a remission in 80 to 90% of patients with advanced disease and results in a median progression-free survival of 12 to 33 months, at which time an androgen independent phenotype usually emerges. This accounts for the median overall survival of 23 to 37 months from the initiation of androgen deprivation. This transition represents an important clinical landmark of an evolving disease that correlates with an increased risk of death and morbidity[2]. This year ~32,000 men are projected to die from prostate cancer, the vast majority of whom will die from metastatic castration resistant disease (mCRPC) with bone metastases[3]. The effective therapies for progressive CRPC are limited with docetaxel and cabazitaxel chemotherapies, the immunotherapy sipuleucel-T, and newer, more potent hormonal therapies abiraterone acetate and enzalutamide as the only currently FDA approved therapies shown to improve patient survival in the CRPC setting [4,5, 6-9].

1.2 Mechanisms of Castrate Resistant Prostate Cancer Growth

Androgen deprivation can be achieved surgically with orchiectomy or by pharmacologic means. Current approaches to ADT use luteinizing hormone releasing hormone (LHRH) agonists. The mechanism of action is by causing the continuous stimulation of the anterior pituitary leading to the inhibition of luteinizing hormone (LH) secretion and ultimately the disruption of testicular production of testosterone. Although ADT has been effective in the majority of patients, studies have shown that extra-testicular sources of testosterone represent an important alternative source of androgen stimulation in a significant proportion of prostate cancer patients. Due to the peripheral conversion of adrenal steroids to testosterone, as much as 10% of baseline circulating testosterone remains in castrate men[10]. In prostate cancer xenograft models, increased levels of androgen receptor (AR) have been observed and appear to be resistant to older antiandrogens such as bicalutamide[11]. This could result in amplified signal output from low levels of circulating adrenal androgens, thus suggesting a role for agents that more potently block the AR[12].

1.3 Enzalutamide: a potent second generation AR antagonist

With the change in fundamental understanding of castration resistant prostate cancer-that AR signaling remains a key component of CRPC progression, investigators set out to rationally design chemical therapeutics that would potently and specifically bind to and block the AR from signaling in CRPC. Older antiandrogens, such as bicalutamide, have mixed agonist/antagonist properties, bind the AR poorly and do not block AR nuclear translocation, leaving multiple facets by which these medications can fail to block AR[12,13]. Based on the crystal structure of the AR, MDV3100 (enzalutamide) was designed to potently bind the AR and prevent activation and nuclear localization [Figure 1][13,14]. Early preclinical evaluation of enzalutamide showed strong binding of the AR, along with inhibition of nuclear localization of the AR upon enzalutamide binding, decreased AR signaling, and preclinical CRPC activity[14]. This led to rapid clinical development of the compound.

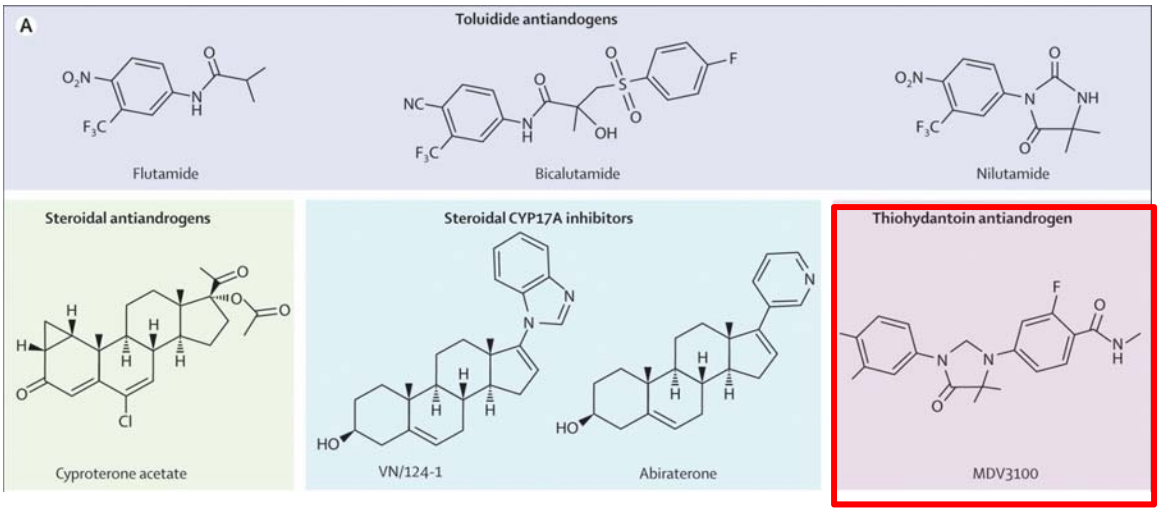


Figure 1. Molecular structure of MDV3100 and other AR antagonists

1.4 Clinical Data with Enzalutamide in Prostate Cancer

Based on the strong preclinical data, enzalutamide quickly moved into a multicenter phase I/II trial. This phase I/II study showed enzalutamide to be well tolerated and to result in AR pathway inhibition, as demonstrated by decrease in prostate specific antigen (PSA) levels in the majority of patients, independent of prior therapy for metastatic CRPC[15]. This trial established the maximum tolerated dose of 240mg/day orally. Most recently, a randomized phase III trial of enzalutamide at 160mg/day confirmed its utility in this disease as it substantially improved overall survival in patients with progressive CRPC compared to placebo[9]. Approximately 1200 patients with progressive CRPC were randomized 2:1 to enzalutamide versus placebo. There was significant improvement in patient outcomes with enzalutamide. The hazard ratio for death versus placebo was 0.63 (nearly 40% improvement in risk of death). It also improved progression free survival, time to skeletal event (e.g. bone fracture or radiation) and quality of life. There were few major adverse events, although there was more low-grade fatigue, diarrhea an hot flashes compared to placebo and rare seizures (0.6% incidence) were identified[9]. Based on these results, enzalutamide was FDA approved and is now a standard of care for progressive CRPC. Although clearly and improvement upon placebo in CRPC, the median progression free survival remains low at 8.3 months and overall survival is still limited to less than 1.5 years despite enzalutamide.

1.5 EnzalutamidePharmacokinetics

Although enzalutamide is generally well tolerated, the highly potent AR antagonists, including enzalutamide are associated with increased risks of seizures, particularly at higher plasma concentrations of the drug and may be less effective at lower blood levels[15,16]. Given the concerns of both over- and under-dosing enzalutamide, careful attention to its pharmacokinetics (PK)is paramount in designing combination therapy clinical trials with the agent. In PK investigations in men with CRPC, enzalutamide was absorbed rapidly after oral administration, with the time to maximum plasma concentration (t_{max}) after a single dose typically occurring at 1 hour post-dose. No major deviations from dose proportionality were observed over the dose range 30 mg to 600 mg. Due to the long terminal half-life (approximately 5.8 days), it took approximately 1 month to reach steady state. With daily oral administration, enzalutamide accumulation was observed at steady state with an 8.3-fold

higher exposure (steady state area under the curve, AUC) relative to a single dose. Based on the mean peak to trough ratio, the average difference between the peak (maximum plasma concentration, Cmax) and trough (pre-dose plasma concentration, C_{trough}) concentrations was ≤ 25%. As a result of the low daily fluctuations, plasma profiles at steady state resembled a constant infusion. The C_{trough} values in individual patients remained constant beyond day 28 of chronic therapy, suggesting time linear PK once steady state was achieved. At steady state, plasma concentrations of enzalutamide and the active metabolite, N-desmethyl enzalutamide (M2), were approximately the same. Given the limited variability in plasma concentration once at steady state, and the linear PK at steady state the C_{trough} for the parent compound and active metabolite is the appropriate PK parameter to follow with respect to potential drug-drug interaction.

In a mass balance and biotransformation study, healthy men received a single oral dose of ^{14}C enzalutamide 160 mg. By 77 days post-dose, 85% of the radioactivity was recovered including 71% in urine (with only trace amounts of enzalutamide and N-desmethyl enzalutamide) and 14% in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide). In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on in vivo and in vitro data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide, M2).

In a drug-drug interaction study in healthy male volunteers, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the composite AUC from time zero to infinity (AUC_∞) of enzalutamide plus M2 by 2.2-fold with minimal effect on C_{max}; therefore, the US product label indicates that strong CYP2C8 inhibitors should be avoided if possible as they can increase plasma exposure to enzalutamide plus N-desmethyl enzalutamide. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide should be reduced to 80 mg once daily. If coadministration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor. In asecond drug-drug interaction assessment, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the composite AUC_∞ of enzalutamide plus M2 by 1.3-fold with no effect on C_{max}[17,18]. For combination drug trials of other medications in combination with enzalutamide, consideration of changes in drug exposure due to CYP3A4 or CYP2C8 interference is critical.

1.6 Glucocorticoid Receptor (GR) Signaling in Prostate Cancer

There have been multiple mechanisms involving AR biology that have been proposed to explain progression of CRPC which include AR splice variants, AR mutations that do not require ligand or are sensitive to non-androgen ligands, and ligand-independent AR activation[19-23]. In addition, alternative signaling pathways inversely linked to AR signaling may also contribute to CRPC progression in the setting of potent AR inhibition[24]. Classically, single agent corticosteroids (ligand for the glucocorticoid receptor) have been shown to have modest activity in CRPC[25,26]. However, these studies were conducted in the setting of intact AR signaling. The central hypothesis underlying this clinical trial is that the glucocorticoid receptor (GR) can compensate for AR signaling to enable CaP cell survival in the context of potent AR pathway blockade. Several lines of evidence support our central hypothesis.For example, GR and AR are in the same nuclear hormone receptor family and in

fact share target DNA sequence binding homology[27,28]. Additionally, the AR has been shown to bind DNA elements associated putative GR regulated genes, including pro-cell survival genes such as *serum-glucocorticoid regulated kinase 1 (SKG1)*[27,29,30]. However, their functional overlap physiologically is less clear. In fact, despite homology in structure and target DNA sequence, the GR and AR often have adversarial effects in normal physiology (e.g. in skeletal muscle with AR activation being anabolic, while GR activation is catabolic), and they may negatively regulate each other[27]. The role of the glucocorticoid receptor in prostate cancer is equally complex. Although in primary prostate cancer specimens, the expression of the GR is relatively low, a recent examinations of prostate cancer samples from patients, published by the principal investigator (PI) and others, demonstrated that in the setting of hormonal therapy targeting androgen signaling, expression of the GR increases significantly[31-33]. This suggests that the GR expression increases to compensate for diminished AR activity in prostate cancer treated with hormonal therapies.

Preclinical evidence also supports a role for the GR in CRPC progression. In commonly utilized prostate cancer cells for preclinical exploration, the expression at baseline is variable and its function within these lines is unclear as the data are limited. Recently, preclinical *in vitro* and *in vivo* data has been presented that demonstrates that in the context of AR antagonism with enzalutamide, or after surgical castration of an immunocompromised mouse harboring a human prostate cancer xenograft, GR expression and/or nuclear localization, indicating activation, increases. Furthermore, GR activation with dexamethasone, a synthetic glucocorticoid receptor agonist, can rescue AR transcription activity of multiple pro-survival target gene, such as *SGK1*, in the setting of enzalutamide[34].

1.7 Study Rationale: Combined AR/GR blockade in CRPC

Further clarifying a potential compensatory role of GR signaling in CRPC in the context of AR inhibition, preclinical work, *in vitro* and *in vivo*, supports that GR expression and activation blunt the therapeutic efficacy of AR targeted therapy leading to CRPC progression [Szmulewitz lab, under review *Molecular Endocrinology*]. In multiple AR expressing CaP cell lines, GR activation confers relative protection from enzalutamide associated cell death. Mifepristone, a potent GR antagonist [see sections 1.8-1.9], was able to mitigate these effects, and potentiated the effects of MDV3100 on CaP cell survival[34]. Furthermore, CRPC progression *in vivo* was delayed when GR was modulated in combination with androgen targeted therapy. In CRPC xenografts engineered to have diminished GR expression, or treated with mifepristone,CRPC progression was impaired compared to control [Szmulewitz lab, under review *Molecular Endocrinology*]. Finally, within the phase III AFFIRM enzalutamide study, it has now been reported that patients who were taking GR agonist corticosteroids within the enzalutamide arm of the study had poorer survival and diminished benefit of enzalutamide than those not taking glucocorticoids[35]. In sum, these data provide a strong rationale for combining enzalutamide AR antagonism with a GR antagonist in CRPC.

1.8 Mifepristone

Mifepristone is a synthetically synthesized hormone receptor modulator derived from the naturally occurring material estrone. Mifepristone is a progesterone and glucocorticoid receptor (GR) antagonist currently FDA approved for emergency contraception and Cushing's disease. It is also know to be a potent inhibitor of the GR[36]. While a single dose of mifepristone 200 mg combined with misoprostol is needed to terminate pregnancy,

potentially higher doses are required for potent anti-GR effects[37]. Mifepristone is now FDA approved for the indication of Cushing's disease at daily doses ranging 300mg-1200mg (Korlym, Corcept). It is also being studied in patients without Cushing's disease for indications including hypercholesterolemia, weight gain, Alzheimer's and psychosis, and has been well tolerated at multiple different doses including ranging from 200-600mg daily[38-40]. With daily dosing, the most common side effects considered related to study drug include headache, dizziness, nausea/vomiting, constipation, fatigue, abdominal cramping, rash, and depression. In the study of Alzheimer's patients who were treated for 16-weeks with 300mg/day there were 4 severe adverse events (SAE's) in the 41 patients on the mifepristone arm 2 of which were considered potentially related to the study drug (rash/nausea/decreased appetite, seizure). Hypokalemia, likely due to mineralocorticoid excess, was observed more frequently in the mifepristone arm of the study then placebo, however there were no high grade hypokalemia events and no clinically serious consequences noted[40]. The other adverse event related to mechanism of action (GR antagonism) is adrenal insufficiency. As of 2013 investigator brochure, with over 1400 subjects enrolled, only 7 cases of adrenal insufficiency have been documented, all in the studies for Cushing's disease. They were mild and treated with supplemental corticosteroids. Although a macular-papular rash with mifepristone is common, it is also typically mild and treated with topical agents, and does not typically recur or escalate with retreatment. Severe rash syndromes and/or adrenal crisis have not been observed[40].

1.8.1 **Mifepristone clinical pharmacology**

Mifepristone has an approximate 40% bioavailability when taken orally at 100mg and ~70% when taken at lower doses. The T_{max} is 1-2 hours. It is highly protein bound. Cytochrome P450 3A4 (CYP3A4) is the major enzyme involved in the metabolism of mifepristone leading to ~90% of elimination through the biliary system into the feces (10% eliminated in the urine). It is metabolized into six metabolites with an approximate half-life of the parent compound ranging 24-50 hours. In volunteer multiple dose studies, approximately 2 weeks is required for elimination of 90% of maximum concentration. Multiple-dose administration results in a plateau of trough concentrations in mifepristone at between 5 and 7 days. No dose adjustments are needed for mild-moderate hepatic impairment or renal impairment. The fed state increases plasma concentrations of mifepristone (however there is not a large effect of high fat diets) and mifepristone is to be taken with meals. Mifepristone is an inhibitor of CYP2A6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4, however it also induces CYP3A4 enzyme expression.

1.8.2 **Mifepristone in CRPC**

Mifepristone as a single agent has been tested in CRPC, with the hypothesis that it would act as an AR inhibitor (given structural similarities between the AR and GR and potential effects of co-regulatory molecules). In this small single agent study, although mifepristone was well tolerated with no significant adverse events at 200mg/day, there were no reported responses as measured by decrease in PSA. However, it was noted that mifepristone led to a significant increase in detectable androgen levels[41]. This may explain the potential occasional palliative benefits seen in CRPC treated with glucocorticoids. In addition to anti-inflammatory effects on bone pain, exogenous glucocorticoids likely decrease androgen levels[42]. Blockade of AR signaling with a potent AR antagonist such as enzalutamide will obviate any effect on systemic androgen levels.

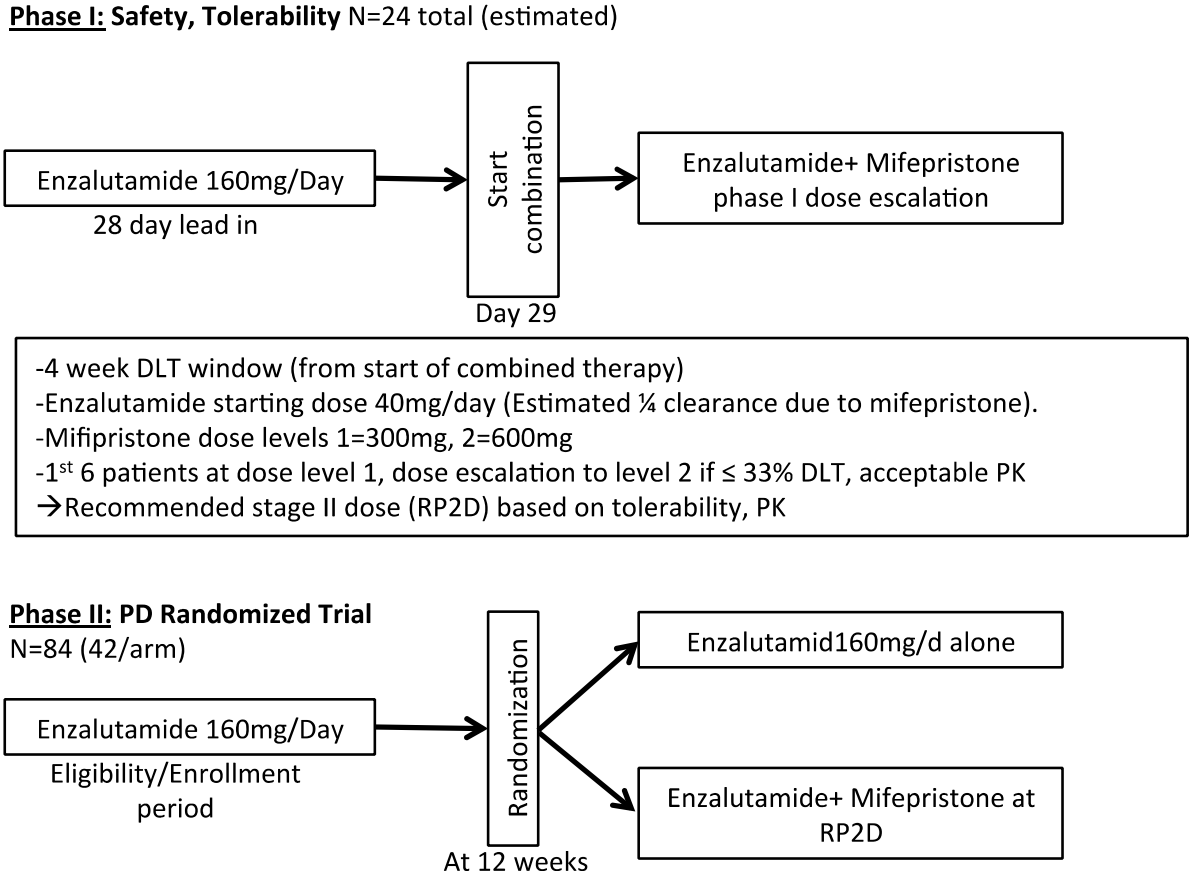
1.9 Rationale for and Description of Study Design

We hypothesize that activated GR compensates for diminished AR signaling in CRPC treated with the potent AR inhibitor enzalutamide, thereby facilitating cancer cell survival and clinical castrate resistant progression. The safe co-administration of the GR antagonist mifepristone with enzalutamide is expected to block this pathway and improve patient outcomes. To adequately test the hypothesis will require several steps-1) Define the effect of mifepristone on enzalutamide exposure.2) Ensure that enzalutamide and mifepristone can be given together, daily in patients with CRPC, at pharmacologically active doses. 3) Evaluate if mifepristone, when added to enzalutamide, prolongs its efficacy in CRPC.

As will be detailed below, the clinical trial centers on a two-part study schematic [Schema-Figure 2]. Mifepristone, being an inhibitor of CYP2C8 and CYP3A4, the two primary enzymes responsible for enzalutamide metabolism may have the potential to increase plasma exposure to enzalutamide active moieties. Furthermore, although the two drugs are very well tolerated alone, with little overlapping toxicity profiles, the combination of enzalutamide and mifepristone may have unanticipated toxicity. Thus the clinical trial will begin with a phase I study to define the effect of mifepristone on enzalutamide metabolism and determine safety of the combination. For the phase I study, subjects will be treated with enzalutamide at standard dose of 160mg/day orally for 28days to achieve steady state. After which, combination dosing with mifepristone will begin. The lead in of enzalutamide alone will allow the drug to achieve steady state plasma concentrations. Plasma levels of enzalutamide and M2 metabolite will be measured at this time point to determine a subject's baseline steady-state $C_{trough.}$ As mifepristone inhibits both CYP2C8 and CYP3A4, after the single agent lead in, study subjects will enter the combination portion of the study, starting at 300mg/day mifepristone along with 40mg/day (1/4 dose) enzalutamide as in Figure 2. 40mg of mifepristone (1/4 standard 160mg/day dose) was chosen as a conservative estimate of the dose that will provide safe and pharmacologically active exposure to the enzalutamide active moieties without risking unsafe high plasma concentrations. The dose of enzalutamide to be used in the phase I/II trial will be informed by the results of the phase PK studies imbedded in this trial, and may need to be modified to achieve appropriate steady state concentrations of enzalutamide active moieties. In addition to PK studies, the phase I study will measure changes in endocrine biomarkers to assess systemic effects of mifepristone on the GR.

The phase II portion of the trial is a randomized study of enzalutamide alone versus the combination of enzalutamide plus mifepristone [Figure 2]. It will utilize pharmacodynamic (PD) endocrine biomarkers to support the underlying hypothesis that under the pressure of potent AR blockade the GR may drive prostate cancer cell survival. Time to PSA progression will be utilized as a PD biomarker of GR antagonism within CRPC tumors as activation of both the GR and the AR can drive PSA expression in prostate cancer[28,34]. Subjects will be enrolled in the phase II trial who are currently on standard of care single-agent enzalutamideand have stable disease or better after 12 weeks of enzalutamide to allow for adaptive upregulation of GR signaling,which is proposed to enrich the patient population. In addition, the 12-week randomization is optimally timed to exclude patients with disease that is entirely refractory to further endocrine manipulation ("androgen independent" disease).

Figure 2. Trial Schema



1.10 Circulating Tumor Cell Evaluation in CRPC

When combining therapies, and therefore potentially introducing additive toxicity, utilization of PD biomarkers will enrich our ability to define the population most likely to benefit from such a combination while also ensuring on-target efficacy. As will be done in this trial of hormonal therapies, interrogation of the endocrine system may define PD markers of target inhibition. However, procurement of bio-specimens representative of a patient's disease at the time of disease progression is a key component to personalizing cancer therapy. Metastatic prostate cancer is particularly challenging as patients routinely metastasize to the bones, a secondary site that is painful to biopsy and unfortunately low relative yield[43]. A potential source of metastatic prostate cancer specimens is cancer cells in the peripheral blood circulation (circulating tumor cells, CTCs). This trial will explore a CTC interrogation platform that will examine intracellular AR expression. While multiple technologies exist for the enumeration of CTCs, very few allow interrogation of cancer biology critical for utilizing CTCs as a therapy specific predictive biomarker. Furthermore, little attention has been paid to the analytic development of these assays, which is critical in the development of any CTC isolation platform. This trial will be essential in clinical validation of a new multi-step technique (see section 12.1 below) that allows for the evaluation of therapeutic target expression within CTCs in real time. State of the art flow cytometry with embedded digital microscopy and recently developed fluorescently conjugated primary antibodies allows the interrogation of intracellular AR and GR simultaneously. The novel multi-marker interrogation methodologies will allow for preliminary studies validating AR/GR status within CTCs as a predictive therapeutic biomarker for targeted therapies. This trial will

analyze the reproducibility and variability of these measures.

2.0 OBJECTIVES

2.1 Primary Objective

- Phase I: To establish the safe and pharmacologically active doses of mifepristone and enzalutamide to use in combination.

- Phase II: To determine if mifepristone in combination with enzalutamide prolongs time to PSA progression compared to enzalutamide alone in patients with metastatic castration resistant prostate cancer

2.2 Secondary Objectives

- To evaluate the effect of mifepristone on endocrine biomarkers such as serum cortisol and thyrotropin.

- To determine the effect of mifepristone on enzalutamide clearance and steady state enzalutamide exposure.

- To determine if mifepristone affects PSA response rate when added to enzalutamide.

- To determine if mifepristone when added to mifepristone prolongs radiographic and clinical progression free survival according to standard working group criteria[44].

- To explore the role of GR and AR protein expression within circulating tumor cells as a pharmacodynamic biomarker for mifepristone and enzalutamide in CRPC.

- To explore the expression of GR and down-stream AR/GR targets in metastatic tumor specimen prior to combination drug administration and at clinical progression.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

1. Histologically or cytologically confirmed prostate cancer

2. Evidence of castrate testosterone level <50ng/dL (or surgical castration)

3. For Phase I portion of the study: Evidence of disease progression:

   - 2 or more new lesions on bone scan or

   - Progressive disease on CT/MRI according to RECIST 1.1 criteria[45] or

   - Rising PSA: PSA evidence for progressive prostate cancer consists of a minimum PSA level of at least 2 ng/ml, which has subsequently risen on at least 2 successive occasions, at least 2 weeks apart.

4. For Phase II portion of the study:

- Subjects must be on enzalutamide for metastatic CRPC and within the first 12 weeks of enzalutamide at 160mg/day
- Record of subject's enzalutamide start date and baseline PSA (within 28 days of starting) before starting enzalutamide available

5. Subjects must have documented clinically stable disease or better during the screening period of the study (see Section 7.1) as defined by all of the following (for Phase II portion of the study):
   - PSA ≤1.25 times the PSA at start of enzalutamide
   - Lack of radiographic progression as defined by RECIST 1.1 and Prostate Cancer Working Group Criteria[44-46]
   - Clinically stable as confirmed by treating physician
6. Any prior therapy for castrate disease is acceptable except prior specific CYP17 antagonists (e.g. abiraterone acetate, orteronel) or prior second generation AR antagonists (e.g. enzalutamide or ARN509) which are excluded other than enzalutamide as specified for phase II portion. A minimum washout of 28 days for any other anticancer therapy prior to first dose of study drug is required (only applicable for phase I).
7. Any other radiotherapy or radionuclide require 28-day washout prior to first dose of study drug.
8. Denosumab or zoledronic acid are allowed.
9. ECOG performance status ≤ 2 (Appendix A).
10. Patients must have normal hepatic function as defined below:
    - Total bilirubin ≤1.5 x the upper limit of normal
    - AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
11. Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

1. Therapy with other hormonal therapy, including any dose of megestrol acetate (Megace), finasteride (Proscar), dutasteride (Avodart), or any herbal product known to decrease PSA levels (e.g., saw palmetto and PC-SPES), or any systemic corticosteroid within 2 weeks prior to first dose of study drug.
2. Inability to swallow capsules or known gastrointestinal malabsorption.
3. History of other malignancies, with the exception of: adequately treated non-melanoma skin cancer, adequately treated superficial bladder cancer, stage 1 or 2 solid tumor

malignancies who are without evidence of disease, or other solid tumors curatively treated with no evidence of disease for ≥ 5 years from enrollment.

4. Blood pressure that is not controlled despite > 2 oral agents (SBP >160 and DBP >90 documented during the screening period with no subsequent blood pressure readings <160/100).

5. History of seizure disorder or active use of anticonvulsants.

6. QTc on EKG >450 msec

7. Serious intercurrent infections or non-malignant medical illnesses that are uncontrolled.

8. Active psychiatric illness/social situations that would limit compliance with protocol requirements.

9. NYHA class II, NYHA class III, or IV congestive heart failure (any symptomatic heart failure).

10. Concurrent therapy with strong inhibitors or inducers of CYP3A4 or CYP2C8 (See Section 9.12below for list of strong inhibitor or inducers) due to concerning possible drug-drug interactions

3.3 Inclusion of Minorities

Men of all races and ethnic groups are eligible for the trial.

4.0 REGISTRATION AND DATA COLLECTION/MANAGEMENT

4.1 Registration Process

Prior to registration, potential patients must have documented ability and willingness to procure standard commercially available enzalutamide (Xtandi®). Prior authorization assistance for commercially available enzalutamide is available through the manufacturer:

http://www.astellasaccess.com/home/pat/xtandi/

The University of Chicago Comprehensive Cancer Center maintains a secure, password protected, and regularly backed up commercial clinical trials database called "Velos." Patients on the trial will be entered into the Velos database centrally at the University of Chicago by the study coordinator. Data will be entered by the study coordinator and stored within the database using the patient-study number as well as a unique identifier generated by Velos.

Study Coordinator:
Jeff Bozeman
University of Chicago, Department of Medicine
Section of Hematology/Oncology

5841 S. Maryland Ave. MC2115
773-834-3095
773-702-4889
jbozema1@medicine.bsd.uchicago.edu

Eligible patients will be entered on study centrally at the University of Chicago by the Study Coordinator. Forms are available to UC Phase II Personalized Cancer Care Consortium (PCCC) Affiliates on the University of Chicago Cancer Research Center website.
http://cancer.uchicago.edu/trials/pccc/index.shtml
Click on the Log in to access
Enter your site specific user name and password

For non-UC Consortium affiliates, forms will be provided by request from the study coordinator.

The following baseline clinical variables will be collected and stored in the database using data entry forms all available in the Velos database (Appendix B):

- Demographics
- Age
- Race
- Performance status
- Primary tumor data
- Diagnosis date
- Baseline staging
- Baseline PSA
- Gleason grade
- Primary tumor treatment
- Systemic therapy administered
- Date of androgen ablation start
- Dates of anti-androgen therapy, and withdrawal
- Dates and types of other systemic therapy
- Dates and types of systemic radiotherapy
- Sites of metastatic disease

Patients can be registered only after the initial IRB approval for the participating site has been forwarded to the Coordinating Center, University of Chicago.

All patients must be registered with the University of Chicago Study Coordinator. The following documents should be completed by the research nurse or data manager and faxed to (773) 702-4889 or emailed to the study coordinator at:
PhaseIICRA@medicine.bsd.uchicago.edu a minimum of 48 hours prior to expected study med start date:

- Provider of information
- Treating Physician (NCI investigator number)
- Patient name and hospital ID number

- Patient's zip code of residence
- Date & copy of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- Complete Phase II Consortium Affiliate Clinical Trial Patient Registration Form
- Source documentation for eligibility and pre-study procedures
- Prior authorization and documentation of enzalutamideavailability

The research nurse or data manager at the participating site will then call the study coordinator to confirm all selection criteria listed in Section 3.0.

To complete the registration process, the UCMC Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Fax or e-mail the patient study number to the participating site
- Fax or e-mail, within 28 hours of completed registration, the assigned treatment dose (for phase I portion) or treatment arm (for phase II portion)
- Call the research nurse or data manager at the participating site and verbally confirm registration.

4.2 Treatment Allocation and RandomizationProcesses

For the phase I portion of the study, based on the dosing schema described below, study subjects will be assigned the applicable doses of mifepristone and enzalutamide. The dose level will be included in the registration information provided by the study coordinator as in Section 4.2 above.

For the phase II portion of the study, eligible registered subjects will be randomized to either continue standard dose enzalutamide at 160mg/day orally or to the enzalutamide and mifepristone at the Recommended Phase II Dose (See Section 5.3). Patients will be randomized by the University of Chicago Cancer Clinical Trials Office (CCTO), in cooperation with the Biostatistics Core Facility of the UCCRC. Patients will remain on their allocated treatment arm throughout the duration of study therapy with no crossover while on study. Participating sites will be notified by the coordinator within 48-hours of registered patient’s open label, randomized treatment group assignment.

5.0 STUDY DRUG ADMINISTRATION

Treatment will be administered on an outpatient basis continuously. Study drug is commercially available and will be procured by the patient through their pharmacy. A specialty pharmacy may be needed. As noted above (Section 4.1), prior authorization and documentation of enzalutamide availability is necessary prior to registration.

Mifepristone will be provided by Corcept Therapeutics and shipped to the University of Chicago for use on site and distribution to participating institutions upon patient registration and treatment allocation. The mifepristone will be provided as 300mg tablets, 30 tablets/bottle. Appropriate number of bottles will be dispersed by the investigator to the patient depending on the treatment dose allocation. Each bottle provided to the subjects will be labeled with the protocol number, dosing and storage instructions, and expiration

date. The contents of the label will be in accordance with applicable regulatory requirements.

The mifepristone may be requested by the Principal Investigator (or their authorized designees) at the University of Chicago. Corcept will only ship the agent directly to the University of Chicago. Other sites who require study agent should submit a completed Clinical Drug Request Forms to the University of Chicago Investigational Drug Service by fax (773) 834-7461. Orders received on Fridays will not be shipped until the following business day.

For questions about drug orders, transfers, returns, or accountability call (773) 834-7466 Monday through Friday between 8:00 am and 4:30 pm (CST) or email IDS.PHARMACY@uchospitals.edu anytime.

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all

As noted in Figure 2 Trial Schema, this clinical trial consists of two parts:

- Phase I portion, in which the doses of enzalutamide and mifepristone will be adjusted based on safety and pharmacokinetics to reach the Recommended Phase II Dose (RP2D)

- Phase II randomized study of mifepristone and enzalutamide at RP2D versus enzalutamide alone

5.1 Study Drug administration for each portion is as follows.

5.1.1 Phase I Study Drug Administration

- The eligible subjects will begin standard of care dosing of enzalutamide at 160mg/day.

- Beginning day 29, subjects will enter phase I combination drug portion of the study beginning at mifepristone dose 0 and at enzalutamide dose A (40mg/day). Dose levels are defined in Table 1.

- After the first 6 patients are evaluated at this dose level, subsequent patients will be enrolled and dosed similarly (after 28 day standard dose lead in) with dose of enzalutamide and mifepristone to be determined based on the following dose escalation/de-escalation rules.

5.1.1.1 Phase I Dose Level Determination

Mifepristone and enzalutamide dose levels (Table 1) will be adjusted by dose cohorts according to the following rules, which are illustrated in the algorithm below (Figure 3). Each cohort will enroll a minimum of six patients, beginning with dose level 0A, with additional patients added or doses adjusted as described in the algorithm by following rules 1-4 in order to take into account dose limiting toxicity (DLT) rate and the change in steady-state (C_{trough}) enzalutamide levels (ř, Figure 3). As noted above, it is estimated that mifepristone at both 300mg and 600mg will increase enzalutamide exposure by approximately 4-fold, with no significant difference in CYP inhibition based on mifepristone

dose. Thus, the initial dose level for enzalutamide, to ensure safety is ¼ the standard dose of 160mg/day. As noted in the Figure 3 rules, if enzalutamide plasma levels are lower then expected, the enzalutamide dose will be increased for the next cohort (e.g. from A to A'), whereas if higher then anticipated, the dose will be decreased (e.g. from A to B). Mifepristone dose will be escalated or decreased based on tolerability (DLT rate-see proceeding section). **The recommended Phase II dose (RP2D) will be the highest mifepristone dose in combination with enzalutamide such that <33% (4/12) experience DLT and ř ≤1.5.** Although we anticipate that a 12 patient cohort will be sufficient to estimate effect of mifepristone on enzalutamide clearance and that the intra-patient comparison will account for variability within each patient in baseline enzalutamide clearance characteristics, it is possible that the variability in affect of mifepristone on enzalutamide metabolism will be larger then anticipated. In this case, dose cohorts will be expanded in a protocol amendment to better characterize PK interactions.

Table 1. Dose levels

Mifepristone		**Enzalutamide**	
Level	Dose	Level	Dose
-1	300 mg/every other day	A'	80 mg/day
0	300 mg/day	A	40 mg/ day
1	600 mg/day	B	40 mg every other day
		C	40 mg every 3rd day

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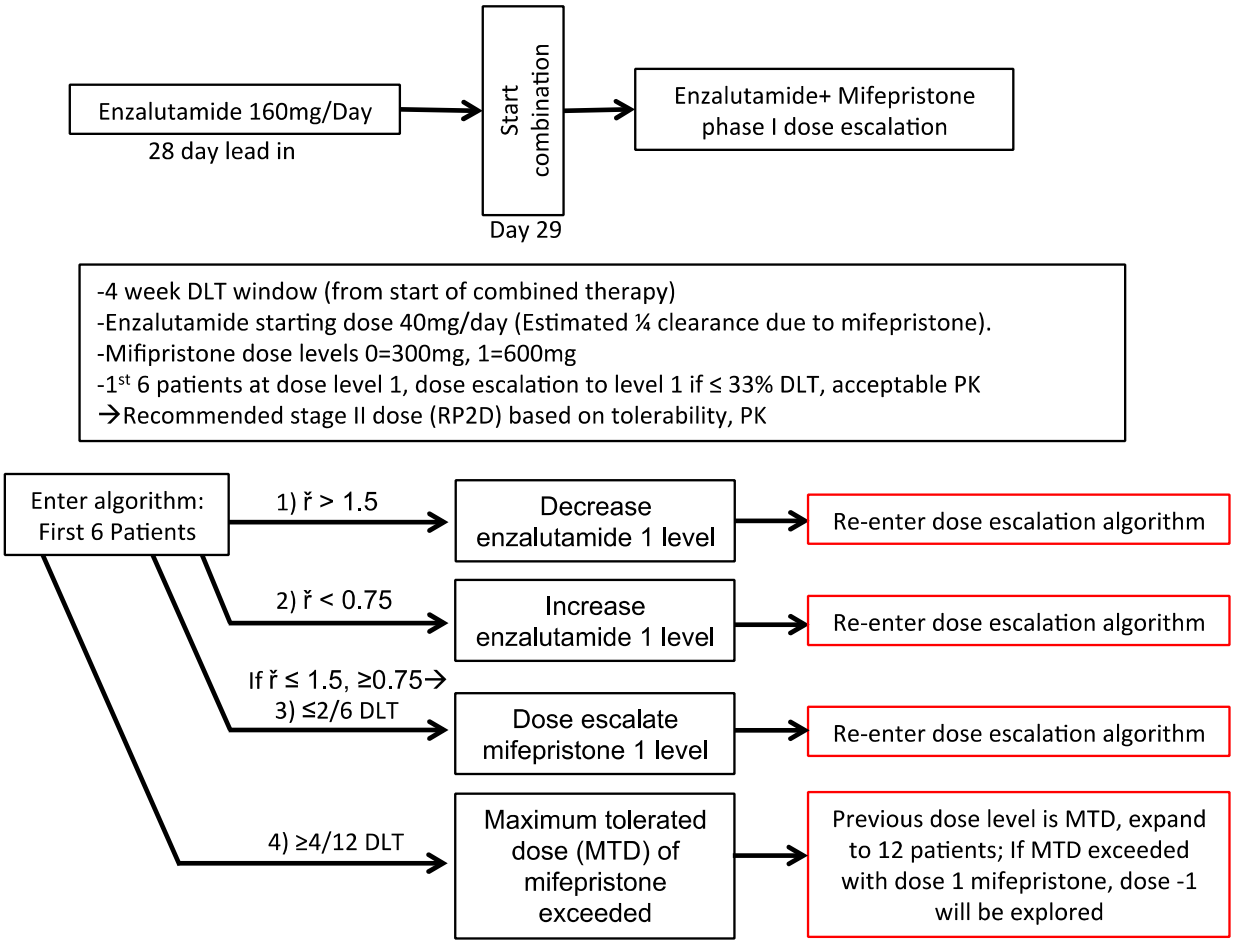
Figure 3. Phase I schema and dose escalation/de-escalation algorithm



r_i = ratio of trough drug concentration after 28 days concurrent dosing divided by trough drug concentration after 28 days enzalutamide alone dosing for an individual patient

= [C_{trough} Enzalutamide + C_{trough} M2 metabolite] day 57 /[C_{trough} Enzalutamide + C_{trough} M2 metabolite] day 29

ř = average of r_i for all patients within a dose cohort (i.e., mean of 6 or 12 patients)

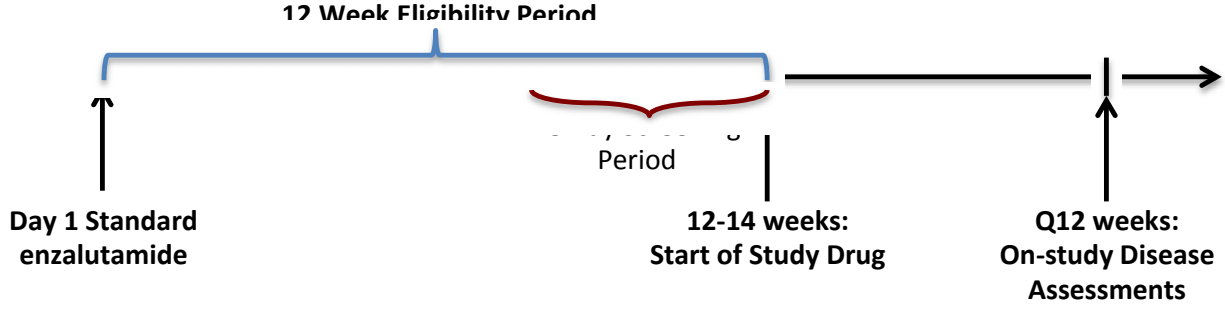
5.2 Dose Limiting Toxicity Definition

A grade 3 or 4 toxicity (CTCAE 4.0, http://evs.nci.nih.gov/ftp1/CTCAE/About.html) that is potentially related to the therapy will be classified as a dose limiting toxicity (DLT). There will be a 28day DLT monitoring period (after combination treatment) during the phase I study in which safety will be examined prior to dose escalation from 300mg to 600mg. A 28 day DLT period was chosen as the majority of dose limiting toxicities seen with enzalutamide, including rare seizures were seen in this period in previous phase I/II studies were seen within 6 weeks of beginning enzalutamide and patients will be on enzalutamide for 28 days prior to combination dosing already[15]. The DLT period begins at day 29, upon the onset of concurrent mifepristone and enzalutamide drug daily administration, and ends at day 57, fourweeks later.

5.3 Phase II Study Drug Administration (Figure 4)

- Eligible subjects will be enrolled and registered within the first 12 weeks of standard of care enzalutamide 160mg/day for CRPC and randomized to one of the following two arms:
  - Arm 1: Enzalutamide 160mg/day standard dose
  - Arm 2: Enzalutamide + Mifepristone at RP2D
- Subjects will begin randomized study treatment after 12 weeks of standard of care enzalutamide lead-in. Treatment on study may start up to 14 weeks after initial enzalutamide (+2 week grace period).

Figure 4: Phase II Enrollment and Study Treatment timeline



6.0 DURATION OF TREATMENT

Therapy with enzalutamide or enzalutamide/mifepristone will continue until one of the following events occurs.

1. Progression of disease according to 2008 PSAWG-2 criteria[47] is met (Appendix C, D). Note-PSA progression (or response) will not be assessed until the patients' first 12-week disease assessment visit.
2. Unacceptable toxicity is encountered.
3. Patient withdraws consent
4. Patient is withdrawn from study at the discretion of the investigator

7.0 STUDY ASSESSMENTS

These assessments are summarized in the study calendar below.

7.1 Pre-treatment Screening Evaluation

Eligible patients who have signed informed consent and have had eligibility confirmed will be seen in the outpatient clinic within two weeks of starting the study. They will undergo a history and physical examination, have ECOG performance status, concomitant medications, and baseline toxicity documented at this visit. In addition, to confirm eligibility, the patient will have standard of care screening labs drawn within four weeks of initiating therapy. These include: CBC (white blood cell count, hemoglobin, platelet count, white blood cell differential) and serum chemistries (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, alkaline phophatase, and albumin), LDH, serum testosterone and

PSA. A whole blood sample for circulating tumor cell correlative study will be performed during the screening period and processed as described in Section 12.1. An optional pre-study tumor biopsy will be obtained during screening period (see section 12.2). Subjects will have an EKG to insure normal QTc prior to enrolling.

Disease burden evaluation with a nuclear medicine bone scan (or Fluoride PET), abdominal/pelvis imaging (CT or MRI), and CT chest (when clinically indicated) must be obtained within 30 days of study entry. Study entry date is defined as day of first on-study treatment as detailed in Section 5.1-5.3.

7.2 On Study Visits

On study visit will every 2 weeks through 8 weeks on study, then monthly. The frequency of visits early in the trial is to ensure adequate patient safety while on study.

For study visits, including day 1, the following full set of blood tests will need to be obtained: CBC, serum chemistries, LDH, PSA. In addition, as mifepristone can affect the hypothalamic-adrenal gland axis and to monitor for endocrine related adverse events, serum cortisol cortisol and thyrotropin will be assessed at day 1 and at the subsequent two monthly (day 29, 57) study visits. A second whole blood sample for circulating tumor cell correlative study will be performed on first day of study drug as described in Section 12.1. Other monthly assessments including ECOG status, concomitant medications etc. to be collected are outlined in the study calendar. To asses for potential QTc prolongation with the combination of study agents, a second EKG will be obtained after both medications at steady state. Note: monthly visits can occur ±3 days of scheduled visit.
Disease assessment with imaging (as in pre-study evaluation) will be repeated every 12 weeks while on study, <u>starting at first day of concomitant daily study drug administration</u>.

7.2.1 Pharmacokinetics sampling:

Plasma samples to determine enzalutamide and M2 metabolite levels within the serum of patients on study will be collected and sent to Medivation Inc. for pharmacokinetic (PK) analysis. Patients should withhold enzalutamide administration prior to visits with PK sampling and should take enzalutamide after the PK sample is collected. The pre-dose PK sample should be taken immediately before enzalutamide administration. The PK sample should be collected even if patient did not withhold enzalutamide.

<u>For the phase I study</u>, the following samples will be collected for PK modeling before enzalutamide, mifepristone dose for each day. Samples will be taken weekly starting at day 29 for the next four weeks.

1. Day 29
2. Day 36
3. Day 43
4. Day 50
5. Day 57 (4 weeks after start of phase I daily concomitant dosing)

For <u>patients in the Phase II portion of the study</u>, PK's will be collected on day 1 of on-study period (steady-state enzalutamide alone) and after 4 weeks on study.

All samples will be shipped to:

Darla Tyrrel, Sample Receiving
inVentive Health Clinical Lab, Inc.
301A College Road East
Princton, NJ 08540
Phone: (609) 951-0005
Fax: (609) 951-0080
Email: Dtyrrel@inventrivhealth.com

7.2.1.1 Collection and Handling of PK Specimen(s)

Blood samples for pharmacokinetic analysis will be processed in the follow manner:

- Completely fill a 2-mL lavender-top, K_2EDTA blood collection tube. Mix immediately by gently inverting the tube at least 8 to 10 times to ensure thorough mixing of the anticoagulant.

- Document the actual time and date of collection on the PK Collection Form (Appendix E).

- Immediately after collection, place the blood sample on ice, in a refrigerator (2°C to 8°C), or in an equivalent cooling device until centrifugation for preparation of plasma. Within 30 minutes of blood collection, centrifuge the blood samples in a refrigerated centrifuge (~4°C) at approximately 2000 x g for 10 minutes.

- Use a new polyethylene disposable pipette to divide the plasma into two pre-labeled screw-cap 2 mL polypropylene cryovial plasma storage tubes (i.e., Primary PK Sample and Backup PK Sample). Ensure equal amounts (approximately 0.5 mL) are transferred to each aliquot tube. If the supernatant is limited (approximately 0.5 mL or lower), it should be transferred entirely to the Primary PK sample tube.

- **Immediately place the PK Samples upright in a sample storage cryobox and transfer them to a -80°C or a –20°C freezer.**

The plasma samples will be labeled with patient's initial and ID number, UC protocol number, initials of phlebotomist, sample ID (i.e. Day 29, Day 50, etc) and date of blood collection. Actual blood sampling times will be noted for each patient in the attached flow sheet (pharmacology referral form, appendix E). Any delays or problems will be carefully noted under comments along with the initials of the phlebotomist.

PK samples obtained of the UC will be transported to the BioFluids Core Facility (Room AB201, Scientific Director, Dr. Michael Maitland) to be stored at –80ºC. For all PK sampling, the time of blood collection will be recorded on the specimen collection sheet as well as tube label by the phlebotomist.

PK samples from participating institutions other than the University of Chicago will be collected and processed according to the same methods and stored at the participating

institutions at –80ºC (or -20ºC if -80ºC not available, provided it is not a "self-defrosting" model due to variability in temperature for these models) for shipment. Cryotubes for plasma storage will be provided by the University of Chicago as will blank labels. Frozen PK samples will be shipped to Dr. Gibbonsin a styrofoam container (not supplied by UC). Samples will be batched and shipped together with each dose level cohort (Phase I) or quarterly (for phase II).

7.3 Off Study Assessments

Patients will be followed with these assessments until taken off study. Upon study discontinuation, subjects will undergo a complete evaluation with a history and physical examination, ECOG performance status, concomitant medications, and toxicity documented at this visit. The subject will also have standard laboratory studies collected at this visit (CBC, serum chemistries, LDH, PSA, testosterone), and have radiologic tumor assessments performed, unless already performed within four weeks of being taken off study. Study participant refusal or inability to undergo these evaluations should be noted. This visit should be done on the day patients are taken off study medication but may be completed within 30 days of coming off treatment. A third CTC sample will be obtained. In addition, a second optional pre-study tumor biopsy will be obtained at time of disease progression for those coming off study for progression.

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8.0 STUDY CALENDAR

	Screening [m]	Day1, 15, 29, 43, 57 then Monthly[g]	Every 3Months[g] (beginning at start of concomitant dosing)	Offstudy visit[j]
Procedures				
Informed Consent[a]	X			
Medical History, including demographics	X			
Physical exam, including height (only at screening) and weight	X	X	X	X
Vital Signs[b]	X	X	X	X
ECOG performance status	X	X	X	X
Concomitant medications	X	X	X	X
Adverse Events		X	X	X
EKG	X	X[l]		
Laboratory Assessments				
CBC with platelets & Differential counts	X	X	X	X
Serum chemistry and electrolytes[c]	X	X	X	X
LDH	X	X	X	X
PSA	X	X	X	X
Testosterone	X		X	X
Hypothalamic-pituitary labs		X[k]		
PK sample-per Sec. 7.2.1		X[h]		
TumorAssessments[d]				
Bonescan/F18 PET[e]	X		X	X
CT or MRI of the abdomen/pelvis	X		X	X
CT chest[f]	X		X	X
Correlative Studies				
Circulating tumor cell (CTC) collection	X	X[i]		X
Tumor biopsies (optional)	X			X

a. Written informed consent must be obtained before any study-specific screening assessments are performed (it can be no more than 28 days prior to starting/beginning study medication).

b. Includes blood pressure, pulse, respiratory rate, and body temperature.

c. Serum chemistry includes BUN, creatinine, ALT, AST, glucose, alkaline phosphatase, total bilirubin, electrolytes (K+, Cl-, Na+,CO2, Ca+).

d. Imaging will be evaluated at screening and for clinical benefit every 12 weeks (3 cycles) of treatment, beginning at start of concomitant drug dosing (day 29 for phase I, day 1 for phase II).

e. Isolated new lesions on bone scan at the first12-week scan will be confirmed with a repeat bone scan at 6 weeks to rule out bone scan flair.

f. Obtain if clinically warranted.

g. +/- 3 days.

h. PK assessments per Section 7.2.1(day 29, 43, 57 then monthly)

i. Whole blood for CTC assessment will be collected on Day 1 of study drug administration.

j. End of study visit – within 30 days of the last enzalutamide dose. Tumor assessment not necessary if done within preceding 30 days.

k. Serum TSH and AM cortisol will be measured at day 1, 29, 57

l. EKG to assess QTcon study will be obtained Day 57 for Phase I, Day 29 for Phase II

m. In calculating days of tests and measurements, the day a test or measurement is done is considered day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered day 28. Eligible patients will be seen in the outpatient clinic within two weeks of starting the study to have history and physical examination, ECOG performance status, concomitant medications, and baseline toxicity documented. To confirm eligibility, the patient will have standard of care screening labs drawn within four weeks of initiating therapy.

9.0 TREATMENT PLAN

9.1 Agent Administration

Treatment will be administered on an outpatient basis as per Section 5.0, Figure 2. The patients on study will procure the enzalutamide as stated above through their standard outpatient pharmacy, but will not take any doses of therapy until instructed to do so, and at doses specified by study nurse and investigator. Study drug administration calendars will be filled out by the patient while on study. The patients' pill bottles will be brought to each study visit for pill counting by the research nurse to validate the calendars.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy with the exception of patients who are chemically castrated who should continue to receive their LHRH agonist/antagonist while on this clinical trial. Medications for bone health (e.g. zoledronic acid or denosumab) should likewise be continued (Section 3.1).

9.2 Management of Castration Related Symptoms:

Treatment with androgens, estrogens, and progestin to control hot flushes is not allowed. However, selective serotonin re-uptake inhibitors (SSRIs) are permitted for the management of hot flashes.

9.3 Dose-Reduction Procedure for Adverse Event Management

In the event where dose-reduction is used for AE management, dose reductions are allowed according to table 2 below, however given the study design, the starting dose for a subject may vary. For mifepristone the dose reduction algorithm is downward from level 1→1'→0→-1; for enzalutamide dose reductions follow A'→A→B→C depending on subjects starting dose. The maximum time a patient's study medication may be held due to toxicity is 28 days. After which, the patient must be discontinued from study participation. A dose delay of 14 days or more will mandate a dose reduction.

All grade 3 or 4 toxicity (CTCAE 4.0, http://evs.nci.nih.gov/ftp1/CTCAE/About.html) that are potentially related to the therapy, unless specifically addressed below, should necessitate holding offending study drug, which can be reintroduced according to the instructions listed below. Holding or reducing dose otherwise (unless specifically addressed below) is at the discretion of the investigator.

- If Grade 1-2 toxicities, give supportive care per institutional guidelines. No study treatment dose reduction.

- If Grade3 or higher toxicities including headache (interferes with ADL), nausea (TPN, IVF), vomiting (>6episodes/24hrs,TP Nor IVF), diarrhea (IVF, hospitalization, hemodynamic collapse),or any other toxicity judged to be related to study treatment is observed where the patient's safety is jeopardized, hold study treatment.

- When toxicity resolves to ≤Grade 1, resume study treatment at full dose.

- If toxicity recurs, hold study treatment, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade1, resume study treatment with the first dose level reduction.

- If toxicity recurs, hold study treatment, and adjust or add medications to mitigate the toxicity. When resolve to ≤ Grade1, resume study treatment with these dose level.

- If toxicity recurs despite aggressive medical management, and two dose level reductions, discontinue study treatment.

Several of the potential adverse events for this study are side effects common to both mifepristone and enzalutamide, such as diarrhea, anhedonia, nausea and fatigue. Given the established efficacy of enzalutamide for patients with CRPC, if dose delays or adjustments necessary for non-specific adverse events, it is recommended that the mifepristone be delayed/reduced first, and if no improvement in adverse event with adjustment of mifepristone, enzalutamide then be delayed/reduced.

Table 2. Dose reduction levels

Mifepristone		**Enzalutamide**	
Level	Dose/Day	Level	Dose
-1	Will be removed from study for toxicity	A’	80 mg/day
0	300 mg/ every other day	A	40 mg/ day
1’	300/600 alternating every other day	B	40 mg every other day
1	600 mg/day	C	40 mg every 3rd day

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9.4 Treatment Management of Hypertension

Hypertension may develop while on mifepristone due to excess mineralocorticoid activity due to treatment dependent increase in ACTH. Because of this, hypertension occurring secondary to mifepristone may be most effectively prevented through the concurrent administration of eplerenone which is capable of inhibiting mineralocorticoid induced hypertension. The following table provides a recommended algorithm for treatment-emergent hypertension management. Decisions to hold or decrease the dose of study treatment must be based on blood pressure (BP) readings confirmed with a second measurement at least 5 minutes after the first measurement.

BP Measurements – Systolic/Diastolic	**Treatment/Dose Modification**
> 140 mm Hg (systolic) and <160 mm Hg OR > 90 mm Hg (diastolic) and < 105 mm Hg OR	• Add new or additional antihypertensive medications or increase dose of existing medications. • Maintain dose of study treatment.
≥ 160 mm Hg (systolic) OR ≥ 105 mm Hg (diastolic)	• **Hold mifepristone.** • **Add new or additional anti-hypertensive medications or increase dose of existing medications.** • **Monitor subject closely for hypotension (if on** anti-hypertensive medications) until study treatment is restarted. • Resume treatment at same dose level when BP falls to < 140/90 mm Hg.

If toxicity occurs, hold study treatment, adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study treatment with first dose level reduction.

If toxicity recurs at the first dose level reduction, hold study treatment, adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study treatment with the second dose level reduction.

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9.5 Treatment-Emergent Edema and Fluid Retention

Fluid retention can similarly be managed with aldosterone antagonists such as eplerenone and other diuretics as needed. Serum potassium level should be monitored closely.

Symptoms	Treatment/Dose Modification
• Pedal Edema	• Management per investigator. No study treatment dose reduction
• Anasarca and/or pulmonary edema requiring supplemental oxygen	• Hold mifepristone. Adjust or add medications to mitigate the toxicity and/or consider specific mineralocorticoid receptor blocker, eplerenone. When toxicity resolves to ≤Grade 1, resume study treatment at full dose.
• Recurrence of anasarca and/or pulmonary edema requiring oxygen.	• Hold mifepristone treatment. Adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study treatment at first dose level reduction.
• Recurrence of anasarca and/or pulmonary edema requiring oxygen at first dose level reduction	• Hold study treatment. Adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study treatment at second dose level reduction
• Recurrence of toxicity despite optimal medical management and with two dose level reductions	• Discontinue study treatment.

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9.6 Management of Hypokalemia

Hypokalemia may occur in patients treated with mifepristone due to mineralocorticoid excess and potentially. Initial management of hypokalemia should include oral K+ supplementation as well as the addition of eplerenone, as appropriate.

Serum K+	Grade	Action	Further Action and/or Maintenance
<3.5mM-3.0mM	Grade 1	Initiate oral K+ Supplements	Titrate K+ dose to maintain serum K+ ≥3.5mM ≤5.0mM (Maintenance of pts at ≥4.0mM is recommended); weekly laboratory studies until K+ ≥3.5mM ≤5.0mM.
<3.0mM–2.5mM	Grade 3	Withhold mifepristone and initiate IV K+ and cardiac monitoring	Restart mifepristone at dose level -1; Titrate K+ dose to maintain serum K+ ≥3.5mM ≤5.0mM; weekly laboratory studies until K+ ≥3.5mM ≤5.0mM.
<2.5mM	Grade 4	Withhold mifepristone and initiate IV K+ and cardiac monitoring	Call study PI prior to re- initiating study treatment.

9.7 ManagementofElevatedLiverFunctionTests

Although elevated liver function studies are an uncommon adverse event for both enzalutamide and mifepristone, given the hepatic metabolism of both drugs, potential for increased toxicity is noted.

- IfGrade1increasesinAST,AL Torbilirubin occur(e.g. increase in AST or ALT from ULN to 2.5 XULN; increase into talbilirubin from ULN to 1.5 XULN): The frequency of liver function test monitoring should be increased per Investigator discretion, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
- If Grade 2 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT to>2.5-5XULN; increase into talbilirubin from > 1.5-3 XULN): The frequency of liver function test monitoring should be increased to ≥ once a week, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
- If Grade3 or higher increases in AST, ALT, o rbilirubin occur (e.g. increase in AST or ALT to>5 XULN; increase in total bilirubin to > 3 XULN), hold mifepristone and

enzalutamide and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1.When liver function studies do normalize, first reintroduce enzalutamide at one dose reduction. If after 2 weeks of single agent enzalutamide, AST/ALT are still grade 1 or better, mifepristone may be introduced at one dose level reduction.

If Grade 3 or higher increases in AST, ALT, or bilirubin recur after the first dose reduction hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the liver function tests return to baseline value or Grade1. Liver enzyme measurements should be made immediately, regardless of when the next study visitor monitoring interval is scheduled.

If study treatment resumption is considered for patients who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, resume study treatment with the second dose level reduction as above when AST, ALT, or bilirubin returns to baseline value or Grade 1.

If Grade 4 increases in AST, ALT, or bilirubin occur (e.g. increase in AST or ALT to > 20X ULN; increase in total bilirubin to >10 XULN), patients must discontinue study treatment immediately and will not be re-challenged. They should be followed until resolution of abnormal liver function tests.

9.8 ManagementofAdrenal Insufficiency

Administration of mifepristone, particularly with long-term dosing, carries a risk of inducing adrenal insufficiency by virtue of blockade of the glucocorticoid receptor. Of note, signs and symptoms of adrenal insufficiency may occur with normal or high cortisol level given the blockade of the GR rather than primary insufficiency of the adrenal gland. Unlike primary adrenal insufficiency, adrenal insufficiency that may be seen with mifepristone is not anticipated to be associated with hyperkalemia given the maintenance, and potential increase, in mineralocorticoid activity in the setting of GR blockade. Throughout the Corcept mifepristone program of over 1200 subjects, there have only been three cases of adrenal insufficiency documented as adverse events[40]. However, the symptoms of adrenal insufficiency can be vague and include fatigue, hypoglycemia, anorexia, constipation, nausea and hypotension, particularly orthostatic hypotension. Should a constellation of these symptoms occur in a subject, no change is necessary other then supportive care for grade 1 and 2 adrenal insufficiency. For grade 3 adrenal insufficiency, for example severe symptoms requiring hospitalization, mifepristone should be held and hydrocortisone initiated for adrenal replacement.

9.9 Management of Rash

Mifepristone is associated with macular-papular eruptive rash on the upper torso, trunk that can extend to extremities and face. It is a relatively frequent adverse event noted with mifepristone (~30%). It typically occurs within the first two weeks of drug exposure, is typically mild (grade 1-2) and associated with pruritis. It should be treated with topical antihistimines ± topical corticosteroids. It is typically self-limited. Should a subject

experience severe rash that does not improve with topical agents, mifepristone can be held, which in most instances leads to resolution. Rechallange of full dose mifepristone should be initiated upon resolution of the rash. Severe (grade 4) rash such as Stevens-Johnson syndrome or Toxic Epidermal Necrolysis has not been observed with mifepristone.

9.10 Chemotherapy and Radiotherapy

If possible, alternative anticancer treatment should not be initiated until PD has been observed by standard guidelines and study treatment has been discontinued. If a subject requires additional systemic anticancer treatment, study treatment must be discontinued. Local intervention (e.g. nephrostomy tube placement, TURP) is discouraged unless medically unavoidable. Subjects receiving local intervention are allowed to continue to receive study treatment at the investigator's discretion.

9.11 Other Medications

Anti-emetics and anti-diarrheal medications should not be administered prophylactically prior to the first dose of study drug. After the first dose of study drug, at the discretion of the investigator and after the onset of symptoms, treatment (or prophylaxis) with anti-emetic and anti-diarrheal medications may be undertaken per standard clinical practice.

Pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. Colony stimulating factors (e.g. granulocyte colony-stimulating factors) administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically before the first dose of study treatment. Erythropoietin should not be used based on a recent report of increased risk of tumor recurrence/progression associated with erythropoietin[48].

No concurrent investigational agents will be permitted.

9.12 Potential Drug Interactions

As noted above, mifepristone is an inhibitor of both CYP3A4 and is also metabolized by CYP3A4. Similarly, enzalutamide is metabolized by CYP3A4 and CYP2C8. Strong inhibitors and inducers of CYP3A4 and CYP2C8 should be avoided. In addition substrates of CYP3A4 or CYP 2C8/9 should be used with caution and at the lowest dose available. The following table should be used as a reference (from http://www.fda.gov/drugs/).**Given the prevalence of CYP3A4 metabolism, all concomitant medications should be evaluated for potential drug-drug interaction.**

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	Strong: Prohibited	**Moderate: Used with caution**
CYP3A4 inducers	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin
CYP3A4 inhibitors	Boceprevir, clarithromycin, conivaptan, **grapefruit juice**, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil
CYP 3A4 substrates	Avoid if possible/use at lowest dose: Alprazolam, erythromycin, felodipine, amlodipine, verapamil, fentanyl, lovastatin, nifedipine, simvastatin,	
CYP2C8/9 inducers		Rifampin, carbamazepine
CYP2C8/9 inhibitors	Gemfibrozil	Amiodorone, fluconazole, miconazole
CYP 2C8/9 substrates	Avoid if possible/use at lowest dose: Warfarin, rosiglitazone, celecoxib, ibuprofen, losartan, naproxen, sulfamethoxazole,	

Although warfarin is not excluded, it should be used with caution and close monitoring of INR.

Additional information with regards to drug-drug interactions is available on the FDA prescribing information for enzalutamide and mifepristone.

- Enzalutamide: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf
- Mifepristone: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202107s000lbl.pdf

10.0 SAFETY

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation of a subject who has been enrolled in a clinical study and who may have been administered an investigational product, regardless of whether or not the event is assessed as related to the study drug treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of whether or not the event is assessed as related to the investigational product. Abnormal laboratory values, ECG findings, or vital signs that are considered clinically significant by the investigator, and pre-existing medical conditions that worsen during a study, should be recorded as AEs.

For the purpose of data collection, all AEs that occur after initiation of study drug through 30 days after last dose of study treatment (or until a subject is determined to be a screening failure) are to be recorded by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

Assessment of toxicities and adverse events will be graded according to the Common Toxicity Criteria (CTC), version 4.03:

- V4.03 (CTCAE): publish date June 14, 2010: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

10.2 Serious Adverse Events

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

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

1. Results in death.
2. Is immediately life-threatening (i.e. in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity.
    - Note: The term "disability" refers to events that result in a substantial disruption of a subject's ability to conduct normal life function.
5. Is a congenital anomaly or birth defect.
6. Is an important medical event (IME)
    - Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of Serious Adverse Event. Examples of IMEs include: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

10.3 Suspected Adverse Reactions

An adverse event (AE) is considered to be a suspected adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls.

10.4 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, investigator brochure, and/or FDA-approved package. This includes adverse events listed in the protocol or consent as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with this investigational agent.

10.5 Serious Adverse Event Reporting

This study will be using MedWatch for SAE reporting.

MedWatch forms and information: http://www.fda.gov/medwatch/getforms.htm

The minimum information required for SAE reporting includes identity of investigator, site number, patient number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (ie the seriousness criteria) and the investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE.

When reporting serious adverse events, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death should not be reported as an SAE, but as an *outcome* of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then Death may be used as an event term and should be reported as "death, cause unknown". If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
- Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair.
- Procedures for pre-existing conditions that have not worsened after initiation of treatment.
- Pre-specified study hospitalizations for observation.
- Events that result in hospital stays of less than 24 hours and that do not require admission, eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics.

- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
- Symptoms related to progressive diseases uc has severe bone pain will not be reported as toxicity or as Serious Adverse Events.
- ALL SAEs, whether or not they are considered related to the study agent MUST be reported to the IND Holder (Rita Nanda, MD) and to the University of Chicago Comprehensive Cancer Center (UCCCC). Refer to Section10.6 for reporting guidelines.
- All serious unexpected adverse drug reactions (see definitions in Section 10.3 and 10.4) must be reported to the FDA by the investigator as required by 21 CFR 312.32 (See **Section 10.6** below for reporting processes).
    - These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form).

10.6 Adverse Event Reporting Process

All SAEs and protocol deviations must be reported to the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO). The responsible Research Nurse or other designated individual should report the SAE/deviation to the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the eVelos database 'Serious Event Report' Form.Each event report must indicate whether the event meets the IRB's Unanticipated Problem reporting criteria. Notification of each reported event to the Study Chair and IND Holder will occur.

When appropriate, the UC IRB's Unanticipated Problem electronic submission form must be completed by the research nurse or other designated individual and submitted by the investigator via the IRB's electronic submission system within **the IRB's designated reporting timeframes**. Details of the IRB's current policy can be found on their website at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html.

For events occurring at a non-UC site (e.g. participating site):

- Multi-center sites participating in the study will notify the UCCCC CCTO via phone at 773-702-5928 and email at qaccto@bsd.uchicago.edu of all serious adverse events within 24 hours of knowledge of the event.
- Each SAE should be reported to the local IRB of record in accordance with their current policies
- These events should also be reported to the UC IRB if the event meets current reporting requirements.

For all Unexpected and Serious Adverse Drug Reactions (i.e. unexpected SAEs that are related to the study agent (mifepristone), in addition to the required reporting to the UCCCC via Velos, the responsible Research Nurse or other designated individual at the treating site should:

- Provide a more complete written report using the FDA MedWatch 3500A form.
- The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu,

within the specified timelines below regardless of whether all information regarding the event is available.
- If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within10 calendar days of treating investigator knowledge of the event

10.7 Adverse Event reporting by the Coordinating Center

The designated UCCCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

10.8 Other Safety Considerations

10.8.1 Laboratory Data

All laboratory data obtained during the course of the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an adverse event or serious adverse event as appropriate, unless this value is consistent with the patient's present disease state or is consistent with values obtained prior to entry into the study.

10.8.2 Medication Errors

Any medication error that results in an adverse event, even if it does not meet the definition of serious, requires reporting to the UCCCC CCTO as above.

10.8.3 Follow-Up of Adverse Events

Any SAE or AE assessed as possibly related that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study treatment must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to possibly-related serious adverse events that occur *greater than 30 days after last dose* of study treatment. The status of all other continuing adverse events will be documented as of 30 days after last dose of study treatment.

10.8.4 Safety Monitoring

According to University of Chicago Cancer Center Guidelines, this protocol will be

classified as moderate risk. Data and Safety Monitoring (DSM) will occur at the weekly University of Chicago Genitourinary Oncology DSM meeting. At each meeting, the study will be reviewed for safety and progress toward completion. Toxicities and adverse events will also be reviewed and a DSM form will be completed at each meeting. Twenty percent of research charts will be audited annually for protocol compliance items including eligibility, completion of procedures, administration of treatment, reporting of toxicities, documentation of response, follow-up, data-collection, record keeping, and the collection of correlative studies. Safety of participating subjects at other sites will also be reviewed at the University of Chicago DSM, however safety will also be monitored locally per each institutions guidelines. During the phase 1 portion of the study, there will be weekly teleconferences between participating centers to review subject safety and study progress. For the phase II portion, there will be a similar monthly teleconference.

10.8.5 **Independent Safety Monitor**

Dr. Sumati Murli, PhD, Director for Clinical Research Operations in the University of Chicago Comprehensive Cancer Center, will serve as the Independent Research Monitor (IRM) for this study as stipulated by DOD Directive 3216.02. The principle role of the IRM within the context of this study will be to oversee study conduct specifically with respect to safety. Given the phase I/II nature of the study, and the potential for dose adjustments based on both pharmacokinetics and safety, the IRM will have direct oversight with respect to assessment of patient safety, independent of the research team. In the case of serious adverse events or subject deaths that she feels meet the criteria to be classified as unanticipated problems, her independent report in the form of a memo will be promptly submitted to the DOD (USAMRMC ORP HRPO) and University of Chicago IRB along with the report of the event. In addition to attending weekly data safety monitoring meetings, she will participate in the regular teleconferences once more than one site is participating in the trial. In the event that she is not able to attend the data safety monitoring meeting in person, she will review the data safety monitoring minutes from that meeting. Specifically, she will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event should she feel it qualifies as an unanticipated problem. For those events qualifying as unanticipated problems, the IRM will comment on the outcomes of the event or problem and, in case of a serious adverse event or death, she will comment on the relationship to participation in the study. The IRM will indicate whether she concurs with the details of the unanticipated problem report provided by the principal investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the USAMRMC ORP HRPO and the University of Chicago IRB. The IRM has the authority to stop this research protocol in progress in parallel with the submission of a UP to the University of Chicago IRB, remove individual human subjects from this research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects participating in this protocol until the University of Chicago IRB assesses the UP and the IRM's report and determines appropriate next steps.

11.0 MEASUREMENT OF EFFECT

Patients with measurable disease will be assessed by standard criteria[45,46](**Appendix C, D**). For the purposes of this study, patients should be re-evaluated every 12 weeks.

11.1 Outcome Measures based on PSA Decline

The following parameters will be recorded after the initial 12 weeks of therapy and at 12-week intervals thereafter.

- PSA decline and response will be measured according to PSAWG-2 (2008) criteria.
- PSA changes from baseline will be calculated for all patients and reported as a waterfall plot.
- Time to progression (TTP) based on revised PSA Working Group-2 criteria (2008 version).
- PSA progression free survival: PSA measurements will be taken at screening (baseline) and subsequently at time points as indicated in the schedule of visits. Any unscheduled PSA measurement will be utilized in the periodic assessment of PSA progression.
- The maximal decline in PSA for each patient will be recorded for each patient.
- The date of the maximal PSA decline (nadir date) will be recorded for each patient, as will the duration from the start of therapy to the nadir PSA.

11.2 Radiographic Tumor Response

Change in measurable disease, when applicable, will be determined according to RECIST 1.1 and PSAWG-2 criteria (Appendix E)[45,46,49]. For the purposes of this study, imaging will be repeated according to the study calendar (Section 8.0) every 12 weeks unless otherwise indicated clinically.

Lymph nodes[46]*:* To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). Lymph nodes that are at least 10 mm but less than 15 mm in short axis may be pathologic and can be considered non-measurable/non-target lesions (that are not measured). At baseline and in follow-up, only the short axis will be measured and followed.

Bone lesions: Bone lesions are by definition non-measurable. If bone lesions are identified on MRI that have soft tissue components that are identifiable and accurately measurable the bi-dimensional measurements of these lesions will be recorded as soft tissue measurable disease. Of note, progression based on bone scan will be assessed according to PSAWG-2 criteria[49]. Isolated new lesions on bone scan at the 12-week scan will be confirmed with a repeat bone scan at 6 weeks to rule out bone scan flair. If no new lesions are seen at the 6-week confirmation, it will be considered flair. All subsequent bone scans will follow standard criteria with regards to progression (two new lesions necessary for progression).

11.3 Duration of Response

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

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.4 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression (by either PSA or RECIST) or death, whichever occurs first.

12.0 CORRETALIVE STUDIES

12.1 Circulating Tumor Cells (CTC)

Circulating Tumor Cell isolation and characterization
CTC are emerging potential source of tumor tissue for therapeutic biomarker interrogation. At present, there is no standard procedure for extracting and evaluating CTC beyond enumeration. This study will utilize methodologies developed in the PI's laboratory[50] for further biomarker validation.

For evaluation of CTC, 15mL of whole blood will be collected in two (7.5mL each) BD CPT vacutainers which will be provided. For this exploratory endpoint, samples will only be collected for University of Chicago study subjects. Samples will processed within 60minutes of sample acquisition.

CPT tubes will be centrifuged at 1500g for 20minutes at room temperature. Following centrifugation, the uppermost plasma layer will be removed and saved for correlative studies. Mononuclear cell layer will be then transferred from both tubes into one new 15ml conical tube. Phosphate buffered saline (PBS) will be added to a total volume of 15ml. The cells will be centrifuged at 450g for 5 minutes at room temperature. The supernatant will be discarded and the washed mononuclear cells will be resuspended in 10ml of PBS for further processing.

Once mononuclear cell fraction isolated, prostate cancer cells will be identified and further characterized using flow cytometry cell sorting (FACS) and analysis. Pellet of cells will be resuspended in cell separation buffer (PBS with 2mM EDTA, 0.5% serum albumin), FcR blocking buffer (Miltenyi), EpCAM (to bind epithelial cells) and CD45 (to bind white blood cells) primary antibodies conjugated to specific fluorescent markers. Cells will then by analyzed in conjunction with the flow cytometry core facility gating for the EpCAM positive, CD45 negative population. The cells will be characterized using multiplex flourescent immunocytochemistry with fluorescently conjugated antibodies to the AR, GR (Cell Signaling) along with DAPI nuclear staining.

Cells will be FACS sorted onto charged glass chamber slides, and then fixed with 3% formalin and stained with ICC antibodies for multiplex fluorescence. The slides will be imaged using the Leica SP2 laser confocal microscope. Alternatively, depending on FACS machine availability, the Image Stream flow cytometer may be used to analyze fixed and stained cells. Captured images will be analyzed for fluorescence intensity and digitally scored using ImageJ software. Positive and negative control cells stained concomitantly will also be digitally analyzed and will provide the reference for staining intensity analysis. In

addition to staining intensity, intra-cellular localization will be described for CTC for each marker. Immunofluorescence will be assessed in conjunction with Dr. Paner in the Pathology Department, University of Chicago.

12.2 Optional Tumor Biopsies

Studies have shown that GR expression increases in response to androgen pathway inhibition in prostate cancer[32]. The GR expression in CRPC is unknown. To better understand the potential compensatory role of the GR in CRPC progression, to explore the role of baseline intra-tumoral GR expression as a predictive biomarker for GR inhibition with mifepristone, and to query other resistance pathway mechanisms, subjects will be asked to contribute an optional tumor core needle biopsy (under CT guidance if necessary). An optional biopsy will be obtained both during the screening period and at the off study visit (Section 7.0above) if possible. While the exact number of specimens obtained depends on the size of the target, the difficulty of the procedure, and risk of complications, the goal is to obtain between 2-3 samples for analysis. A full standard operating procedure (SOP) for biopsy acquisition and handling will be provided to study sites. The primary sample will be fixed in paraformaldehyde, decalcified (if needed) and embedded in formalin. Samples will be processed for immunohistochemistry (IHC) and assessed for standard pathologic parameters (with H&E staining), AR and GR staining. These pathology parameters will be assessed in conjunction with Dr. Paner in the Pathology Department, University of Chicago. If a second core biopsy is obtained, it will be embedded in Tissue Tek™ OCT and frozen at -80°C for future molecular analysis of AR pathway resistance.

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample Size/Primary Endpoint

Within the phase I portion of the study, steady-state C_{trough} for Enzalutamide and the active metabolite will be determined for each patient and means and standard deviations calculated. As described above, the mean of the ratio of C_{trough} for Enzalutamide and the active metabolite will be calculated for each dosing cohort, and mean value will be used for dos adjustment determinations. Standard deviation and range of the C_{trough} and ratio will also be calucalated and reported.

The randomized phase II study, will be conducted with appropriate sample size to power primary endpoint- to determine if mifepristone in combination with enzalutamide prolongs time to PSA progression compared to enzalutamide alone in patients with metastatic castration resistant prostate cancer. The primary statistical consideration will be PSA progression-free survival (PFS) post randomization, defined as the time to PSA progression or death, whichever comes first. PSA progression will be defined as a PSA (confirmed 2 weeks later) that is ≥1.25 times (25% increase) the PSA at randomization (week 12). We assume the median time to PSA progression in the control (enzalutamide alone) arm will be 6 months post randomization. The rationale for this assumption is as follows. In the phase III enzalutamide (AFFIRM) trial[13], ~10% of treated patients had PSA progression prior to 12 weeks. The PSA progression-free rate was ~42% at 9 months, which would correspond to a 6-month rate, conditional on no event at 12 weeks, of 0.42/0.9=0.47. Thus our enrichment strategy should lead to a patient population with a median PFS of 6 months (24 weeks) in the control arm post randomization. In order to detect a hazard ratio (HR) of 0.60, which corresponds to an increase in the median from 24 to 40 weeks, with 80% power, a sample

size of 84 patients (42/arm) is required, using a one-sided test at the α=0.10 significance level. This assumes a two-year accrual period and a subsequent one-year follow-up period. Kaplan-Meier[41] curves will be generated and the two treatment arms compared using a logrank test. Median time to event in each group will be estimated along with 90% confidence intervals using the method of Brookmeyer and Crowley[42]. Cox[43] proportional hazards regression models will be fit to assess and adjust for the effects of baseline covariates. Overall survival and radiographic progression-free survival will be analyzed similarly. The relative PSA change within each arm will also be reported using a waterfall plot according to working group recommendations for phase II studies in CRPC, as a secondary endpoint[44]. Adverse events will be summarized by grade and type and compared between groups using chi-square or Fisher's exact tests.

For the secondary endocrine PD endpoint, we will compare endocrine PD marker differences between the enzalutamide alone versus the Enzalutamide + Mif treatment arms. In previous placebo controlled trials of Mif, serum cortisol levels reliably doubled from a baseline of approximately 15 μg/dL to >30 μg/dL after treatment with mifepristone[38,39]. Based on the reported interquartile ranges, and assuming normality of the distribution, the coefficient of variation is estimated at 50%. An interim futility analysis will be conducted after half (35) of the expected 70 PSA events are observed. At this stage we will conduct an interim analysis of the difference in cortisol levels; a lack of biomarker effect would provide justification for closing the trial. Thus, assuming a true mean for the control arm of 15 and standard deviation of 7.5 on day 29 post randomization, our sample size will provide 90% power to detect a difference of 15 vs. 22 μg/dL between the two treatment arms, based on t-test at a two-sided alpha level of 0.05. This calculation allows for a 15% missing data rate prior to day 29 post randomization. The other endocrine laboratories collected at day 29, will be similarly compared between treatment groups.

In addition, if at the interim analysis the conditional power for the primary PSA endpoint is <25%, we will consider terminating the trial for futility. This stopping rule will provide minimal power loss (<3%)[44].

13.2 Randomization

Upon documented and confirmed eligibility, the patient will be enrolled and randomized. Randomization for phase II portions of the study will be done through Dr. Karrison and colleagues in the biostatistics core at the University of Chicago in a 1:1 fashion. There will be no specific stratification as the 12-week standard of care enzalutamide lead in for the phase II study we hypothesize will add homogeneity to the population. As only patients with stable disease or better at 12 weeks are randomized any affect of prior therapy, etc. on the study population will be mitigated.

13.3 Analysis of Secondary Endpoints

The stratified log-rank will be used to compare the two treatment arms with respect to progression-free survival (PFS). PFS is defined above. For patients without disease progression at the time of analysis, PFS will be censored at the time of the patient's last tumor assessment. The Kaplan-Meier approach will be used to estimate PFS distribution and the proportional hazards model will be used to assess the importance of treatment arm in predicting PFS.

The pharmacokinetic data will be obtained from PK samples described above (Section 7.2.1.).These PK parameters will be summarized using standard descriptive methods (means, standard deviations, medians and ranges).

The primary objective of the exploratory CTC aim is to assess intra- and inter-patient variability in AR and GR expression within CTCs from patients with progressive CRPC. The second objective of this aim is to explore the correlation between baseline AR and GR expression and PSA progression-free survival in patients treated with enzalutamide ± mifepristone. The median/range, mean/standard deviation of expression (relative fluorescence) for AR and GR will be summarized for each patient (intra-patient variability) and for the entire population (inter-patient variability). The components of variability will be estimated using analysis of variance. In addition percent nuclear/cytoplasmic/both cellular localization will be calculated for both receptors. Finally, Cox regression models for time to PSA progression will be fit using the expression of AR and GR as covariates incorporating treatment-by-marker interaction terms to determine whether they have prognostic and/or predictive value. Based on prior studies in this patient population ~50-60% of patients enrolled will have CTCs isolated and available for imaging. The percentage of patients with CTC's following 12 weeks of enzalutamide is unknown, but likely lower, and thus we will assume 30% will have evaluable CTC's at the time of randomization. This should provide ~25 patients (.3x82) for analyses.

12.4 Safety Evaluation and Analysis

Safety analysis will be conducted on the full analysis set. All AEs occurring on study will be listed by subject in a data listing. The type of adverse events (AEs), severity, and incidence rates will be presented in all treated subjects. Comparison of the frequency of adverse events (for example, percentage of patients with worst toxicity grade 2 or higher) will be conducted using chisquare or Fisher exact tests.

APPENDIX A

Performance Status Criteria

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

APPENDIX B

Sample Data Capture Forms

Patient Baseline Data

Diagnostic PSA: ☐
Use PSA value closest to the date of the initial local tumor therapy.

Clinical T stage: ☐ Surgery date: ☐
Clinical N stage: ☐ Surgical T stage: ☐
Biopsy date: ☐ Surgical N stage: ☐
Biopsy primary Gleason score: ☐ Surgical primary Gleason score: ☐
Biopsy secondary Gleason score: ☐ Surgical secondary Gleason score: ☐

☐ Capsule invasion ☐ Seminal vesical invasion ☐ Margin positive

Primary Tumor Therapy

Primary tumor therapy #: ☐

Primary tumor therapy type: ☐
Primary tumor therapy start: ☐
Primary tumor therapy end: ☐

Assoc hormone therapy? ○ Yes ○ No
Assoc hormone therapy type: ☐
Assoc hormone therapy start: ☐
Assoc hormone therapy stop: ☐

Androgen Ablation

INSTRUCTION

The use of an anti-androgen (e.g. bicalutamide) as part of combined androgen ablation should be recorded on the 'Other Hormonal Therapy' form.

Androgen ablation start: ☐

Androgen ablation administered for local disease should be entered under 'Tumor Therapy' form

Intermittant androgen ablation? ◯Yes ◯No

If yes, continuous androgen ablation start: ☐

Other Hormonal Therapy

INSTRUCTION

Each additional hormonal therapy should be listed separately. Anti-androgren therapy (e.g. bicalutamide) administered with androgen ablation should be listed here.

Other hormonal therapy #: ☐

Other hormone type: ☐

Therapy start: ☐

Therapy stop: ☐

Withdrawal response? ◯Yes ◯No

Treatment History

Form Name: Treatment History Form

Treatment Details

Therapy Code* * Select Therapy

Therapy Start Date

Approximate? ☐

If approximate, enter the exact month (if known) and the year Month: Year:

Therapy Start Date*

Therapy End Date

Approximate? ☐

If approximate, enter the exact month (if known) and the year Month: Year:

Therapy End Date

Agent Select Agent

Cumulative Dose Units

If applicable, site of therapy: ○ Primary ○ Other

Timing:

Palliative?

Best Response:

Resection:

Notes

Appendix C

PROSTATE-SPECIFIC ANTIGEN WORKING GROUP CRITERIA[49]

Progressive Disease after Androgen Deprivation Eligibility Criteria:

PSA evidence for progressive prostate cancer consists of a PSA level of at least 5 ng/ml which has risen on at least 2 successive occasions, at least 2 weeks apart. If the confirmatory PSA (#3 below) value is less (i.e., #3b) than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression.

Procedures for Assessing PSA Progression Post Study Treatment

PSA measurements will be taken on a monthly basis. PSA increases and decreases will be tracked in order to assess disease response.

PSA partial response is defined by at least a 50% decline from screening (baseline) PSA value. The declined must be confirmed by a second PSA value obtained 4 or more weeks later.

PSA progressive disease may be defined in both patients who have not shown a decrease in their PSA and those who have. For patients who have not shown a decrease, progressive disease is defined as an increase of 25% over the screening (baseline) PSA value and an increase in the absolute-value PSA level by at least 5ng/mL. This increase should be confirmed by a second value.

For those patients whose PSA have decreased but has not reached response criteria, progressive disease is defined as 25% increase over the nadir PSA value provided that the increase is at least 5ng/mL and is confirmed.

Duration of PSA Response

Duration of PSA Response is measured from the time when the PSA value first declines by at least 50% of the screening (baseline) and that was eventually confirmed by a second value. It is calculated until the time at which there is an increase of 50% of PSA nadir, provided the absolute increase is at least 5 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 50% above the nadir.

If the PSA never shows a 50% increase over the nadir value, then the patient will be censored at the last PSA measurement.

Time to Disease Progression

For patients who have achieved a $\geq$ 50% decrease from the screening (baseline) PSA, assessment of time to disease progression is when the PSA has increased 50% above the nadir and at a minimum of 5ng/mL. For patients without a PSA decrease of this magnitude or without a decrease, the time for progression is calculated at the time a 25% increase from screening (baseline) PSA has been achieved.

Appendix D

RESPONSE EVALUATION CRITERIA in SOLID TUMORS (RECIST) [45,46]

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions (non-lymph nodes) - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Lymph nodes*:* To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). Lymph nodes that are at least 10 mm but less than 15 mm in short axis may be pathologic and can be considered non-measurable/non-target lesions (that are not measured). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Evaluation: Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target 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

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to

document the objective progression even after discontinuation of treatment.

- 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 (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Appendix E

PHARMACOKINETIC SAMPLE COLLECTION SCHEME

A phase I/II trial of enzalutamide plus the glucocorticoid receptor antagonist mifepristone for patients with metastatic castration resistant prostate cancer (CRPC)

ENZALUTAMIDE PREDOSE PK SAMPLES TO BE COLLECTED AT:
Phase I: Day 29 (day 1 of concomitant dosing), Day 36, Day 43, Day 50, Day 57
Phase II: Day 1, Day 29 (month 2)

All PK samples prior to that day's enzalutamide administration

PATIENT NAME: PATIENT ID:

DATE:

No	SampleID	Date of Sample Draw	Actual Clock Time	Calculated Clock Time (with respect to dose)	Initials of Sample Collector	Comments
Phase I						
1	Pre-dose, **Day 29**					
2	**Day 36**					
3	**Day 43**					
4	**Day 50**					
5	**Day 57**					
PHASE II						
1	Pre-dose, **Day 1**					
2	Pre-dose, **Day 29**					

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