

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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**PHASE III TRIAL OF ENZALUTAMIDE (NSC # 766085) VERSUS ENZALUTAMIDE, ABIRATERONE AND PREDNISONE FOR CASTRATION RESISTANT METASTATIC PROSTATE CANCER**

*Investigational agent: Enzalutamide (IND exempt) supplied by Astellas and distributed by Biologics*

*ClinicalTrials.gov Identifier: NCT01949337*

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<b>To submit site registration documents:</b>	<b>For patient enrollments:</b>	<b>Submit study data directly to the Lead National Clinical Trial Network (NCTN) Group unless otherwise specified in the protocol:</b>
<p>Regulatory documentation must submitted to the CTSU via the Regulatory Submission Portal:</p> <p>Regulatory Submission Portal (Sign in at <a href="http://www.ctsu.org">www.ctsu.org</a>, and select the Regulatory Submission sub-tab under the Regulatory tab.)</p> <p>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [REDACTED] to receive further instruction and support.</p> <p>Contact the CTSU Regulatory Help Desk at [REDACTED] for regulatory assistance.</p>	<p>Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at [REDACTED].</p>	<p>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</p>
<p>The <b>study protocol and all related forms and documents</b> must be downloaded from the protocol-specific page of the CTSU Member website located at <a href="https://www.ctsu.org">https://www.ctsu.org</a>. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignments house in the CTSU RSS.</p>		
<p><b><u>For clinical questions</u></b> see the Protocol Contacts, Page 2.</p>		
<p><b><u>For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)</u></b> contact the CTSU Help Desk by phone or e-mail:  CTSU General Information Line – [REDACTED] All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
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**PHASE III TRIAL OF ENZALUTAMIDE (NSC # 766085) VERSUS ENZALUTAMIDE, ABIRATERONE AND PREDNISONE FOR CASTRATION RESISTANT METASTATIC PROSTATE CANCER**

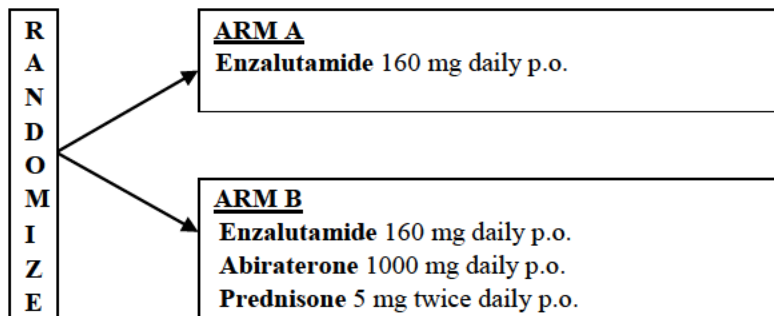
**ELIGIBILITY CRITERIA** (see [Section 4.0](#))

Progressive CRPC with histologically or cytologically confirmed adenocarcinoma of the prostate  
 Must have measurable or non-measurable disease (see [§4.2](#))  
 Patients must have progressive disease defined as one or more of the following that occurred while the patient was on ADT:  
 - PSA progression defined by a minimum of two rising PSA levels with an interval of at least 1 week between each determination. (see [§4.3.1](#))  
 - Soft tissue disease progression defined by [Section 13.2.3](#).  
 - Bone disease progression defined by PCWG2 (see [§4.3.3](#))

Required Initial Laboratory Values	
Granulocytes	≥ 1500/mcL
Platelet Count	≥ 100,000/mcL
Hemoglobin	≥ 9 g/dL
Creatinine	≤ 2.0 x ULN
Bilirubin	≤ 1.5 x ULN
AST or ALT	≤ 2.0 x ULN
Albumin	≥ 3 g/dL
Total Testosterone	≤ 50ng/dL (1.7 nmol/L)

No treatment with prior taxane-based chemotherapy for metastatic disease (see [§4.4.1](#))  
 No prior enzalutamide, abiraterone, or other novel antiandrogen or androgen synthesis inhibitor.  
 No treatment with any of the following for prostate cancer within 4 weeks prior to enrollment: Hormonal therapy, Chemotherapy, Biologic therapy, Investigational therapy, Immunotherapy (see [§4.4.3](#))  
 No use of herbal products that may decrease PSA levels within 4 weeks prior to enrollment  
 No chronic use of systemic steroids > 10 mg of prednisone/prednisolone per day within 4 weeks prior to enrollment  
 No prior use of ketoconazole for greater than 7 days.  
 No prior RT for the treatment of metastasis within four weeks prior to enrollment (see [§4.4.7](#))  
 Patients receiving bisphosphonates or denosumab must be on a stable dose for at least 4 weeks prior to enrollment  
 Patients must maintain ongoing androgen deprivation therapy with a GnRH analogue, antagonist, or bilateral orchiectomy (i.e., surgical or medical castration)  
 No known or suspected brain metastases  
 No planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery  
 No structurally unstable bone lesions suggesting impending fracture  
 No history of seizure or any condition that may increase the patient’s seizure risk (e.g., prior cortical stroke, significant brain trauma). No history of TIA within 12 months of enrollment.  
 No clinically significant cardiovascular disease including: MI within 6 months; uncontrolled angina within 3 months; CHF with NYHA class 3 or 4; history of clinically significant ventricular arrhythmias; history of Mobitz II second degree or third degree heart block without a permanent pacemaker in place; or bradycardia (<50 bpm)  
 No hypotension (systolic BP < 86 mmHg) or uncontrolled hypertension (systolic BP > 170 or diastolic BP > 105)  
 No GI disorder that negatively affects absorption  
 No major surgery within 4 weeks prior to enrollment  
 Age ≥ 18 years of age; ECOG Performance Status 0-1  
 Asymptomatic or mildly symptomatic from prostate cancer; i.e., BPI-SF score = 0-3

**Schema**  
**1 Cycle = 4 weeks**



\* See [Section 8.0](#) for complete treatment details.

Treatment is to continue until disease progression or unacceptable toxicity.

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## 1.0 INTRODUCTION

Prostate cancer is the second leading cause of cancer-related death in American men. In 2011, it is anticipated that 33,720 men will die of this disease, nearly all of them from bone metastases that are responsible for pain, spinal cord compression, bone fractures, and blood dyscrasias.<sup>1</sup>

Prostate cancer growth is dependent on androgens and androgen receptor activation. Depleting or blocking androgen action has been a mainstay of treatment for over 6 decades. Traditional hormonal therapies include GnRH analogues, anti-androgens, androgen synthesis inhibitors, and estrogens. Despite the early sensitivity of tumors to hormonal strategies, tumors that progress despite androgen deprivation generally represent a transition to the terminal form of the disease, for which limited treatment options are available. Docetaxel and prednisone prolong survival on the order of 2-3 months in such patients when compared to mitoxantrone and prednisone, and to this day, docetaxel is a standard first-line chemotherapy for patients with CRPC.<sup>2</sup> Cabazitaxel was recently shown to prolong survival for patients with progressive disease following docetaxel, but cabazitaxel has significant side effects, including a 5% toxic death rate due to neutropenic sepsis.<sup>3</sup> The vaccine sipuleucel-T also prolongs survival in CRPC, but patients with pain, visceral disease, or who use steroids are precluded from receiving treatment. Alternatives to chemotherapy and immune therapy for treatment of patients with CRPC are greatly needed.

Results of clinical trials and studies on the molecular profiles of progressing tumors have shown that the androgen receptor actively signals and induces tumor growth throughout the natural history of prostate cancer, even in patients with CRPC. The mechanisms by which the AR continues to actively signal in the castration-resistant state are multifold, but include upregulation of androgen biosynthesis, overexpression of androgen receptors, and mutation.<sup>4-6</sup> These pathways have provided a wide variety of potential therapeutic approaches targeting the AR axis, with two approaches (and two specific agents, abiraterone acetate [hereafter, “abiraterone”] and enzalutamide) shown to prolong life in these patients:

### 1.1 Targeting AR Activation:

The fact that the AR actively signals despite castrating therapy makes the AR-axis a prime therapeutic target. First-generation non-steroidal anti-androgens such as bicalutamide, nilutamide, and flutamide have long been part of the clinical armamentarium, and have been extensively explored in conjunction with castration or as second line therapy after patients have progressed through castration.<sup>7</sup> These relatively low-affinity ligands bind to the C-terminal portion of the AR ligand-binding domain, and function both by passively competing with patients' endogenous androgens, or by active mechanisms such as recruiting corepressor or inhibiting coactivator binding.<sup>8-10</sup> However, these agents have the capacity to function as agonists as well as antagonists via diverse mechanisms.

Novel antiandrogens, however, have been developed to overcome these mixed agonist/antagonist properties. Enzalutamide is an oral agent that appears to bind to the AR with five to eight times the affinity of bicalutamide and two to three times the affinity of DHT. The anti-tumor effects of enzalutamide appear to be mediated by inhibiting AR nuclear translocation, DNA binding, and coactivator peptide recruitment. In contrast to bicalutamide, enzalutamide exhibits no agonistic properties and does not recruit coactivator proteins. In a human prostate cancer cell line that overexpresses AR, termed VCaP, enzalutamide suppressed growth and induced apoptosis, even when bicalutamide did not. Similarly, in vivo tumor suppression was evidenced in castration-resistant AR-overexpressing LNCaP/AR xenograft models, revealing tumor reduction. Mice treated with enzalutamide had prolonged time to tumor progression relative to bicalutamide as well.<sup>6</sup>



Enzalutamide was tested in a recently reported phase III trial involving patients with CRPC who had received prior treatment with docetaxel. The primary endpoint of the study was overall survival, with secondary endpoints of time to progression, radiographic progression-free survival, and post-treatment PSA and circulating tumor cell alterations. The study was positive, demonstrating that the patients who had received enzalutamide enjoyed a risk of death 37% lower than those who received a placebo (HR 0.63, 13.6 vs. 18.4 months median survival for each arm), conferring a 4.8 month overall survival advantage.<sup>11</sup> The FDA has approved enzalutamide for patients with metastatic CRPC who have received prior docetaxel.

## 1.2 Targeting Androgen Synthesis

Although androgen deprivation therapy (using luteinizing hormone-releasing hormone agonists or antagonists) decreases total serum testosterone levels by approximately 95%, this intervention primarily inhibits gonadal androgen synthesis and does not affect extra-gonadal androgens. It is now established that, in CRPC, there is continuous production of androgens by the adrenal glands as well as the prostate cancer itself.<sup>12,13</sup> Moreover, in the castrate state, intraprostatic concentrations of testosterone and dihydrotestosterone remain sufficient to stimulate AR. The main mechanisms by which CRPC is able to overcome low circulating androgen levels are local conversion of adrenal androgens (e.g. androstenedione) to testosterone, and de novo intratumoral synthesis of androgens through increased expression of steroidogenic enzymes such as cytochrome P450 17 (CYP17).<sup>14,15</sup>

Abiraterone is a selective inhibitor of androgen biosynthesis that potently blocks CYP17, which is critical to testosterone synthesis by the adrenals, testes, and within the prostate tumor.<sup>16,17</sup> In phase 1-2 trials, treatment with abiraterone resulted in significant antitumor activity in both taxane naïve and taxane treated patients.<sup>18,19</sup> The most common adverse events were associated with increased mineralocorticoid levels, including hypokalemia, fluid retention, and hypertension; these were largely abrogated by co-administering low-dose glucocorticoids. Two phase III trials have been undertaken with abiraterone. In Cougar 301, patients with progressive CRPC following treatment with docetaxel were treated with abiraterone and prednisone or prednisone alone. A total of 1195 men were randomized, with a primary endpoint of overall survival. Men who received the abiraterone enjoyed a significant reduction in the risk of death, with a hazard ratio of 0.65, associated with a median survival of 14.8 months as opposed to 10.9 months ( $P < 0.001$ ).<sup>20</sup> As a result, abiraterone and prednisone was approved by the FDA for patients with CRPC who have progressed despite prior treatment with docetaxel in April 2011.

In Cougar 302, 1088 patients with CRPC who were chemotherapy naïve were randomized to abiraterone and prednisone vs. prednisone alone. On March 8, 2012 the independent data monitoring committee (IDMC) unblinded the study as a planned interim analysis. Patients who received a placebo and prednisone had a median survival of 27.2 months. Patients who received abiraterone and prednisone had a 25% risk reduction for dying (median OS not reached, HR 0.75 (0.61-0.93),  $p = 0.0097$ ). The FDA has expanded the indication of abiraterone to include patients with CRPC who are chemotherapy naïve.<sup>21</sup>

## 1.3 Rationale for combining abiraterone/prednisone and enzalutamide in the chemotherapy naïve population

Both abiraterone/prednisone and enzalutamide prolong survival in patients with CRPC that have progressed despite prior treatment with docetaxel. These drugs work by two distinct mechanisms, both of which reduce AR signaling: the former, by reducing the primary ligand of the AR and the latter, by inhibiting AR activation. Both drugs prolong survival in patients who have been treated with prior docetaxel.

The rationale for this trial is predicated on the demonstrated pathway addiction in CRPC, and the hypothesis that inhibition of the involved pathway (AR signaling) with two separate

inhibitors that act at different levels of the pathway will be more effective than single inhibition at one level. In addition, there is no *a priori* reason to believe that the impact of these agents would be different in patients who have or have not been treated with prior docetaxel, and it is generally recognized that the testing of these agents in the post-docetaxel setting was largely a regulatory construct. Support for the value of anti-AR strategies in the chemotherapy naïve population has been evidenced by an interim analysis of Cougar 302, in which patients with CRPC who were chemotherapy naïve received abiraterone/prednisone vs. prednisone alone. The interim analysis suggested an improved PFS and OS in favor of abiraterone/prednisone.<sup>21</sup> Based on these data, the IDMC recommended unblinding of this study in order to allow the men receiving placebo to receive abiraterone/prednisone. The labeled indication of abiraterone has been expanded to include chemotherapy naïve patients. Abiraterone is now commonly used in chemotherapy naïve patients as part of routine practice. A phase III study of enzalutamide in the pre-chemotherapy population has completed accrual, although results are not anticipated to be available for several years. Furthermore, most investigators generally agree that the most rational place for the use of these agents is in the pre-chemotherapy setting. Certainly, the capacity to delay the use of chemotherapy would be considered to represent significant clinical benefit by patients and physicians alike.

The combination of abiraterone/prednisone and enzalutamide has not yet been tested. However, both drugs have highly favorable safety profiles individually, and historically do not have overlapping toxicity profiles that should preclude therapy. The immediacy of the need to develop combinatorial strategies of these agents is strong enough, and the likelihood of seeing toxicity marginal enough, to justify up-front testing in the phase III setting in order to preserve precious patient resources. However, a safety early stopping rule is built into the study.

#### **1.4 Rationale for the correlative studies**

Correlative studies embedded in this trial will provide insight into sub-populations within the broader CRPC population that might optimally benefit from one of the specific treatment strategies being tested, as well as begin to define the processes at play at the time of developing resistance to these therapies. These studies will involve analyses of circulating androgen levels, microRNA, RNA profiles, and serum angiokine levels that will identify independent prognostic biomarkers of overall survival and progression-free survival in men with metastatic CRPC, as well as potentially predict for the benefit associated with combined enzalutamide/abiraterone therapy over single agent sequential therapy. In addition, in collaboration with the Alliance Imaging Committee, the study contains a correlative study of bone imaging by Tc-99 or sodium fluoride F-18 (NaF) PET/CT imaging techniques, to develop optimized prognostic and predictive imaging biomarkers for castration-resistant metastatic disease. The background and details, rationale, and statistical plan are found in an Appendix to this document.

#### **1.5 Rationale for the conduct of this trial in the cooperative groups**

From a clinical standpoint, the question of whether enzalutamide vs. enzalutamide and abiraterone/prednisone should be the treatment of choice as first-line therapy for CRPC is one that the cooperative groups can well answer. Both drugs are highly sought by patients at academic centers and in the community, especially before chemotherapy.

The clinical and scientific importance of this study has also been recognized by the other cooperative groups beyond the Alliance. SWOG and ECOG will be participants in the study, and the study has been endorsed by NCIC as well.

#### **1.6 Registration fatigue/uniscale assessment**

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that

baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. (50)

## 2.0 OBJECTIVES

### 2.1 Primary Objective

To compare the overall survival of patients with progressive metastatic CRPC treated with either a) enzalutamide only or b) enzalutamide with abiraterone and prednisone

### 2.2 Secondary Objectives

- 2.2.1 To assess the grade 3 or higher toxicity profile and compare safety by treatment arm
- 2.2.2 To assess and compare post-treatment PSA declines by treatment arm
- 2.2.3 To compare radiographic progression free survival defined by Prostate Cancer Working Group 2 (PCWG2), and objective response rate, by treatment arm.
- 2.2.4 To test for rPFS treatment interaction in predicting overall survival.
- 2.2.5 To assess pre- and post-treatment measures of tumor burden and bone activity using NaF PET/CT and Tc MDP bone scintigraphy and correlate these measures with overall survival.
- 2.2.6 To develop and validate prognostic and predictive models of overall survival that include baseline clinical and molecular markers.

#### Correlative Study objectives

- 2.2.7 To determine whether pre-treatment serum adrenal androgen (SA) levels are prognostic factors of overall survival and to test whether SA levels are predictive factors of overall survival.
- 2.2.8 To evaluate specific pre-treatment RNA levels as prognostic factors for OS, including the 6- and 9-gene signatures, the CTC RNA profile, and the circulating tumor stem cell RNA profile.
- 2.2.9 To evaluate the predictive ability of specific pre-treatment and post-treatment RNA, levels on the OS and PFS.
- 2.2.10 To evaluate specific pre-treatment microRNA levels as prognostic factors for OS.
- 2.2.11 To test whether the microRNA are predictive factors for overall survival.
- 2.2.12 To determine whether pre-treatment angiokine levels are prognostic factors for OS and PFS.
- 2.2.13 To test whether pretreatment angiokine levels are predictive factors for OS and PFS and to assess whether post-treatment angiokine levels are predictive factors for OS and PFS.
- 2.2.14 To investigate a drug by *CYP17A1* interaction with respect to overall survival.
- 2.2.15 To assay candidate variants and loci hypothesized to be associated with other clinical phenotypes (e.g., progression-free survival or toxicity) or other eQTLs.

- 2.2.16** To identify specific SNPs and/or copy number variations that are associated with the response to and toxicity associated with therapy
- 2.2.17** To define the effect of abiraterone on reducing enzalutamide metabolic clearance (i.e. increasing enzalutamide AUC) when the drugs are used in combination.
- 2.2.18** To define the exposure (AUC) toxicity and exposure (AUC) anti-tumor effect relationship, including biomarkers for enzalutamide alone and enzalutamide combined with abiraterone in prostate cancer patients.
- 2.2.19** To develop a population pharmacokinetic model for enzalutamide alone and enzalutamide combined with abiraterone taking account of relevant intrinsic and extrinsic factors.
- 2.2.20** To determine the inpatient and outpatient variability of abiraterone exposure (AUC) in prostate cancer patients receiving abiraterone when combined with enzalutamide
- 2.2.21** To determine the intra-patient and inter-patient variability of enzalutamide exposure (AUC) in prostate cancer patients receiving enzalutamide alone and abiraterone plus enzalutamide.

### **3.0 ON-STUDY GUIDELINES**

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness, which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers or non-invasive bladder cancers or other in-situ or non-invasive malignancies. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for  $\geq 3$  years.
- Estimated life expectancy of  $< 6$  months.

#### **In addition,**

- Men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
- Abiraterone is an inhibitor of CYP2D6. Avoid coadministration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). Abiraterone is a substrate of CYP3A4. Avoid strong inhibitors and inducers of CYP3A4.
- Co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) should also be avoided. In addition, concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine,

ergotamine, fentanyl, pimozone, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided.

- Because of the potential risk of seizures (0.9% of patients in the randomized trial) with enzalutamide, the use of drugs that may lower seizure threshold potential should be minimized if possible.
- Patients should have the ability to swallow study medications.

#### 4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Alliance Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

##### 4.1 Documentation of Disease:

Progressive castration-resistant metastatic prostate cancer with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.

##### 4.2 Patients must have Measurable or Non-measurable Disease

###### 4.2.1 Measurable Disease

For **visceral or extra-nodal lesions** to be considered measurable, they must be  $\geq 10$  mm in one dimension, using spiral CT.

For **lymph nodes** to be considered measurable (i.e., target or evaluable lesions), they must be  $\geq 20$  mm in at least one dimension, using spiral CT.

###### 4.2.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm with spiral CT scan) and truly non-measurable lesions.

Lesions that are considered non-measurable include bone lesions (only).

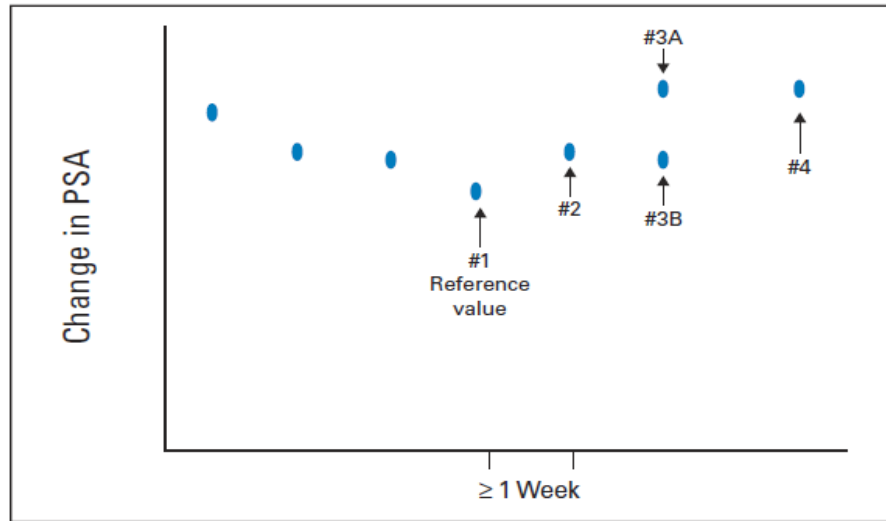
###### 4.2.3 Patients with node only disease (i.e. no presence of visceral, extra nodal lesions or bone lesions) must have node(s) that measure $\geq 15$ mm in short axis.

##### 4.3 Progressive disease

Patients must have progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy. For patients enrolling on the basis of soft tissue or bone progression, the baseline scan must show progression relative to a comparison scan. If the comparison scan is not available, the baseline scan report must reference the previous scan to document progression.

###### 4.3.1 PSA progression defined by a minimum of two rising PSA levels with an interval of $\geq 1$ week between each determination. Patients who received an anti-androgen must have progression documented by a minimum of two rising PSA levels with an interval of $\geq 1$ week between each determination such that at least the second of these rises is $\geq 4$ weeks

since last flutamide, bicalutamide or nilutamide. The PSA value at the screening should be  $\geq 2 \mu\text{g/L}$  (2 ng/mL)



**Fig 2.** Eligibility based on prostate-specific antigen (PSA) changes. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 2 ng/mL or higher, a reduction from the 5 ng/mL specified in the previous guidelines.<sup>1</sup> Reprinted from Bubley et al.<sup>1</sup>

(from PCWG2)<sup>22</sup>

#### 4.3.2 Soft tissue disease progression defined by Section 13.2.3.

#### 4.3.3 Bone disease progression defined by PCWG2 with two or more new lesions on bone scan

### 4.4 Prior Treatment

#### 4.4.1 No treatment with prior taxane-based chemotherapy for metastatic disease.

- i. Patients who received prior taxane-based chemotherapy as neoadjuvant or adjuvant therapy for local disease, or who received taxane-based therapy in the PSA clinical (non-metastatic) state is allowable provided that the total duration of exposure was six cycles or less and chemotherapy was completed more than 6 months prior to registration.
- ii. Taxane-based chemotherapy that was aborted due to allergic reactions or intolerance to chemotherapy and therefore received 1 cycle of prior therapy is allowable.

#### 4.4.2 No prior enzalutamide, abiraterone, or other novel antiandrogen or androgen synthesis inhibitor

#### 4.4.3 No treatment with any of the following for prostate cancer within 4 weeks prior to enrollment:

- Hormonal therapy (e.g., AR antagonists, 5 alpha reductase inhibitors, estrogens).  
Note: Treatment with bicalutamide and nilutamide within 4 weeks prior to enrollment is not allowed. Treatment with flutamide within 4 weeks prior to enrollment is

not allowed. Treatment with all other GnRH analogues or antagonists is allowed.

- Chemotherapy
- Biologic therapy
- Investigational therapy
- Immunotherapy

- 4.4.4 No use of herbal products that may decrease PSA levels within 4 weeks prior to enrollment
- 4.4.5 No chronic use of systemic steroids greater than the equivalent of 10 mg of prednisone/prednisolone per day within 4 weeks prior to enrollment
- 4.4.6 No prior use of ketoconazole for greater than 7 days.
- 4.4.7 No prior radiation therapy or radionuclide therapy for the treatment of metastasis within four weeks prior to enrollment
- 4.4.8 Patients receiving bisphosphonate therapy or denosumab must have been on a stable dose for at least 4 weeks prior to enrollment
- 4.4.9 Patients must maintain ongoing androgen deprivation therapy with a GnRH analogue, antagonist, or bilateral orchiectomy (i.e., surgical or medical castration)

#### 4.5 Patient History

- 4.5.1 No known or suspected brain metastases (NOTE: patients with treated epidural disease are allowed)
- 4.5.2 No planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery
- 4.5.3 No structurally unstable bone lesions suggesting impending fracture
- 4.5.4 No history of seizure or any condition that may increase the patient's seizure risk (e.g., prior cortical stroke, significant brain trauma). No history of TIA within 12 months of enrollment.
- 4.5.5 No clinically significant cardiovascular disease including:
  - MI within 6 months
  - Uncontrolled angina within 3 months
  - CHF with NYHA class 3 or 4, or patients with NYHA class 3 or 4 in the past, unless a screening echo or MUGA performed within three months demonstrates an EF>45%
  - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes)
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place
  - Hypotension (systolic BP <86 mmHg) or bradycardia (<50 bpm) at screening
  - Uncontrolled hypertension (systolic BP >170 mmHg or diastolic BP >105 mmHg at screening)
- 4.5.6 No GI disorder that negatively affects absorption
- 4.5.7 No major surgery within 4 weeks prior to enrollment

**4.6 Age and performance status****4.6.1** Age  $\geq$  18 years of age**4.6.2** ECOG Performance Status 0-1**4.6.3** Asymptomatic or mildly symptomatic from prostate cancer.

A score of 0-1 on BPI-SF Question #3 (worst pain in last 24 hours) will be considered asymptomatic, and a score of 2-3 will be considered mildly symptomatic (see Appendix II)

**4.7 Required Initial Laboratory Values:**

Granulocytes	$\geq$ 1,500/ $\mu$ L
Platelet count	$\geq$ 100,000/ $\mu$ L
Hemoglobin	$\geq$ 9 g/dL
Creatinine	$\leq$ 2 x upper limits of normal (ULN)
Bilirubin	$\leq$ 1.5 x ULN
AST or ALT	$\leq$ 2 x ULN
Albumin	$\geq$ 3 g/dl
Total Testosterone	$\leq$ 50 ng/dL (1.7 nmol/L)

**5.0 REGISTRATION/RANDOMIZATION AND STRATIFICATION****5.1 CTEP Investigator Registration Procedures**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at [REDACTED]. For questions, please contact the CTEP Investigator Registration Help Desk by email at [REDACTED].

**5.2 CTEP Associate Registration Procedures / CTEP-IAM Account**

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.



Additional information can be found on the CTEP website at [REDACTED] For questions, please contact the *CTEP Associate Registration Help Desk* by email at [REDACTED]

### 5.3 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

**IRB Approval:** Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

#### 5.3.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A031201 protocol page located on the CTSU members' website. Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol # A031201
- Click on the Site Registration Documents link

#### 5.3.2 Requirements for A031201 Site Registration

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

#### 5.3.3 Submitting Regulatory Requirements

Submit completed forms along with a copy of your IRB Approval (for sites not participating via the NCI CIRB), Model Informed Consent (for sites not participating via the NCI CIRB), and any other required documentation (see above) to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

[REDACTED]  
Phone: [REDACTED]  
Fax: [REDACTED]  
E-mail: [REDACTED] (for regulatory document submission only)

### 5.3.4 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

Click on the Regulatory tab at the top of your screen

Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

### 5.4 Patient Registration Requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

- **Determination of Risk Using Halabi Nomogram:** patients will be categorized into one of three risk groups using the following link:

<https://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html>

See Appendix IV for instructions for using the nomogram.

Variables for the nomogram include: ECOG performance status (0, 1, or 2), baseline PSA, LDH, alkaline phosphatase, albumin, hemoglobin, opioid analgesic use, presence of bone metastases, presence of lymph node metastasis, and presence of visceral metastases (defined as lung, liver, or adrenal).

- **Assurance of drug provision:** As abiraterone will be used on-label, patients and their treating physicians will secure their own supply of the drug. Arrangements with third party insurers, private or public, should be made prior to registration/randomization. The patient must be willing to pay for the balance of the drug's cost that is not covered by third party insurance.

### 5.5 Patient Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>. A user manual is available for OPEN users on the CTSU site.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.

All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at [REDACTED]

## 5.6 Registration to Correlative and Companion Studies

### 5.6.1 Registration to Substudies described in Section 10

There are four substudies within Alliance A031201:

- Alliance A031201-IM1: Imaging science studies in Alliance A031201 ([Section 10.1](#))
- Alliance A031201-ST1: Correlative science studies in Alliance A031201 (Sections [10.2](#) – [10.6](#))
- Alliance A031201-PP1: Pharmacogenomic studies in Alliance A031201 ([Section 10.7](#))
- Alliance A031201-PP2: Pharmacokinetic studies in Alliance A031201 ([Section 10.8](#))

#### **Mandatory companion study:**

Participation in **A031201-IM1** is required for all patients enrolled to A031201. All patients enrolled to this treatment trial will be registered to this companion at the same that he is registered to A031201.

#### **Optional companion studies:**

The three additional substudies **A031201-ST1**, **A031201-PP1**, **A031201-PP2**, must be offered to all patients enrolled on Alliance A031201 (although patients may opt not to participate).

If a patient answers “yes” to “I agree that my specimens may be used for the research studies described above.” (Question #1) in the Model Consent, he has consented to participate in the biomarker, pharmacogenomic, and pharmacokinetic studies described in Sections [10.2](#) through [10.8](#). The patient should be registered to Alliance A031201-ST1, A031201-PP1, and A031201-PP2 at the same time that he is registered to the treatment trial (Alliance A031201) and samples submitted per [Section 6.2](#).

## 5.7 Stratification Factors and Treatment Assignments

Randomization will be stratified on:

- 1) Prior chemotherapy:

Yes, No

- 2) Risk Group determined using the nomogram developed by Halabi, et al<sup>55</sup> (See Section 5.1.2):

Low, Intermediate, High

## 6.0 DATA AND SPECIMEN SUBMISSION

### 6.1 Data submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and the appropriate Rave role (Rave CRA, Read-

Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at [www.ctsu.org/RAVE/](http://www.ctsu.org/RAVE/) or by contacting the CTSU Help Desk at [REDACTED] or by e-mail a [REDACTED].

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

All radiology reports must be uploaded via the Supporting Documentation page associated with the current cycle folder in Medidata Rave® (See [Section 7.0](#)).

**6.1.2 Adverse event data collection and reporting**, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. [Section 16.0](#) provides information about expedited reporting. Institutions that do not submit adverse event forms in a timely manner may be denied future registrations to this study.

**Common Terminology Criteria for Adverse Events:** This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and adverse event reporting. However, beginning April 1, 2018, CTCAE v5.0 must be used for expedited adverse event reporting via CTEP-AERS.

### 6.1.3 Routine Adverse Event Reporting

Solicited Adverse Events: The following adverse events are considered “expected” and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

- Fatigue (see CTCAE General disorders and administration site conditions)
  - Diarrhea
  - Vomiting
  - Edema limbs (see CTCAE General disorders and administration site conditions)
  - Arthralgia
  - Myalgia
  - Headache (see CTCAE Nervous system disorders)
  - Insomnia (see CTCAE Psychiatric disorders)
  - Hot flashes (see CTCAE Vascular disorders)
  - Hypertension
  - Dyspnea
  - Hyperglycemia (see CTCAE Metabolism and nutrition disorders)
  - Hypokalemia (see CTCAE Metabolism and nutrition disorders)
  - Alanine aminotransferase increased (see CTCAE Investigations)
  - Aspartate aminotransferase increased (see CTCAE Investigations)
  - Blood bilirubin increased (see CTCAE Investigations)
- Constipation
- Dyspepsia
- Bone pain
- Seizure
- Cough

## 6.2 Specimen Submission for Correlative Studies:

All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A031201, although patient participation is optional. Biomarker, pharmacogenetic, and pharmacokinetic studies will be performed. Rationale and methods for the scientific components of this study is described in [Section 10.0](#).

Specimen	Baseline#	Cycle 3 Day 1*	At Progression*	Ship:
Serum (red top) <sup>1</sup>	2 x 6 mL	2 x 6 mL	2 x 6 mL	On dry ice to OSU
Whole blood PAXgene <sup>2</sup>	2 x 2.5 mL	2 x 2.5 mL	2 x 2.5 mL	On dry ice to OSU
Plasma EDTA (lavender) <sup>3</sup>	8-10 mL	8-10 mL	8-10 mL	On dry ice to OSU
and Citrate (light blue) <sup>3</sup>	8-10 mL	8-10 mL	8-10 mL	
Whole Blood EDTA (lavender) <sup>4</sup>	10 mL			On same day on cold pack to OSU
Specimen	Baseline	Prior to Cycles 2 through 6		Ship:
Plasma (lavender) <sup>5</sup>	4 mL	4 mL		On dry ice to University of Pittsburgh

\* (+/- 7-day window is permitted)

# To be collected after registration but prior to the initiation of protocol treatment

1. To be used for measurement of adrenal androgen levels and circulating miRNA described in [Sections 10.2](#) and [10.4](#).
2. To be used for circulating RNA studies described in [Section 10.3](#).
3. To be used for circulating angiokine studies described in [Section 10.5](#).
4. To be used for pharmacogenetic studies described in [Section 10.7](#).
5. To be used for pharmacokinetic studies described in [Section 10.8](#).

### 6.2.1 Specimen registration and tracking

**Use of the alliance biospecimen management system (BioMS) is mandatory and all specimens must be logged and shipped via this system.**

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [REDACTED] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors or for assistance in using the application or questions or problems related to specific specimen logging, please call [REDACTED].

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.



**Instructions for the collection of samples are included below.** Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

**Labeling:** Blood specimens must be labeled with the following information (using a Sharpie or Cryopen):

1. Alliance study number (i.e., A031201)
2. Alliance patient ID number
3. Patient's initials
4. Date and time of specimen procurement
5. Sample type (i.e. whole blood, plasma-EDTA, plasma-citrate, serum)

**Shipment** on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays.

All specimens except pharmacokinetic samples should be sent to the following address:



#### 6.2.2 Specimen Submission for Correlative Studies

**Serum (for adrenal androgens and circulating miRNA, Sections [10.2](#) and [10.4](#)):** Collect approximately 12 mL peripheral venous blood divided into 2 plain red top vacutainer tubes. Gently invert approximately 5 times to mix clot activator with blood. Let blood clot for 30 minutes. Observe a dense clot. Centrifuge at approximately 2500 x g for 15 minutes at room temperature. After centrifugation, place 0.5 mL aliquots of serum into 1.8 mL cryovials\*. Store the vials at -70°C or colder until shipping. Samples should be shipped within 30 days on dry ice by overnight express courier. If a -70° or colder freezer is not available, temporary storage at -20° C prior to shipment is acceptable for up to 72 hours.

\* Cryovial Choices: Some examples of acceptable 1.8 mL cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

**Whole blood in PAXgene tubes (for circulating RNA, [Section 10.3](#)):** Collect approximately 2.5 mL peripheral venous blood into each of two 5 mL PAXgene tubes. Gently invert the tube 5-10 times and freeze (within 1 hour of collection) in a -70° Celsius or colder freezer. Once frozen, the PAXgene tubes should be shipped within 30 days of collection on dry ice by overnight express courier. If a -70° C or colder freezer is not available, temporary storage at -20° C prior to shipment is acceptable for up to 72 hours.

\* PAXgene tubes: PAXgene tubes must be obtained from the Alliance Biorepository at Ohio State University (see “Protocol Resources” on the second cover page of protocol for contact information). No starter kits are available for this study. Once a patient has been registered to the study, institutions requesting tubes must provide the patient study ID number to the Alliance Biorepository at Ohio State University, and kits will be shipped to the site upon confirmation of registration.

**Plasma (for angiokine SearchLight assay, [Section 10.5](#)):**

1. For EDTA plasma, draw 8-10 mL of peripheral blood into a lavender top vacutainer(s) (K2EDTA anticoagulant). Invert approximately 8 times and centrifuge for 15 minutes at approximately 2500 x g at room temperature. Remove plasma and transfer to a clean tube (plastic or glass). Repeat centrifuge at 2500 x g for 15 minutes at room temperature. Aliquot 1 mL plasma into each 1.8 mL cryovial.\*
  2. For citrate plasma, draw 8-10 mL of peripheral venous blood into a light blue top vacutainer(s) (3.2% sodium citrate anticoagulant). Invert approximately 8 times and centrifuge for 15 minutes at approximately 2500 x g at room temperature. Remove plasma and transfer to a clean tube (plastic or glass). Repeat centrifuge at 2500 x g for 15 minutes at room temperature. Aliquot 1 mL plasma into each 1.8 mL cryovial.\*
  3. Label and freeze cryovials at  $-70^{\circ}\text{C}$  or colder. Samples should be shipped within 30 days on dry ice by overnight shipping service to the appropriate Alliance biorepository. If  $-70^{\circ}\text{C}$  or colder freezer is not available, temporary storage at  $-20^{\circ}\text{C}$  prior to shipment is acceptable for up to 72 hours.
- \* Cryovial Choices: Some examples of acceptable 1.8 mL cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

**Whole blood (for pharmacogenomics sample, [Section 10.7](#)):** Collect 10 mL of venous blood in lavender top (EDTA anticoagulant) vacutainer tube(s). The tubes should be inverted approximately 10 times to mix the EDTA. Refrigerate sample until shipping. The sample should be placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn on a cold pack by overnight courier service to the appropriate Alliance biorepository.

Note: It is strongly encouraged that samples for pharmacogenomics testing are collected prior to the initiation of study treatment. However, sample collection and registration to a pharmacogenetic sub-study may take place within 60 days of registration to the treatment trial if permitted by the study protocol.

**Plasma (for pharmacokinetics sample, [Section 10.8](#)):**

Prior to Cycles 2 through 6, patients enrolled to the pharmacokinetics substudy will be asked to complete a questionnaire form (see [Appendix II](#)), which will provide information about the prior 48-hour dosing of enzalutamide or abiraterone and enzalutamide (details of dose, time and relationship to food).

Collect 4 mL of blood in lavender top tubes at baseline, prior to first enzalutamide or abiraterone/enzalutamide dose, and at each subsequent clinic visit through Cycle 6 while on study treatment.

Samples should be collected into 4 mL lavender top vacutainers (BD367862). Fill the tubes completely. Mix immediately by gently inverting the tube at least 8 to 10 times to ensure thorough mixing of the anticoagulant and then tubes should be placed on ice for less than 30 minutes during the sampling period. Samples should be centrifuged at  $4^{\circ}\text{C}$  at 2,000 g x for 10 minutes to separate plasma from red cells. Aliquot 1 mL plasma into 1.8 mL cryovials that are clearly labeled with appropriate patient ID, the date of the sample, and the time of sample acquisition. Sample timing should be indicated as actual time the sample was obtained. Sample handling from collection to storage should not exceed 60 minutes.



Care must be taken to ensure that labels are carefully attached to the tubes and are not likely to fall off when frozen or during shipping.

Samples should be stored at or below  $-70^{\circ}\text{C}$  and shipped to the PK lab as soon as possible after collection. If a  $-70^{\circ}\text{C}$  freezer is not available please store at  $-20^{\circ}\text{C}$  and ship within a few days of collection. Please place samples in a plastic bag, surrounded by paper toweling prior to placing in dry ice, so that the plastic tubes containing plasma will not crack. Samples should be shipped Monday-Thursday for next day delivery. **DO NOT SHIP SAMPLES ON A FRIDAY OR A WEEKEND OR BEFORE A HOLIDAY.**

Send samples to the following address:



### 6.3 Imaging credentialing and submission

#### 6.3.1 Institutional credentialing procedures for imaging

Prior to the enrollment of patients, institutions that have not previously been credentialed for any other Alliance trials must be credentialed to participate in the trial by the Alliance Imaging Core Laboratory (ICL) at The Ohio State University Medical Center. If the site has previously been credentialed by the ICL to participate in imaging studies, the ICL will provide a brief A031201 protocol refresher prior to the site enrolling patients for this trial.

Institutions should contact the Alliance ICL directly to complete credentialing or a refresher for A031201. See [Section 6.3.3](#) for the Alliance ICL contact information.

#### 6.3.2 Individual training for bone scan interpretation

Bone imaging will be interpreted in accordance with modified PCWG2 progression criteria, as described in [Section 13](#). For the purposes of determining progression, the following individuals will perform bone imaging interpretation (in order of preference), and will undergo training in correctly identifying bone scan progression using modified PCWG2 criteria. These individuals are:

- A **reference radiologist** designated by the participating institution or;
- The **local PI or designated local investigator** or;
- In the absence of either a reference radiologist or local investigator, the **Alliance Imaging Core** will perform the interpretation.

Prior to the first scan interpretation (week 9 / end of cycle 2) for the first patient enrolled, institutions should contact the Alliance ICL directly to provide the name and contact information for the reference radiologist or local PI/designated local investigator that will perform the scan interpretation. Alternatively, institutions may choose to indicate the need for the Alliance ICL to perform the interpretation.

Upon contacting the Alliance ICL, institutions will be provided with instructions for either completing the training for bone scan interpretation using modified PCWG2 criteria or for the submission of scans to allow the Alliance ICL to perform the interpretation. See [Section 6.3.3](#) for the Alliance ICL contact information.

To complete the training, the PI/designated local investigator is to view a webinar recording describing the PCWG2 interpretation procedures. This recording is available as a download on the A031201 study page on the Alliance and CTSU web sites. Additionally, this recording is available for download to all sites that are able to submit data electronically through the Alliance Imaging Core Lab. Upon completion, the Alliance Imaging Core Lab should be notified via e-mail to [REDACTED] by the PI/designated local investigator that they have viewed the webinar. A pdf of the presentation slides seen in the webinar can be provided for reference. This pdf is also available on the A031201 study page on the Alliance and CTSU web sites.

If the designated reference radiologist, local PI or designated local investigator who is to interpret the bone scans of patients on study changes, the institution must inform the Alliance ICL. Additionally, the Alliance ICL should be provided notification that the PCWG2 webinar training has been completed for the new bone scan interpreter designee.

Sites that lack the resources for either a designated reference radiologist or a local investigator at their institution to interpret bone scans using PCWG2 criteria and that require the Alliance Imaging Core Lab to perform the interpretation need to inform the Alliance ICL of this arrangement prior to the enrollment of their first patient. The request and rationale for the request should be sent via e-mail to [REDACTED] for review and consideration.

For sites that utilize the Alliance Imaging Core Lab to interpret the bone scans, the ICL will provide results to the site using the PCWG Bone Scan Assessment Tool Guide found in [Appendix V](#). Once received, the site is responsible for entering the results and data into Medidata Rave.

### 6.3.3 Scan submission instructions

All MRI, CT, PET/CT and planar/SPECT images will be collected digitally for archival and retrospective central review purposes. The following images will be collected digitally:

- **Baseline (within 28 days prior to patient registration)**  
Chest x-ray, PA & Lateral, or Chest CT (MRI), Bone Imaging (Tc-99m MDP planar/SPECT or NaF PET/CT) and CT or MRI abd/pelvis
- **Treatment monitoring (every 8 weeks for the first 6 cycles, then every 12 weeks, and at end of treatment)**  
Chest x-ray, PA & Lateral, or Chest CT (MRI), Bone Imaging (Tc-99m MDP planar/SPECT or NaF PET/CT) and CT or MRI abd/pelvis
- **Post-treatment follow-up (every 12 weeks after discontinuation of treatment until progression or 5 years after randomization)**  
Chest x-ray, PA & Lateral, or Chest CT (MRI), Bone Imaging (Tc-99m MDP planar/SPECT or NaF PET/CT) and CT or MRI abd/pelvis

The complete CT, MRI, PET/CT and/or planar/SPECT scan data in digital **DICOM** format will be submitted to Alliance Imaging Core Laboratory within **5 business** days once the image acquisition is completed at site. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the Imaging Core Laboratory. The Imaging Core Lab will notify site and Alliance A031201 imaging committee within **2 business days** of the data receipt, and then, within **3 business days** following the data receipt, of the quality check report.

Sites need to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g., 112136) and protocol number (e.g., A031201), respectively.

For baseline staging, treatment monitoring and follow-up CT, MRI, PET/CT and/or planar/SPECT scans, imaging data must be submitted to the Imaging Core Lab via Web-based data transfer, FTP data transfer approaches or CD/DVD Shipment is acceptable. Electronic data submission is the preferred method and the Alliance Imaging Core Lab can assist sites in accomplishing electronic data submission.

**Web-based data transfer:**

Any PCs with Internet access can be used to upload images to the Imaging Core Lab via this approach. The standard Web access information will be provided separately through the specific trial e-mail [REDACTED], per the request by participating sites before their first data submission.

**FTP Transfer:**

Any FTP software can be used to upload images to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail [REDACTED] per the request by participating sites before their first data submission.

**Shipment/Mail Transfer:**

If the electronic data transfer approaches cannot be achieved at sites, the de-identified digital images in DICOM format can be burned to CDs, labeled with Alliance A031201 patient ID (e.g., 112136), date of study and study period (e.g., baseline, DX, post therapy) and mailed to the Imaging Core Lab at:

[REDACTED]

Send an e-mail notification to inform the Imaging Core Lab at [REDACTED] of the imaging data submission once the data transfer is completed. Any questions or problems about the data transfer to the Imaging Core Lab, call the Core Lab IT group at [REDACTED] for help.

**7.0 REQUIRED DATA****Pre-Study Testing Intervals**

To be completed within 16 DAYS before registration:

- All laboratory studies, history and physical

To be completed within 28 DAYS before registration:

- ECG, Chest CT or x-ray (CT is preferred); CT/MRI chest/abd/pelvis; and Bone imaging. PET scans are not allowed for tumor measurement.

Evaluations may be performed +/- 3 days except for imaging and correlative substudies, for which a 7-day window is allowable.

	Prior to Registration	Day 1 of each cycle and at end of treatment*	Post Treatment Follow up**
<b>Tests &amp; Observations</b>			
History and Physical Exam	X	X	X
Pulse, Blood Pressure	X	X	
Height, Weight	X		
Performance Status	X	X	
12-Lead ECG	X		
BPI (Question 3 only)	X		
Fatigue/Uniscale Assessment	C		
Drug Toxicity Assessment		X	
Opioid Analgesic Use Assessment	X		
<b>Laboratory Studies</b>			
CBC, Differential, Platelets	X	X	
Creatinine, NA, K, glucose	X	X	
PSA	A	A	
Total Testosterone	X		
AST/ALT, Alk. Phos., Bili	X	X (1)	
Albumin, LDH	X		
<b>Staging</b>			
Chest CT (preferred); or Chest x-ray, PA & Lateral	B	B (2)	X
Bone Imaging***	X	X (2)	X
CT or MRI abd/pelvis†	X	X (2)	X
<b>Correlative studies‡</b>			
Blood samples	See <a href="#">Section 6.2</a> .		

\* Pre-registration labs and H&P may be used for day 1 of cycle 1 tests if obtained within 16 days prior to day 1 of Cycle 1. For subsequent cycles labs may be obtained within 48 hours prior to day of treatment.

\*\* Imaging must be repeated after the end of protocol treatment unless performed within the prior 4 weeks; then every 12 weeks until progression or until 5 years after randomization, whichever comes first. After progression, follow the patient for survival and second malignancy every 6 months until death or 5 years after registration.

\*\*\* Patients can obtain either sodium fluoride (NaF) PET/CT imaging or Tc-99 bone scintigraphy at the discretion of the treating physician. However, all follow-up bone imaging must be the same modality as the baseline modality.

† Either diagnostic CT or MRI, however, follow-up studies should be the same modality as the baseline study. CT scan obtained as part of the NaF PET/CT does not substitute for the CT done for staging/response evaluation unless it is performed using standard diagnostic algorithms.

‡ For patients who consent to each substudy.

A PSA is to be collected at pre-registration, Day 1 of each cycle, and at end of treatment. Additional pre-registration PSA values are required for those patients demonstrating PSA progression for eligibility. The last PSA value recorded prior to the initiation of treatment will be considered the baseline PSA for this study. PSA will not be used for documenting progressive disease. No patient is to end treatment on the basis of a change in PSA only.

B Chest imaging is required at baseline and at all restaging time points. Patients who have received a chest CT (or MRI) need not have a chest x-ray. Patients who have findings suspicious for metastatic disease on a chest x-ray at baseline should have a confirmatory CT of the chest at baseline. Patients who have findings suspicious for metastatic disease at baseline on CT should have CT scans at follow-up tumor assessments.

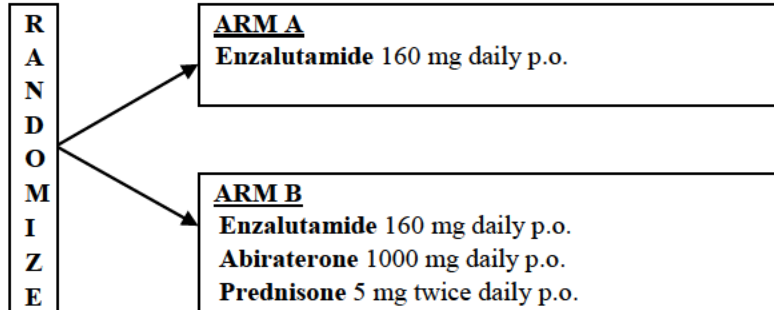
C Within 21 days prior to registration (see [Appendix I](#)).

1 Arm A: Day 1 of each cycle. Arm B: For patients receiving abiraterone, every two weeks for the first 3 months of treatment, then Day 1 of each cycle.

2 Tumor assessments will be performed every 8 weeks for the first 6 cycles (i.e., weeks 9, 17, 25 +/- 1 week), then every 12 weeks (i.e., weeks 37, 48, etc. +/- 1 week) from the initiation of treatment regardless of treatment interruptions or holds until the PCWG2 or RECIST criteria in [Section 13.0](#) have been met. Note: Upload all radiology reports via the Supporting Documentation page associated with the current cycle folder in Medidata Rave® (See [Section 6.1](#)).

## 8.0 TREATMENT PLAN

Protocol treatment is to begin within 14 days of registration. Questions regarding treatment should be directed to the Alliance Study Chair.



Protocol therapy will consist of 28-day cycles.

Treatment will continue until confirmed disease progression (see [Sections 13.2.3](#) and [13.3.3](#)) or unacceptable toxicity. PSA will NOT be used to define disease progression.

Patients randomized to both arms of the study are to be asked to maintain a medication log and bring it with them to clinic visits.

### 8.1 Arm A: Enzalutamide alone

Patients randomized to Arm A will be instructed to take 160 mg **enzalutamide** by mouth daily. Study drug doses should be taken as close as possible to the same time each day. Study patients will take four capsules of enzalutamide once daily. Enzalutamide can be taken with or without food.

If dosing is missed on one day for any reason, double dosing should NOT occur the following day.

**Inducers and inhibitors of CYP enzymes:** In vitro drug metabolism studies suggest that enzalutamide may have the potential to induce CYP3A4 and to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; therefore, concomitant medications that are substrates of any of these enzymes should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, because the possibility of drug-drug interactions cannot be fully excluded. Since the metabolism of enzalutamide is not known, caution should be taken for the concomitant use of strong inhibitors and inducers of CYP enzymes and alternative products used when available.

### 8.2 Arm B: Enzalutamide, abiraterone, and prednisone

Patients assigned to Arm B should start all components of the regimen: abiraterone, prednisone, and enzalutamide on the same day. Per [Section 5.1.3](#), patients are required to secure their own supply of the abiraterone. Arrangements with third party insurers, private or public, should be made prior to registration/randomization.

If dosing of enzalutamide, abiraterone, and/or prednisone is missed on one day for any reason, double dosing should NOT occur the following day.

**Inducers and inhibitors of CYP enzymes:** In addition to the information above regarding the interaction of CYP enzymes and enzalutamide, abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose

reduction of the CYP2D6 substrate. Additionally, abiraterone is a substrate of CYP3A4 in vitro. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

### 8.2.1 Enzalutamide

**Patients will be instructed to take 160 mg enzalutamide by mouth daily, every morning.** Enzalutamide should be taken as close as possible to the same time each day. Study patients will take four capsules of enzalutamide once daily. Enzalutamide can be taken with or without food.

### 8.2.2 Abiraterone

**Patients will be instructed to take 1000 mg Abiraterone daily, every evening.** Abiraterone must be taken on an empty stomach. No food should be consumed for at least two hours before, and for at least one hour after the dose of abiraterone is taken. The tablets should be swallowed whole with water.

### 8.2.3 Prednisone:

**Patients will be instructed to take 5 mg p.o. twice daily, once in the morning and once in the evening.** The dose of prednisone will be gradually reduced if clinically indicated. It is not required for the prednisone to be taken at the same time as enzalutamide and abiraterone. The dose of prednisone will remain unchanged in the event that the enzalutamide and/or abiraterone doses are changed.

## 8.3 Maintenance of castrate testosterone levels

All patients who have not undergone an orchiectomy must be maintained on either a **GnRH analogue or GnRH antagonist** during treatment.

## 8.4 Bone protection

**Bisphosphonates or other approved bone-targeting agents** for the treatment of metastatic prostate cancer should be maintained during the screening period and while actively being treated on the study regimen as clinically indicated for patients with bone metastases.



## 9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

The following general guidelines apply to all dose modifications listed below

- Doses will not be re-escalated once reduced
- If dose reduction below dose level -2 is required, treatment with that agent will be discontinued.
- The dose of prednisone can be gradually reduced if clinically indicated.
- If treatment is held for more than four weeks due to toxicity, discontinue protocol therapy
- Each cycle is always 28 days regardless of dose interruption. (i.e., a 7 day interruption of a dose starting on day 15 of a cycle would mean that the dose is restarted on day 22 of the same cycle)

**Dose level table for enzalutamide**

Dose Level	enzalutamide
<b>0 (starting dose)</b>	160 mg/day
<b>-1</b>	120 mg/day
<b>-2</b>	80 mg/day

**Dose level table for abiraterone**

Dose Level	abiraterone
<b>0 (starting dose)</b>	1000 mg/day
<b>-1</b>	750 mg/day
<b>-2</b>	500 mg/day

### 9.1 Hepatic Toxicity

**For  $\geq$  grade 3 ALT or AST or Bilirubin (see Investigations in CTCAE v. 4.0),** interrupt enzalutamide and abiraterone. Check liver function labs weekly. Restart both enzalutamide and abiraterone at one dose level reduction when ALT, AST, and bilirubin recover to grade 1. Monitor serum transaminases and bilirubin every two weeks for three months and monthly thereafter.

**For hepatic failure (see Hepatobiliary Disorders in CTCAE v. 4.0),** discontinue protocol therapy.

### 9.2 Neurologic toxicity

Discontinue protocol treatment for any seizure.

### 9.3 Reversible posterior leukoencephalopathy syndrome (RPLS)

For signs and symptoms suggestive of reversible posterior leukoencephalopathy syndrome (RPLS) such as confusion, headache, seizures, and cortical blindness, hold enzalutamide for up to 4 weeks. Suspected RPLS should be investigated with MRI. If diagnosis of RPLS is confirmed, enzalutamide should be permanently discontinued. If RPLS is ruled out via MRI and signs and symptoms attributed to another cause, enzalutamide should resume. If enzalutamide is held or permanently discontinued for RPLS, continue abiraterone and prednisone.

### 9.4 Other Non-Hematologic Grade 3 or 4 Toxicity

For patients on both arms who experience a grade 3 or greater toxicity attributed to enzalutamide, enzalutamide should held for one week or until symptoms improve to  $\leq$  grade 2. Patients may be re-started on enzalutamide at one dose level reduction. If treatment is held for more than 4 weeks, discontinue protocol therapy.

For patients on Arm B who experience a grade 3 or greater toxicity attributed to abiraterone, abiraterone should be held for one week or until symptoms improve to  $\leq$  grade 2. Patients may be re-started on abiraterone at one dose level reduction. If treatment is held for more than 4 weeks, discontinue abiraterone and continue enzalutamide.

For non-hematologic grade 3 or 4 toxicity where the attribution to either abiraterone or enzalutamide cannot be determined, both drugs should be held for one week or until symptoms improve to  $\leq$  grade 2. Patients may be re-started on abiraterone and prednisone at one dose level reduction. If appearance of previous toxicity does not reappear, then patients may be re-started on enzalutamide at one dose level reduction.

## 10.0 CORRELATIVE STUDIES

Correlative studies embedded in this trial will provide insights into sub-populations within the broader CRPC population that might optimally benefit from one of the specific treatment strategies being tested, as well as begin to define the processes at play at the time of development of resistance to these therapies. These studies will involve analyses of circulating androgen levels, microRNA, RNA profiles, and serum angiokine levels that will identify independent prognostic biomarkers of overall survival and progression-free survival in men with metastatic CRPC, as well as potentially predict for the benefit associated with combined enzalutamide/abiraterone therapy over single agent sequential therapy. These biomarkers will be associated with both AR-dependent and AR-independent signaling pathways and are described briefly below. In addition, in collaboration with the Alliance Imaging Committee, the study contains an imaging correlative study of bone imaging by Tc-99 MDP or sodium fluoride F-18 (NaF) PET/CT imaging techniques, to develop optimized imaging prognostic and predictive biomarkers for castration-resistant metastatic disease.

### 10.1 Biomarker development/validation of technetium bone scintigraphy and sodium fluoride (NaF) PET/CT for CRPC

#### 10.1.1 Background and hypotheses

Despite decades of use, bone imaging has never been developed as either a prognostic or predictive biomarker for prostate cancer. The Prostate Cancer Working Group 2 (PCWG2) criteria were formulated as a semiquantitative scale for examining post-treatment bone scan changes, with a standard definition for progression and a standard means of controlling for flare. The PCWG2 standard for defining progression is two new confirmed lesions, except during the early post-treatment period when flare may occur during which two new lesions must be followed by two additional lesions on the next scan to qualify for progression. PCWG2 is the first successful attempt to create a set of criteria for data collection and interpretation for the purposes biomarker development and clinical trial conduct. PCWG2 criteria were standardized for reproducibility of imaging measurements but not necessarily optimized for biologic relevance and correlation with outcome. PCWG2 criteria, however, were developed using standard Tc-99 bone scintigraphy. Sodium fluoride (NaF) PET/CT imaging, however, is increasingly being used as routine bone imaging in the community. The potential advantages of NaF PET/CT bone imaging include the ability to quantitate the amount of tracer uptake in each lesion and of the patient's disease burden, and more precise anatomic localization. Both Medicare and many private insurances are reimbursing for NaF PET/CT bone imaging. From a clinical trial standpoint, the imaging is integral to the conduct of the study, and the study will not dictate to the treating physician which type of bone imaging to order, but will leave the choice of Tc-99 or NaF PET/CT to the physician in accordance with his/her institutional or community standards. We anticipate that approximately 25% of the patients will undergo NaF PET/CT imaging. The imaging data will be collected in real time and audited. Retrospectively, the optimal definitions of



progression and the optimal quantitative imaging biomarker for prediction and prognostication using NaF PET/CT or Tc-99 bone definition will be established, by comparing the imaging data with overall survival.

We hypothesize that clinical bone imaging, integral to the conduct of the clinical trial for assessing eligibility and response, can be used to develop prognostic and predictive biomarkers for metastatic CRPC using optimized quantitative assessments.

We hypothesize that the definitions of progression embedded in PCWG2 can be applied to NaF PET/CT, and that these definitions can be similarly optimized in order to serve as prognostic and predictive biomarkers.

PCWG2 was developed with Tc bone scintigraphy as a standard. Clinicians are increasingly using NaF PET/CT without a reference database or analysis to associate these imaging findings with clinical outcomes, and that at present there is no plan other than this proposal to associate and validate these findings. We do not know a priori which parameter of NaF PET/CT will most closely be prognostic or predictive.

We hypothesize NaF PET/CT can be used to develop fully quantitative measures of tumor burden (such as MTV) or of bone activity (such as SUVmax), and these measures will be prognostic and that changes with treatment will be predictive.

PCWG2 is only semi-quantitative in that it relies on lesion counting to establish disease progression. A major advantage of NaF PET/CT is that as a positron emitter, lesional uptake can be fully quantitated, which is not routinely possible with Tc bone scintigraphy. These quantitative measures of baseline bone activity and disease burden at baseline and after treatment, offer the potential to create prognostic and predictive models for survival, which previously were not possible with imaging data.

At the same time, such questions apply to Tc bone scanning as well. However, NaF PET/CT and Tc bone scanning are different technologies and measure different biologic processes. They cannot be compared head to head. We hypothesize that the basic measure of burden will be prognostic and predictive and will therefore examine lesion number, and, if feasible, bone scan index.

### **10.1.2 Objectives**

To assess pre- and post-treatment measures of tumor burden and bone activity using NaF PET/CT and Tc bone scintigraphy and correlate these measures with overall survival.

### **10.1.3 Methods**

**A. Image acquisition:** Patients in this study must undergo bone imaging in order to establish eligibility criteria for this trial, and further, they will undergo bone imaging as part of standard response assessments at regularly scheduled intervals (Every 8 weeks for the first 6 cycles, then every 12 weeks). The patient's treating physician will order the type of bone imaging that represents standard practice at their institution. These scans may either be NaF PET/CT or traditional technetium bone scintigraphy. According to current practice, we anticipate that 25% of these will be NaF PET/CT and 75% will be bone scintigraphy.

Individual sites will perform the imaging studies and investigators will complete the specialized CRF that incorporates PCWG2-dictated data capture. In close collaboration with the Alliance Imaging Committee, under the leadership of Dr. Lawrence Schwartz, and in conjunction with the Alliance imaging core facility, we will collect in real time the imaging data and the specialized CRF that captures PCWG2-defined critical imaging data

elements. The image acquisition quality of the bone imaging will be performed in real time. The accuracy of the response assessments will be audited by an expert panel in real time.

**B. Analysis of PCWG2 progression criteria and optimizing the definition of progression to predict for survival:** We will compare PCWG2 definition of progression with alternative imaging definitions of progression on both NaF PET/CT and technetium bone scintigraphy. These alternate definitions of progression will include, but may not be limited to, differing lesion numbers to define progression, the need for confirmatory scans, and quantitative measures of tumor burden.

**C. Analysis of quantitative imaging assessments of NaF PET/CT and Tc bone scintigraphy as measured by:**

- i. For NaF PET/CT we will analyze SUV<sub>max</sub>, SUV<sub>max</sub>avg, SUV peak, metabolic tumor volume, and other parameters to determine which of these best associates with survival as a baseline prognostic biomarker and the change analysis as a dynamic post-treatment predictive parameter.
- ii. For bone scintigraphy, we will examine lesion number, skeletal distribution, and bone scan index as a prognostic and predictive biomarker.
- iii. For both studies, we will examine flare on the first post-treatment scan as a potential positive prognostic biomarker.

#### 10.1.4 Statistical design

One of the two main objectives is to test whether rPFS defined per PCWG2 at 6 months will predict overall survival.

Using the data from COU-302, rPFS rates at 3-months and at 6-months in patients treated with AA plus prednisone are estimated to be 98% and 80%, respectively. Thus, the landmark at 6 months is chosen based on the bone scan assessment and clinical relevance. We do not know the proportion of rPFS rate at 6 months in patients treated with enzalutamide plus/or minus AA, but it will be assumed to be the same as in COU-302. It is expected that 25% of the patients will undergo NaF/PET scan imaging and the remaining 75% will undergo scan using the standard Tc-99. It is assumed that the hazards of death in institutions where patients will undergo NaF/Pet scan will be the same as institution where the patients will undergo Tc-99 scan. For simplicity in the power computation, rPFS rate at 6 months will be used as a binary variable. We do not know the number of deaths among the patients who will undergo either NaF/Pet or Tc-99 bone scan. A total of 616 deaths are expected at the end of the trial and rPFS at 6 months is 80%. Accounting for censoring and deaths before 6 months, it will be assumed that there are 129 deaths and 385 deaths for patients undergoing NaF/PET scan and Tc<sub>99</sub>, respectively.

The table below provides the minimum hazard ratio detectable, assuming power of 0.80, and proportion of radiographic progression at 6-months ranging from 0.20-0.35, a two-sided type I error rate of 0.05, and 129 and 385 patients undergoing NaF/PET and Tc-99, respectively for the NAF/PET and Tc-99 imaging modalities.

<b>Proportion who progress radiographically at 6-months</b>	<b>NaF/PET (129 deaths)</b>	<b>Tc-99 (385 deaths)</b>
0.20	1.88	1.42
0.25	1.79	1.39
0.30	1.74	1.36
0.35	1.69	1.34

**Table 1**

In addition, the other main objective is to test for treatment-rPFS interaction using NAF/PET and Tc-99 scans in predicting overall survival.

The sample size for this study is 1,224 patients. Power calculations based on testing treatment by rPFS at 6 months using NaF/PET scans interaction is provided in the table below and will be exploratory. It is assumed that the OS distribution follows an exponential distribution, an accrual rate of 306 patients (25% of 1,224 patients) over 36-months period, and 24 months post-accrual follow-up. Adequate power will be detected for only large interactions terms. The table below presents the power for testing the null of no treatment by rPFS interaction using a two-sided type I error rate of 0.05. Let  $\Delta_1$  and  $\Delta_2$  be the hazard ratios for treatment effect within patients who do not (non-progressors) and do progress (progressors) radiographically at 6-months, respectively. The assumed median OS is 33 months for the enzalutamide arm. No discrepancy in OS distributions of the non-radiographic progressors and radiographic progressors at 6-months is expected for this treatment arm.

<b>Proportion of patients who progress radiographically at 6-months by NaF/PET scans</b>	$\Delta_1$	$\Delta_2$	$\Delta$	Power
0.25	1.2	3.0	2.5	0.67
	1.2	3.5	2.9	0.78
	1.2	3.6	3.0	0.80
0.30	1.2	3.0	2.5	0.70
	1.2	3.5	2.9	0.82
	1.2	3.6	3.0	0.83

**Table 2**

In addition, power calculations based on testing treatment by rPFS at 6 months interaction using the Tc-99 scans is provided in the table below and will be exploratory because of the limited sample size. It is assumed that the OS endpoint follows an exponential distribution, an accrual rate of 918 patients (75% of 1,224 patients) over 36-months period, and 24 months post-accrual follow-up. Adequate power will be detected for moderate to large interactions terms. The table below presents the power for testing the null of no treatment by rPFS interaction using a two-sided type I error rate of 0.05. Let  $\Delta_1$  and  $\Delta_2$  be the hazard ratios for treatment effect for non-progressors and progressors at 6 months, respectively. The assumed median OS is 33 months for the enzalutamide arm. No discrepancy in OS distributions of the non-radiographic progressors and radiographic progressors at 6-months is expected for this treatment arm.

Proportion of patients who progress radiographically at 6 months by Tc-99 scans	$\Delta_1$	$\Delta_2$	$\Delta$	Power
0.25	1.2	2.0	1.7	0.67
	1.2	2.1	1.7	0.74
	1.2	2.2	1.8	0.80
0.30	1.2	2.0	1.7	0.71
	1.2	2.1	1.7	0.78
	1.2	2.2	1.8	0.84

**Table 3****Data Analysis for imaging objectives**

The proportional hazards model will be used to assess whether the rPFS rate at 6 months as defined by the PCWG2 will predict overall survival. In addition, the PH model will be used to test for treatment by rPFS rate at 6-month interaction. If there is a suggestion that there are treatment by rPFS interactions, then the estimates of HR and 95% CI will be presented separately within each treatment group.

Exploratory analyses will be performed with the proportional hazards model will be used to assess the prognostic importance of SUVmax, SUVmaxavg, SUVpeak, metabolic tumor volume, and other parameters as predictors of overall survival. Potential markers will be identified based on their associations with PFS where the c-index will be the primary measure of predictive discrimination. The c-index will be used to compare whether the predictions of rPFS at 6 months from NaF/PET scans will be higher than the standard Tc-99 scans.

Exploring the association between rPFS and OS is a complex problem. Part of the difficulty of assessing this relationship is that both endpoints are time to event outcomes with censoring. This is statistically challenging because of issues related to interval censoring and informative censoring. The problem is simplified by assuming that there is no informative censoring and thereby we can apply the Kendall tau to explore the relationship between OS and rPFS rate at 6 months.

**10.2 Serum Androgen Levels****Validation Study of the Prognostic and Predictive Significance of Baseline and on-Treatment Serum levels of Testosterone, DHEA and Androstenedione****10.2.1 Background and specific hypotheses**

Patients with higher baseline androgens treated with abiraterone/enzalutamide have a superior median survival than patients with a similar androgen level who are treated with enzalutamide alone. This hypothesis is based on need to validate the observations made in patients treated with abiraterone versus placebo on the COU-301 study in which all three androgens (testosterone, DHEA and androstenedione), when stratified at the median, were associated a difference in survival. For example the hazard ratio for survival was 0.64 (<0.0001) comparing high versus low testosterone in abiraterone treated patients. In placebo treated patients the hazard ratio was 0.51 (p=0.0004) suggesting that even in patients who did not receive abiraterone therapy that there is a prognostic importance of baseline androgen levels. However, a caveat with that study was that the control arm received both placebo and prednisone, and prednisone is associated with modest reductions in androgens, therefore it is not possible to conclude that baseline androgen levels are completely independent of therapy, as all patients in that trial received some form of

androgen reduction therapy. The current study will compare both abiraterone/enzalutamide treated patients to those who receive enzalutamide alone allowing for the opportunity to test whether OS is impacted to a similar extent in patients who are not treated with an agent that lowers androgen levels. Prospective validation of the data from the abiraterone versus placebo data will serve to determine if future studies with androgen synthesis inhibitors and androgen receptor antagonists will require stratification on the basis of androgen levels in addition to confirming that this statistical association exists in the pre-chemotherapy setting as well as in the post chemotherapy setting.

Reduction in androgen levels during treatment with Abiraterone/enzalutamide therapy to undetectable levels is associated with higher proportions of PSA response, longer progression free survival than in patients treated with enzalutamide monotherapy. Data from the randomized placebo controlled trial of abiraterone and prednisone compared to prednisone and placebo demonstrated that abiraterone therapy leads to a reduction in average serum androgen levels for the treated population and to undetectable levels in a large proportion of patients, and that this is associated with PSA decline. Despite this association it was observed that there were patients who experienced a PSA decline while on abiraterone who did not experience a decline in serum androgens to undetectable levels and there were others who experienced a significant decline in androgens who did not experience a 50% decline in PSA. Subsequent analyses have confirmed that androgen decline occurs as a continuous variable. In this analysis we will determine the associations between treatment arms, change in androgen on treatment, and clinical outcome.

#### 10.2.2 Objective

To determine whether pre-treatment serum adrenal androgen (SA) levels are prognostic factors of overall survival and to test whether SA levels are predictive factors of overall survival.

#### 10.2.3 Methods

Serum androgen levels will be measured during screening and will be measured by Liquid Chromatography/Mass Spectroscopy. Subsequently serum androgen levels will be measured after 8 weeks on therapy to determine the change in androgen levels over time. Androgen quantification will be performed by Esoterix incorporated, who has performed a similar analysis on COU-301, a phase III study of abiraterone/prednisone versus placebo/prednisone.

#### 10.2.4 Statistical design:

The primary objective is to test and validate the prognostic significance of SA in predicting of overall survival in men with CRPC. We expect to have 75% available serum samples of patients who will consent to their specimen being used for this objective. We do not know the number of deaths among patients with anticipated samples, but it will be assumed to be 462 deaths (75% of 616 deaths the target deaths). The samples will be randomly divided into training (n=308 deaths) and testing (n=154 deaths) datasets. Using the training dataset, we will test if SAs will predict OS. For simplicity in the power computation, SA levels will be dichotomized at the median value and patients will be classified as having low (below or equal to the median value) or high (above the median) levels. Assuming that the OS follows an exponential distribution, 308 deaths, a two-sided type-I error rate of 0.0167 (= 0.05/3), power = 0.80, and prevalence of 0.50, the minimum detectable hazard ratio is 1.44.

**Data Analysis:** The Kaplan-Meier product-limit approach will be used to estimate the OS and PFS distributions. In addition, the proportional hazards (PH) model will be used for assessing the prognostic significance of SA for predicting OS. Furthermore, the PH model

will be used to assess the prognostic importance of SAs in predicting OS adjusting on treatment arm, baseline characteristics and stratification factors.

Moreover, stratified PH regression models will be performed to test for treatment-SA biomarker interaction. Estimates of HR of OS (and 95% CI of the HRs) will be presented separately within each treatment arm if there is a suggestion that there is a treatment-SA interaction. Using the testing dataset, the time-dependent area under the curve (tAUC) will be computed as a measure of prognostic discrimination and the 95% CI will be computed by the bootstrapped approach. In addition, the PH model will be used to assess whether changes in SA at 8-weeks from baseline are associated with OS.

### **10.3 Development and validation of a circulating RNA profile as a prognostic and predictive biomarker of AR-targeted therapy in men with CRPC**

#### **10.3.1 Background and hypothesis**

Circulating tumor cells are known to be prognostic in metastatic CRPC and multiple other tumor types.<sup>24-26</sup> However, their utility requires human pathology review and real time analysis (i.e. < 72 hours) and is expensive and not readily exportable to community sites. In addition, the currently FDA-approved methodology for CTC capture and enumeration (Veridex Cellsearch method) relies on EpCAM expression in circulating tumor cells and CTCs are not reliably detected in over 50% of men with docetaxel-naïve metastatic CRPC.<sup>27</sup> More sensitive methods for CTC detection that are exportable, simple, and have less subjective variability are needed. In addition, we have shown that men with metastatic CRPC have CTCs that co-express stem cell-like biomarkers such as CD133 and epithelial-mesenchymal transition (EMT) biomarkers such as N and O cadherin and vimentin, suggesting that these CTCs may have a variety of phenotypes that may be variably sensitive to targeted therapies.<sup>28</sup> It has been demonstrated that androgen-deprivation therapy (ADT) leads to induction of EMT and stem cell-like biomarkers in prostate cancer cell lines, xenografts, and patient specimens, and may thus be a mechanism of ADT resistance and CRPC progression.<sup>29</sup> In addition, the development of a stable RNA profile that is able to associate with prognosis to the same degree or better than the current FDA approved Cellsearch assay would be a significant advance that may also permit biologic insight into mechanisms of tumor progression.

We have also developed and validated a multiplex PCR based assay for PAXgene samples that detects CTC RNA in patients with favorable (4 or fewer cells/7.5 mL of blood) CTC counts using the Veridex CellSearch assay. The assay is currently being evaluated on samples from patients enrolled on trials of abiraterone and enzalutamide. The results will enable more precise estimates of the number of samples needed to explore associations with prognosis at baseline and following treatment with these agents. Potential predictive markers are also under study. We will evaluate this multiplex assay in the current trial as both a prognostic and predictive biomarker. In addition, whole blood RNA biomarker panels (6 and 9 gene) that have been developed and externally validated in men with mCRPC will be analyzed in this trial for similar prognostic and predictive value using the same PAXgene samples.<sup>33,34</sup>

Linuma et al., have developed and validated an rtPCR-based strategy for the detection of cytokeratin (CK) + CD133+ CEA + CTCs from the whole blood of colorectal cancer patients undergoing adjuvant therapy.<sup>30</sup> This stem-like CTC biomarker was highly prognostic in this setting and validated in several external data sets. RTPCR for PSA has been validated in CRPC and the evaluation of CK+/PSA+/CD133+ expression in whole blood from patients is thus feasible.<sup>31</sup> Finally, prostate stem cells have been shown to express CD133 in preclinical models, suggesting that this biomarker may be an indicator

of stemness in prostate cancer stem cells, linking stemness to prostate growth and treatment resistance.<sup>28, 30-32</sup> We will test this RNA profile and other validated RNA profiles in mCRPC<sup>33, 34</sup> in a test dataset within this trial and validate their prognostic and predictive role in the entire available trial dataset. For the nine-gene and six-gene signatures, we hypothesize that the high risk predictive population identified by these biomarkers will have a poor prognosis in this trial, but will also be predictive of the benefit of combination abiraterone/enzalutamide therapy over single agent therapy.

We hypothesize that high levels of CK+/PSA+/CD133 (circulating prostate cancer stem cell (CSCs) biomarker levels) and other RNA profiles associated with prostate cancer will be adversely prognosis in men with metastatic CRPC from each arm and have a shorter time on study drug (shorter PFS and OS). We hypothesize that high levels of CSCs will be predictive of the benefit of combination enzalutamide/abiraterone over enzalutamide alone, given that these patient will have a poorer prognosis that will be improved with more aggressive combination therapy.

### 10.3.2 Objectives

- To evaluate specific pre-treatment RNA levels as prognostic factors for OS, including the 6- and 9-gene signatures, the CTC RNA profile, and the circulating tumor stem cell RNA profile.
- To evaluate the predictive ability of specific pre-treatment and post-treatment RNA, levels on OS and PFS.

### 10.3.3 Methods

Duplicate baseline, cycle 3, and progression blood samples for rtPCR analysis of circulating tumor RNA will be collected with 2.5 mL PAXgene tubes and stored and analyzed for both prognostic and potentially predictive value. Thus a total of 6 PAXgene tubes will be collected per patient on this study. [See [Section 6.2.2](#) for PAXgene sample collection and submission procedures.]

An independently run 40-sample pilot feasibility study using whole blood from existing studies in CRPC will be performed to evaluate the reliability and ranges for the circulating CTC stem cell assay in CRPC and establish values that will permit estimates for sample size calculations and power estimates for the larger development and validation cohorts within this trial. In these 40 subjects, the duplicate samples at baseline and each time point will be collected and analyzed for an association with outcome. Several indicators of reproducibility will be computed; such as coefficient of variation, correlation coefficient, limits of agreement, and the Bland-Altman plots. If the correlation coefficient between the replicates is at least 0.9, then the assay will be considered “reproducible.” However, if the correlation coefficient is less than 0.90, the study team will discuss how to proceed with these assays. Recommendations may include modifying the assay, or training the laboratory personnel who are performing these assays. The reproducibility rates will be reported at the end of the study.

External validation of this cancer stem cell and circulating tumor RNA biomarker in the current trial is planned, evaluating both prognostic and predictive associations.

Extraction of total RNA and cDNA synthesis will be performed as a batch using primers established against known prostate cancer, EMT, and stemness genes (PSA, CK, CD133, others). The expression of PSA, CK19, CK20, and CD133mRNA of blood samples will be examined; target genes of CTCs and glyceraldehydes-3-phosphate-dehydrogenase (GAPDH) mRNA were used as internal control genes. The expression levels of these mRNA were measured by real-time quantitative RT-PCR. All baseline samples will be

measured in duplicate. The levels of PSA, CK19, CK20, and CD133 mRNA will be normalized by GAPDH mRNA and their association with outcomes will be performed. mRNA profiles validated in CRPC will also be tested at baseline for prognostic associations with PFS and OS as well as predictive of PFS and OS in the current trial.<sup>33, 34</sup>

#### 10.3.4 Statistical design:

The primary objective is to identify and validate the prognostic significance of CSC RNA profile in predicting overall survival in men with mCRPC. We expect to have 75% available RNA PAXgene samples of patients who will accept that their specimen be used for this objective. We do not know the number of deaths among patients with anticipated samples, but it will be assumed to be 462 deaths (75% of 616 deaths). The samples will be randomly divided into training stratified by deaths (n=308 deaths) and testing (n=154 deaths) datasets. Using the training dataset, we will test if CSCs predict OS. For simplicity in the power computation, RNA expression will be dichotomized at the median value and patients will be classified as having low (below or equal to the median value) or high (above the median) levels. Assuming that OS follows an exponential distribution, 308 deaths, a two-sided type-I error rate of 0.0125 (type I error rate = 0.05/4 biomarkers), power = 0.80, and prevalence of 0.50, the maximum detectable hazard ratio is 1.46.

**Data Analysis:** The Kaplan-Meier approach will be used to estimate the OS and PFS distributions. In addition, the proportional hazards (PH) model will be used for assessing the prognostic significance of individual RNA biomarker for predicting OS. The PH model will be used to assess the prognostic importance of individual RNA in predicting OS adjusting on treatment arm, baseline characteristics and stratification factors.

Moreover, stratified PH regression models will be performed to test for treatment-RNA biomarker interaction. Estimates of HR of OS (and 95% CI of the HRs) will be presented separately within each treatment arm if there is a suggestion that there is a treatment-RNA biomarker interaction. Using the testing dataset, the time-dependent AUC as a measure of prognostic discrimination will be computed and the 95% CI for the time-dependent AUC will be computed by the bootstrapped approach.

### 10.4 Development and validation of a circulating microRNA profile as a prognostic and predictive biomarker of AR-targeted therapy in men with CRPC

#### 10.4.1 Background and hypothesis

Circulating microRNA provide a robust potential prognostic and predictive biomarker.<sup>35</sup> Our group has recently developed and validated a fluid-capillary, quantitative polymerase chain reaction (qPCR) platform to robustly measure circulating microRNA from the serum of men with prostate cancer.<sup>36</sup> In this study, patterns of circulating microRNA were found to be associated with the presence of prostate cancer and, importantly, distinguished between low and high risk localized prostate cancer based upon the CAPRA scoring system.<sup>36</sup> In castration resistant prostate cancer, persistent AR activity despite low levels of circulating testosterone is a common mechanism driving persistent growth.<sup>37,38</sup> The common dependence on persistent AR activity likely explains the success of drugs such as abiraterone.<sup>39</sup> and enzalutamide<sup>40</sup> in castration resistant prostate cancer. However, not all patients with metastatic castration resistant prostate cancer have a sustained response to these agents (Median time to progression is about 4 months with abiraterone) and biomarkers that anticipate the dependence of a tumor on persistent AR activity may improve our ability to choose the most appropriate treatment for patients in a timely manner. While PSA is androgen regulated, it has been found insufficient as a predictive biomarker for hormonal therapy in prostate cancer. Similarly, circulating adrenal



androgens are associated with prognosis in men with mCRPC who receive abiraterone and were found to be predictive to response to ketoconazole in a CALGB correlative study,<sup>41</sup> they do not have sufficient specificity and sensitivity to be used to guide therapy.

Specific microRNAs are known to both control AR activity (e.g. Let-7 microarray family)<sup>42</sup> and others are known to be regulated by AR (such as miR-101 and miR-21).<sup>43,44</sup> Importantly, Let-7 family members have been found to antagonize self-renewal in stem cells and higher levels may not only impact AR activity but impact the ability of mCRPC to adapt during enzalutamide with or without abiraterone by manifesting stem cell-like characteristics. These microRNAs are reliably detected in the serum of men with prostate cancer<sup>36</sup> and we will test the hypothesis that pre-treatment and dynamic levels of AR associated microRNAs will be predictive for response to enzalutamide and/or the combination of enzalutamide and abiraterone.

**Specific hypotheses:** Patients with high levels of androgen-regulated miRNA will have greater benefit from AR targeted therapy.

We hypothesize that:

- 1) Patients with circulating levels of miR-21 that are above the median of expression for men with mCRPC will have a greater benefit from enzalutamide and enzalutamide + abiraterone than patients with circulating levels of miR-21 below the median.
- 2) Patients with circulating levels of miR-101 that are above the median of expression for men with mCRPC will have a greater benefit from enzalutamide and enzalutamide + abiraterone than patients with circulating levels of miR-101 below the median.
- 3) Patients with circulating levels of Let-7 miRNA family members that are above the median of expression for men with mCRPC will have a greater benefit from enzalutamide and enzalutamide + abiraterone than patients with circulating levels of Let-7 miRNA family members below the median.

#### 10.4.2 Objectives

- To evaluate specific pre-treatment microRNA levels as prognostic factors for OS.
- To test whether the microRNA are predictive factors for overall survival.

#### 10.4.3 Methods

[See [Section 6.2.2](#) for serum sample collection and submission procedures.]

Thaw a single 500  $\mu$ L sample on ice and mix 300  $\mu$ L with an equal volume (300  $\mu$ L) of 2X Denaturing Solution (at room temperature); re-freeze and store the residual 200  $\mu$ L. Additional aliquots of serum may be used if the yield of RNA is too low. Follow the MirVana PARIS Kit manufacturer's protocol as previously published [Mitchell et al, 2008]. Concentrate RNA using Microcon reservoirs; elute into 20  $\mu$ L final volume. Perform the reverse transcription (RT) with MMLV-RT and reverse stem-loop primers to amplify specific microRNA species (List of primers can be found at <http://urology.ucsf.edu/blellochlab/protocols.htm>). Pre-Amplification is necessary to enhance signal strength and the input RNA level determines the optimal number of Pre-PCR cycles. Using serum as starting material, 12 cycles results in detectable miRNA levels, but 15 cycles appeared to be superior. For our protocol, we will use 15 cycles of pre-amplification using previously developed primers (Forward primers at <http://urology.ucsf.edu/blellochlab/protocols.htm>). Product from the 15 cycles is gel purified, re-extracted, and purified after gel extraction with MinElute columns. Final eluted volume is 10  $\mu$ L in DEPC treated water. The 10  $\mu$ L is then used to assay microRNA levels with the Fluidigm 96.96 qRT-PCR Profiling platform. After samples are loaded onto the

chip it is placed in the BioMark system for amplification and analysis. After RT-PCR the proprietary software provides amplification curves, heat maps and Ct values for each well. A detailed protocol including all steps is provided in Moltzahn et al., J Vis Exp (2011); 54:2552.

#### 10.4.4 Statistical design

The primary objective is to test and validate the prognostic significance of microRNA in predicting of overall survival in men with CRPC. We expect to have 75% available serum samples of patients who will accept that their specimen be used for this objective. We do not know the number of deaths among patients with anticipated samples, but it will be assumed to be 462 deaths (75% of 616 deaths the target deaths). The samples will be randomly divided into training (n=308 deaths) and testing (n=154 deaths) datasets. Using the training dataset, we will test if microRNA predict OS. For simplicity in the power computation, microRNA will be dichotomized at the median value and patients will be classified as having low (below or equal the median value) or (above the median) levels. Assuming that OS follows an exponential distribution, 308 deaths, a two-sided type-I error rate of 0.0167, power = 0.80 and prevalence of 0.50, the minimum detectable hazard ratio is 1.44.

In addition, power calculations based on testing micro-RNA treatment interaction is provided in Table 4, below, and will be exploratory because of the limited sample size. It is assumed that the OS endpoint follows an exponential distribution, and accrual rate of 1224 patients over a 36-month period, and 24-month post-accrual follow up. Adequate power will be detected for moderate to large interactions terms. Table 4 presents the power for testing the null of no treatment by micro-RNA interaction using a two-sided type I error rate of 0.05 and assuming positive marker prevalence of 50% (since the micro-RNA is dichotomized at the median). The assumed median OS is 36 months for Arm A. No discrepancy in OS distributions is expected for this arm.

	$\Delta_1$	$\Delta_2$	$\Delta$	Power
0.5	1.2	2.0	1.7	0.42
	1.2	2.1	1.8	0.50
	1.2	2.2	1.8	0.57
	1.2	3.0	2.5	0.84
	1.2	3.3	2.9	0.96

**Table 4**

**Data Analysis:** The Kaplan-Meier approach will be used to estimate the OS and PFS distributions. In addition, the proportional hazards (PH) model will be used for assessing the prognostic significance of individual microRNA for predicting OS. The PH model will be used to assess the prognostic importance of individual microRNA in predicting OS adjusting on treatment arm, baseline characteristics and stratification factors.

Moreover, stratified PH regression models will be performed to test for treatment-microRNA interaction. Estimates of HR of OS (and 95% CI of the HRs) will be presented separately within each treatment arm if there is a suggestion that there is a treatment-microRNA interaction. Using the testing dataset, the tAUC as a measure of prognostic discrimination will be computed and the 95% CI for the tAUC will be computed by the bootstrapped approach.

## 10.5 Analysis and Confirmation of Prognostic Blood-based Angiokine Biomarkers in Men with Metastatic Castration-Resistant Prostate Cancer

### 10.5.1 Background and hypothesis

Evolving data strongly suggests that genetic alterations within the tumor epithelium, as well as variations in host microenvironment factors in the setting of chronic castration, lead to prostate cancer progression through multiple divergent biologic pathways. Serum and plasma prognostic factors may help to identify subgroups of metastatic castration-resistant prostate cancer (CRPC) with prognostic significance. In prior CALGB studies we have identified plasma vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), chromogranin A (CgA), and hepatocyte growth factor (HGF) to have independent prognostic significance.<sup>46-49</sup> In particular, these factors are part of a larger set of angiogenic and cytokine factors that may play an important role in the prognosis of CRPC, independent of the testosterone – androgen receptor (AR) signaling axis.

Recently, multiplex ELISA approaches have been utilized for the analysis of a broader array of plasma and serum of cancer patients. Compared to tumor biopsies, analyses of blood samples have the marked advantages of minimal risk, greater convenience, reduced cost, universal availability in clinical trials, and the ability to be collected at multiple time-points, including before treatment and along the continuum of disease response and progression. Building off of our previous studies, we have performed broad analysis of 32 angiogenic and cytokine analytes in 2 cooperative group studies (CALGB 80303 and CALGB 90206) with plans to run samples across our recently completed Phase III study in patients with mCRPC (CALGB 90401) to identify potential prognostic analytes for overall survival in patients receiving either docetaxel/prednisone/bevacizumab or docetaxel/prednisone.<sup>50</sup>

Angiokine and cytokine analytes have independent prognostic significance in patients with mCRPC, independent of androgen and AR inhibition.

### 10.5.2 Objectives

- To determine whether pre-treatment angiokine levels are prognostic factors for OS and PFS.
- To test whether pretreatment angiokine levels are predictive factors for OS and PFS and to assess whether post-treatment angiokine levels are predictive factors for OS and PFS.

### 10.5.3 Methods

**Proposed analytes:** These cover multiple categories of angiogenic factors: VEGF family members, non-VEGF classical angiogenic factors, inflammatory factors, stromal factors, and coagulation factors as shown in the following Table below. Overall, assays had excellent sensitivity and low variability. Several factors were highly prognostic for outcome in general, including IGBP-1, ICAM-1, Ang-2, CRP, IL-8, TSP-2, VCAM-1, PAI-1 active, IGF-1, and IL-6.

**Assay:** From a quality control standpoint, our multiplex array has been optimized for use in cancer patients and utilizes the SearchLight® multiplex ELISA platform (Aushon Biosystems, Inc.). This novel multiplexing technology allows for the measurement of up to 16 different analytes simultaneously in a single microplate well. The assay design is similar to a sandwich ELISA where the capture antibodies are pre-spotted into individual wells of a 96-well plate. We have developed the current profile via extensive collaboration with Aushon, both in the selection of important angiogenic factors and in the technical

validation of the assay in plasma of cancer patients. All plate designs have already been validated in order to 1) limit cross-reactivity of the antibodies 2) optimize sensitivity and specificity and 3) maximize the linearity of the assay's dynamic range. Any study samples that fall outside the linear portion of the standard curve are retested. Samples that read below the limit of detection are retested, if possible. Samples that read above the linear portion of the standard curve are serially diluted and retested to obtain accurate measurements. Any analyte that does not meet the aforementioned criteria will result in the sample being re-evaluated.

Soluble angiogenic Factors	Matrix-derived Angiogenic Factors	Markers of Coagulations	Markers of vascular activation and Inflammation
bFGF	TGFb1	PAI-1 Active	Gro-a
HGF	TGFb2	PAI-1 Total	IL-6
PIGF	Osteopontin	CRP	IL-8
VEGF-A	BMP9		P-selectin
VEGF-C	TSP2		SDF-1b
VEGF-D	PEDF		ICAM-1
ANG-2	sEndoglin		VCAM-1
PDGF-AA			MCP-1
PDGF-BB			
IGFBP1			
IGFBP2			
IGFBP3			
sVEGFR1			
sVEGFR2			

**Table 5: Angiogenic and Cytokine factors**

#### 10.5.4 Statistical design

The primary objective is to identify and validate the prognostic significance of analytes in predicting overall survival in men with CRPC. We expect to have 75% available plasma samples of patients who will accept that their specimen be used for this objective. We do not know the number of deaths among patients with anticipated samples, but it will be assumed to be 462 deaths (75% of 616 deaths). The samples will be randomly divided into training (n=308 deaths) and testing (n=154 deaths) datasets. Using the training dataset, we will identify analytes that significantly predict OS. For simplicity in the power computation, analyte levels will be dichotomized at the median value and patients will be classified as having either low (below or equal to the median value) or high (above the median) levels. Assuming that OS follows an exponential distribution, 308 deaths, a two-sided type I error rate of 0.00125 (type I error rate = 0.05/40), power = 0.80, and prevalence of 0.50, the minimum detectable hazard ratio is 1.59.

The primary objective of the prognostic studies will be to explore the association of angiokine biomarker levels with overall survival, and secondary endpoints will be progression-free survival. The Kaplan-Meier product-limit approach will be used to estimate the OS and PFS distributions. In addition, the proportional hazards (PH) model will be used for assessing the prognostic value of individual and combination blood analytes for predicting OS. The PH model will be used to assess the prognostic importance

of individual and combination analytes in predicting OS adjusting on treatment arm, baseline characteristics and stratification factors.

Moreover, PH regression models will be performed to test for treatment-analyte interaction in predicting overall survival. As a first step, models with individual analytes will be considered. The interaction terms for treatment analytes that have p-values less than 0.10 will be jointly modeled adjusting for treatment and stratification factors. Estimates of HR of OS (and 95% CI of the HRs) will be presented separately within each treatment arm if there is a suggestion that there is a treatment-analyte interaction. The parameter estimate from the final model will be applied to the testing set and the tAUC as a measure of prognostic discrimination will be computed and the 95% CI for the tAUC will be bootstrapped.

#### **10.6 To develop and validate prognostic and predictive models of overall survival and will include baseline clinical and molecular markers.**

Currently, there are three prognostic models of overall survival that have been developed and validated in chemotherapy naïve patients.<sup>51-53</sup> The CALGB model is developed in a large multi-center cohort and was based on 760 patients enrolled on six trials, and identified seven variables: LDH, PSA, alkaline phosphatase, hemoglobin, performance status, presence of visceral disease and Gleason score. The model developed by Smaletz et al. was based on data from 409 men treated at the Memorial Sloan Kettering Cancer Center and also identified seven prognostic factors: age, Karnofsky performance status, LDH, albumin, alkaline phosphatase, and hemoglobin. Armstrong and colleagues developed and validated a prognostic model that was based on the TAX 327 trial. In addition to the known prognostic factors, they identified pain, PSADT, liver metastases and number of metastatic sites as independent factors of OS. 29 It is noteworthy that the model developed by Armstrong et al. was based on patients treated with docetaxel and yielded a c-index of 0.69. The difference in the parameters in the final models may have arisen from different patient population, different sample sizes, and different sets of assumptions made in model building and in the data that were available. Nevertheless, all models selected variables that were representative of host factor and tumor burden and had similar statistics in terms of predictive accuracy. The predictive discrimination (the area under the receiver operating characteristic [ROC] curve was 0.68 in both models) was not close to one, suggesting that models need to improve their predictive accuracy.

#### **Power Computation**

We would like to accurately estimate the tAUC and the 95% CI for the tAUC will be bootstrapped. Using Gonen and Heller approach,<sup>23</sup> extensive simulations studies were performed to estimate the c-index and variance of the c-index were conducted. The results of these simulations showed that the c-index ranged from 0.69-0.99 depending on the individual parameters and the shape parameter of the Weibull distribution. Regardless the c-index can be estimated with simulated variance of 0.0041.

#### **Data Analysis**

The trial dataset will be randomly divided into a 2:1 allocation ratio with 2/3 of the patients going into the training set and 1/3 will be used in the validation.

A penalized Cox proportional hazard models using adaptive LASSO penalty will be considered. Unlike other methods, the main advantage of using penalized methods is that they simultaneously select important prognostic factors and estimate their associated regression coefficients. Furthermore, the identification of prognostic factors is not based on the p-values. Adaptive weights were given by the reciprocal of absolute parameter estimates from an unpenalized Cox model fitted with all baseline covariates. The final model will be evaluated for its discriminative ability in two ways. First, the time dependent area under the curve (AUC) will

be computed in the training sample. Second, the model will be assessed for its calibration by plotting the predicted probability based on the final model vs. the observed probability at time (24, 30, 36 months). A risk score will be computed for each patient in the training set from the estimated regression coefficients.

To examine the prognostic ability of the fitted model, we will apply the parameter estimates on the testing set and calculated the risk score for every patient in the testing data sets based on the estimated regression parameters from the training set. We will then evaluate its discriminative ability based on the time dependent AUC (21). The 95% CI for the AUC will be computed based on the bootstrapped method.

## 10.7 Pharmacogenomic studies

### 10.7.1 Background and hypothesis

Abiraterone is a selective inhibitor of androgen biosynthesis that potently blocks CYP17A1, which is critical to testosterone synthesis by the adrenals, testes, and within the prostate tumor. Genetic variation in expression of CYP17A1 is regulated in part by promoter sequence variation, including a T>C change at nucleotide -34.

The primary statistical objective for this companion study is to investigate a drug by *CYP17A1* interaction with respect to overall survival. Specifically, we hypothesize that patients on the enzalutamide/abiraterone arm (Arm B) with a homozygous -34T genotype (Genotypic Group 1, 43% of the population) will have an inferior overall survival to patients with a heterozygous or homozygous -34C genotype (Genotypic Group 2, 57% of population). No genotype effect is expected in Arm A (enzalutamide alone).

As secondary objectives, we will assay candidate variants and loci hypothesized to be associated with other clinical phenotypes (e.g., progression-free survival or toxicity) or other eQTLs.

In addition, we may use the DNA collected to consider other candidate SNPs or to conduct a genome-wide association study (GWAS) to validate other or identify novel candidates, or, as next generation sequencing platforms become more cost effective, consider exome or whole- genome sequencing. As a randomized trial with uniform assessment and follow-up this represents an important opportunity to better understand the relationships among germline genetic variation, disease, and treatment-response phenotypes. At this time, the Population Pharmacology and Pharmacogenomics Committee of Alliance is conducting genomewide analyses of previously completed CALGB trials using The Illumina 1M platform in collaboration with the RIKEN Center for Genomic Medicine. More than 1,000,000 SNPs are simultaneously genotyped. In addition, there are 4,300 SNPs in regions of copy number variations (CNVs), thus allowing for the detection of CNVs as well. Near the completion of this clinical trial, specific hypotheses based on currently evolving findings will be formulated and a detailed investigational plan will be submitted as an amendment to this investigation. This flexible, anticipatory design is not only conventional, but also necessary in cancer pharmacogenomics.

#### 10.7.2 Objectives:

1. To investigate a drug by *CYP17A1* interaction with respect to overall survival.
2. Assay candidate variants and loci hypothesized to be associated with other clinical phenotypes (e.g., progression-free survival or toxicity) or other eQTLs.
3. To identify specific SNPs and/or copy number variations that are associated with the response to and toxicity associated with therapy

**10.7.3 Methods:**

All patients enrolled in the accompanying randomized phase III study will be given the option to consent for germline DNA analysis. A single blood sample (10 ml in a lavender top) will be collected at baseline (or any follow-up visit) for pharmacogenetic analysis. Germline DNA will be extracted using standard techniques and genetic testing appropriate to specific study questions will be performed. The concentration and quality of DNA will be quantified by ultraviolet spectroscopy. All DNA samples and unprocessed blood will be frozen and will be stored at the Alliance Biorepository at Ohio State University (OSU) until they are distributed to the appropriate laboratory for analysis. The typical yield of DNA from a 10ml blood sample is 100 ug (range of 80-150 ug). For the studies described below we will need up to 5 ug for both the candidate gene analysis as well as the whole genome analysis, leaving the majority of the sample stored at the OSU and available for additional future genotyping projects.

**10.7.4 Statistical design**

According to the clinical design of this study the number of patients to be evaluated clinically is 1224. For simplicity, will assume that the median OS for Arm A is 27 months and that the median OS for Arm B is 35.1 months, and that the patients are accrued uniformly over a period of 36 months and that the last patient will be followed for at least 14 months. This is the scenario described in the first row of [Table 9](#) in Section 15.1

It is assumed that at least 85% of the patients are self-reported non-Hispanic whites, and that at least 85% of the patients will consent and provide usable samples for the proposed analyses. The power calculations shown below will be based on the assumption that 884 ( $1224 \times 0.85 \times 0.85$ ) patients will be available for these analyses. It is noted that this the smallest expected sample size. All patients who provide consent and usable samples will be included in the proposed pharmacogenomic studies.

The analysis will be carried out within a framework of a multiplicative two-way Cox proportional hazards model. The inference will be conducted with respect to the interaction term in this model. For the power calculation, we will assume that the time to event distribution for Arm B is a two-component mixture of exponential laws of the form  $0.5 = 0.43 \cdot \exp(-\lambda_{1B} \cdot MB) + 0.57 \cdot \exp(-\lambda_{1B} \cdot HRB \cdot MB)$  where MB is the median for arm B and  $\lambda_{1B}$  is the exponential hazard rate for the TT genotype in Arm B. HRB quantifies the hazard ratio between the two genotypic groups. It is noted that the corresponding hazard ratio in Arm A is assumed to be one as no genotypic effect is expected. Therefore the effect size is  $HRB/HRA = HRB/1 = HRB$ . The power, at the two-sided 0.05 level, is 0.67 if  $HRB = 0.63$ , 0.77 if  $HRB = 0.60$  and 0.82 if  $HRB = 0.57$ .

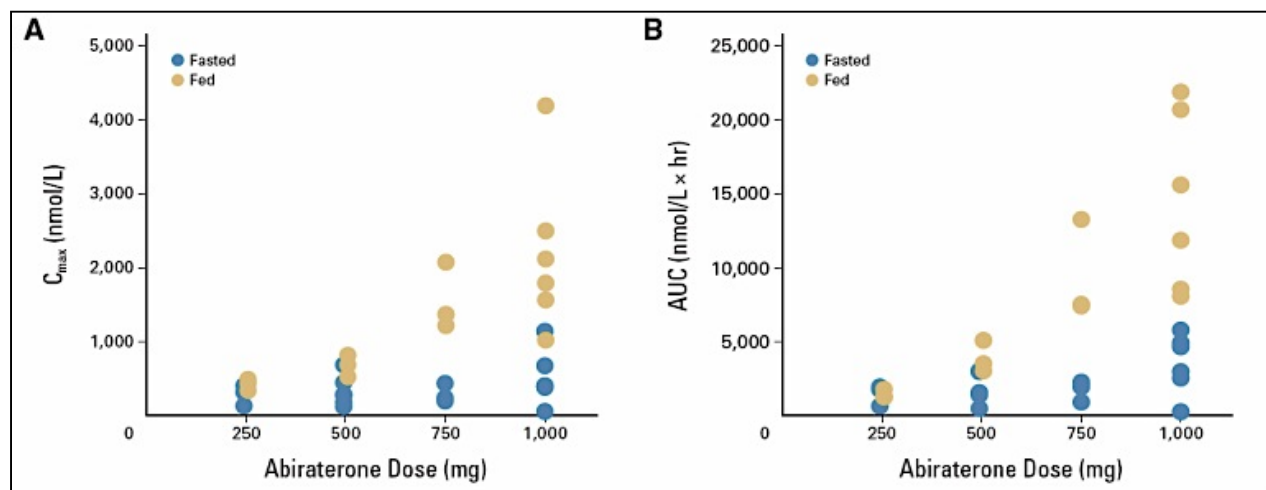
## 10.8 Population Pharmacokinetics of abiraterone and enzalutamide

### 10.8.1 Background and hypothesis:

Abiraterone Pharmacokinetics: The abiraterone pharmacokinetic parameters across dose levels tested in the Phase I studies show considerable variability between patients and are presented in the Table below. In a phase I study of abiraterone conducted across four sites in the US, pharmacokinetics were evaluated for all 33 patients. The parent compound, abiraterone, was not detected in any sample, suggesting rapid and complete conversion to abiraterone. Maximum drug concentrations ( $C_{max}$ ) were achieved within 1.5 to 4 hours ( $T_{max}$ ). When administered with food that had high-fat content (per FDA guidance), drug exposure was significantly increased (by 4.4-fold) compared with fasting administration ( $P=0.049$ ; Figure 1). Less than proportional increases in both  $C_{max}$  and  $AUC_{0-\infty}$  were observed across dose levels in fed and fasted patients (Figure 1), but was less pronounced among fed patients. The small number of patients per cohort and the high degree of inter-patient variability, often approaching 50%, limits further interpretation. Nonetheless, abiraterone exposures (AUCs) appeared to be consistently higher in fed compared to fasted patients (Figure 1) possibly suggesting food may aid drug absorption. Abiraterone terminal elimination half-life across all groups ranged from 5 to 14 hours. At subsequent cycles, concentrations were lower (approximately 10-15%) than the highest concentration observed in cycle 1. <sup>1-3</sup>

Parameter	Abiraterone Dose (mg)							
	250		500		750		1000	
	Fasted (n = 3)	Fed (n = 3)	Fasted (n = 6)	Fed (n = 3)	Fasted (n = 3)	Fed (n = 3)	Fasted (n = 6)	Fed (n = 6)
$T_{max}$ , h								
Mean	2.0	2.0	1.5	2.7	2.0	2.0	1.8	4.0
SD	0	0.1	0.5	1.2	0.1	0	0.4	0
% CV	0	3.8	36.5	43.3	2.8	0	22.3	0
$C_{max}$ , nM/L								
Mean	283	421	331	676	290	1552	510	2194
SD	142.2	75.8	204.9	147.9	126.6	458.1	366.5	1096.9
% CV	50.3	18.0	62.0	21.9	43.7	29.5	71.9	50.0
$AUC_{0-\infty}$ , nM/L•hr								
Mean	1411	1387	1781	3840	1665	9359	3478	14404
SD	697.2	290.2	986.8	1080.9	704.6	3338.6	2012.2	5971.0
% CV	49.4	20.9	55.4	28.2	42.3	35.7	57.9	41.5
$T_{1/2-\lambda}$ , h								
Mean	5.3	5.1	10.6	6.9	7.1	7.9	14.4	12.5
SD	1.7	1.0	6.3	5.7	3.4	2.6	7.7	1.2
% CV	31.7	20.3	59.8	82.7	48.6	33.2	53.3	9.8
Apparent Clearance, L/h								
Mean	4288	530	5441	391	1519	247	2650	231
SD	1319.3	99.5	4844.5	99.1	822.7	73.0	4617.0	97.7
% CV	30.8	18.8	89.0	25.4	54.2	29.6	174.2	42.2
Apparent Vd, L								
Mean	654	3940	10252	3418	13688	2740	25494	4069
SD	447.3	1275.4	12268.8	1934.4	4265.4	1084.7	18670.2	1462.6
% CV	68.4	32.4	119.7	56.6	31.2	39.6	73.2	36.0





**Figure 1: Effect of food intake on Abiraterone C<sub>max</sub> and AUC**

Abiraterone is primarily cleared by hepatic metabolism, abiraterone sulphate is formed by SULT2A1 and this metabolite is further metabolized to N-oxide abiraterone sulphate, by CYP3A4. Approximately 5% of the radioactivity of a <sup>14</sup>C labeled dose of abiraterone is found in urine. In vitro studies with hepatic microsomes revealed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6, and notably CYP2C8 (which metabolizes enzalutamide) [abiraterone product insert].

**Enzalutamide (MV3100) Pharmacokinetics and Metabolism:** Following oral administration of enzalutamide at 160 mg in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations is 1 hour (range 0.5 to 3 hours). The enzalutamide mean terminal elimination half-life (T<sub>1/2</sub>), in patients with metastatic CRPC, following a single oral dose is 5.8 days (range 2.8 to 10.2 days). With daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide shows approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. In patients with metastatic castration resistant prostate (MCRP) cancer, the mean (%CV) predose C<sub>min</sub> values for enzalutamide and its major M2 metabolite were 11.4 (25.9%) µg/mL and 13.0 (29.9%) µg/mL, respectively.

In vitro, enzalutamide is metabolized by CYP2C8 and CYP3A4. In vivo results further suggest that CYP2C8 is primarily responsible for the formation of the active metabolite - N-desmethyl enzalutamide (M2). In vivo, the sum of enzalutamide and M2 exposure was increased by 2.2-fold and 1.3-fold when it was co-administered with gemfibrozil (strong CYP2C8 inhibitor) or itraconazole (strong CYP3A4 inhibitor), respectively. If the co-administration of enzalutamide with a strong CYP2C8 inhibitor cannot be avoided, the daily enzalutamide dose should be reduced to 80 mg. In vitro, enzalutamide, M1 and M2 caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Enzalutamide also caused time- dependent inhibition of CYP1A2. Among these enzymes, the IC<sub>50</sub> of CYP2C8 was the lowest. However, enzalutamide at steady state did not cause a clinically relevant change in the AUC of pioglitazone (CYP2C8 substrate) in vivo.

In vitro, enzalutamide caused induction of CYP3A4. In vivo, enzalutamide can be classified as a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer.

Therefore, co-administration of enzalutamide with CYP3A4, 2C9, and 2C19 substrates with a narrow therapeutic index should be avoided.

**Potential pharmacokinetic drug-drug interactions between enzalutamide and abiraterone:** We hypothesize that there will be a significant pharmacokinetic drug-drug interaction between enzalutamide and abiraterone because abiraterone is a strong inhibitor of CYP2C8 (in vitro) and enzalutamide is metabolized to N-desmethylenzalutamide in via CYP2C8 (and CYP3A4) thus potentially increasing enzalutamide AUC due to decreased metabolic clearance (enzalutamide product insert). In vivo, gemfibrozil an inhibitor of CYP2C8 increased enzalutamide + N desmethyl enzalutamide by 2.2 fold without a significant effect on C<sub>max</sub>. Additionally enzalutamide is a strong inducer of CYP3A4 in vitro and in vivo, this will increase the degradative metabolism of abiraterone sulfate (abiraterone metabolite) and indirectly effect abiraterone metabolism. In vivo, strong CYP3A4 inducers (Rifampin) decreased abiraterone AUC by 55%. [abiraterone and enzalutamide product inserts]

### 10.8.2 Objectives

1. To define the effect of abiraterone on reducing enzalutamide metabolic clearance (i.e. increasing enzalutamide AUC) when the drugs are used in combination.
2. To define the exposure (AUC) toxicity and exposure (AUC) anti-tumor effect relationship, including biomarkers for enzalutamide alone and enzalutamide combined with abiraterone in prostate cancer patients.
3. To develop a population pharmacokinetic model for enzalutamide alone and enzalutamide combined with abiraterone taking account of relevant intrinsic and extrinsic factors.
4. To determine the inpatient and outpatient variability of abiraterone exposure (AUC) in prostate cancer patients receiving abiraterone when combined with enzalutamide
5. To determine the intra-patient and inter-patient variability of enzalutamide exposure (AUC) in prostate cancer patients receiving enzalutamide alone and abiraterone plus enzalutamide.

### 10.8.3 Methods

For patients in the study who are receiving enzalutamide alone or enzalutamide plus abiraterone, venous blood samples for abiraterone/enzalutamide concentrations will be obtained at baseline, and at each scheduled follow-up clinic visit for up to six months while still receiving study drug therapy. These samples will have the time of day they were obtained documented. At these follow up visits a Patient Pharmacokinetic Questionnaire (see [Appendix II](#)) will be filled in which will request information about the prior 48h dosing of abiraterone/enzalutamide. This will detail the time of day the last two doses of study drug were taken, and relationship of when the doses were taken in relation to meals.

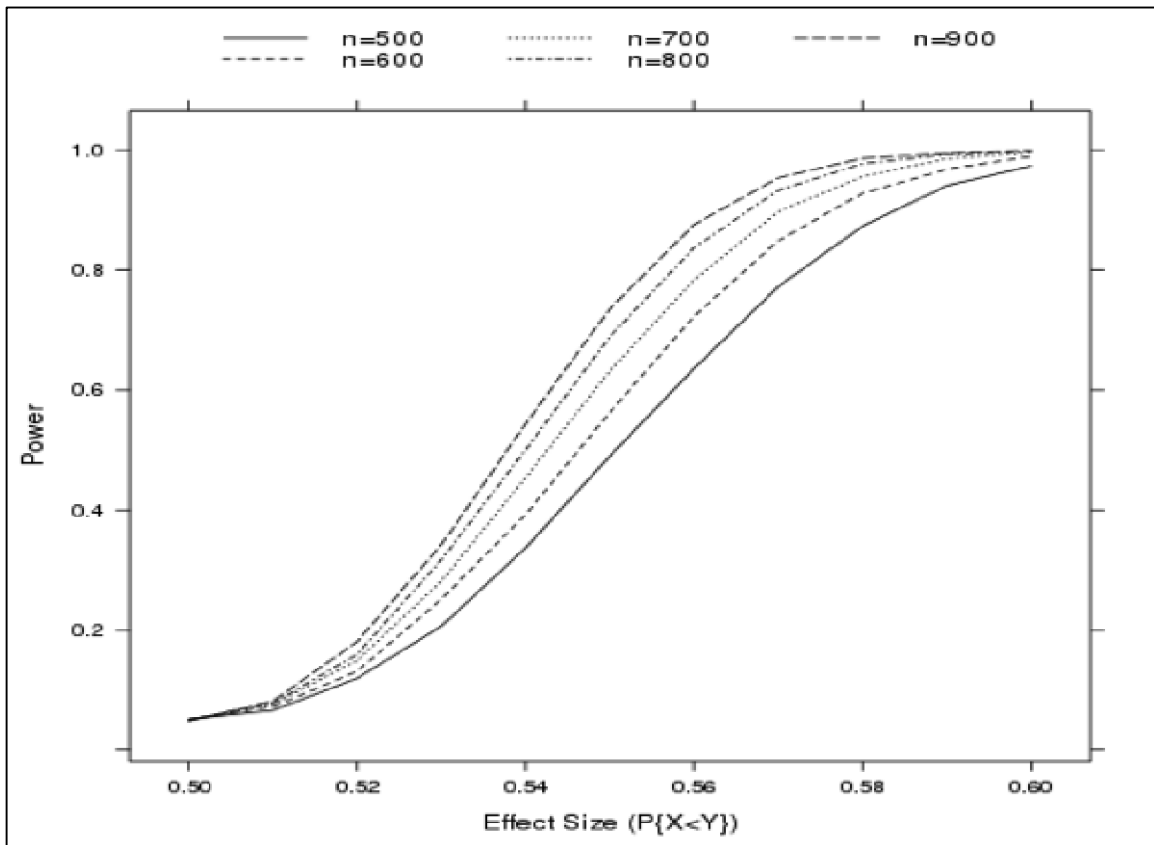
Drug concentrations will be measured using an LC-MS-MS assay validated in the Alliance Pharmacology/Pharmacokinetic core lab at the Univ. of Pittsburgh using a modification of the assay published by Gurav S., et al. Biomed Chromatogr. 2011. PMID: 22002259 for abiraterone, and a validated LC-MS-MS method for enzalutamide and the n-desmethyl-enzalutamide metabolite.

Pharmacokinetic population data modeling of the multiple drug concentrations will be performed using NONMEM to derive enzalutamide and abiraterone specific AUCs and the intra and inter-patient variability (see below for details).

#### 10.8.4 Statistical design:

The primary scientific hypothesis is that the metabolic clearance of enzalutamide is reduced when administered concomitantly with abiraterone. The corresponding statistical hypothesis is that the distribution of enzalutamide metabolic clearance is stochastically smaller in the combination arm.

We will test this hypothesis formally using the Wilcoxon rank sum test. The canonical effect size in this context is  $P[X < Y]$  where  $X$  and  $Y$  are random variates from the two population respectively. We propose to evaluate all con. We anticipate that the range for the sample size will be between 500 and 900 but will not exceed the study sample size based on the primary clinical study endpoint. For the power calculation illustrations, we will assume that  $X$  and  $Y$  are random variables from normal distributions with unit variance. The power as a function of the effect size, at the two-sided 0.05 level, for  $n=500, 600, 700, 800$  and  $900$  is shown in Figure 2 below. Each illustration is based on  $B=10000$  simulation replicates. The effect size will be visualized using a receiver operating characteristic (ROC) curve.



**Figure 2.**

We will also explore the relationship between toxicity and exposure, and anti-tumor effect and exposure. To incorporate additional baseline co-variates, including clinical risk factors, demographics and biomarkers, we will employ a standard regression framework

Population Pharmacokinetic Modeling: We will develop parametric population pharmacokinetics models for the exposure of enzalutamide alone and enzalutamide combined with abiraterone. To capture both between and within-subject variabilities in

both enzalutamide and abiraterone exposures, a non-linear mixed effects model will be used. In particular, we will consider models of the form

$$y_i [t] = \Psi [t, \theta, \eta_i; D, x] + \varepsilon_i [t]$$

where  $y_i [t]$  denotes the observed plasma concentration at time  $t$ ,  $t \in \{t_1, \dots, t_k\}$ , obtained through sparse sampling as previously described, for the  $i$ -th individual and  $\theta$  denotes the vector of population parameters of size  $p$ . The quantity  $D$  denotes the dose level and  $x$  is a vector of additional covariates. The random vectors  $\eta_i$  and  $\varepsilon_i = (\varepsilon_i[t_1], \dots, \varepsilon_i[t_k])$  account for the between and within subject variabilities respectively. If possible, non-linearities with respect to time will be explored. The model will be fitted using first-order conditional maximum likelihood estimation in the NONMEM program (version 5) [Reference: Beal, S. and L. Sheiner, NONMEM Users Guide. 1992, NONMEM Project Group, University of California at San Francisco: San Francisco]. For this purpose it will be assumed that the random effects  $\eta_1, \dots, \eta_n$  are independent  $q$ -variate mean-zero normal random variables with common variance  $\Sigma$  where  $q$  is at most equal to  $p$  (the dimension of the population parameter vector  $\theta$ ). It is also assumed that the measurement errors  $\varepsilon_1, \dots, \varepsilon_n$  are independent  $k$ -variate mean-zero normal vectors with common covariance matrix. Individual pharmacokinetic parameter estimates will be obtained from the estimated population PK model for both enzalutamide and abiraterone.

Covariate testing will be performed to identify sources of variability in exposure to enzalutamide and abiraterone among individuals. Covariates that will be tested include: demographic characteristics, organ function markers, disease severity, genetic markers, and concomitant medications and time relationship to ingestion of the previous meal. All derived PK parameters will be summarized using standard numerical and graphical displays.

**Pharmacometric Analyses:** Patients with pharmacokinetic, efficacy and key toxicity data will be included in the pharmacometric analyses. First a population pharmacokinetic approach will be employed to analyze the concentration-time data for enzalutamide and abiraterone. Relevant demographic and intrinsic/extrinsic factors will be explored for covariate relationship. Different empirical Bayesian PK parameters will be correlated with toxicity and efficacy endpoints such as the overall survival and safety endpoints. Pharmacokinetic-biomarker relationships using key markers will also be conducted.

## 11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

### 11.1 Qualified personnel

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

### 11.2 Enzalutamide (NSC #766085)

Enzalutamide, or MDV3100, has the chemical name 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide. The drug substance has no chiral centers and no salt forms are available at ~ pH 2 to 10. It is essentially insoluble in water, but partially soluble in lipid-based solutions. The drug substance is formulated in the surfactant Labrasol to create a self-emulsifying (or microemulsifying) dosage form.

Please refer to the package insert for additional information.

#### *Availability*

#### **For US Sites:**

Enzalutamide will be provided by Astellas directly to Investigators engaged in research under the Protocol, whose current IRB status has been verified by the Alliance. Enzalutamide may be ordered by completing the US order form provided by Astellas and posted on the CTSU Web site study page for A031201. For Canadian sites: Enzalutamide is supplied as 40 mg soft gelatin capsules in bottles containing 120 capsules.

The FDA has determined that enzalutamide is IND exempt for this study.

#### **For Canadian Sites:**

Enzalutamide will be provided by Astellas and distributed by Biologics. Enzalutamide may be ordered by completing the order form found at the CTSU Web site study page for A031201. Enzalutamide is supplied as 40 mg soft gelatin capsules in bottles containing 120 capsules.

The FDA has determined that enzalutamide is IND exempt for this study.

#### *Storage and Stability*

Enzalutamide should be stored at room temperature (68°- 77°F), with excursions permitted to 59°F to 86°F (15°C to 30°C).

#### *Drug accountability and returns*

The investigator, or designated qualified personnel must maintain an accurate record of the receipt, dispensing and disposal of enzalutamide using the NCI Investigational Agent Accountability Record Form for oral agent available at <http://ctep.cancer.gov/forms>. Drug returned by patients should be recorded on the Investigational Agent Accountability Record Form and disposed on site per local institutional standard of practices. Unused or expired drug should be destroyed per local institutional practice. U.S. sites are to provide Investigational Agent Accountability Record Forms to Astellas upon request and at study conclusion.

#### *Administration*

Enzalutamide will be administered once daily, orally. It may be administered without regard to meals. Capsules should be swallowed whole and not chewed or crushed. If dosing is missed on one day for any reason, double dosing should NOT occur the following day.

#### *Toxicities*

Enzalutamide is generally well tolerated.

Fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache have been seen at higher rates than with placebo for any grade toxicity. In addition, 7 cases of seizure (<1%) were seen in the enzalutamide group in the randomized clinical trial, with no cases in the placebo group.

The adverse events listed below are of interest to Astellas:

- Anorexia
- Asthenia/fatigue
- Dyspnea
- Renal failure/insufficiency
- Hepatic failure/insufficiency
- Neutrophil count decreased
- Cognitive impairment
- Spinal cord compression and cauda equina syndrome
- Seizure
- Fall
- Fracture
- Hallucination
- Nausea
- Vomiting
- Edema
- Hypokalemia
- Hypertension
- Cardiac failure
- Insomnia
- Rash
- Diarrhea
- Pruritus

For this trial, report adverse events as described in Sections [6.1.3](#) and [16.0](#).

#### *Potential drug interactions*

##### Drugs that Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers. Co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of enzalutamide with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of enzalutamide.

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

##### Drugs that Inhibit or Induce CYP3A4

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3 fold in healthy volunteers.

The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided if possible.

##### Effect of enzalutamide on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, enzalutamide reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

### 11.3 Abiraterone Acetate

Abiraterone acetate (hereafter, “abiraterone”) is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

Please refer to the package insert for additional information.

#### *Availability*

Abiraterone is commercially available as 250-mg tablets: oval, white to off-white and contain abiraterone and compendial (USP/NFIEP) grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified water, in descending order of concentration (the water is removed during tableting).

#### *Dosage and Administration:*

Abiraterone 1,000 mg will be administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone is taken and for at least one hour after it is taken.

#### *Warnings and Precautions:*

**Mineralocorticoid excess:** Use abiraterone with caution in patients with a history of cardiovascular disease. The safety of abiraterone in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established.

**Adrenocortical insufficiency:** Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

**Hepatotoxicity:** Increases in liver enzymes have lead to drug interruption, dose modification and/or discontinuation.

**Food Effect:** Abiraterone must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone is taken with meals.

#### *Toxicities:*

The most common adverse reactions ( $\geq 5\%$ ) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

#### *Drug interactions:*

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

#### Effects of Abiraterone on Drug Metabolizing Enzymes

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C<sub>max</sub> and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone 1,000 mg daily and prednisone 5 mg twice daily. Avoid coadministration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

### Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on in vitro data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone treatment.

## **11.4 Prednisone**

Please refer to the FDA-approved package insert for prednisone for product information, extensive preparation instructions, and a comprehensive list of adverse events.

### *Availability*

Prednisone is commercially available in 5 mg tablets.

### *Storage and stability*

Prednisone should be stored at room temperature.

### *Administration*

Prednisone is administered orally.

### *Toxicity*

Short-term use of prednisone (e.g.,  $\leq 4$  weeks) may be associated with gastrointestinal side effects (dyspepsia, ulceration); insomnia, nervousness, and occasionally, psychosis; and hyperglycemia. Immunosuppression with an increasing risk of infection is also seen.

More prolonged use may be associated with, in addition to the above, muscle weakness and muscle wasting; osteoporosis and fractures; hirsutism, acne, skin atrophy and easy bruising; sodium and water retention. Adrenal suppression can occur with long-term use, necessitating tapering rather than abrupt discontinuation, and the need for steroid coverage during stress. Occasionally, a withdrawal syndrome manifest by muscle aches and pains is seen upon discontinuation.

## **12.0 ANCILLARY THERAPY**

### **12.1 Supportive Care**

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate.

In addition, treatment of chronic and/or comorbid issues as they arise are permissible as long as they do not interfere with study treatments. For example, the following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:

- Steroids given at a maximum equivalent daily dose of 10 mg of prednisone;
- Pain therapy per standard of care and institutional guidelines for pain felt not to be due to progressive disease (e.g., for fragility fracture or pathologic fracture of an existing bone lesion without documentation of new lesions);
- Palliative surgical procedures to treat skeletal related events that are felt not to represent progressive disease (e.g., kyphoplasty for restoration of a fragility fracture or surgery and/or radiation therapy to address a pathologic fracture of an existing bone lesion in the absence of other indices of progressive disease).



## 12.2 Treatment with other chemotherapeutic agents

The concurrent administration of any other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists or antagonists), or immunotherapy is prohibited during protocol treatment. Use of other investigational drug therapy for any reason is prohibited.

## 12.3 Radiation therapy

Radiation therapy, including external beam radiotherapy, may not be administered except for the specific circumstance described in [Section 12.1](#) as part of supportive care.

Radium-223 may not be administered.

## 12.4 Growth Factors

The use of growth factors is not allowed for patients enrolled to this study. It is not anticipated that the treatments in this study will necessitate their use.

## 12.5 Zoledronic acid and denosumab

Treatment with zoledronic acid and/or denosumab may be initiated once patients has been on study treatment for at least two months and tolerance to study treatment has been established.

## 13.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE (SOLID TUMORS)

For the purposes of this study, patients should be reevaluated every 8 weeks for 6 cycles, then every 12 weeks. The timing of scans should be based off the initiation date of protocol treatment. The restaging schedule should be adhered to regardless of treatment holds or interruptions. In addition to a baseline scan, confirmatory scans should also be obtained at least 6 weeks following initial documentation of objective response.

### 13.1 Prostate Cancer Working Group 2 (PCWG2) response criteria

This study makes use of the PCWG2 response criteria, which is comprised of three distinct evaluation schemes:

- **Visceral lesions** will be assessed using a modified form of the RECIST 1.1 criteria as specified in [Section 13.2](#).
- **Lymph nodes** will not be assessed using RECIST 1.1; instead, customized criteria are specified in [Section 13.2](#).
- **Bone metastases** will be assessed using the PCWG2 criteria specified below in [Section 13.1](#).

PCWG2 discourages the use of overall response criteria, and in this protocol, overall response criteria will only apply to soft tissue lesions, will not incorporate bone lesions, and will not incorporate changes in tumor markers.

Tumor markers: neither PSA nor any other tumor marker will be used in this protocol for either defining in part or in whole progression or response. PSA will not be used to make treatment decisions either.

Bone lesions: Post-treatment changes will be described as “new lesions” or “no new lesions.” There will be no descriptions of post-treatment “responses” for bone metastases. As such, only progression will be defined in regards to bone lesions, using the following table as a descriptor.

Patients are defined as progressing when they meet bone or soft tissue progression (both are not required).

Please refer to [Appendix VI](#) for specific examples of how bone lesion progressions should be tracked and reported.

### Documentation for Radiographic Evidence of Disease Progression

Date Progression Detected (Visit) <sup>a</sup>	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9	Bone lesions: Two or more new lesions compared to <u>baseline</u> bone scan by PCWG2.	Timing: at least 6 weeks after progression identified or at Week 17 visit. <sup>b</sup>	Two or more new bone lesions on bone scan (compared to Week 9 scan).
	Soft tissue lesions: Progressive disease on CT or MRI per <a href="#">Section 13.2.3</a> .	Confirmation required for soft tissue disease (scan of same modality as demonstrated progression). <sup>b</sup>	Confirmation of progressive soft tissue disease per <a href="#">Section 13.2.3</a> .
Week 17	Bone lesions: Two or more new lesions on bone scan compared to <u>Week 9 bone scan</u> .	Timing: at least 6 weeks after progression identified or at Week 25 Visit. Required for bone lesions observed on bone scan. <sup>b</sup>	Persistent <sup>c</sup> or increase in number of bone lesions on bone scan compared to Week 17 scan.
	Soft tissue lesions: Progressive disease on CT or MRI per <a href="#">Section 13.2.3</a> .	No confirmatory scan required for soft tissue disease progression.	-----
Week 25 or later	Bone lesions: Two or more new lesions compared to <u>Week 9 bone scan</u> .	Timing: at least 6 weeks but no later than 12 weeks after progression identified. Required for bone lesions observed on bone scan. <sup>b</sup>	Persistent <sup>c</sup> or increase in number of lesions on bone scan compared to prior scan.
	Soft tissue lesions: Progressive disease on CT or MRI per <a href="#">Section 13.2.3</a> .	No confirmatory scan required for soft tissue disease.	-----

a Progression detected at an unscheduled visit either prior to Week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

b Confirmation must occur at the next available scan.

c For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

**Note:** For patients with a superscan (confluence of lesions across the axial skeleton such that distinguishing any new lesions is not possible), progression will be defined by clinical progression or progression by RECIST criteria.

## 13.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be chosen based on their suitability for accurate repetitive measurements. Lymph nodes need to be  $\geq 20$  mm in at least one dimension to be considered target or evaluable lesions to assess changes in size.

It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for all lesions, including nodes) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

**13.2.1 Complete Response:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in long axis to  $< 10$  mm.

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

**13.2.3 Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new non-osseous lesions is also considered progression). Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and at least 10 mm in diameter as assessed using calipers (e.g., skin nodules). Per PCWG2 and Cou302: Visceral (lung, liver adrenal) or extranodal lesions need to be  $\geq 10$  mm in one dimension, using spiral CT. However, lymph nodes need to be  $\geq 20$  mm in at least one dimension to be considered new.

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

### 13.3 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up. Non-target lesions include bone lesions.

**13.3.1 Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm long axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

**13.3.2 Non-complete response (non-CR)/Non-progression (non-PD):** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

**13.3.3 Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Whether new or pre-existing, lesions must be measurable per [Section 13.2.3](#) to be used to measure progression. For new bone lesions, adhere to bone progression criteria specified in [Section 13.1](#).

### 13.4 Evaluation of Best Overall Response

Measurable disease will be evaluated using the PCWG2 criteria in [Section 13.1](#).

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥ 4 wks confirmation*
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	≥ 4 wks confirmation*
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline*
PD	Any	Yes or No	PD	
Any	PD**	Yes or No	PD	No prior SD, PR or CR
Any	Any	Yes	PD	

\* Only for non-randomized trials with response as the primary endpoint.

\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-measurable (Non-Target) Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

\* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

### 13.5 Guidelines for Evaluation of Measurable Disease

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- 13.5.1 Clinical Lesions** will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- 13.5.2 Chest X-ray:** Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- 13.5.3 Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Visceral (lung, liver, adrenal) or extranodal lesions need to be  $\geq 10$  mm in one dimension if slice thickness is  $\leq 5$  mm; however, lymph nodes need to be  $\geq 20$  mm in at least one dimension to be considered evaluable lesions to assess for changes in size. MRI is also acceptable in certain situations (e.g., for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- 13.5.4 PET-CT** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.
- 13.5.5 Ultrasound (US)** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- 13.5.6 Endoscopy and Laparoscopy** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- 13.5.7 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.

## **13.6 Confirmation Measurement/Duration of Response**

### **13.6.1 Confirmation**

To confirm progressive measurable disease, it is recommended that confirmatory scans be performed after at least 6 weeks.

### **13.6.2 Duration of Overall Response**

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) 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).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

### **13.6.3 Duration of Stable Disease**

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.

## 14.0 END OF TREATMENT

### 14.1 Duration of treatment

Protocol therapy should be continued as long as the patient is tolerating the study drug and continues androgen deprivation therapy (i.e., surgical castration or ongoing GnRH analogue therapy) until confirmed radiographic disease progression AND one of the two following events: 1) initiation of other standard treatments for prostate cancer or 2) initiation of investigational agent for treatment of prostate cancer. Initiation of bisphosphonates or other approved bone protective agents are allowed as supportive treatment for worsening bone mineral density or fragility fracture during treatment and should not result in discontinuation of study drug therapy.

Patients who discontinue treatment will continue to be followed for radiographic progression (until disease progression has been confirmed, additional treatments for prostate cancer, and survival [5 years]).

### 14.2 Disease progression

Patients should continue protocol treatment until confirmed radiographic or unequivocal clinical progression. If the patient has radiographic progression but no unequivocal clinical progression and alternate treatment is not initiated, the patient may continue on study treatment, at the investigator's discretion. However, if patients have unequivocal clinical progression without radiographic progression, these patients are indicated for the current standard of care. Study treatment should be stopped and patients advised regarding available treatment options.

### 14.3 Extraordinary Medical Circumstances:

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on forms.
- Follow the patient for survival and secondary malignancy for a minimum of 5 years following registration.

## 15.0 STATISTICAL CONSIDERATIONS

This is a randomized, prospective phase III trial in which 1224 patients will be randomized will be randomized in 1:1 ratio to one of two treatment arms: arm A (enzalutamide) or Arm B (abiraterone plus enzalutamide). Randomization will be stratified on patients who received prior chemotherapy (yes, no) and risk-group stratification defined as low, intermediate, or high using the Halabi et al. nomogram<sup>55</sup>. Assignment to treatment arm will be performed centrally at the Alliance Statistical Center following determination of eligibility.

### 15.1 Sample Size Determination

The null and alternative hypotheses can be written as  $H_0: \Delta=1$  or  $H_a: \Delta=0.77$ , where  $\Delta$  is the hazard ratio defined as  $\lambda_{ArmB} / \lambda_{ArmA}$ .  $\lambda_{ArmA}$  represents the hazard of death for Arm A and  $\lambda_{ArmB}$  represents the hazard of death for Arm B. Under the alternative hypothesis, the expected number of deaths is 616 in the two arms. With this information, assuming failure time that follows an exponential distribution and a one-sided type I error rate = 0.025, the log-rank test has 90% power to detect a hazard ratio of 0.77 taking into account the planned schedule of the interim analyses. The median OS time in patients randomized to enzalutamide (arm A) who have not received first line chemotherapy is 35.3 months, but this is based on 200 events in the COU302. The target sample size will be 1,224. Regardless what the observed median OS time is in patients randomized to arm A, the final analysis will be conducted when 616 deaths has been observed.

Assuming a monthly accrual of rate of 34 patients, the target 616 deaths are expected to occur anywhere from 14 to 24 months post enrollment period depending on what the observed median OS time are in patients randomized to arms A and B.

Median OS time in Arm A (months)	Expected Median OS time in Arm B (months)	Sample Size	Accrual Period (months)	Follow-up (months)	Trial Duration (months)
27	35.1	1,224	36	14	50
30	39	1,224	36	18	53
33	42.9	1,224	36	21	57
36	46.8	1,224	36	24	60

**Table 7: Sample size and trial duration for various median OS time assuming a one-sided type I error rate of 0.025, power of 0.90, HR = 0.77, and accrual rate of 34 patients/month**

## 15.2 Interim Analysis

Efficacy (overall survival) results will be conducted on semiannual basis to coincide with the semiannual meetings of the Alliance Data and Safety Monitoring Board (DSMB). Under the alternative hypothesis, six hundred sixteen events (deaths) are expected at the end of the follow-up period. Assuming the accrual rate and failure rate in row 1 (Table 7), the first interim analysis for OS will be performed at about 37% of the full information (approximately 24 months after study activation). Other interim analyses will be performed at 55% (approximately 30 months), at 72% of the total information (approximately 36 months), at 87% (approximately 42 months), and at 100% (approximately 48 months after study activation). No interim analysis will be performed if there is not at least 10% increment in the information proportion compared to the previous interim analysis. To help insure complete data on which to base the interim analyses, institutions will be asked to submit survival status updates on their patients on a semi-annual basis while the trial is being monitored by the DSMB.

A Lan-Demets spending function analogue of a one-sided O'Brien-Fleming will be used to stop the trial early to reject the null hypothesis. Assuming the above percent information available at each look and a one-sided type I error rate = 0.025, the z-score boundaries for stopping for superiority for the OS endpoint and the z-score boundaries for stopping for futility under the alternative hypothesis using Friedlin et al., futility guidelines are presented in the table below. Should any boundary be crossed, accrual to the trial may be stopped.

Interim Analysis	Percent information (Number of deaths)	Boundaries for Interim Analysis for the OS endpoint Z value, nominal significance levels, and hazard ratio	
		For Superiority	For Futility
1 (18 months)	22% (135)		-1.645, 0.472, 1.012
2 (24 months)	37% (228)	3.392, 0.0003, 0.638	0.003, 0.501, 1.000
3 (30 months)	55% (339)	2.782, 0.003, 0.739	0.140, 0.556, 0.985
4 (36 months)	72% (444)	2.431, 0.008, 0.794	0.309, 0.621, 0.971
5 (42 months)	87% (536)	2.211, 0.013, 0.826	0.482, 0.685, 0.959
6 (Final)	100% (616)	2.063, 0.020, 0.847	2.063, 0.020, 0.847

**Table 8: Superiority and futility boundaries for each interim analysis**

## 15.3 Toxicity Monitoring

Extensive clinical data is available on enzalutamide and abiraterone/prednisone. We have no reason to believe that the combination of the two drugs will lead to increased toxicity, and there is no plan to do a separate phase I/II study of the combination. Given that the safety of



enzalutamide is well established, safety parameters will apply to the combination arm. Monthly conference calls (including the Study Chair, Committee Chair, study statisticians, data coordinator, protocol coordinator, and Alliance Executive Officer) will be held to monitor the first 120 patients randomized to the trial treated for 4 cycles due to unacceptable treatment-related events. Unacceptable toxicity will be defined as: treatment-related death and seizures.

It is assumed that the incidence of unacceptable toxicity in patients treated with enzalutamide is 1%. Unacceptable toxicity rates will be compared by the two treatment arms for the first 120 randomized patients to the study. We expect to accrue the first 120 patients at about 3.5 months after institutions have their IRBs approved the study. Three analyses at 50% (60 patients), 80% (72 patients), and 100% (120 patients) will be performed and will be discussed at all scheduled conference calls. If at any scheduled time of analysis the lower boundary of a one-sided 90% confidence interval for the difference in unacceptable toxicity exceeds 10%, accrual to the trial will be immediately suspended. The trial will remain closed until the review of all toxicity data is completed and a decision is made about whether it is safe to resume accrual. This decision will be made by consensus of the study team, the Alliance DSMB and CTEP. Institutions that do not submit adverse event forms in a timely manner may be denied future registrations to this study.

#### **15.4 Data Analysis**

An intent-to-treat approach will be used in this phase III study to analyze clinical outcomes (OS, PFS, radiographic PFS, post treatment decline in PSA and ORR) except toxicity. Patients who withdraw consent for treatment or withdraw from the study due to toxicity will continue to be followed for overall survival, even if they begin another therapy. The stratified log-rank statistic will be the primary analysis to compare the hypothesis on OS and PFS adjusting on the stratification factors (prior chemotherapy and risk group as determined by the Halabi nomogram<sup>55</sup>).

The Kaplan-Meier product-limit estimator will be used to estimate the OS, PFS and radiographic PFS distributions. In addition, the proportional hazards model will be used to assess the importance of each comparison adjusting on patient characteristics and stratification factors in predicting OS, PFS, and radiographic PFS.

Landmark analyses of rPFS at 6 months from randomization/registration will be performed to minimize lead-time bias. The associations between OS and PFS, and between OS and rPFS progression, will be investigated using a statistic that estimates Kendall's tau measure of association for bivariate time to event outcomes subject to censoring.

Furthermore, the Cochran-Mantel-Haenszel test will be used to compare the two arms on the proportion of patients who experience an objective response (defined as either a confirmed CR or a PR) and post-treatment decline in PSA adjusting on the stratification factors.

#### **15.5 Accrual Rate**

Based on previous data from patients enrolled on CALGB 90401, the accrual rate was 34 patients/month, accrual to this trial is expected to be completed in about 36 months within study activation as outlined in Table 10.

### 15.6 Inclusion of Women and Minorities

Minorities will be eligible for this study without alteration in eligibility criteria. We expect that the racial and ethnic composition of the patient group for the current trial will be similar to that seen in CALGB 90401.

Accrual Targets					
Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	0	+	51	=	51
Not Hispanic or Latino	0	+	1173	=	1173
<b>Ethnic Category: Total of all subjects</b>	0	+	1224	=	1224
Racial Category					
American Indian or Alaskan Native	0	+	5	=	5
Asian	0	+	9	=	9
Black or African American	0	+	126	=	126
Native Hawaiian or other Pacific Islander	0	+	1	=	1
White	0	+	1083	=	1083
<b>Racial Category: Total of all subjects</b>	0	+	1224	=	1224

### 16.0 EXPEDITED ADVERSE EVENT REPORTING

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the NCI CTEP Adverse Event Reporting System (CTEP-AERS).

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

**Please note that toxicity and routine AE reporting through RAVE will continue to use v4.0 after April 1, 2018.**

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance coordinated studies.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. Note that the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

**16.1 Alliance A031201 Reporting Requirements**

**Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of treatment<sup>1</sup>**

<p><b>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</b></p> <p><b>NOTE:</b> Investigators <b>MUST</b> immediately report to the sponsor (NCI) <b>ANY</b> Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</p> <p>An adverse event is considered serious if it results in <b>ANY</b> of the following outcomes:</p> <ol style="list-style-type: none"> <li>1) Death</li> <li>2) A life-threatening adverse event</li> <li>3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for <math>\geq 24</math> hours</li> <li>4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions</li> <li>5) A congenital anomaly/birth defect.</li> <li>6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).</li> </ol>				
<p><b>ALL SERIOUS</b> adverse events that meet the above criteria <b>MUST</b> be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.</p>				
<b>Hospitalization</b>	<b>Grade 1 Timeframes</b>	<b>Grade 2 Timeframes</b>	<b>Grade 3 Timeframes</b>	<b>Grade 4 &amp; 5 Timeframes</b>
Resulting in Hospitalization $\geq 24$ hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization $\geq 24$ hrs	Not required		10 Calendar Days	
<p><b>Expedited AE reporting timelines are defined as:</b></p> <ul style="list-style-type: none"> <li>o “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.</li> <li>o “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.</li> </ul>				
<p><sup>1</sup> Serious adverse events that occur more than 30 days after the last administration of treatment require reporting as follows:</p> <p><b>Expedited 24-hour notification followed by complete report within 5 calendar days for:</b></p> <ul style="list-style-type: none"> <li>• All Grade 4, and Grade 5 AEs that are at least possibly related to treatment</li> </ul> <p><b>Expedited 10 calendar day reports for:</b></p> <ul style="list-style-type: none"> <li>• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, and that are at least possibly related to treatment</li> <li>• Grade 3 adverse events that are at least possibly related to treatment</li> </ul>				

## 16.2 Additional Instructions or Exclusions

### **Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:**

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Note: A death on study requires both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.
- After April 1, 2018, death due to progressive disease should be reported as Grade 5 “Disease progression” in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.
- Treatment expected adverse events include those listed in [Section 6.1.3](#) and in the package insert.
- Any seizures occurring on A031201 should be reported via CTEP-AERS within 10 calendar days.
- When evaluating hypertension, consider the description of severity grade 3 relative to the last AE reporting period. That is, for “more than one drug or more intensive therapy than previously used,” “previously” should be considered the last reporting period. A regimen more intensive than a previous reporting period need only prompt expedited reporting the first time that it is used. If BP is stable on the more intensive regimen, do not continue to report grade 3 HTN via CTEP-AERS.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e., solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and in situ tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified—other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how it was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in the partner of a male patient during therapy or within 28 days after completion of treatment on A031201 must be reported via CTEP-AERS. In CTCAE version 4.0 (until March 31, 2018) or version 5.0 (after April 1, 2018), use the event term, “*pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade 4)*”.
  - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
  - The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring

after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP-AERS.

- After April 1, 2018, pregnancy loss is defined in CTCAE as “Death in utero.”
  - Any pregnancy loss should be reported expeditiously, as Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
  - A neonatal death should be reported expeditiously as Grade 4, “Death neonatal) under the General disorders and administration SOC.
  - In the case of partners of male patients, no interaction with the pregnant partner is required. It is anticipated that any information about these pregnancies will be obtained from the patient.
- The reporting of adverse events described above is in addition to, and does not supplant, the reporting of adverse events as part of the reporting of the results of the clinical trial, e.g. routine reporting.

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**APPENDIX I: REGISTRATION FATIGUE/UNISCALE ASSESSMENT**

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded in Medidata Rave®.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

A translator may be used to administer the assessment. Additionally, since NCIC is participating in A031201, a French version of the assessment has been provided on the following page.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be



**APPENDIX II: BPI-SF QUESTION #3 AND PHARMACOKINETICS PATIENT QUESTIONNAIRE**

**Brief Pain Index-Short Form Question #3**

Prospective patients for this study should be asked the question below for the purposes of determining eligibility per [Section 4.6.3](#):

Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours:

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7	<input type="checkbox"/> 8	<input type="checkbox"/> 9	<input type="checkbox"/> 10
No pain										Pain as bad as you can imagine

**Pharmacokinetics Patient Questionnaire**

**Date:**

**The following questions refer to the day before yesterday (2 days ago):**

- What time did you take your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
- What time did you last eat before taking your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
- What time did you first eat after taking your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM

**The following questions refer to yesterday (1 day ago):**

- What time did you take your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
- What time did you last eat before taking your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
- What time did you first eat after taking your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM

**The following questions refer to today (ONLY APPLIES IF YOU HAVE TAKEN YOUR STUDY MEDICATION BEFORE BEING SEEN IN THE CLINIC TODAY):**

- What time did you take your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
  - What time did you last eat before taking your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
  - What time did you first eat after taking your study medication (*enzalutamide*)?      \_\_ : \_\_    AM / PM
- 

**The following questions only need to be answered if you are taking abiraterone.**

**The following questions refer to the day before yesterday (2 days ago):**

- What time did you take your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM
- What time did you last eat before taking your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM
- What time did you first eat after taking your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM

**The following questions refer to yesterday (1 day ago):**

- What time did you take your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM
- What time did you last eat before taking your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM
- What time did you first eat after taking your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM

**The following questions refer to today (ONLY APPLIES IF YOU HAVE TAKEN YOUR STUDY MEDICATION BEFORE BEING SEEN IN THE CLINIC TODAY):**

- What time did you take your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM
- What time did you last eat before taking your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM
- What time did you first eat after taking your study medication (*abiraterone*)?      \_\_ : \_\_    AM / PM

**APPENDIX III: PATIENT MEDICATION LOGS**

**Enzalutamide Medication Log (Arms A and B)**

Number of Pills Given: \_\_\_\_\_  
Total Daily Dose: \_\_\_\_\_

Pill Bottle(s) returned: Circle Yes or No  
Number of Pills returned: \_\_\_\_\_

*(To be completed by RN)*

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

**SPECIAL INSTRUCTIONS**

1. Take enzalutamide capsules orally in the morning with or without food. The capsules should be swallowed whole and must not be crushed or broken.
2. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose.
  - a. If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled
  - b. Remember to record missed doses
3. If vomiting occurs after taking enzalutamide, do not take a replacement dose on that day. Resume at the next scheduled dose
4. Enzalutamide capsules should be stored at room temperature



CYCLE #: \_\_\_\_\_ # of WEEKS \_\_\_\_\_

DAY	Medication	DATE	TIME		Number of 40 mg capsules taken	Comments
<i>Example</i>	Enzalutamide	07/01/2012	9:00	AM	4	
1	Enzalutamide			AM		
2	Enzalutamide			AM		
3	Enzalutamide			AM		
4	Enzalutamide			AM		
5	Enzalutamide			AM		
6	Enzalutamide			AM		
7	Enzalutamide			AM		
8	Enzalutamide			AM		
9	Enzalutamide			AM		
10	Enzalutamide			AM		
11	Enzalutamide			AM		
12	Enzalutamide			AM		
13	Enzalutamide			AM		
14	Enzalutamide			AM		
15	Enzalutamide			AM		
16	Enzalutamide			AM		
17	Enzalutamide			AM		
18	Enzalutamide			AM		
19	Enzalutamide			AM		
20	Enzalutamide			AM		
21	Enzalutamide			AM		
22	Enzalutamide			AM		
23	Enzalutamide			AM		
24	Enzalutamide			AM		
25	Enzalutamide			AM		
26	Enzalutamide			AM		
27	Enzalutamide			AM		
28	Enzalutamide			AM		

Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Consenting Professional/Research RN Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Comments: \_\_\_\_\_

**Abiraterone Medication Log (Arm B)**

Number of Pills Given: \_\_\_\_\_

Total Daily Dose: \_\_\_\_\_

*(To be completed by RN)*

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

**SPECIAL INSTRUCTIONS**

1. Abiraterone must be taken on an empty stomach. Take abiraterone tablets orally in the evening without food at least 1 hour before OR 2 hours after a meal. The tablets should be swallowed whole and must not be crushed or broken.
2. If a dose is missed, please take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose
  - a. If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled
3. If vomiting occurs after taking abiraterone, do not take a replacement dose on that day. Resume at the next scheduled dose
4. Abiraterone tablets should be stored at room temperature

CYCLE #: \_\_\_\_\_ # of WEEKS \_\_\_\_\_

DAY	Medication	DATE	TIME		Number of 250 mg tablets taken	Comments
<i>Example</i>	Abiraterone	07/01/2012	9:00	PM	4	
1	Abiraterone			PM		
2	Abiraterone			PM		
3	Abiraterone			PM		
4	Abiraterone			PM		
5	Abiraterone			PM		
6	Abiraterone			PM		
7	Abiraterone			PM		
8	Abiraterone			PM		
9	Abiraterone			PM		
10	Abiraterone			PM		
11	Abiraterone			PM		
12	Abiraterone			PM		
13	Abiraterone			PM		
14	Abiraterone			PM		
15	Abiraterone			PM		
16	Abiraterone			PM		
17	Abiraterone			PM		
18	Abiraterone			PM		
19	Abiraterone			PM		
20	Abiraterone			PM		
21	Abiraterone			PM		
22	Abiraterone			PM		
23	Abiraterone			PM		
24	Abiraterone			PM		
25	Abiraterone			PM		
26	Abiraterone			PM		
27	Abiraterone			PM		
28	Abiraterone			PM		

Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Consenting Professional/Research RN Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Comments: \_\_\_\_\_

**Prednisone Medication Log (Arm B)**

Number of Pills Given: \_\_\_\_\_

Total Daily Dose: \_\_\_\_\_

*(To be completed by RN)*

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

**SPECIAL INSTRUCTIONS**

1. Take one prednisone tablet orally in the morning and in the evening with or without food.
2. If a dose is missed, please take the dose as soon as possible, but only if there are 6 or more hours remaining before the next dose
  - a. If the dose is due in less than 6 hours, skip the missed dose and take the next dose as scheduled
3. If vomiting occurs after taking prednisone, do not take a replacement dose on that day. Resume at the next scheduled dose
4. Prednisone tablets should be stored at room temperature

CYCLE #: \_\_\_\_\_ # of WEEKS \_\_\_\_\_

DAY	Medication	DATE	TIME		TIME		Number of 5 mg tablets taken (AM/PM)	Comments
<i>Example</i>	Prednisone	07/01/2012	9:00	AM	9:00	PM	1/1	
1	Prednisone			AM		PM		
2	Prednisone			AM		PM		
3	Prednisone			AM		PM		
4	Prednisone			AM		PM		
5	Prednisone			AM		PM		
6	Prednisone			AM		PM		
7	Prednisone			AM		PM		
8	Prednisone			AM		PM		
9	Prednisone			AM		PM		
10	Prednisone			AM		PM		
11	Prednisone			AM		PM		
12	Prednisone			AM		PM		
13	Prednisone			AM		PM		
14	Prednisone			AM		PM		
15	Prednisone			AM		PM		
16	Prednisone			AM		PM		
17	Prednisone			AM		PM		
18	Prednisone			AM		PM		
19	Prednisone			AM		PM		
20	Prednisone			AM		PM		
21	Prednisone			AM		PM		
22	Prednisone			AM		PM		
23	Prednisone			AM		PM		
24	Prednisone			AM		PM		
25	Prednisone			AM		PM		
26	Prednisone			AM		PM		
27	Prednisone			AM		PM		
28	Prednisone			AM		PM		

Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Consenting Professional/Research RN Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Comments: \_\_\_\_\_

**APPENDIX IV: GUIDE TO THE HALABI NOMOGRAM ON-LINE CALCULATOR**

1. Access the Halabi Nomogram at:  
<https://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html>
2. In the top right, ensure that “NO” is selected for “Display Output?” This will remove redundant statistical details from the output and just provide the results needed for this trial.
3. For “Risk Group Classification Question”, ensure that “3 Groups” is selected.
4. Respond to all of the remaining questions. Note that you can view the valid lab ranges by hovering your pointer over the lab name. Those valid ranges are:
  - a. Albumin: 0 - 10 g/dL
  - b. Hemoglobin: 6.0 - 17.0 g/dL
  - c. Alkaline Phosphatase: 1.0 - 9,000.0 U/L
  - d. PSA: 1.0 - 9,000.0 ng/mL
  - e. Opioid Analgesic use (yes, no)
  - f. LDH > 1 X ULN (yes, no)
5. Once all questions have been answered, click the “Validate!” button. This will refresh the screen with the predicted risk grouping for the patient based on the provided data.
6. Save the results as a PDF by clicking the “PDF” link and upload the PDF via Medidata Rave® into the form for “Supporting Documentation” in the Baseline folder.
7. Note the risk grouping marked “Yes”: Low, Intermediate, or High. This is the value that must be entered as a stratification factor during Step 1 of the OPEN registration process.

**APPENDIX V: PCWG2 BONE SCAN ASSESSMENT TOOL GUIDE**

This study will use the Prostate Cancer Working Group 2 (PCWG2) response criteria for evaluating bone metastases for progression. This study will use Medidata Rave® for remote data capture of all study data.

This appendix includes the official validated forms on which the A031201 data collection is based. The forms within this appendix are provided for your information and guidance only. You may use these forms at your discretion for local record keeping, but these forms are not required for A031201 data capture and if used these forms should not be uploaded to Medidata Rave®.

**In the Week 9 and Post Week 9 Bone Scan Assessment Forms, the tracer uptake question is asking if what is viewed on the bone scan is related to metastatic disease, as opposed to arthritic lesions or traumatic injuries.**

**If a patient has metastatic disease on the scans but no new lesions in comparison to the appropriate reference scan, the tracer uptake question may be answered “yes,” new regions may be left blank, and the number of new lesions would be zero.**


**The baseline scan serves as the "reference" scan at Week 9 restaging. The Week 9 scan serves as the "reference" scan for all subsequent scans. Please reference [Section 13.1](#) for further details.**

NOTE: Medidata Rave® does not collect exact locations of new metastases using a skeletal template for this study, as is depicted in these forms. It is sufficient to collect region of new disease in Medidata Rave®.

**Baseline Bone Scan Assessment Form**


<b>PCCTC Bone Scan Assessment Tool</b>			
<b>BASELINE Scan</b> Date: (    /    /    )			
Patient Identifier:			
Protocol Number:		Protocol Start Date:	
<b>Is tracer uptake related to metastatic disease?</b> <input type="radio"/> Yes <input type="radio"/> No <small>NOTE: If "NO", do not fill out the form below</small>			
<b>If yes, indicate total number of lesions related to metastatic disease</b> (select one)			
<input type="radio"/> 1 <input type="radio"/> 2-4 <input type="radio"/> 5-9 <input type="radio"/> 10-20 <input type="radio"/> >20			
Comments		Investigator's Signature	
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Week 9 Bone Scan Assessment Form

<b>PCCTC Bone Scan Assessment Tool</b>	
<b>Week 9 Scan</b> Date: ( ___ / ___ / ___ )	
Patient Identifier:	
Protocol Number:	Protocol Start Date:
<p><b>Is tracer uptake related to metastatic disease?</b></p> <p style="text-align: center;"><input type="radio"/> Yes <input type="radio"/> No</p> <p style="text-align: center;"><i>NOTE: If "NO", do not fill out the form below</i></p>	
<b>Draw site(s) of NEW lesion(s) on skeleton</b>	
<p><b>Check Region(s) of NEW Disease:</b></p> <p><input type="checkbox"/> Skull</p> <p><input type="checkbox"/> Thorax</p> <p><input type="checkbox"/> Spine</p> <p><input type="checkbox"/> Pelvis</p> <p><input type="checkbox"/> Extremities</p>	
<p><b>If yes, indicate total number of NEW lesions compared to <u>Baseline Scan</u> (Date: ___ / ___ / ___ )</b></p> <p style="text-align: center;">(select one)</p> <p style="text-align: center;"> <input type="radio"/> 0                    <input type="radio"/> 1                    <input type="radio"/> 2                    <input type="radio"/> 3                    <input type="radio"/> 4                    <input type="radio"/> 5                    <input type="radio"/> &gt;5             </p>	
<i>*Presence of new lesions at this time does not confirm progression *</i>	
<p><b>Clinical Impression (circle one)</b></p> <p style="text-align: center;"> <input type="radio"/> Improved                    <input type="radio"/> Stable                    <input type="radio"/> Progression             </p>	
Comments	Investigator's Signature
<p><small>Version 2.0</small> <span style="float: right;"><small>© 2010, MCRCC</small></span></p>	



Post-Week 9 Bone Scan Assessment Form

<b>PCCTC Bone Scan Assessment Tool</b>			
<b>_____ Week Scan</b> Date: ( ___ / ___ / ___ ) <b>**To be compared to Week 9 Scan**</b>			
Patient Identifier:			
Protocol Number:		Protocol Start Date:	
<b>Is tracer uptake related to metastatic disease?</b> <input type="radio"/> Yes <input type="radio"/> No <i>NOTE: If "NO", do not fill out the form below</i>			
<b>Draw site(s) of NEW lesion(s) on skeleton</b>			
<b>Check Region(s) of NEW Disease:</b> <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities			
If yes, indicate total number of NEW lesions compared to <u>Week 9 Scan</u> (Date: ___ / ___ / ___ ) (select one)			
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> >5			
<b>Clinical Impression (circle one)</b> <input type="radio"/> Improved <input type="radio"/> Stable <input type="radio"/> Progression			
Comments			Investigator's Signature
Version 2.0 <span style="float: right; font-size: small;">© 2010, MRCOC</span>			

Progression Assessment Worksheet

<b>PCCTC Bone Scan Assessment Tool</b>			
<b>Progression Assessment Worksheet</b>			
Patient Identifier:			
Protocol Number:		Protocol Start Date:	
Date of Scan: _____ / _____ / _____			
<p><b>1. Are there 2 or more new lesions compared to the WEEK 9 SCAN?</b></p> <p><input type="radio"/> Yes    <input type="radio"/> No</p> <p><i>If YES, proceed to question 2.</i></p> <p><i>If NO, the patient does not have radiographic progression by bone scan.</i></p>			
<p><b>2. Is this the first scan performed POST the WEEK 9 SCAN?</b></p> <p><input type="radio"/> Yes    <input type="radio"/> No</p> <p><i>If YES, proceed to question 3A. If NO, proceed to question 3B.</i></p>			
<p><b>3A. Were there 2 or more new lesions at the WEEK 9 SCAN compared to the BASELINE SCAN?</b></p> <p><input type="radio"/> Yes    <input type="radio"/> No</p>		<p><b>3B. Does this scan confirm the presence of 2 or more new lesions seen since the WEEK 9 SCAN?</b></p> <p><input type="radio"/> Yes    <input type="radio"/> No</p>	
<p><i>If YES, patient has met conditions for radiographic progression by bone scan.</i></p> <p><i>If NO, the patient does not have radiographic progression by bone scan.</i></p>			
Comments		Investigator's Signature	
Version 2.0		© 2010, MSKCC	

**APPENDIX VI: PCWG2 PROGRESSION SCENARIOS**