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TITLE: A Pilot Study of Dexamethasone Therapy Prior to Rechallenge with Enzalutamide in Men with Metastatic Castration-Resistant Prostate Cancer

Dex **EXT**ends **E**nza **R**esponse (The **DEXTER** Trial)

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SYNOPSIS

Title: A Pilot Study of Dexamethasone Therapy Prior to Rechallenge with Enzalutamide in Men with Metastatic Castration-Resistant Prostate Cancer

Phase of Study: Pilot

Objectives: To determine if treatment with dexamethasone (Dex) followed by enzalutamide (Enza) provides PSA and objective response, in patients who have previously had disease progression after Enza. Prior treatment with docetaxel is allowed but not required.

Study Design: The study is a single arm, open-label study wherein patients with metastatic castrate resistant prostate cancer (mCRPC) will be treated with Dex 2mg PO daily until PSA progression, then treated with Enza 160mg PO daily.

Treatment Plan: Patients will be prescribed Dex 2mg tablets to take daily by mouth with food. All patients will receive a minimum of two months of Dex. Following PSA or radiographic progression of disease, patients will be prescribed Enza 160 mg (40 mg tablets x4) by mouth daily. Dex will be tapered and stopped over a one week period. Enza will be continued for three months, after which time patients will be assessed for response. All patients will come off study after 3 months of Enza. Patients without evidence of response to Enza will be offered other standard of care therapy or additional clinical trial. Patients demonstrating Enza response will come off trial and be allowed to continue Enza as standard of care therapy. Blood Samples for assessment of AR and AR-V expression will be taken at baseline and at time of initiation of Enza.

Assessment of Response: Patients will have monthly PSA measurements. Disease will be assessed with bone scan and CT C/A/P at baseline, prior to initiation of Enza and at study conclusion. Progression will be defined by RECIST 1.1 and PCWG-2 criteria for soft tissue and bone metastasis, respectively. PSA response will be defined as 50% decrease in PSA from initiation of Enza. PSA progression will be defined by PCWG-2 criteria.

Rationale: The treatment options are very limited for patients with metastatic prostate cancer whose disease has become resistant to hormonal therapy and chemotherapy. Initially, the disease responds to drugs such as Enza, which block the androgen receptor. However, prostate cancer becomes resistant to this therapy through several mechanisms, including changes in the cancer's expression of the androgen receptor.

Dex and other glucocorticoids are an established treatment for prostate cancer; they can provide pain control, relief of other cancer-related symptoms like anorexia and fatigue, as well as have a direct anti-cancer effect. The receptor for glucocorticoids is expressed on many advanced prostate cancers, and recent work has theorized that there is interaction between the glucocorticoid receptor and androgen receptor pathways. It is thought that using a drug to affect one of the receptors may change the expression patterns and signaling of the other receptor.

Given that Dex has a known benefit, and that there is a likely interaction between the androgen

receptor and glucocorticoid receptor, this research aims to treat patients with medicines in sequence to attempt to achieve better responses to the therapies. By giving Dex and then transitioning to Enza at time of progression, patients may respond to Enza who may otherwise not have been responders to the therapy. In addition, the study will seek to identify whether there are characteristics of the cancer cells (specifically with regard to the androgen receptor expression and splicing) that predict response to the sequence of therapies.

Study Population: Men with metastatic castration-resistant prostate cancer with progression after prior treatment with Enza. Prior treatment with docetaxel is allowed but not required.

Number of Patients: 20

Treatment Sites: The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; The Akron General Medical Center, Akron, OH

Inclusion Criteria:

1. Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate
2. Patients must have metastatic disease radiographically documented by CT/MRI or bone scan; measurable disease is not necessary for inclusion.
3. Age ≥18 years.
4. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
5. Life expectancy of greater than 3 months in the opinion of the investigator
6. Patients must have acceptable organ and marrow function as defined below:
   - absolute neutrophil count ≥1,500/mcL
   - platelets ≥100,000/mcL
   - hemoglobin ≥ 8; transfusion is allowed
   - total bilirubin ≤1.5 × institutional upper limit of normal
   - AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
   - Creatinine clearance ≥30 by Cockcroft-Gault formula
7. Patients must have progression after prior treatment with Enza at any point in the disease course (pre- or post-chemotherapy).
8. Prior treatment with docetaxel is allowed but not required.
9. Prior treatment with other second line hormone therapy is allowed (e.g. flutamide, bicalutamide, nilutamide, ketoconazole, abiraterone, ARN-509). Patients must be off these therapies for at least 4 weeks prior to starting treatment
10. Prior treatment with Xofigo (^{223}Radium), Provenge, mitoxantrone and cabazitaxel is allowed.
11. Patients must have rising PSA on two successive measurements, at least 2 weeks apart.
12. Patient must be treated with continuous androgen ablative therapy (e.g. goserelin, leuprolide, triptorelin, or degarelix, if he has not had prior surgical castration) and have castrate levels of testosterone (<50 ng/dL or 1.7 nmol/L).
13. Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria:

1. Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier (persistent toxicity ≥ Grade 1) .
2. Patients who are receiving any other investigational agents.
3. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Dex or Enza.
4. Any use of systemic corticosteroids in the prior 4 weeks.
5. Uncontrolled diabetes mellitus
6. History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, and brain arteriovenous malformations.
7. Patients receiving any medications or substances that are inhibitors or inducers of CYP2C8 are ineligible (e.g. gemfibrozil, rifampin, trimethoprim, pioglitazone).
8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations or geographical condition that would limit compliance with study requirements.

Study Endpoints:

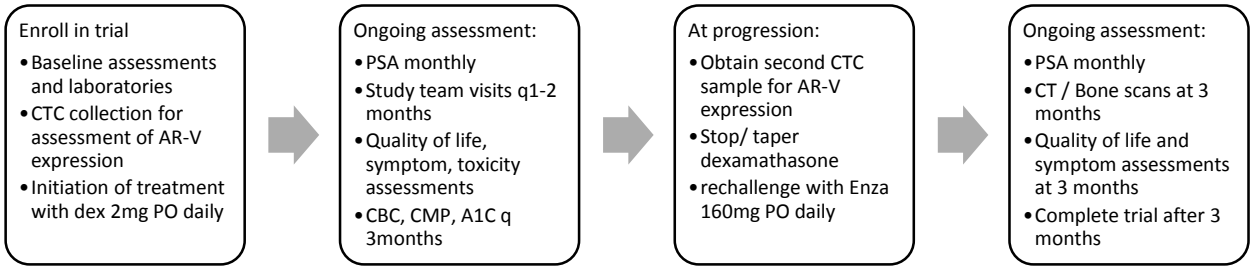
The primary endpoint:

- Response rate to Enza after treatment with Dex therapy. Responses will be determined by PSA criteria as defined by Prostate Cancer Working Group (PCWG2) criteria. The baseline will be defined as the initiation of Enza. The percentage of patients with >50% PSA response on rechallenged with Enza will be the primary endpoint.

The secondary endpoints/analysis:

- Objective response rate to Enza in patients with measurable disease on CT scan using RECIST criteria.
- Time to PSA progression (based upon PCWG2 criteria) for treatment with Dex.
- Effect of each treatment on quality of life as assessed by patient completion of validated instruments. Quality of life assessments will be taken at study entry, periodically while on Dex and Enza, at time of progression on Dex, and at study completion.
- PSA response rates to Dex for patients who are AR-V7 positive and AR-V7 negative, respectively, at study entry.
- Response rates to Enza for patients who are AR-V7 positive and AR-V7 negative, respectively, at study entry.
- Percentage of patients who are AR-V7 positive at study entry who are AR-V7 negative at time of initiation of Enza, and vice-versa.

Study Scheme:



Statistical Plan:
The primary endpoint will be the PSA response rate with the re-challenge of Enza following Dex, which is defined as the proportion of subjects with a ≥50% PSA decline from baseline and maintained for ≥4 weeks at any time-point after receiving Enza. The treatment regimen would be considered of insufficient activity for further study in this population if PSA response rate is 5% or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 25% PSA response rate. The sample size is calculated to detect an improved PSA response rate from 5% to 25%. A minimax Simon two-stage design is planned. A total of 13 patients will be entered in the first stage. If none of them show PSA response after Enza, the treatment regimen will be terminated and we will conclude the regimen is ineffective. If >=1 subjects has PSA response, then additional 7 patients will be studied. If a total of 2 or fewer subjects achieve PSA response in stage one and two combined, we consider this regimen ineffective. If a total of 3 or more respond, we conclude the regimen is promising and warrant further study. The trial could be terminated early also as soon as 3 PSA responses with the post-Dex Enza treatment are confirmed.

The maximum sample size will be 20. Patients who receive at least one dose of Dex will be evaluable for PSA response. This design provides 90% power to reject a 5% PSA response in favor of 25% response rate, with a type I error of 0.1. The chance of early stopping is 0.51 when the response rate is less than 5%.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the PSA response rate to Enza after treatment with Dex (Dex) therapy. Responses will be determined by PSA criteria as defined by Prostate Cancer Working Group (PCWG2) criteria. The baseline will be defined as the initiation of Enza. The percentage of patients with >50% PSA response will be the primary endpoint.

1.2 Secondary Objectives

1.2.1 Objective response rate to Enza in patients with measurable disease on CT scan using RECIST criteria.

1.2.2 Time to PSA progression (based upon PCWG2 criteria) for treatment with Dex.

1.2.3 Effect of each treatment on quality of life as assessed by patient completion of validated instruments (FACIT-Fatigue Scale, RANDSF-36) Quality of life assessments will be taken at study entry, during second on-treatment visits for both Dex and after 3 cycles of Enza.

1.2.4 PSA response rates to Dex for patients who are AR-V7 positive and AR-V7 negative, respectively, at study entry.

1.2.5 Response rates to Enza for patients who are AR-V7 positive and AR-V7 negative, respectively, at study entry.

1.2.6 Percentage of patients who are AR-V7 positive at study entry who are AR-V7 negative at time of initiation of Enza, or vice-versa.

2. BACKGROUND

2.1 Study Disease

Prostate cancer remains the second leading cause of cancer death among men in the United States. Initially, most patients with metastatic prostate cancer will respond to androgen-deprivation therapies. Inevitably, resistance to this therapy develops and patients experience progression of disease. Over the past several years, new treatments have been introduced that have prolonged the overall survival for patients with metastatic castration-resistant prostate cancer. After patients develop castration-resistant metastatic disease, options include treatment with secondary androgen synthesis suppression, anti-androgens, chemotherapy, radiotherapy, or immunotherapy. The basis for the several of these novel therapies is that prostate cancer remains dependent on androgens despite the development of a “castration-resistant” phenotype. As patients are treated with these novel hormonal therapies and chemotherapy, responses are transient. While the treatments have been shown to prolong survival in patients, all are non-

curative. Patients eventually are challenged with the available therapies and exhaust their treatment options.

A common sequence of treatment for a patient who develops castration-resistant disease, but remains minimally symptomatic from his disease, would to first be treated with abiraterone acetate and then Enza after progression. After a patient has progressed on these secondary hormonal therapies, chemotherapy with docetaxel is administered. Patients who then experience progression after treatment with both Enza and docetaxel are faced with more limited options. For those that are were not treated with abiraterone prior to Enza and docetaxel, it is known that response rates are reduced when compared with responses as first- or second-line therapy.[1] As patients are challenged with subsequent therapies (including Enza as third-line agent), responses become increasing limited both in terms of percentage of patients who respond and length of progression-free and overall survival.

There is a great need, not only for the development of novel therapeutics, but also for strategies to potentially re-sensitize the patients so that they again may respond to the established therapies.

2.2 Study Agents

2.2.1 Dexamethasone (Dex)

Dex is an FDA-approved corticosteroid that is used for a variety of clinical indications. Specifically for oncology patients, it is commonly used as an anti-emetic for prevention of chemotherapy-induced nausea and vomiting, as an anti-inflammatory agent to palliate pain due to cancer, and as an anti-cancer agent in hematologic malignancies, most commonly multiple myeloma. It is readily bioavailable after oral administration.

In the case of prostate cancer, glucocorticoids such as Dex have long been used in advanced cases.[2] Beyond the palliative effects of glucocorticoids for relief of pain, studies have repeatedly demonstrated PSA responses and clinical benefit. Clinical trials that use continuous low-dose Dex have reported >50% PSA response rates ranging from 32 – 62% (See Table 1).

While some portion of this effect may be attributable to adrenal suppression due to the exogenous glucocorticoids, responses are reported even in patients on potent suppressants of adrenal androgens. For example, Lorente et al. recently reported a small trial of patients with metastatic castration-resistant disease who were experiencing progression of disease while on abiraterone and prednisone.[3] By performing the intervention of changing prednisone 5mg twice daily to Dex 0.5mg while continuing abiraterone, 25% of patients (5 / 20) had a PSA response. Cell-based disease models of prostate cancer have demonstrated downstream effects from activation of the glucocorticoid receptor includes arresting cell growth in the G0 phase of the cell cycle via activation of TGF-b and suppression of NF-kb and IL6, among other functions.[4]

Table 1. Studies of PSA response to Dex and mifepristone in castrastion-resistant prostate cancer

Study	Treatment	N	**PSA Response (>50%)**
Storlie et al. 1995[5]	Dex 1.5-2.25mg daily	38	61%
Nishiyama et al. 1998[6]	Dex 0.5-1.5mg daily	7	57%
Nishimura et al. 2000[7]	Dex 0.5-1mg daily	37	62%
Saika et al. 2001[8]	Dex 1.5mg daily	19	26%
Morioka 2002[9]	Dex 1.5mg daily	27	59%
Venkitaraman et al. 2007[10]	Dex 0.5mg daily	102	49%
Attard et al. 2009[11]	Dex 0.5mg daily	30	32%
Komiya et al. 2010[12]	Dex 0.5-1.5mg daily	99	40%
Shamash et al. 2011[13]	Dex 2mg daily	133	50%
Study	GR antagonist treatment		
Taplin et al. 2008[14]	Mifepristone 200 mg/day	19	0%

It has been postulated that glucocorticoid receptor antagonists may reverse resistance in advanced disease,[15] yet the only clinical trial in metastatic prostate cancer using mifepristone, an anti-progestin that also antagonizes the glucocorticoid receptor, had a 0% response rate (Taplin study in Table 1), and mifepristone can offer no palliative effects. Studies examining use of glucocorticoid antagonists in combination with Enza are ongoing.

2.2.2 Enzalutamide (Xtandi)

Enza is a potent small molecule androgen receptor antagonist that was FDA-approved for treatment of patients with metastatic castration-resistant prostate cancer in 2012. The first indication for the drug's use was after treatment with docetaxel chemotherapy. In the 1199 patient phase III AFFIRM study, Scher et al. demonstrated increased survival for treatment with Enza versus placebo.[16] Patients who were treated with Enza had longer overall survival (18.4 vs 13.6 months), improved median progression free survival (radiographic: 8.3 vs. 2.9 months; PSA: 8.3 vs 3.0 months), and improved PSA response rates (54% vs 2%).

The FDA updated the approval for Enza to allow for its use before treatment with chemotherapy after the results from the PREVAIL study were released. In that phase III study, 1717 patients were randomized to receive Enza or placebo.[17] Those receiving Enza compared to placebo had a greater overall survival (32.4 vs 30.2 months), improved median progression free survival (radiographic: not reached vs 3.9 months; PSA: 11.2 vs 2.8), and improved PSA response rates (78% vs 3%).

Based upon these trials, Enza is increasingly being used as prostate cancer treatment prior to docetaxel therapy for castration-resistant disease.

2.3 Study Rationale

We now understand some of the resistance mechanisms of the cancer to hormonal therapies. Prostate cancer develops resistance as it adapts to the low androgen environment.[18] Yet, the prostate cancer cells remain dependent on the androgen receptor signaling pathway for growth.[19] This ongoing dependence on androgen signaling is the basis for clinical responses to further anti-androgen therapies even after development of castration-resistant disease.[20] These therapies act through either direct antagonism (i.e. bicalutamide or Enza) or indirectly through suppression of synthesis of non-prostate sources of androgen (i.e. ketoconazole or abiraterone). Several mechanisms have been proposed for resistance to these treatments, including overexpression of androgen receptor via increased transcription and gene amplification or expression of ligand-independent androgen receptor splice variants.[21]

In addition, the glucocorticoid receptor pathway is thought to interplay with the androgen signaling pathway since the glucocorticoid receptor is able to bind to androgen response elements.[4] Glucocorticoid receptor overexpression has been demonstrated as a common feature in heavily treated metastatic prostate cancer. In one series of 45 patients who underwent prostate biopsies after androgen deprivation therapy and / or chemotherapy, 25 (56%) co-expressed androgen receptor and glucocorticoid receptor while 5 (11%) expressed only the glucocorticoid receptor and exhibited loss of androgen receptor.[22] Two studies have examined glucocorticoid receptor expression at patients with metastatic prostate cancer, including in response to therapy on Enza.[15,23] Arora et al. observed up-regulation of glucocorticoid receptor in patients who were poor responders to Enza.[15]

It is postulated that there is interplay between the androgen receptor and glucocorticoid receptor, and that the glucocorticoid receptor expression and activation represents an additional resistance mechanism for Enza. Given our expanding knowledge of mechanisms of resistance to anti-androgen therapy, coupled with the prior observed benefits in a subset of patients of glucocorticoid therapy, we are studying treatment with glucocorticoid agonist therapy prior to rechallenge with Enza.

2.4 Study Hypothesis

The hypothesis of the study is that Dex-mediated down-regulation of the glucocorticoid receptor could reverse one resistance mechanism to Enza therapy and allow for renewed therapeutic sensitivity to Enza.

2.5 Correlative Studies Background

We will study expression of AR-V7 and its association with response to Dex and subsequent response to Enza.

The androgen receptor is a 110-kDa protein with several functional domains. Anti-androgen drugs such as Enza target the highly conserved C-terminal ligand binding domain. Transcripts that are produced by alternative splicing of the androgen receptor mRNA transcript can lead to protein products that lack the target for androgen receptor antagonists. While a total of 15

androgen receptor variants have been described, the most important variant is AR-V7. Our institution recently examined associations between AR-V7 status and PSA response rates and progression-free survival (PSA and radiographic), using multivariable cox regression analysis to determine the independent effect of AR-V7 expression on clinical outcomes.[24] In this study, 31 patients treated with Enza were enrolled, of which 12 (38.7%) were positive for expression of AR-V7. Patients that were positive for AR-V7 had a 0% PSA response rate to Enza compared to 52.6% for those that were negative. Other poorer outcomes similarly were associated with AR-V7 positivity including progression free survival (PSA: 1.4 vs 5.9 months; radiographic/clinical: 2.1 vs 6.1 months). The presence of AR-V7 in circulating tumor cells was found to be associated with poor response to Enza.

In preclinical cell-based prostate cancer assays performed in our laboratory, AR-V7 expressing cell-lines (VCaP and CWR22Rv1) can be growth inhibited by Dex exposure at high doses. Given that there is a previously demonstrated benefit to administration of Dex to patients with advanced disease, including PSA responses as discussed above, and there is preclinical data showing growth inhibition of cell lines, even expressing AR-V7, we will perform the correlative study to track AR-V7 expression with response Dex and Enza.

The methods have been previously described and published. Circulating tumor cells are enriched from peripheral blood collected from patients via a modified commercially available AdnaGen Prostate Cancer Select kit, wherein circulating prostate cancer cells are isolated with ligand-coated magnetic beads and lysed yielding mRNA. The cells are isolated using magnetic beads coated with 3 different antibodies (EPCAM and 2 proprietary antibodies). Quantitative RT-PCR is subsequently performed on the samples to evaluate mRNA expression of full length androgen receptor and AR-V7.

Technology to assay for changes in glucocorticoid receptor expression and glucocorticoid receptor splice variants in circulating tumor cells currently does not exist.

3. PATIENT SELECTION

Eligible patients will have with metastatic castration-resistance prostate cancer who have experienced disease progression after treatment with Enza. . Prior treatment with Enza pre or post-chemotherapy is required. Prior treatment with docetaxel is allowed but not required. Patients will have been treated with continuous ADT. Patients will continue on ADT with LHRH agonist (i.e. Zoladex, Trelstar, Eligard or Lupron) or LHRH antagonist (Degarelix) if not surgically castrated throughout the duration of the study to inhibit endogenous testosterone production. Patients will be treated in a single–arm study sequentially with Dex then Enza. A total of 13 patients will be recruited across 2 treatment sites in the initial phase of the trial, after which an additional 7 patients will be recruited if initial benchmarks for non-futility are met.

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed adenocarcinoma of the prostate

3.1.2 Patients must have metastatic disease radiographically documented by CT/MRI or bone scan; measurable disease is not necessary for inclusion.

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Life expectancy of greater than 3 months in the opinion of the investigator

3.1.6 Patients must have acceptable organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- hemoglobin ≥ 8; transfusion is allowed
- total bilirubin ≤1.5 × institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- Creatinine clearance ≥30 by Cockcroft-Gault formula

3.1.7 Patients must have progression after prior treatment with Enza at any point in the disease course (pre- or post-chemotherapy).

3.1.8 Prior treatment with docetaxel is allowed but not required.

3.1.9 Prior treatment with other second line hormone therapy is allowed (e.g. flutamide, bicalutamide, nilutamide, ketoconazole, abiraterone, ARN-509). Patients must be off these therapies for at least 4 weeks prior to starting treatment.

3.1.10 Prior treatment with Xofigo (^{223}Radium), Provenge, mitoxantrone and cabazitaxel is allowed.

3.1.11 Patients must have rising PSA on two successive measurements, at least 2 weeks apart.

3.1.12 Patient must be treated with continuous androgen ablative therapy (e.g. goserelin, leuprolide, triptorelin, or degarelix, if he has not had prior surgical castration) and have castrate levels of testosterone (<50 ng/dL or 1.7 nmol/L).

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

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier (persistent toxicity ≥ Grade 1) .

3.2.2 Patients who have received any other investigational agents within the last 4 weeks.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Dex or Enza.

3.2.4 Any use of systemic corticosteroids in the prior 4 weeks.

3.2.5 Uncontrolled diabetes mellitus

3.2.6 History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastates, and brain arteriovenous malformations.

3.2.7 Patients receiving any medications or substances that are inhibitors or inducers of CYP2C8 are ineligible (e.g. gemfibrozil, rifampin, trimethoprim, .pioglitazone). Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations or geographical condition that would limit compliance with study requirements.

3.3 Inclusion of Women and Minorities

This study is focused on prostate cancer, therefore is applicable to men only. Women and children will not be included on this study. Men from all ethnic and race groups are eligible for this study.

4. PATIENT REGISTRATION AND ENROLLMENT PLAN

4.1 Registration Procedures

4.1.1 All patients must sign a written informed consent form before study specific screening procedures are performed. Screening procedures to evaluate patient eligibility for the study will be conducted within 28 days prior to Cycle 1 Day 1. If the patient meets eligibility and screening requirements he will initiate on therapy. All required screening, treatment and post-treatment study procedures and assessments must be done within 7 days (+/-) of the specified study visit date.

4.1.2 Initial Registration Process: Eligible patients will be registered on study centrally at the Sidney Kimmel Comprehensive Cancer Center by the Lead Site Study Coordinator.

To register a patient, the following documents must be completed and emailed to the Lead Center Program Coordinator at Johns Hopkins, Yan Tian, at yantian@jhmi.edu:

- Signed/dated patient consent form
- Eligibility checklist
- Copies of the prostate cancer pathology report
- Copies of pre hormone therapy/chemotherapy or radiation therapy
- Screening labs
- CT and bone scan reports
- Other materials may also be sent if considered pertinent for confirming patient eligibility

The Lead Center (Johns Hopkins) will review the documents to confirm eligibility. To complete the registration process the Lead Center will:

- Assign a patient study number
- Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log
- Once eligibility is confirmed, all patients must commence treatment within 7 calendar days.

4.2 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Study Design

Patients with metastatic castration-resistant prostate cancer who are treated with continuous androgen-deprivation therapy and have progressed after prior treatment with Enza will be treated on a single-arm, open-label, multi-site study to determine the response rate of Enza after treatment with Dex. Prior treatment with docetaxel is allowed but not required. Secondary objectives will be radiographic response rates to Enza for patients with measurable disease, response rates to Dex, progression-free survival (PSA and radiographic) for treatment with Dex, AR-V7 positivity with correlation to response to Dex and Enza, and any change in AR-V7 positivity occurs as a result of treatment with Dex.

5.2 Study Treatments and Scheme

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2.1 Study Treatments

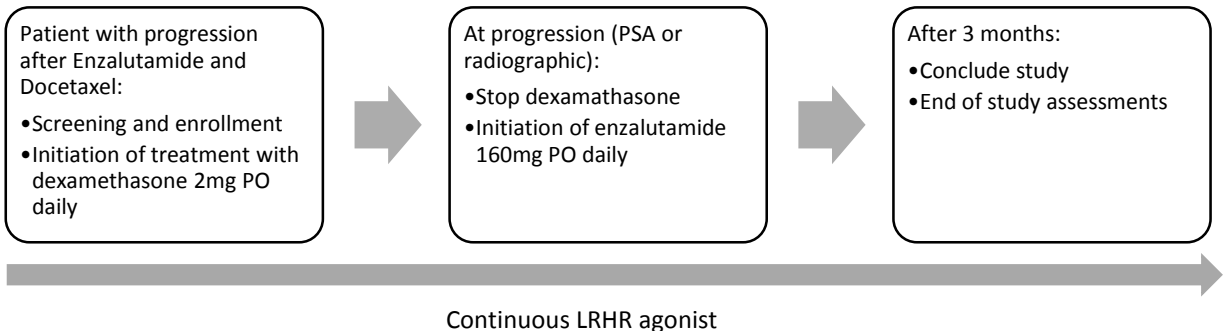
Patients will continue on ADT with LHRH agonist (i.e. Zoladex, Trelstar, Eligard or Lupron) or LHRH antagonist (Degarelix) if not surgically castrated throughout the duration of the study.

Patients will be prescribed Dex 2mg tablets to take once daily orally with food for 28 days/cycle continuously. Patients who have PSA progression after one cycle will continue on Dex for a second cycle. Patients with continued increase in PSA (if satisfies progression based upon PCWG2 definition) will begin Enza. Patients with declining PSA after 2 cycles of Dex will continue on Dex until PSA progression. Every 3 cycles patients will have repeat bone/CT scans to evaluate treatment response. Patients will remain on treatment with Dex until evidence of PSA progression (per the PCWG2 definition) or disease progression on CT scan (per RECIST criteria), or progressive bone metastatic disease (per the PCWG2 definition).

At time of progression, Dex will be stopped via a rapid taper over one week if patients were treated for >30 days. Patients will be instructed to take 1 mg Dex for 7days, then stop. However, ongoing use of corticosteroids will be allowed if indicated for bone pain or adrenal suppression.

Patients will then be prescribed Enza 40 mg tablets and instructed to take 4 tablets per day orally with or without food for 28 days/cycle continuously. Dose adjustments and delays will be allowed as per standard of care with treatment with Enza. Patients will have PSA checked monthly. All patients will remain on Enza for 3 cycles regardless of PSA response. At the end of 3 cycles of Enza all patients will come off study. Those patients with PSA or radiographic progression will come off study and be offered standard of care or another clinical trial. Those patients with PSA or radiographic response after 3 cycles will be offered to remain on Enza as standard of care therapy.

5.2.2 Treatment Scheme



5.3 Duration of Follow Up

Patients will be followed for 4 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.4 Criteria for Removal from Study

A patient may be removed from the study for a variety of reasons, including:

1. As defined by the protocol, evidence of disease progression based on radiographic progression or worsening symptoms while on Enza.
2. Unacceptable adverse events
3. Intercurrent illness that prevents further participation
4. Experiencing a treatment delay of longer than 2 weeks due to drug toxicity attributed to Dex. Patients who experience treatment delay while on Enza will remain on study as per protocol.
5. Patient refuses further treatment through the study and/or withdraws consent to participate
6. Need for "stress dose" glucocorticoids due to a life threatening medical condition.
7. Patients is noncompliant with respect to taking drugs, keeping appointments, or having tests required for the evaluation of drug safety and efficacy
8. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in this study in the judgment of the investigator
9. Under no circumstance will care of a withdrawn patient be adversely affected by a decision to withdraw or be withdrawn from the study.
10. Ongoing response after 12 cycles of dexamethasone.

5.5 Concomitant Therapy

The use of any concurrent medication from screening and while on study, prescription or over-the-counter, is to be recorded on the patient's CRF along with the reason the medication was taken. In addition, tobacco and alcohol use will be collected. Concurrent use of another clinical investigational drug or device while on study is prohibited. Supportive care medications are

permitted with their use following institutional guidelines. For patients who did not undergo orchiectomy, concurrent treatment with LHRH analogue is mandatory and must be recorded.

The following supportive care medications are considered permissible during the study.

- Conventional multivitamins, selenium and soy supplements
- Dutasteride or finasteride if being used to treat BPH and only if patients are on the medication for at least 3 months prior to Study Day 1
- Bisphosphonate and denosumab usage is allowed only if patients are on the medication for at least 3 months prior to Study Day 1
- Transfusions and hematopoietic growth factors per institutional practice guidelines

5.6 Prohibited Concomitant Medications

Concomitant therapy during the treatment phase of the study with any of the following listed is prohibited:

- Chemotherapy
- Immunotherapy
- Bicalutamide, nilutamide, flutamide
- Systemic ketoconazole (or other azole drugs such as fluconazole and itraconazole)
- Abiraterone acetate
- Prednisone or other glucocorticoids, except if indicated for bone pain or adrenal suppression at the time of tapering of dexamethasone
- Diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- Radiopharmaceuticals such as xofigo (223Ra), strontium (89Sr) or samarium (153Sm)
- Other experimental drugs or treatments

5.7 Dosing Delays / Modifications

During treatment with Dex, any interruption in treatment due to treatment toxicity for greater than 2 weeks will result in removal from study. No dose modifications are otherwise allowed.

During treatment with Enza, patients will remain on study for three months, regardless of dose intensity, treatment modifications or delays. While the standard dose of 160mg by mouth daily is initiated, the investigator may dose adjust for toxicities and interactions per standard protocols for Enza. These dose delays and modifications will be tracked and reported.

6. STUDY ACTIVITIES

6.1 Screening

All patients must sign a written informed consent form before study specific screening procedures are performed. Screening procedures to evaluate patient eligibility for the study will be conducted within 28 days prior to Cycle 1 Day 1. Prior to enrollment, patient must have documented insurance coverage demonstrating ability to pay for Enza. If the patient meets eligibility and screening requirements he will be initiated on study. All required screening, treatment and post-treatment study procedures and assessments must be done within 7 days (+/-) of the specified study visit date.

6.1.1 Screening studies (Screening assessments must begin within 28 days prior to Cycle 1, Day 1)

- Comprehensive medical history and physical exam, including height and weight, and medications.
- ECOG Performance status (PS)
- CBC (Complete blood count) with differential and platelet count
- CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, HCO3)
- Serum PSA
- Serum testosterone
- Hemoglobin A1C
- Staging imaging with CT if not already performed within 4 weeks and bone scintigraphy if not already performed within 8 weeks

6.2 Treatment Period

Patients will have continuous treatment of outpatient therapy. Patients who are not surgically castrated will continue to receive ongoing GnRH agonist or antagonist therapy as prior. Patients will be assessed every 1-3 cycles at a clinic visit.

6.2.1 Cycle 1 Day 1 visit:

- Physical exam, including weight, ECOG performance status, vital signs
- CBC (Complete blood count) with differential and platelet count (Not needed if performed within the last 2 weeks at screening)
- CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, HCO3) (Not needed if performed within the last 2 weeks at screening)
- Serum PSA
- Hemoglobin A1 (Not needed if performed within the last 2 weeks at screening)
- Blood drawn for to assess level of full length and androgen receptor variant in circulating tumor cells (CTC AR-V7)

- Quality of life surveys (FACIT-Fatigue Scale, RANDSF-36)

6.2.2 Ongoing assessments while on Dex

- Clinic visit after cycle 1 and then every third cycle for patients who are responding after 2 cycles.
    - Physical exam, including weight, ECOG performance status, vital signs
    - Assessment of toxicity
    - Quality of life surveys
- PSA every cycle
- CBC, Comprehensive Metabolic Panel, Hemoglobin A1c every 3 cycles
- CT scan and bone scan every 3 cycles
- Blood drawn for research testing to assess level of full length and variant androgen receptor at time of progression on Dex (at time of initiation of Enza).

6.2.3 Ongoing assessment while on Enza

- Clinic visit every cycle.
    - Physical exam, including weight, ECOG performance status, vital signs
    - Assessment of toxicity
    - Quality of life surveys
- PSA every cycle

6.3 End of Study

- Clinic visit
    - Physical exam, including weight, ECOG performance status, vital signs
    - Assessment of toxicity
    - Quality of life surveys
- PSA
- CBC, Comprehensive Metabolic Panel, Hemoglobin A1C
- CT scan and bone scan

6.4 Early Discontinuation

- Clinic visit
- If early discontinuation is due to an adverse event or toxicity of any of the study treatments, the patient should be followed until resolution of the adverse event/toxicity or at least one month, whichever is later.

7. SAFETY AND ADVERSE EVENTS

Safety will evaluated based on the incidence, severity, duration, causality, seriousness, and type of adverse events (AEs), and changes in the patient's physical examination, vital signs, and clinical laboratory results. Investigators will use the NCI CTCAE version 4.0 published 28 May 2009 to assess the severity of adverse events and toxicities (see Appendix B). All observed or volunteered adverse events regardless of treatment group or causal relationship to study drug will be recorded on the adverse event pages of the case report form.

8. PHARMACEUTICAL INFORMATION

8.1 Enza

8.1.1 Administration

Enza 160 mg daily (the current FDA approved dose), or four 40 mg capsules by mouth daily, will be administered. A 30 day supply will be prescribed at the beginning of each month. The study will not pay for supply of Enza.

8.1.2 Supply

Enza, marketed as Xtandi, comes in 40 mg capsules and are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with MDV. Enza capsules are available in bottles of 120 capsules (NDC 0469-0125-99).

8.1.3 Storage

Store Enza capsules at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

8.2 Dex

8.2.1 Administration

Dex 2 mg daily by mouth will be administered.

8.2.2 Supply

Dex, marketed as Decadron, comes in 2 mg tablets in generic formulations. A 90 day supply will be prescribed every 3rd cycle.

8.2.3 Storage

Store Dex tablets at 20° to 25°C (68° to 77°F). Protect from moisture.

9. STUDY CALENDAR

Baseline screening evaluations are to be conducted within 28 days prior to Cycle 1, Day 1. Cycles are 28 days. Return visits after initiation of therapy can be done be done within 7 days (+/-) of the specified study visit date.

	Screening[1]	Dex C1	Dex C2	Dex C3	Dex C4 -> ongoing	Progression (post Dex)	Enza C1	Enza C2	Enza C3 (Study Conclusion Visit)
Dex		X	X	X	X				
Enza							X	X	X
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X
Vital signs[8]	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X
CBC w/diff, plts[2]	X	X[4]		X	X[6]	X			X
Serum chemistry[3]	X	X[4]		X	X[6]	X			X
Hemoglobin A1C	X	X[4]		X	X[6]	X			X
PSA	X	X	X	X	X	X	X	X	X
Serum testosterone	X								
Adverse event evaluation		X	X	X	X	X	X	X	X
CT Scan (C/A/P)	X[9]			X[5]	X[6]	X			X
Bone Scan	X[9]				X[6]				X
QOL (FACIT, RAND SF-36)		X	X	X	X	X	X	X	X
AR-V7 CTC measurement		X[7]				X[7]			

1 Screening assessments must begin within 28 days prior to Cycle 1, Day 1
2 CBC (Complete blood count) with differential and platelet count
3 CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, HCO3)
4 Not needed if performed within the last 2 weeks at screening
5 CT scan post-cycle 2 on Dex if evidence of PSA progression
6 CBC, CMP, Hgb A1C and Radiologic Evaluation (CT scan, bone Scan) will be performed every 3 cycles while responding to Dex.
7 Blood Samples for assessment of AR and AR-V expression will be taken at baseline and at time of initiation of Enza.
8 Vital signs: Temperature, blood pressure and pulse rate will be measured.
9 Screening Radiologic Evaluation with CT of the chest, abdomen and pelvis within 4 weeks and bone scan within 8 weeks prior to C1 D1.

10. STUDY ASSESSMENTS

10.1 Assessing PSA response

PSA response and progression will be defined per PCWG2 criteria (Appendix E). PSA response is defined as a 50% decline in baseline PSA. PSA progression is defined as an elevation of 25% and an absolute increase of at least 2ng/dl over the nadir, confirmed by a second measurement at least 3 weeks apart. Patients will have PSA measurements taken every cycle of therapy.

10.2 Assessing response in measurable disease

In patients with measurable disease, tumor response will be evaluated using CT and bone scan. Patients will undergo screening CT scan and bone scan. CT scan is repeated after 2 cycles of Dex if evidence of PSA progression, otherwise CT and bone scan are performed every 3 months to determine disease response/progression to Dex or Enza. Progression for soft tissue lesions will be based on RECIST 1.1 criteria (Appendix C) and for bone lesions based on PCWG2 criteria.

10.2.1 AR-Variant Studies

To determine levels of full length AR and AR-V7, blood will be obtained from patients at screening and after 2 cycles of Dex therapy. Blood samples are collected and shipped to the Johns Hopkins Laboratory within 24 hrs according to standard procedure (Appendix D).

11. DATA REPORTING / REPORTING REQUIREMENTS

Data and safety monitoring will follow SKCCC Data and Safety Monitoring Plan. Additionally, scheduled meetings will take place monthly and will include the protocol principal investigator, research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.
During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.
This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The Clinical Research Office will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study."

11.1 Adverse Event Monitoring and Reporting

An Adverse Event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). The PI and/or the research nurse will monitor each patient closely for the development of adverse events and toxicities and record all such events. Patients will be evaluated for toxicity if they have received one dose of Dex. The timely reporting of adverse events (including toxic deaths) is required by the Food and Drug Administration (FDA).

11.2 Evaluating Adverse Events

The grade and severity of the event will be determined using the DCT/NCI Common Terminology Criteria, CTCAE v.4.0. Links to CTCAE version 4.0 can be found in Appendix B. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. Study staff must use one of the CTCAE criteria to define the event. Adverse events not included in the CTCAE v.4.0 should be reported and graded under the "Other" adverse event within the appropriate category and grade 1 to 5 according to the general grade definitions, mild, moderate, severe, life-threatening, fatal or disabling, as provided in the CTCAE.
The event will be determined to be expected or unexpected.
The event will be evaluated for relationship to the medical treatment or procedure. The Investigator should document his/her opinion of the relationship of the event to study medication as follows:

- Unrelated- The adverse event is clearly not related to the investigational agent(s).
- Unlikely- The adverse event is doubtfully related to the investigational agent(s).
- Possible-The adverse event may be related to the investigational agent(s).
- Probable-The adverse event is most likely related to the investigational agent(s).
- Definite- The adverse event is clearly related to the investigational agent(s).

Based on this information, a decision will be made whether an adverse event should be reported as an expedited report (Serious Adverse Event, section 3.0) in addition to the routinely reported clinical data. All expedited adverse event reports should be submitted to the JHM Institutional Review Board (IRB) and to the FDA.

11.3 Documenting Adverse Events

Each individual sign or symptom must be documented separately. All adverse events (both expected and unexpected) will be captured on the appropriate study-specific case report forms (CRFs). CRFs must be signed and dated by person conducting evaluation to be used as source documentation
The attribution of all adverse events must be verified by an investigator. Evaluation of laboratory toxicities may be documented directly on a printed laboratory report or CRF provided it is signed by the investigator. However, if an action was conducted due to this abnormality (e.g. RBC transfusion due to low Hgb) this would be recorded on the AE form also.

11.4 Serious Adverse Events

A SAE is any sign, symptom or medical condition that emerges during treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and is not a chronic condition that was part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory criteria:
• is fatal (i.e., results in death from any cause at any time) or life-threatening (i.e., the patient was in the view of the investigator, at immediate risk of death from the reaction as it occurred)
• required or prolonged hospitalization (see exclusions below)
• results in persistent or significant disability/incapacity
• constitutes a congenital anomaly or a birth defect
• is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
Events not considered to be serious adverse event are hospitalizations for the:
• Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
• Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
Any serious adverse event occurring in a patient from the first day of treatment and until 4 weeks after the last dose of treatment must be reported. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated. All serious adverse events must be followed to resolution (≤ 1 or baseline) or until considered stable or irreversible.

11.5 Expedited Reporting of Serious Adverse Events

Serious adverse events and protocol problems will be reported in compliance with JHM IRB guideline, "Organization Policy on Reports of Unanticipated Problems Involving Risks to Participants or Others" [Policy No. 103.6(b)] (most current version). A copy of this document is located at http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/103_6b.html

All deaths on study regardless of attribution must be reported by the Principal Investigator Dr. Denmeade and to the JHM IRB. In addition, all serious adverse events, regardless of causality to study drug and/or administration device, will be reported promptly to the Lead Study Coordinator within 24 hours of being made aware of the SAE. If the Lead Study Coordinator cannot be reached within 24 hours, SAE will be reported promptly to Dr. Denmeade (fax: 410-614-8397, e-mail: denmesa@jhmi.edu) within 24 hours of recognition of the serious adverse event.If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

Investigators will be notified by the Principal/Co-Principal Investigator and/or by the CRO of all SAEs that are unexpected (ie, not previously described in the Pharmaceutical Characterization of each drug in section 9 of this protocol), and definitely, probably, or possibly related to Dex or Enza. This notification will be in the form of an expedited safety report (ESR) that is to be faxed

to the investigators and the study coordinators within 48 hours. Upon receiving such notices, the site investigator must review and retain the notice and where required by local site regulations, the site investigator will submit the ESR to the site IRB. The site investigator and IRB will determine if the informed consent requires revision. The site investigator should also comply with the site IRB procedures for reporting any other safety information. Where required, submission of ESRs by the investigator to Health Authorities should be handled according to local regulations.

11.6 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the site IRB before implementation.

11.7 Informed consent:

Written informed consent will be obtained by a study investigator or study research nurse working on this study. An explanation of the nature of study, its purpose, procedures involved, expected duration, potential risks and benefits will be provided to each participant by the investigator or the research nurse. Each participant will be informed that participation in the study is voluntary and that he may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment. Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent before signing the consent form. Consent forms will be filed with the Clinical Research Office and copies stored securely with the study coordinator. No patient will enter the study before his informed consent has been obtained.

11.8 Multicenter Guidelines:

The Protocol Chair
The Protocol Chair, Samuel Denmeade, MD, is responsible for performing the following Tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the current IRB approved version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs) from all sites
- Reviewing all study data from all sites

Coordinating Center Responsibilities (SKCCC)
Coordinating Centers must:

- Verify that each participating institution has a Federal Wide Assurance (FWA) number.
- Confirm that IRB approval has been obtained at each participating site prior to their first patient registration
- Maintain copies of IRB approvals from each site
- Implement central patient registration

- Prepare all submitted data for review by the Protocol Chair (Samuel Denmeade, MD)
- Establish procedures for documentation, reporting, and submitting of adverse events to the Protocol Chair (Samuel Denmeade, MD) and all applicable parties
- Facilitate audits by securing selected source documents and research records from participating sites for audit, or by conducting audits at participating sites.

Participating Sites:
Participating sites are responsible for performing the following tasks:

- Follow the protocol as written and conduct the study within the guidelines of Good Clinical Practice.
- Collect and submit data, and report adverse events according to the schedule specified by the protocol.
- Register all patients with the Lead Center (SKCCC) by submitting patient registration forms, and signed informed consents promptly.
- Provide sufficient experienced clinical and administrative staff; as well as adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintain regulatory binders on site, and provide copies of all required documents to the Lead Center (SKCCC)

Case report forms
Case report forms will be generated by Staff at the Lead Site Coordinating Center at SKCCC for the collection of all study data. The data should be entered in eCRF in a timely manner, (within 2 weeks of the visit). All relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted via email to the Lead Study Coordinator, Yan Tian, at yantian@jhmi.edu. All patient names or other identifying information will be removed prior to being sent to the Coordinating Center (SKCCC) or non- redacted source documents can be sent via a password -protected/ secured document transfer based on each institution's guidelines.
Investigators will be responsible for ensuring that the eCRFs are kept up-to-date.
Authorized representatives of the Coordinating Center (SKCCC) may visit the satellite sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Source documents
Study personnel will record clinical data in each patient's source documents (ie, the patient's medical record). Source documentation will be made available to support the patient research record. Study monitors will review entries on the CRFs at regular intervals, comparing the content with source documents.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

We will conduct a single arm trial to determine if treatment with Dex followed by Enza provides PSA and objective response in patients who have previously had disease progression after Enza. Prior treatment with docetaxel is allowed but not required.

The primary endpoint will be the PSA response rate with the re-challenge of Enza following Dex, which is defined as the proportion of subjects with a ≥50% PSA decline from baseline level when starting Enza and maintained for ≥4 weeks at any time-point after receiving Enza.

The secondary endpoints will include objective response rate to Enza in patients with measurable disease on CT scan, time to PSA progression (based upon PCWG2 criteria) for treatment with Dex, quality of life assessment using FACIT-Fatigue Scale and RANDSF-36 surveys, and response rate with Dex and Enza by AR-V7 status at study entry.

12.2 Sample Size/Accrual Rate

The treatment regimen would be considered of insufficient activity for further study in these population if PSA response rate is 5% or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 25% PSA response rate. The sample size is calculated to detect an improved PSA response rate from 5% to 25%. A minimax Simon two-stage design is planned. A total of 13 patients will be entered in the first stage. If none of them show PSA response after Enza, the treatment regimen will be terminated and we will conclude the regimen is ineffective. If >=1 subjects has PSA response, then additional 7 patients will be studied. If a total of 2 or fewer subjects achieve PSA response in stage one and two combined, we consider this regimen ineffective. If a total of 3 or more respond, we conclude the regimen is promising and warrant further study. The trial could be terminated early also as soon as 3 PSA responses with the post-Dex Enza treatment are confirmed.
The maximum sample size will be 20. Patients who receive at least one dose of Dex will be evaluable for the primary endpoint of PSA response. Those who do not start Enza subsequent to Dex will be considered as non-responders in the analysis. This design provides 90% power to reject a 5% PSA response in favor of 25% response rate, with a type I error of 0.1. The chance of early stopping is 0.51 when the response rate is less than 5%.

12.3 Analysis Method

We will determine the PSA response rate with the re-challenge of Enza following Dex as the proportion of subjects with a ≥50% PSA decline from baseline level when starting Enza and maintained for ≥4 weeks at any time-point after receiving Enza, and its corresponding 95% confidence interval.

For the secondary endpoints, we will estimate objective response rate to Enza in patients with measurable disease on CT scan and its 95% confidence interval. Time to PSA progression and Radiographic Progression for treatment with Dex will be summarized using Kaplan-Meier

approach. Quality of life will be assessed via FACIT-Fatigue Scale and RANDSF-36 questionnaires. Summary statistics of the scores will be reported at baseline before starting Dex and each follow-up time during the treatment of Dex and Enza. Changes in quality of life scores over the course of the study will be computed and their significance will be evaluated by paired-sample t-tests. Response rate to Dex and Enza will also be reported by AR-V7 status at baseline of study entry.

12.4 Reporting and Exclusions

12.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Dex.

12.4.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate.

REFERENCES

1. Caffo O, De Giorgi U, Fratino L, et al. Clinical Outcomes of Castration-resistant Prostate Cancer Treatments Administered as Third or Fourth Line Following Failure of Docetaxel and Other Second-line Treatment: Results of an Italian Multicentre Study. *European urology* 2014.
2. Fakih M, Johnson CS, Trump DL. Glucocorticoids and treatment of prostate cancer: A preclinical and clinical review. *Urology* 2002; **60**(4): 553-61.
3. Lorente D, Weatherstone K, Omlin A, et al. Tumor responses after steroid switch of prednisolone (P) to dexamethasone (D) in castration-resistant prostate cancer (CRPC) patients (pts) on abiraterone acetate (AA). *Eur J Cancer* 2013; **49**: S703-S.
4. Kassi E, Moutsatsou P. Glucocorticoid receptor signaling and prostate cancer. *Cancer Lett* 2011; **302**(1): 1-10.
5. Storlie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, Richardson RL. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. *Cancer* 1995; **76**(1): 96-100.
6. Nishiyama T, Terunuma M. Hormone/antihormone withdrawal and dexamethasone for hormone-refractory prostate cancer. *International journal of urology : official journal of the Japanese Urological Association* 1998; **5**(1): 44-7.
7. Nishimura K, Nonomura N, Yasunaga Y, et al. Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. *Cancer* 2000; **89**(12): 2570-6.
8. Saika T, Kusaka N, Tsushima T, et al. Treatment of androgen-independent prostate cancer with dexamethasone: a prospective study in stage D2 patients. *International journal of urology : official journal of the Japanese Urological Association* 2001; **8**(6): 290-4.
9. Morioka M, Kobayashi T, Furukawa Y, et al. Prostate-specific antigen levels and prognosis in patients with hormone-refractory prostate cancer treated with low-dose dexamethasone. *Urologia internationalis* 2002; **68**(1): 10-5.
10. Venkitaraman R, Thomas K, Huddart RA, Horwich A, Dearnaley DP, Parker CC. Efficacy of low-dose dexamethasone in castration-refractory prostate cancer. *BJU international* 2008; **101**(4): 440-3.
11. Attard G, Reid AHM, A'Hern R, et al. Selective Inhibition of CYP17 With Abiraterone Acetate Is Highly Active in the Treatment of Castration-Resistant Prostate Cancer. *J Clin Oncol* 2009; **27**(23): 3742-8.
12. Komiya A, Shimbo M, Suzuki H, et al. Oral low-dose dexamethasone for androgen-independent prostate cancer patients. *Oncol Lett* 2010; **1**(1): 73-9.
13. Shamash J, Powles T, Sarker SJ, et al. A multi-centre randomised phase III trial of Dexamethasone vs Dexamethasone and diethylstilbestrol in castration-resistant prostate cancer: immediate vs deferred Diethylstilbestrol. *Brit J Cancer* 2011; **104**(4): 620-8.
14. Taplin ME, Manola J, Oh WK, et al. A phase II study of mifepristone (RU-486) in castration-resistant prostate cancer, with a correlative assessment of androgen-related hormones. *BJU international* 2008; **101**(9): 1084-9.
15. Arora VK, Schenkein E, Murali R, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell* 2013; **155**(6): 1309-22.
16. Scher HI, Fizazi K, Saad F, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. *New Engl J Med* 2012; **367**(13): 1187-97.
17. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in Metastatic Prostate

Cancer before Chemotherapy. *New Engl J Med* 2014; **371**(5): 424-33.
18. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nature medicine* 2004; **10**(1): 33-9.
19. Yuan X, Cai C, Chen S, Chen S, Yu Z, Balk SP. Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. *Oncogene* 2014; **33**(22): 2815-25.
20. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. *New Engl J Med* 2011; **364**(21): 1995-2005.
21. Hu R, Denmeade SR, Luo J. Molecular processes leading to aberrant androgen receptor signaling and castration resistance in prostate cancer. *Expert review of endocrinology & metabolism* 2010; **5**(5): 753-64.
22. Yemelyanov A, Bhalla P, Yang X, et al. Differential targeting of androgen and glucocorticoid receptors induces ER stress and apoptosis in prostate cancer cells: a novel therapeutic modality. *Cell cycle* 2012; **11**(2): 395-406.
23. Efstathiou E, Titus M, Wen S, et al. Molecular Characterization of Enzalutamide-treated Bone Metastatic Castration-resistant Prostate Cancer. *European urology* 2015; **67**(1): 53-60.
24. Antonarakis ES, Lu CX, Wang H, et al. AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer. *New Engl J Med* 2014; **371**(11): 1028-38.

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 NCI COMMON TOXICITY CRITERIA, VERSION 4.0

Version 4.0 of the NCI CTC, dated May 28, 2009, may be viewed and/or downloaded by accessing the following websites:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf

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

APPENDIX C RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

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 –

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.

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.

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.
Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
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 Criteria
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

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 over-estimating 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

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

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

The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response Review
For trials where response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of patients' files and radiological images is the best approach.

Reporting of Results
All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
All conclusions should be based on all eligible patients.
Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
The 95% confidence intervals should be provided.

APPENDIX D CIRCULATING TUMOR CELL (CTC) BLOOD COLLECTION AND SHIPPING

Blood draws should be scheduled on Monday-Thursday to allow overnight shipping and receiving on weekdays before the weekend.

Instructions for Collecting Blood Samples (Circulating Tumor Cells):

1. Collect Blood in 2 Becton Dickinson (BD) Vacutainer ACD Solution A tubes (BD ACD-A). Product # for the BD ACD-A tube is 364606.

2. Ensure that at least 8.5 mL of blood is drawn into each tube. Avoid low volume to minimize agitation during shipping.

3. Invert the tubes gently 180 degree and back 3-4 times.

4. Store samples until shipping at 4-8ºC in a refrigerator. Do not put on ice. Do not leave the samples O/N in a refrigerator.

Instructions for Shipping:

1. Activate the FEDEX cold box and place the tubes wrapped in bubble wraps (or inserted into plastic tube holders) snugly in the shipping box.

2. Ship the two tubes by FEDEX to the address below the same day of blood draw. Notify the recipient of the tracking number on the day of shipment by email.

The Fedex cold boxes are available at

http://images.fedex.com/us/healthcare/pdf/Cold_Shipping_Info_Sheet.pdf

Bubble wraps can be purchased from Staples or other shipping supply stores.
Plastic tube holders can be purchased at https://www.therapak.com/catalog/tube_mailers

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APPENDIX E PROSTATE CANCER WORKING GROUP 2 (PCWG2) CRITERIA

Pathology response criteria

When evaluating measurable soft-tissue target lesions, the RECIST definitions will apply. The first assessment must show an increase in the sum longest diameter (LD) of both preexisting and new lesions of ≥ 20% when compared with the smallest sum LD recorded since treatment started.
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 further (*e.g.* by aspirate/biopsy) before confirming the complete response status.

Evaluating non-target lesions

When assessing non-target lesions, the following RECIST definitions will apply:

Complete response:	Disappearance of all non-target lesions, and normalization of tumor marker levels.
Progressive disease:	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.
Stable disease:	Persistence of one or more non-target lesions and/or maintenance of tumor marker above the normal limits.

Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence. The investigator's determination of best overall response will be based on the response criteria and will not require confirmation scans. For defining disease progression, confirmation scans will only be required in the case where progression is seen on the first follow-up bone scan, but not if progression is shown on CT.
Patients with global deterioration of health status who require discontinuation of treatment without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuation of treatment.
The table below summarized the recommendations of the PCWG2 for measuring response/progression outcomes in phase II clinical trials of prostate cancer. Although these guidelines have been largely followed in the design of the present trial, this table should not be used as a substitute for the clinical protocol.

Prostate Cancer Clinical Trials Working Group (PCWG2) Outcome Measures

Variable	Control/Relieve/Eliminate	Prevent/Delay
PSA	Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot	**Decline from baseline:** Record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (*i.e.* a confirmed rising trend). Recording the duration of PSA decline of little value **No decline from baseline:** PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	Use RECIST with caveats Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot	Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later (particularly important for biologic therapies) Note that for some treatments, a lesion may first increase in size before it decreases
Bone	Record outcome as new lesions or no new lesions *First scheduled reassessment:* No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: No new lesions: continue therapy Additional new lesions: progression *Subsequent re-assessments:*	The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions The date of progression is the date of the first scan that shows the change

	No new lesions: continue New lesions: progression
Symptoms	Consider independently of other outcome measures Document pain and analgesia at entry with a lead in period and measure repeatedly at 3- to 4-week intervals Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy Ignore early changes (< 12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression Confirm response or progression of pain or HRQOL end points > 3 weeks later

Abbreviations: PSA, prostate-specific antigen; HRQOL, health-related quality of life