TITLE: A prospective randomized pilot study evaluating the food effect on the pharmacokinetics and pharmacodynamics of abiraterone acetate in men with castrate resistant prostate cancer

Coordinating Center: University of Chicago

***Principal Investigator:**
Russell Szmulewitz, MD
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115
Chicago, IL 60637
773-702-7609
773-702-3163
rszmulew@medicine.bsd.uchicago.edu

Co-Investigators:
Mark J. Ratain, MD
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115

Walter M. Stadler, MD
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115

Peter O'Donnell, MD
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115

Olwen Hahn, MD
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115

William Douglas Figg Sr., Pharm.D., M.B.A
Senior Scientist and Head of the Clinical Pharmacology Program and Molecular Pharmacology Section,
Medical Oncology Branch
National Cancer Institute
National Institutes of Health
Bldg 10/Room 5A01
9000 Rockville Pike
Bethesda, MD 20892

Statistician:
Theodore Karrison, PhD
Dept. of Health Studies, MC2007
5841 S. Maryland Avenue
Chicago, IL 60637
tkarrison@health.bsd.uchicago.edu

Responsible Research Nurse:
Elia Martinez, R.N.
University of Chicago, Department of Medicine

Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115
773-702-4135
emartinez1@medicine.bsd.uchicago.edu

Responsible Data Manager/Study Coordinator:

Jaclyn D. Peterson
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115
773-834-1746
773-702-4889
jdpeterson@medicine.bsd.uchicago.edu

Pharmacokinetic Laboratory Coordinator :

Cody Peer
National Cancer Institute
National Institutes of Health
Bldg 10/Room 5A01
9000 Rockville Pike
Bethesda, MD 20892

Co-Investigator	Maha Hussain, M.D. University of Michigan Comprehensive Cancer Center
Co-Investigator	Bruce Brockstein, M.D. NorthShore Healthcare
Co-Investigator	John Godwin, M.D. Southern Illinois School of Medicine
Co-Investigator	Sreenivasa Nattam, M.D. Fort Wayne Oncology/Hematology
Co-Investigator	Mark K. Kozloff, M.D. Ingalls Cancer Research Center
Co-Investigator	Sachdev Thomas, M.D. Illinois Cancer Care Peoria
Co-Investigator	Tim Kuzel, M.D. Northwestern Memorial Hospital
Co-Investigator	Bradley Carthon, MD, PhD Emory University
Co-Investigator	Yong Wei Peng, M.D. National University Cancer Institute, Singapore (NCIS)

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SUMMARY

Study Design: In this open label, two-arm study, patients with castrate resistant prostate cancer will be randomized to administer abiraterone acetate 1000mg by mouth daily in the fasting state or abiraterone acetate 250mg by mouth daily with a conventional low fat breakfast. In addition, pharmacokinetic samples and standard laboratory studies will be collected.

Eligible Patients: Patients must have histologically confirmed prostate cancer with evidence of castration resistance defined as rising PSA or clinical/radiographic progression following androgen deprivation, as well as anti-androgen therapy and anti-androgen withdrawal. Patients must have an ECOG performance status of ≤ 2 and have adequate bone marrow, liver and renal function.

Primary Objective: To compare the effect of a lower dose (250mg) of abiraterone acetate in the prandial state to the currently recommended higher dose (1000mg) taken in the fasting state, with prostate specific antigen (PSA) response rate as a pharmacodynamic marker.

Secondary Objectives: To evaluate the effect of prandial states on the pharmacokinetic properties (T_{Max}, C_{Max} means and variability), pharmacodynamic properties (change in extra-gonadal androgen levels), progression-free survival, and safety profile of abiraterone acetate.

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1. BACKGROUND

1.1. Castrate Resistant Prostate Cancer (CRPC)

Although most men are diagnosed with early stage, curable prostate cancer, unfortunately, prostate cancer recurrence is seen in ~40% of patients over time[1]. Androgen deprivation therapy (ADT) remains the mainstay of treatment and induces a remission in 80 to 90% of patients with advanced disease and results in a median progression-free survival of 12 to 33 months, at which time an androgen independent phenotype usually emerges. This accounts for the median overall survival of 23 to 37 months from the initiation of androgen deprivation. This transition represents an important clinical landmark of an evolving disease that correlates with an increased risk of death and morbidity[2]. This year ~32,000 men are projected to die from prostate cancer, the vast majority of whom will die from metastatic castration resistant disease (mCRPC) with bone metastases[3]. The effective therapies for progressive CRPC are limited with docetaxel and cabazitaxel chemotherapies, the novel immunotherapy sipuleucel-T, and the steroidal enzyme inhibitor abiraterone acetate as the only currently FDA approved therapies shown to improve patient survival in the CRPC setting [4,5, 6-8].

1.2. Mechanisms of Castrate Resistant Prostate Cancer Growth

Androgen deprivation can be achieved surgically with orchiectomy or by pharmacologic means. Current approaches to ADT use leutinizing hormone releasing hormone (LHRH) agonists. The mechanism of action is by causing the continuous stimulation of the anterior pituitary leading to the inhibition of leutinizing hormone (LH) secretion and ultimately the disruption of testicular production of testosterone. Although AD has been effective in the majority of patients, studies have shown that extratesticular sources of testosterone represent an important alternative source of androgen stimulation in a significant proportion of prostate cancer patients. Due to the peripheral conversion of adrenal steroids to testosterone, as much as 10% of baseline circulating testosterone remains in castrate men[9]. In prostate cancer xenograft models, increased levels of androgen receptor have been observed and appear to be resistant to antiandrogens[10]. This could result in amplified signal output from low levels of circulating adrenal androgens, thus suggesting a role for agents that target the adrenal androgen synthesis pathway.

1.3. Adrenal Androgens Production

If adrenal androgen production is an important cause of relapse after primary hormonal treatment, inhibitors of 17a-hydroxylase/$C_{17,20}$-lyase, may prove useful as a second-line treatment. The adrenal steroid synthesis pathway is shown below in Figure 1. The CYP17 complex of enzymes, (c17-lyase and 17,20 hydroxylase) are the primary enzymes responsible for extra-gonadal, adrenal androgen production in that they lead to the production of dihydroepiandrostenedione and androstenedione. As the figure demonstrates, inhibition of CYP17 will lead to a reduction of adrenal androgen production (dihydroepiandrostenedione, androstenedione).

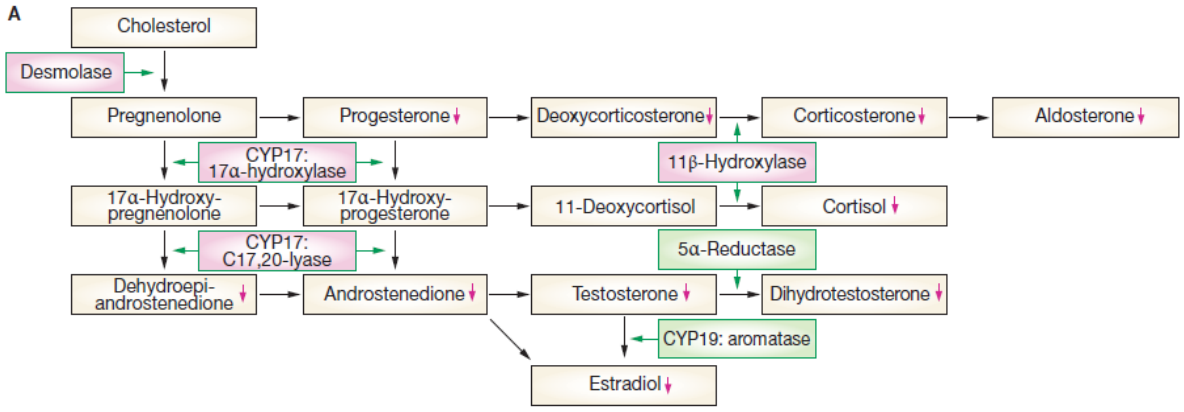

Figure 1: The adrenal steroid synthesis pathway, adapted from Reid et al[11].

1.4. Abiraterone Acetate (CB7630)

Abiraterone Acetate (CP7630) is the 3-acetate and prodrug of CB7598 suitable for oral administration. Abiraterone [CB7598, 17-(3-pyridyl) androsta-5,16-dien-3β-ol] was developed as a tight-binding steroidal inhibitor of CYP17 (17α-hydroxylase/$C_{17,20}$-lyase), with two important enzymatic activities in the synthesis of testosterone, based on the observation that nonsteroidal 3-pyridyl esters had improved selectivity for inhibition of 17α-hydroxylase/$C_{17,20}$-lyase (12). CP7598 is a potent inhibitor with an apparent inhibition constant of 0.5 nM. The chemical nomenclature of CB7630 is 3β-acteoxy-17-(3-pyridyl)androsta-5,16-diene; its empirical formula is $C_{26}H_{33}NO_2$. It has a molecular weight of 381.55. Once absorbed after oral administration, CB7630 is rapidly converted to the active form, CB7598 (Figure 2). CB7598 was the predominant, if not the only form of abiraterone detected in blood both in preclinical studies and in previously conducted clinical studies.

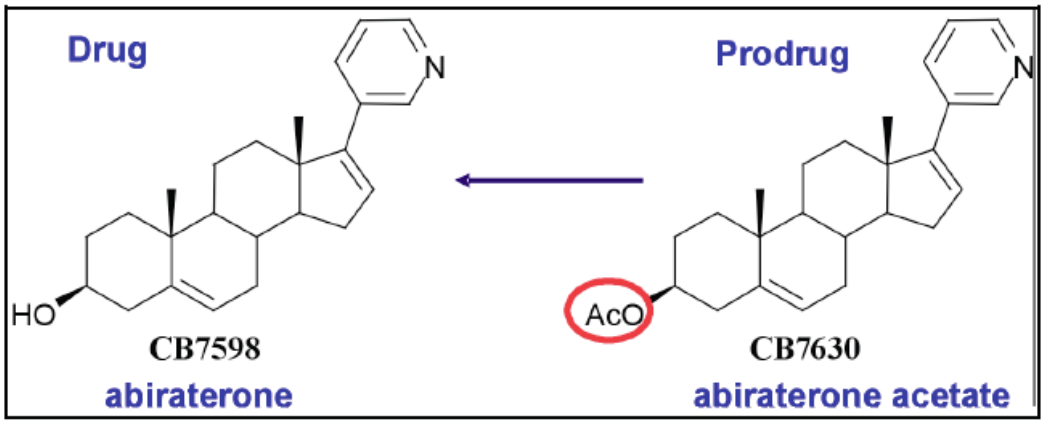

Figure 2: Prodrug abiraterone acetate conversion to abiraterone after absorption.

1.5. Clinical Data with Abiraterone Acetate in Prostate Cancer

To determine if inhibition of 17alpha-hydroxylase/C17,20 lyase could indeed suppress adrenal testosterone production in humans as predicted from mechanism of action and animal models, three phase I exploratory studies of CB7630 (abiraterone acetate) were conducted in the United Kingdom in castrated or non-castrated patients with prostate cancer. Overall, the results of these studies showed that abiraterone acetate was safe and well tolerated, and resulted in a significant

PSA response rate[12,13]. Based on these preliminary studies, several phase II clinical trials in castrate resistant prostate cancer were undertaken and confirmed the impact of abiraterone acetate on PSA in both chemotherapy naïve and treated patients[14,15]. Most recently, the seminal phase III study of abiraterone acetate versus placebo in patients with CRPC with previous failure of docetaxel based chemotherapy reported a significant improvement in overall survival benefitting abiraterone (14.8 vs. 10.9 months, P<0.001)[8]. Abiraterone acetate is well tolerated with the most common toxicities being those of mineralocorticoid excess, including hypertension, edema, and hypokalemia, with no adverse event in either arm of the phase III study seen in >2% of patients.. Abiraterone with prednisone is also effective in the chemotherapy naïve population, where it was proven superior to prednisone alone[16] Based on these studies, abiraterone acetate at 1000mg daily dose in the fasting state, along with 5mg twice-daily prednisone was approved by the Food and Drug Administration (FDA) for use in patients with metastatic CRPC after failure of docetaxel chemotherapy[17]. It is now a standard of care in this patient population.

1.6 Clinical Pharmacokinetics

Blood specimens from phase I studies were analyzed for CB7598 (abiraterone). The pharmacokinetic parameters all show considerable variability between patients and are presented in Table 1. The mean Tmax was 2.70 hours (± SD 2.71) with a mean elimination half-life of 27.6 hours (± SD 20.2). A range of up to 10-fold in AUC was seen for a given dose. The level of inter-patient variability made analysis of dose-dependent pharmacokinetic relationships difficult. Further investigation is required in clinical trials, especially with administering abiraterone with food.

1.7 Clinical Pharmacokinetics with Food

While oral drugs are generally easier for patients, they are much more complex from a pharmacokinetic perspective. In particular, one needs to be concerned regarding low and/or variable bioavailability, drug-food interactions, and a greater potential for drug-drug interactions[18].

Food can alter pharmacokinetics of a drug and subsequently have clinically significant consequences. Various mechanisms have been proposed as a means by which food can alter pharmacokinetics of a drug. These include: delayed gastric emptying, increased biliary flow, changes in gastrointestinal pH, increased splanchnic blood flow, or change in luminal metabolism of a drug. Generally, food effects on pharmacokinetics have the highest impact when the drug is administered shortly after a meal. It is also known that calorie and fat contents of meals would have significant implications on the bioavailability of a drug as different types of meals are likely to have varying impacts on gastrointestinal physiology in relation to a drug disposition[18,19].

A significant food effect on pharmacokinetic profiles of orally administered anticancer agents and their metabolites have been observed with existing oral anticancer agents. As an example, high fat meals have been shown to significantly increase Lapatinib's bioavailability and systemic exposure[20]. However, this significant effect on pharmacokinetics of lapatinib was not appropriately addressed in its registration trial and in the subsequent FDA label[21]. Consequently, the efforts to optimize the drug efficacy and safety by taking advantage of this knowledge have been delayed: a study of lower dose of lapatinib with food for example. This missed opportunity is the result of inadequately addressing critical pharmacokinetics issues early on in the drug development process before undertaking large phase III trials[22].

1.7.1 Abiraterone pharmacokinetics with food

The effect of food on abiraterone administration has been tested previously in two phase I studies. In a UK study, patients who received abiraterone at 1000mg or 2000mg were randomly assigned to receive single dose abiraterone five days apart either after an overnight fast or with a high-fat meal prior to continuous dosing. Pharmacokinetic samples were obtained and showed that when administered with a high-fat meal, abiraterone drug exposure was increased by 4.4-fold (P = 0.049). There was no significant increase in C_{max}, but absorption was significantly extended after food[13]. Similarly, in a phase I study conducted in the US, the effect of food with abiraterone was examined after single dose administration either in the fasting state or with a high calorie breakfast in four escalating dose cohorts (250, 500, 750, and 1000mg). The small number of patients per cohort and the high degree of inter-patient variability limited further interpretation. However, the authors did find that abiraterone exposures appeared to be higher in fed patients, suggestive of a food effect[23]. Currently, the FDA label for abiraterone states that though there is food effect seen with this drug, abiraterone is recommended only to be taken on an empty stomach[17]. Further rationale for performing a food effect study with abiraterone is warranted because the pharmacokinetics of this drug has not been examined with continuous dosing, nor have the pharmacodynamic effects of lower dose with food been assessed in comparison to standard dosing.

1.8 Adherence to Oral Oncology Medications

Over the last decade oral anticancer medications (OAMs), including abiraterone acetate, represent a major shift in the management of cancer patients from directly observed intravenous therapy to self-administered oral chronic therapy[24]. Adherence, broadly defined by the International Society for Pharmacoeconomics and Outcome Research as "the degree of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency" has been a factor for decades in many other chronic diseases, and is now becoming relevant in oncology[25,26]. Physicians are poor at recognizing nonadherence and techniques to quantify adherence are imperfect[27]. Much of the literature in this area has focused on adjuvant treatment of breast cancer as well as chronic myelogenous leukemia (CML) and one representative study showed that only 47% of breast cancer patients took adjuvant hormonal therapy for the full duration at the optimal schedule and early discontinuation and nonadherence was associated with increased mortality[28,29]. In CML nonadherence was seen in over 30% and adversely affected event free survival[30,31]. Many factors can be an obstacle to adherence, including the complexity of the regimen and dietary restrictions[24]. This study will explore adherence to abiraterone acetate in men with CRPC to determine if lower-dose abiraterone taken with food will lead to increased self-reported adherence.

1.9 Study Rationale

The current FDA labeling for abiraterone mandates the drug be taken fasting, which is complicated for patients and often difficult for patients to comply with. There are data to support increased absorption of abiraterone when taken with food. We therefore hypothesize that lower-dose abiraterone taken with food will have a similar effect on CRPC as full-dose taken fasting. We will use serum PSA as a pharmacodynamic marker of abiraterone effect.

Table1: Summary of Pharmacokinetic Data for Abiraterone Acetate Measured as Abiraterone in Plasma[12]

Patient	Dose (mg/m^2)	AUC µM.h	C_{max} µM	T_{max} h	$T_{1/2_\alpha}$ h	$T_{1/2_\beta}$ h	K_{abs} h
1	10	ND	ND	ND	ND	ND	ND
2	10	ND	0.001	2	ND	ND	ND
3	10	ND	0.018	11	ND	ND	ND
4	30	ND	ND	ND	ND	ND	ND
5	30	ND	0.004	4	ND	ND	ND
6	30	ND	0.006	1	ND	ND	ND
7	100	0.15	0.012	13	6.5	ND	6.5
8	100	0.09	0.011	0.16	0.97	26.5	0.03
9	100	0.12	0.019	3.7	2.0	28	1.8
10	200	0.39	0.061	2.8	1.59	25.8	3.87
11	500	0.25	0.063	0.8	0.28	29	0.01
12	500	1.68	0.139	3.7	1.83	21	1.8
13	500	0.73	0.06	3.6	1.73	74	1.71
14	500	0.67	0.066	4	1.43	18	1.41
15	500	0.42	0.077	2	0.29	13.4	1.00
16	500	1.38	0.167	2.7	0.05	13.3	1.15
17	200	0.23	0.037	0.69	1.49	28	0.03
18	500	1.23	0.054	1.7	0.19	14.6	0.3
19	500	1.101	0.183	1.51	0.71	14	0.7
20	500	2.08	0.30	1.41	1.59	24	0.12
21	500	3.54	0.62	1.70	1.07	23.2	0.82
22	500	0.34	0.07	2.30	0.79	12.0	0.80
23	500	NE	NE	NE	NE	NE	NE
24	800	11.66	1.19	3.02	1.32	87	1.34
25	800	2.32	0.43	1.20	0.45	19.9	0.45
26	800	2.84	0.18	3.10	1.73	26.2	1.82

Details of patients: PT 1-16: single dose study in castrate males
PT 17-20: single dose in non-castrate males
PT 21-26: multi-dose study in non-castrate males

Abbreviations: NE – non evaluated due to problems with assay; ND – non-detectable, plasma concentrations below the permit estimation of the pharmacokinetic behavior or drug; AUC – area under the concentration time curve; C_{max} – maximum concentration; T_{max} – time to maximum concentration, $T_{1/2\alpha}$ – initial half-life; $T_{1/2\beta}$ – terminal half-life; K_{abs} – absorption rate constant.

2. OBJECTIVES

2.1. Primary Objective

- The primary objective of the study is to compare the pharmacodynamic effect of reduced dose (250mg daily) abiraterone acetate in the prandial state (250mg-Fed) to the full, standard 1000mg daily dose in the fasting state (1000mg-Fasting) as assessed by change in serum PSA.

2.2. Secondary Objectives

- To evaluate the effect of prandial states on plasma levels and the intra-patient pharmacokinetic variability of abiraterone acetate
- To evaluate the safety profile of reduced dose abiraterone acetate taken in the prandial state.
- To evaluate the pharmacodynamic effect of reduced dose abiraterone acetate in the prandial state as assessed by reduction in the extra-gonadal androgen dihydroepiadrosterone sulfate (DHEA-S) and dihydroepiandrostenedione (DHEA).
- To evaluate the effect of prandial state on time to disease progression (Working group criteria[32]).
- To assess and describe medication adherence to abiraterone acetate for both dosing schedules

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Histologically or cytologically confirmed prostate cancer with progressive disease defined as either:

- 2 or more new lesions on bone scan or
- Progressive disease on CT/MRI according to RECIST 1.1 criteria[33] or
- Rising PSA: PSA evidence for progressive prostate cancer consists of a minimum PSA level of at least 2 ng/ml, which has subsequently risen on at least 2 successive occasions, at least 2 weeks apart.

3.1.2. Evidence of castration resistance defined as disease progression despite a testosterone level <50ng/dL (or surgical castration)

3.1.3. Any prior therapy for castrate disease is acceptable except prior abiraterone, which is excluded. A minimum washout of 28 days for any other anticancer therapy prior to first dose of study drug is required.

- Any other radiotherapy or radionuclide require 28-day washout prior to first dose of study drug.
- Denosumab or zoledronic acid are allowed.

3.1.4. ECOG performance status ≤ 2 (**Appendix A**).

3.1.5. Patients must have normal hepatic function as defined below:

- Total bilirubin ≤1.5 x the upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal

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

3.2. Exclusion Criteria

3.2.1. Therapy with other hormonal therapy, including any dose of megestrol acetate (Megace), finasteride (Proscar), dutasteride (Avodart), or any herbal product known to decrease PSA levels (e.g., saw palmetto and PC-SPES), or any systemic corticosteroid (other than prednisone ≤10mg/day) within 4 weeks prior to first dose of study drug.

3.2.2. Therapy with supplements or complementary is excluded with the following exceptions. All other supplements must be discontinued prior to initiation of study drug.
- Conventional multivitamin supplements
- Selenium
- Lycopene
- Soy supplements

3.2.3. Inability to swallow capsules or known gastrointestinal malabsorption.

3.2.4. History of other malignancies, with the exception of adequately treated non-melanoma skin cancer or adequately treated superficial bladder cancer or other solid tumors curatively treated with no evidence of disease for ≥ 5 years from enrollment.

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

3.2.6. Serum K+ < 3.5 mmoL/L. Patients with a K+ < 3.5 mmoL/L are required to have a documented subsequent K+ >3.5 prior to enrollment to be eligible.

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

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

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

3.2.10. Concurrent therapy with strong inhibitors or inducers of CYP3A4 (See Section 8.12 below for list of strong inhibitor or inducers) due to concerning possible drug-drug interactions with abiraterone.

3.3. Inclusion of Minorities

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

4. REGISTRATION AND DATA COLLECTION/MANAGEMENT

4.1. Registration Process

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

- www.centocoraccessone.com/assets/zytiga/PEF.pdf

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

Study Coordinator:

Jaclyn D. Peterson
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115
773-834-1746
773-702-4889
phaseIICRA@medicine.bsd.uchicago.edu

Eligible patients will be entered on study centrally at the University of Chicago by the Study Coordinator. Forms are available to UC Phase II Consortium Affiliates on the University of Chicago Cancer Research Center website.

- http://cancer.uchicago.edu
- Click on the **Intranet** (top right corner).
- Enter your site specific user name and password
- Click on **Phase II Website**
- Click on **Forms**

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

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

- Demographics
- Age
- Race
- Performance status
- Primary tumor data
- Diagnosis date
- Baseline staging
- Baseline PSA

- Gleason grade
- Primary tumor treatment
- Systemic therapy administered
- Date of androgen ablation start
- Dates of anti-androgen therapy, and withdrawal
- Dates and types of other systemic therapy
- Dates and types of systemic radiotherapy
- Sites of metastatic disease

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

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

- Provider of information
- Treating Physician (NCI investigator number)
- Patient name and hospital ID number
- Patient's zip code of residence
- Date & copy of signed informed consent
- Race, gender, date of birth of patient
- Diagnosis and date of initial diagnosis
- Complete **Phase II Consortium Affiliate Clinical Trial Patient Registration Form**
- Source documentation for eligibility and pre-study procedures
- Prior authorization and documentation of abiraterone availability

The research nurse or data manager at the participating site will then call the study coordinator to confirm all selection criteria listed in Section 3.
To complete the registration process, the UCMC Coordinator will:

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

4.2. Randomization process

All patients with will be randomized to 250mg-Fed versus 1000mg-Fasting after successful registration by the Study Coordinator. Patients will be randomized by the University of Chicago Cancer Clinical Trials Office (CCTO), in cooperation with the Biostatistics Core Facility of the UCCRC. Patients will remain on their allocated treatment arm throughout the duration of study therapy with no crossover while on study. Participating sites will be notified by the coordinator within 48-hours of registered patient's open label, randomized treatment group assignment.

Following registration, patients should begin treatment within 14 days. Issues that would cause a

delay in treatment initiation (e.g. delay in procurement of commercially available abiraterone) should be discussed with the Principal Investigator.

5. STUDY DRUG ADMINISTRATION

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

5.2 Therapy will consist of:

5.2.1 For fasting patients: abiraterone acetate 1000mg per day (in the form of four 250mg tablets), plus prednisone 5 mg po bid. The abiraterone will be taken first thing in the morning after an overnight fast of a minimum 8 hours. It will be taken at least 2 hours prior to any food intake.

5.2.2 For fed patients (not fasting): abiraterone acetate 250mg per day (in the form of one 250mg tablet), plus prednisone 5mg po bid. The abiraterone will be taken either concomitantly or within 30 minutes of a conventional low-fat breakfast. The nature of the breakfast is at the discretion of the patient, however, high fat food items (foods with 250 or more calories from fat-e.g. sausage, bacon, etc.) should not be consumed with abiraterone.

5.2.3 All patients will be treated with prednisone 5mg twice daily obtained through their standard pharmacy.

6. DURATION OF TREATMENT

Therapy with abiraterone acetate will continue until one of the following events occurs.

1. Progression of disease according to 2008 PSAWG-2 criteria[34] is met (**Appendix D, E**). Note-PSA progression (or response) will not be assessed until the patients' first 12-week disease assessment visit .
2. Unacceptable toxicity is encountered.
3. Patient withdraws consent
4. Patient is withdrawn from study at the discretion of the investigator

Note that if the patient discontinues abiraterone therapy, he should continue to be followed for PSA levels unless he has withdrawn consent for further follow-up.

7. STUDY ASSESSMENTS

These assessments are summarized in the study calendar below.

7.1. Pre-treatment Evaluation

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

alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, alkaline phophatase, and albumin), serum testosterone and DHEA-S (Quest diagnositics).

Disease burden evaluation with a bone scan, abdominal/pelvis imaging (CT or MRI), and CT chest (when clinically indicated) must be obtained within 30 days of study entry

7.2 On Study Visits

On study visit will occur weekly for two weeks, at week 4 and then monthly. After patients have been on the study for more than 12 months, on-study visit intervals may be changed from monthly to every 12 weeks at the discretion of the treating investigator. The blood draw at day 8 will be limited to steady state PK samples. The draw on day 15 will be limited to serum chemistries for toxicity assessment.

For the monthly visits, including day 1, the following full set of blood tests will need to be obtained: CBC, serum chemistries, LDH, PSA. Other monthly assessments including ECOG status, concomitant medications etc. to be collected are outlined in the study calendar. Note: monthly visits can occur ±3 days of scheduled visit.

Disease assessment with imaging (as in pre-study evaluation) will be repeated every 12 weeks while on study. A testosterone and DHEA-S level (Quest) will also be obtained at each 3 month visits (month 4, 7, 10, etc.).

7.2.1 Adrenal androgen sampling:

Plasma and serum will be collected at the day 1 visit and month 2 visit and stored to assay for pertinent endocrine labs (e.g. Androstenedione, and DHEA) using a highly sensitive diagnostic assay in the future. For these samples, approximately 7-10 ml of blood will be collected into one sodium EDTA (lavender top-for plasma) vacutainer tube and one serum separator tube (red-grey speckled, SST- for serum). Tubes will be centrifuged (2500 rpm, 20 min, 4ºC) and plasma/serum immediately separated and transferred as two aliquots into storage cryotubes. The plasma samples will be labeled with patient's initial and ID number, UC protocol number, initials of phlebotomist, and sample ID (e.g. baseline, month 2). Samples will be transported to the BioFluids Core Facility (Room AB201, Scientific Director, Dr. Michael Maitland) to be stored at –80ºC.

Frozen plamsa samples from participating institutions will be shipped on dry ice to the University of Chicago in Styrofoam container to the Study Coordinator who will log and transport the samples to the UC BioFluids Facility for storage:

Jaclyn Peterson
University of Chicago, Department of Medicine
Section of Hematology/Oncology
5841 S. Maryland Ave. MC2115
jdpeterson@medicine.bsd.uchicago.edu

7.2.2 Pharmacokinetics sampling:

All abiraterone acetate and abiraterone PK assays will be conducted within the Pharmacology Laboratory at the National Cancer Institute within the National Institutes of Heath (Laboratory Director Dr. William Douglas Figg Sr., Pharm. D) by solid phase extraction after plasma acidification and quantified using a calibration curve. Samples will

be analyzed using LC/MS/MS with electrospray ionization[35]. Stored frozen samples (see 7.2.1.1) will be sent to the Figg laboratory for batch processing at the following address:

Cody Peer
Center for Cancer Research
National Cancer Institute
National Institute of Health
Bldg 10/Room 5A01
Bethesda, MD 20892

Blood samples will be collected according to the following schedule for PK studies (steady state C_{max}, T_{max}):

1. Day 1, time zero: before ingestion of fist abiraterone.
2. Day 8, time zero: before ingestion of abiraterone.
3. Day 8, 2h: two hours post ingestion of abiraterone.
4. Day 8, 3h: three hours post ingestion of abiraterone.
5. Day 8, 4h: four hours post ingestion of abiraterone.
6. Month 2, time zero: before ingestion of abiraterone dose
7. Month 2, 2h: two hours post ingestion of abiraterone.
8. Month 3, time zero: before ingestion of abiraterone dose
9. Month 3, 2h: two hours post ingestion of abiraterone.
10. Month 4, time zero: before ingestion of abiraterone dose
11. Month 4, 2h: two hours post ingestion of abiraterone.

7.2.1.1 Collection and Handling of Specimen(s)

Blood samples for pharmacokinetic analysis will be processed in the follow manner: Approximately 7 ml of blood will be collected into sodium heparinized (green top) vacutainer. Green top tubes will be centrifuged (2500 rpm, 20 min, 4ºC) and plasma immediately separated and transferred as two aliquots into storage cryotubes. The plasma samples will be labeled with patient's initial and ID number, UC protocol number, initials of phlebotomist, sample ID (i.e. baseline, 0.5 hrs, etc) and actual time and date of blood collection. Actual blood sampling times will be noted for each patient in the attached flow sheet (pharmacology referral form, appendix F). Any delays or problems will be carefully noted under comments along with the initials of the phlebotomist. Samples will be transported to the BioFluids Core Facility (Room AB201, Scientific Director, Dr. Michael Maitland) to be stored at –80ºC. For all PK sampling, the time of blood collection will be recorded on the specimen collection sheet as well as tube label by the phlebotomist.

PK samples from participating institutions other then the University of Chicago will be collected and processed according to the same methods and stored at the participating institutions at –80ºC for batched shipment. Cryotubes for plasma storage will be provided by the University of Chicago as will blank labels. Frozen PK samples will be shipped on dry ice to the University of Chicago in a styrofoam container (not supplied by UC) to the Study Coordinator. Samples can be batch shipped to the University of Chicago at quarterly intervals.

7.2.3 Medication adherence questionnaire:

For those patients still on study at 60 days, a questionnaire addressing issues of adherence to abiraterone acetate will be administered either in person or over the phone (Appendix G).

7.3 Off Study Assessments

Patients will be followed with these assessments until taken off study. Upon study discontinuation, subjects will undergo a complete evaluation with a history and physical examination, ECOG performance status, concomitant medications, and baseline toxicity documented at this visit. The subject will also have standard laboratory studies collected at this visit (CBC, serum chemistries, LDH, PSA, testosterone, adrenal androgen studies), and have radiologic tumor assessments performed, unless already performed within four weeks of being taken off study. Study participant refusal or inability to undergo these evaluations should be noted. This visit should be done on the day patients are taken off study medication but may be completed within 30 days of coming off treatment. At the time of study completion for any reason, patients will once again be asked to partake in a questionnaire (Appendix G). If a patient completed the questionnaire less than 30 days prior as part of their on-study visit, they will not be asked to participate.

7.4 Study Calendar

	Pre-treatment	**Day 1 & Monthly**[j] ±3 Days	**Month 1, Day 8**	**Month 1, Day 15**	**Every 3 Months (Month 4, 7, 10…)**	**Off study visit**[k]
Procedures						
Informed Consent[a]	X					
Medical History, including demographics	X	X				
Physical exam, including height (only at screening) and weight	X	X		X		X
Vital Signs [b]	X	X	X	X		X
ECOG performance status	X	X		X		X
Concomitant medications	X	X		X		X
Concurrent Anti Cancer Therapies[c]		X				X
Medication Compliance Questionnaire		X				X
Adverse Events		X		X		X
Laboratory Assessments						
CBC with platelets & differential counts	X	X[l]	X	X		X
Serum chemistry and electrolytes[d]	X	X[l]	X	X		X
AST, ALT, total bilirubin, alk. phos.	X	X				
PSA		X				X
Testosterone, DHEA-S	X				X	X
Adrenal Androgen Levels[e]		X				X
LDH		X				
PK sample		X[f]	X			
Tumor Assessments[g]						

Bone scan[h]	X				X	X
CT or MRI of the abdomen/pelvis	X				X	X
CT chest[i]	X				X	X

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

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

[c] Other than LHRH agonists that are required to maintain castrate levels of testosterone, anti-cancer therapies are excluded during this study. These include chemotherapy, radiotherapy, immunotherapy, ketoconazole, diethylstilbesterol, PC-SPES, and other experimental anticancer medications, such as herbal preparations.

[d] Serum chemistry includes BUN, creatinine, ALT, AST, glucose, alkaline phosphatase, total bilirubin, electrolytes (K+, Cl-, Na+,CO_2, Ca+). Serum AST/ALT should be measured at a minimum day 1 each month. Current FDA guidance suggests every two weeks for first 12 weeks. More frequent AST/ALT monitoring, especially during the first 12 weeks on study is thus at the investigator discretion

[e] Day 1, Month 2 visits and end of study visit only- Androstenedione, DHEA

[f] PK samples will be obtained at the Month 2, Month 3, Month 4 visits in addition to Month 1, Day 1, 8 visits

[g] Imaging will be evaluated at screening and for clinical benefit every 12 weeks (3 cycles) of treatment

[h] Isolated new lesions on bone scan at the 12-week scan will be confirmed with a repeat bone scan at 6 weeks to rule out bone scan flair.

[l] Obtain if clinically warranted.

[j] +/- 3 days.

[k] End of study visit – within 30 days of the last abiraterone dose. Tumor assessment not necessary if done within preceding 30 days.

[l] These test will be performed at your monthly doctor visits. In addition, during the first month on the study, subjects will have these tests performed during two extra weekly visits (after 1 week and after 2 weeks of taking the study drug). After patients have been on the study for more than 12 months, on-study visit intervals may be changed from monthly to every 12 weeks at the discretion of the treating investigator.

[m] Questionnaire will only be performed at day 60 (month 3 day 1) and at the end of the study

8. TREATMENT PLAN

8.1. Agent Administration for patients in the US and Other Participating Countries

Treatment for all patients will be administered on an outpatient basis as per Section 5.

The patients on study will procure the abiraterone as stated above through their standard outpatient pharmacy, but will not take any doses of therapy until instructed to do so, and until after randomization.

For patients participating outside of the US, 250mg tablets of abiraterone acetate will be dispensed in accordance with their site's standard practice. Regardless of location, all subjects are required to complete a daily medication log (Appendix C) to document appropriate medication adherence.

Patients randomized to the 250mg fed state arm will have 90 extra 250mg tablets at the end of each 28 day cycle. Study drug administration calendars will be filled out by the patient while on study. The patients' pill bottles will be brought to each study visit for pill counting by the research nurse to validate the calendars.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy with the exception of patients who are chemically castrated who should continue to receive their LHRH agonist while on this clinical trial. Medications for bone health (e.g. zoledronic acid or denosumab) should likewise be continued (Section 3.1.5).

8.2. Management of Castration Related Symptoms:

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

8.3. Dose-Reduction Procedure for Adverse Event Management

In the event where dose-reduction is used for AE management, 2 dose reductions are allowed according to the following table. The maximum time a patient's study medication may be held due to toxicity is 14 days. After which, the patient must be discontinued from study participation.

Dosing Cohort	Starting Dose	Dose level -1	Dose level -2
Fasting State	1000mg daily	750mg daily	500mg daily
Fed State	250mg daily	250mg every other day	250mg every third day

8.4. Treatment Management of Hypertension

Hypertension may develop while on abiraterone due to excess mineralocorticoid activity arising from a compensatory increase in deoxycorticosterone as a result of the inhibition of the 17''-hydroxylase at an earlier point in the steroid synthesis pathway. Because of this, hypertension occurring secondary to abiraterone may be most effectively prevented through the concurrent administration of corticosteroids, which are given to all patients concomitant with abiraterone therapy. Further treatment of hypertension is not restricted; however consideration should be given to the use of eplerenone which is capable of inhibiting mineralocorticoid induced hypertension. The following table provides a recommended algorithm for treatment-emergent hypertension management. Decisions to hold or decrease the dose of study treatment must be based on blood pressure (BP) readings confirmed with a second measurement at least 5 minutes after the first measurement.

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

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

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

8.5. Treatment-Emergent Edema and Fluid Retention

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

Symptoms	Treatment/Dose Modification
• Pedal Edema	• Management per investigator. No study treatment dose reduction
• Anasarca and/or pulmonary edema requiring supplemental oxygen	• Hold study treatment. Adjust or add medications to mitigate the toxicity and/or consider specific mineralocorticoid receptor blocker, eplerenone. When toxicity resolves to ≤Grade 1, resume study treatment at full dose.
• Recurrence of anasarca and/or pulmonary edema requiring oxygen.	• Hold study treatment. Adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study treatment at first dose level reduction (for fasting patients, 3 tablets or 750 mg of abiraterone, 250mg every other day for fed state patients).
• Recurrence of anasarca and/or pulmonary edema requiring oxygen at first dose level reduction	• Hold study treatment. Adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤Grade 1, resume study treatment at second dose level reduction (for fasting patients, 2 tablets or 500 mg of abiraterone; 250mg every third day for fed state patients)
• Recurrence of toxicity despite optimal medical management and with two dose level reductions	• Discontinue study treatment.

8.5 Management of Hypokalemia

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

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

8.6 Management of Elevated Liver Function Tests

- If Grade 1 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT from ULN to 2.5X ULN; increase in total bilirubin from ULN to 1.5X ULN): The frequency of liver function test monitoring should be increased per Investigator discretion, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
- If Grade 2 increases in AST, ALT or bilirubin occur (e.g. increase in AST or ALT to >2.5-5X ULN; increase in total bilirubin from >1.5-3X ULN): The frequency of liver function test monitoring should be increased to ≥once a week, if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
- If Grade 3 or higher increases in AST, ALT, or bilirubin occur (e.g. increase in AST or ALT to >5X ULN; increase in total bilirubin to >3X ULN), hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the liver function tests return to baseline value or Grade 1.

  If study treatment resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, resume study treatment with the first dose level reduction (Section 8.8 below) when Grade 3 toxicities resolve to Grade 1 or baseline.

If Grade 3 or higher increases in AST, ALT, or bilirubin recur after the first dose reduction hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the liver function tests return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.

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

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

8.7 Management of Non-Mineralocorticoid Based Side Effects

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

- If Grade 3 or higher toxicities including headache (interferes with ADL), nausea (TPN, IVF), vomiting (>6 episodes/24hrs, TPN or IVF), diarrhea (IVF, hospitalization, hemodynamic collapse), or any other toxicity judged to be related to study treatment is observed where the patient's safety is jeopardized, hold study treatment.

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

- If toxicity recurs, hold study treatment, and adjust or add medications to mitigate the toxicity. When resolved to ≤ Grade 1, resume study treatment with the first dose level reduction.
- If toxicity recurs, hold study treatment, and adjust or add medications to mitigate the toxicity. When resolve to ≤ Grade 1, resume study treatment with the second dose level.
- If toxicity recurs despite aggressive medical management and two dose level reductions, discontinue study treatment.

8.8 Concomitant Medication and Treatment

If the subject must use a concomitant medication during the study, it is the responsibility of the investigator to ensure that details regarding the medication are recorded.

8.9 Chemotherapy and Radiotherapy

If possible, alternative anticancer treatment should not be initiated until PD has been observed by standard guidelines and study treatment has been discontinued. If a subject requires additional

systemic anticancer treatment, study treatment must be discontinued. Local intervention (e.g. nephrostomy tube placement, TURP) is discouraged unless medically unavoidable. Subjects receiving local intervention are allowed to continue to receive study treatment at the investigator's discretion.

8.10 Other Medications

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

Pain medications administered as dictated by standard practice are acceptable while the subject is enrolled in the study. Colony stimulating factors (e.g. granulocyte colony-stimulating factors) administered as dictated by standard practice are acceptable while the subject is enrolled in the study. However, colony stimulating factors should not be administered prophylactically before the first dose of study treatment. Erythropoietin should not be used based on a recent report of increased risk of tumor recurrence/progression associated with erythropoietin[36].

No concurrent investigational agents will be permitted.

8.11 Potential Drug Interactions

Potent inhibition of P450 CYPs 2D6 and 1A2 by abiraterone acetate was observed in *in vitro* preclinical studies. Moderate inhibition of P450 CYPs 2C9, 2C19, and 3A4 was also observed. However, investigators should keep in mind the possibility that abiraterone acetate may interact with concomitant medications, particularly those that are metabolized or activated by P450 CYPs 2D6 and 1A2 and, less likely, P450 CYPs 2C9, 2C19, and 3A4.

Abiraterone is a substrate of CYP3A4, in vitro. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution. The following table should be used as a reference (from http://www.fda.gov/drugs/).

	Strong: Prohibited	**Moderate: Used with caution**
CYP3A4 inducers	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin
CYP3A4 inhibitors	Boceprevir, clarithromycin, conivaptan, **grapefruit juice**, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir,verapamil

Although no known interaction with warfarin is known, given its narrow therapeutic window, it should be used with caution due to potential drug-drug interaction.

Additional information with regards to drug-drug interactions is available online through the manufacturer (http://www.zytiga.com/hcp/druginteractions) and on the FDA prescribing information.

- http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf.

9. SAFETY

9.1. Adverse Events

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

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

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

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

9.2. Serious Adverse Events

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

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

1. Results in death.
2. Is immediately life-threatening (i.e. in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity.
    - Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.
5. Is a congenital anomaly or birth defect.
6. Is an important medical event (IME)

- Note: The term "important medical event" refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of Serious Adverse Event. Examples of IMEs include: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of product dependency or product abuse.

9.3. Serious Adverse Event Reporting

This study will be using MedWatch for SAE reporting.

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

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

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

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

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death should not be reported as an SAE, but as an *outcome* of a specific SAE, unless the event preceding the death is unknown. In the exceptional case where the events leading to death are unknown, then Death may be used as an event term and should be reported as "death, cause unknown". If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
- Elective or previously scheduled surgery, e.g., a previously scheduled ventral hernia repair.
- Procedures for pre-existing conditions that have not worsened after initiation of treatment.
- Pre-specified study hospitalizations for observation.
- Events that result in hospital stays of less than 24 hours and that do not require admission, eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics.
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
- All serious unexpected adverse drug reactions (unexpected related SAEs) must be reported to the FDA by the investigator as required by 21 CFR 312.32 (See **Section 9.4.2** below).
- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form).

9.4. Other Reporting Requirements

9.4.1. University of Chicago Comprehensive Cancer Center

All serious adverse events and protocol deviations must also be reported to the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO) via email at qaccto@bsd.uchicago.edu and copied to the study nurse and PI. Events will be reported to the University of Chicago Institutional Review Board (UCIRB) in accordance with their current policies. The Research Nurse or other designated individual should report the SAE/deviation to the UCCCC Quality Assurance (QA) Coordinator by the end of the business day when s/he becomes aware of the event. Events occurring after business hours will be reported to the CCTO by 12pm (noon) the next business day. Each event report must indicate where the event meets the IRB's Unanticipated Problem reporting criteria.

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

9.4.2. Reporting Requirements for Participating Sites

Any Serious Adverse Event (SAE) will be reported to the local institution's IRB and the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO) as specified below. UCCCC will circulate all SAE's to the participating centers.

Any adverse event falling under the definition of Serious will be reported immediately to the Study Chairman who, in turn, must notify the UCCCC IRB per IRB policy. Symptoms related to progressive disease such as severe bone pain will not be reported as toxicity or as Serious Adverse Events.

Multi-center sites participating in the study will notify the UCCCC CCTO via phone at 773-702-5928 and email at qaccto@bsd.uchicago.edu of all serious adverse events within 24 hours of knowledge of the event. The UCCCC clinical research staff will immediately notify the principal investigator (PI) or his designee of the SAE. The participating institutions will submit the SAE to their own IRB. The participating institution must forward a copy of the report filed with their local IRB to UCCCC within 5 calendar days. After the UCCCC clinical research staff receives and processes the initial SAE report from the participating institution, it will be forwarded to the PI or his designee for review and signature.

9.5. Other Safety Considerations

9.5.1. Laboratory Data

All laboratory data obtained during the course of the study should be reviewed. Any abnormal value that leads to a change in subject management (e.g., dose reduction or delay, requirement for additional medication or monitoring) or is considered to be of clinical significance by the investigator should be reported as an adverse event or serious adverse event as appropriate,

unless this value is consistent with the patient's present disease state or is consistent with values obtained prior to entry into the study.

9.5.2. Medication Errors

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

9.5.3. Follow-Up of Adverse Events

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

9.5.4 Safety Monitoring

According to University of Chicago Cancer Center Guidelines, this protocol will be classified as moderate risk. Data and Safety Monitoring (DSM) will occur at the weekly University of Chicago Genitourinary Oncology DSM meeting. At each meeting, the study will be reviewed for safety and progress toward completion. Toxicities and adverse events will also be reviewed and a DSM form will be completed at each meeting. Twenty percent of research charts will be audited annually for protocol compliance items including eligibility, completion of procedures, administration of treatment, reporting of toxicities, documentation of response, follow-up, data-collection, record keeping, and the collection of correlative studies.

10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria[33,37](**Appendix D, E**). For the purposes of this study, patients should be re-evaluated every 12 weeks.

10.1. Outcome Measures based on PSA Decline

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

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

10.2. Radiographic Tumor Response

Change in measurable disease, when applicable, will be determined according to RECIST 1.1 and PSAWG-2 criteria (Appendix E)[33,37,38]. For the purposes of this study, imaging will be repeated according to the study calendar (Section 5.5) every 12 weeks unless otherwise indicated clinically.

Lymph nodes[37]*:* To be considered pathologically enlarged and measurable, a lymph node must be at least 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). Lymph nodes that are at least 10 mm but less than 15 mm in short axis may be pathologic and can be considered non-measurable/non-target lesions (that are not measured). At baseline and in follow-up, only the short axis will be measured and followed.

Bone lesions: Bone lesions are by definition non-measurable. If bone lesions are identified on MRI that have soft tissue components that are identifiable and accurately measurable the bi-dimensional measurements of these lesions will be recorded as soft tissue measurable disease. Of note, progression based on bone scan will be assessed according to PSAWG-2 criteria[38]. Isolated new lesions on bone scan at the 12-week scan will be confirmed with a repeat bone scan at 6 weeks to rule out bone scan flair. If no new lesions are seen at the 6-week confirmation, it will be considered flair. All subsequent bone scans will follow standard criteria with regards to progression (two new lesions necessary for progression).

10.3. Duration of Response

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

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

10.4. Progression-Free Survival

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

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size/Primary Endpoint

The primary endpoint of the study is change in PSA level from baseline to 12 weeks (analyzed on a log scale). The benchmark data for our power calculations are taken from the phase II open label abiraterone trial by Danila and colleagues[15] and the much larger, randomized phase III abiraterone vs. placebo trial conducted by de Bono et al[8], which used the standard, high-dose fasting regimen. In Danila et al, which allowed prior ketoconazole exposure, 21 of 58 patients (36%) exhibited a 50% or greater decline in PSA. Among 797 patients randomized to abiraterone in the de Bono study, 29% had a confirmed PSA response. Pooling these data (weighted by sample size) yields an historical 29.5% PSA response rate.

We will conduct a randomized, phase II, non-inferiority trial, using a non-inferiority margin of 15%.

Specifically, letting p_L denote the true response rate for the low-dose fed regimen and p_H the response rate for the high-dose fasting treatment, we will test H_0: p_L-p_H= -0.15 vs. H_A: p_L-p_H > -0.15. However to reduce sample size requirements we will analyze change in PSA measured on a continuous scale. Assuming the log ratio of the 12-week to baseline PSA levels, i.e., log (PSA_{12}/PSA_0), is approximately normally distributed, a 30% vs. 15% rate difference maps into a -0.525- (-1.035) = 0.51 SD difference in means. Letting μ_1 and μ_2 denote the respective true means, we have H_0: $\mu_1 - \mu_2 \geq 0.51$ SD vs. H_A: $\mu_1 - \mu_2 < 0.51$SD. Assuming the PSA response rates are truly equivalent, a total sample size of 72 patients (36) per treatment arm, will provide 80% power for the non-inferiority test, using a one-sided alpha level of 0.10. A significant number of patient dropouts is unexpected before the 12-week endpoint. However, if there is a dropout rate seen that will impact the statistical power, the sample size will be increased accordingly to compensate for unevaluable patients.

An interim futility analysis will be performed midway through the trial. If the observed difference in means exceeds 0.75SD (i.e., if the low-dose regimen is performing more than 0.75SD *worse* than the high-dose treatment on the log ratio scale), the trial will be terminated and the low-dose regimen will be considered inferior. This criterion will reduce the power only very slightly below 80%.

11.2. Randomization and stratification

Randomization to either the fasting or fed state treatment groups will be done through Dr. Karrison and colleagues in the biostatistics core at the University of Chicago in a 1:1 fashion. The only stratification factor will be prior history of high dose ketoconazole treatment for CRPC given the potential variability in PSA response rate based on this factor. Upon documented and confirmed eligibility, the patient will be enrolled and randomized.

11.3. Analysis of Secondary Endpoints

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

The pharmacokinetic data will be obtained from steady states PK samples from day 8 and the three subsequent visits. (Section 7.2.). The steady state C_{max} and T_{max} will be imputed by Kehua Wu within the PK laboratory at the University of Chicago and summarized using standard descriptive methods (means, standard deviations, medians and ranges). We will compare mean plasma levels between the two treatment arms using a two-sample t test. Our sample size of 36 patients per group will provide 80% power to detect a 0.66 standard deviation (SD) difference in the means. We will compare interpatient (between patient) and intrapatient (within one patient) steady state abiraterone and abiraterone acetate C_{max} variability between the two treatment groups using Levene's test. The variability will also be summarized by calculating the coefficient of variation (SD/mean x 100) for each group.

To assess the pharmacodynamic effects of dosing arm on adrenal androgen production (DHEA, DHEA-S), descriptive statistics will be employed to note the maximal percentage change from baseline, as well as the mean, median, and range of percentage change within each dosing group. Group comparisons will be performed using two-sample t tests or nonparametric, Wilcoxon rank-sum tests.

To assess degree of adherence, medication diaries will be examined and a questionnaire will be administered up to two times throughout the study (Appendix G). Questions were derived from previously validated instruments of adherence in various other medical settings with an addition of several new questions (ASK-12, BMQ-Specific, Basel Assessment of Adherence Scale, VAS scale of adherence, Morisky Adherence Scale). A composite index of nonadherence using multiple scales will be determined and the two sample t-test will be used to compare the low-dose and standard dose abiraterone groups. Baseline to follow-up comparisons will be done using the paired t-test or its nonparametric analog (Wilcoxon signed rank test). Associations between adherence and other variables such as socioeconomic status and beliefs about abiraterone will be determined by the Pearson product moment correlation coefficient.

11.4 Safety Evaluation and Analysis

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

APPENDIX A

Performance Status Criteria

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

APPENDIX B

Sample Data Capture Forms

Patient Baseline Data

Diagnostic PSA: ☐

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

Clinical T stage: ☐ Surgery date: ☐

Clinical N stage: ☐ Surgical T stage: ☐

Biopsy date: ☐ Surgical N stage: ☐

Biopsy primary Gleason score: ☐ Surgical primary Gleason score: ☐

Biopsy secondary Gleason score: ☐ Surgical secondary Gleason score: ☐

☐ Capsule invasion ☐ Seminal vesical invasion ☐ Margin positive

Primary Tumor Therapy

Primary tumor therapy #: ☐

Primary tumor therapy type: ☐

Primary tumor therapy start: ☐

Primary tumor therapy end: ☐

Assoc hormone therapy? ○ Yes ○ No

Assoc hormone therapy type: ☐

Assoc hormone therapy start: ☐

Assoc hormone therapy stop: ☐

Androgen Ablation

INSTRUCTION

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

Androgen ablation start: ☐

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

Intermittant androgen ablation? ◯Yes ◯No

If yes, continuous androgen ablation start: ☐

Other Hormonal Therapy

INSTRUCTION

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

Other hormonal therapy #: ☐

Other hormone type: ☐

Therapy start: ☐

Therapy stop: ☐

Withdrawal response? ◯Yes ◯No

Treatment History

Form Name: Treatment History Form

Treatment Details

Therapy Code* * Select Therapy

Therapy Start Date

Approximate?

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

Therapy Start Date*

Therapy End Date

Approximate?

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

Therapy End Date

Agent Select Agent

Cumulative Dose Units

If applicable, site of therapy: Primary Other

Timing:

Palliative?

Best Response:

Resection:

Notes

APPENDIX C
SUBJECT'S STUDY DRUG/MEAL DIARY

Subject Name_____ (*initials acceptable)* **Subject Study ID** _____

MEDICATION & FOOD DIARY

INSTRUCTIONS TO THE SUBJECT :

1. Complete one form for each month of drug administration.
2. You will take **Abiraterone Acetate** capsules once daily. You should take the capsules at approximately the same time each morning as instructed by your doctor.

   Dose (circled by your nurse/MD): Take one (1) 250 mg capsule or (4) 1000mg

3. Record the date, the number of capsules that you took, and when you took them.
4. Record the date, time of your meal (starting time and finishing time), and content of meal.
5. Please bring this form and your bottles of **Abiraterone Acetate** capsules when you return each appointment.

If you are in the Fasting arm: Following an overnight fast of at least 8hours, you should take the study drug Abiraterone Acetate with 240 mL (8 fluid ounces) of water first thing in the morning. No food is allowed for at least 2 hours after you ingest the study drug. You may drink water as desired. Please record your first meal after taking your medication.
If you are in the Fed arm: Following an overnight fast of at least 8 hours, you should take the study drug with breakfast (or within 30 minutes). The abiraterone should be administered with 240 mL (8 fluid ounces) of water.

Day	Date	# of Pills Taken	Time Pills Taken	Time of Meal	Content of meal
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					

12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Subject's signature: _____

Physician's Office will complete this section:

1. Date subject started protocol drug administration _____
2. Date subject was removed from study _____
3. Subject's planned total daily dose _____
4. Total number of capsules taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

Appendix D

PROSTATE-SPECIFIC ANTIGEN WORKING GROUP CRITERIA[38]

Progressive Disease after Androgen Deprivation Eligibility Criteria:

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

Procedures for Assessing PSA Progression Post Study Treatment

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

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

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

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

Duration of PSA Response

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

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

Time to Disease Progression

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

Appendix E

RESPONSE EVALUATION CRITERIA in SOLID TUMORS (RECIST) [33,37]

Eligibility

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

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

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

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

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

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

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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

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

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

Response Evaluation: Evaluation of target lesions

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

Evaluation of non-target lesions

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

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

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

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

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

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

Confirmation

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

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

Appendix F

PHARMACOKINETIC SAMPLE COLLECTION SCHEME
UC PROTOCOL# 11-0709

A randomized phase II study evaluating the food effect on the pharmacokinetics and pharmacodynamics of abiraterone acetate in men with castrate resistant prostate cancer

SAMPLES TO BE COLLECTED AT: Day 1, Day 8, Month 2, Month 3, Month 4

PATIENT NAME: PATIENT ID:

DATE:

DOSING TIME:

No	SampleID	Date of Sample Draw	Actual Clock Time	Calculated Clock Time (with respect to dose)	Initials of Sample Collector	Comments
1	Pre-dose, **Day 1**					
2	Pre-dose, **Day 8**					
3	2 hours Post dose, **Day 8**					
4	3 hours Post dose, **Day 8**					
5	4 hours Post dose, **Day 8**					
6	Pre-dose, **Month 2**					
7	2 hours Post dose, **Month 2**					
8	Pre-dose, **Month 3**					
9	2 hours Post dose, **Month 3**					
10	Pre-dose, **Month 4**					
11	2 hours Post dose, **Month 4**					

Appendix G

Subject Questionnaire
Principle Investigator: Russell Szmulewitz, MD
Adherence Interview of CRPC Patients on Abiraterone Phase II Trial

Patient Name: _____ Date: _____
ID Number (Medical Record Number): _____
Treatment Arm: _____

Hello my name is _____. I am from the University of Chicago and I work with some of the doctors and other health care workers involved in the Abiraterone Acetate trial in which you are participating.

May I please talk with you for a few moments? I would like to talk with you about your adherence to abiraterone acetate as mentioned in the consent form for the trial. The information gained from talking with you will help us to better care for and talk with cancer patients like yourself in the future. I know this may be a very difficult time for you, but I would like to ask if it would be all right to talk with you now for about 20 to 30 minutes. In answering my questions, you would be participating in a research study that we hope will help to improve the care of cancer patients. There are no benefits to you by participating in the study. There are no physical risks to you by participating in this study. The only risk is that it might be slightly uncomfortable to talk about your illness. Your participation is completely voluntary and you can withdraw at any time. Any answers you might give would be kept entirely confidential and would not affect your care in any way. If you do not wish to talk with me, I would certainly understand and respect your decision.

I want to emphasize that the questions that I will ask are entirely confidential and you should not think that the answers you provide will impact the care your doctor or clinical team provide for you or your participation in the clinical trial that you are enrolled in. We are asking these questions in order to help understand how we can take care of other patients in the future.

Would it be an inconvenience if we talk?

Accepts _____

Declines_____

Reason:

Revised 2.4.12

Adherence to Abiraterone Acetate Questionnaire

Patient Name Date

Section One: Demographic information

To start off, I would like to ask you a few questions about yourself:

1. What is your age in years?

2. **Interviewer**: Is the respondent male or female?

3. Which of the following best describes you? Are you… (**interviewer**: read responses out loud)
    a. Asian or pacific islander
    b. Black or African American
    c. Latino, Hispanic or of Spanish origin or descent
    d. Native American or Alaskan native
    e. White
    f. Some other race, specify

4. What is the last grade or year that you completed in school? (**interviewer**: read responses out loud)
    a. Some high school
    b. High school or graduate school
    c. Some college
    d. College graduate
    e. Some post graduate
    f. Postgraduate or professional degree
    g. Other, specify

5. Which of the following best describes your employment status prior to your illness? Were you employed…(**interviewer**: read responses out loud)
    a. Full-time

b. Part-time
c. Retired
d. Not employed

6. How much are you working now?
    a. Full-time
    b. Part-time
    c. Not working/retired/on disability

7. Which category best describes your combined family income in the last year (before taxes) (**interviewer**: read responses out loud)
    a. less than $5,000
    b. $5,001-$19,999
    c. $20,000-$39,999
    d. $40,000-$59,999
    e. $60,000-$79,999
    f. greater than $80,000
    g. don't know
    h. refused

8. How would you rate your current health status? Would you say that your health is…(**interviewer**: read responses out loud)
    a. Excellent
    b. Very good
    c. Good
    d. Fair
    e. Poor

9. What is your marital status
    a. Married
    b. Divorced/Separated
    c. Widowed

d. Single

Section two: Adherence

I would like to now ask you a few questions about you taking your abiraterone acetate. We would be surprised if people took 100% of their medications. This information is confidential, but if you let me know that you have some difficulty with taking your medications, I will ask your permission to let your treatment team know so they can better assist you. If you do not wish me to discuss this with your team I will not.

10. Do you ever forget to take your abiraterone?
    a. Yes
    b. No

11. Have you skipped several doses in a row of your abiraterone?
    a. Yes
    b. No

12. Have you lowered or raised the prescribed amount of your abiraterone on your own?
    a. Yes
    b. No

13. Do you recall talking your abiraterone more than 2 hours earlier or later than the prescribed dosing time?
    a. Yes
    b. No

14. When you feel better do you sometimes stop taking your abiraterone?
    a. Yes
    b. No

15. I run out of my abiraterone because I don't get refills on time.

a. Strongly agree
b. Agree
c. Neither agree nor disagree
d. Disagree
e. Strongly disagree

16. Have you skipped or stopped abiraterone because you didn't think it was working?
    a. In the last week
    b. In the last two weeks
    c. In the last month
    d. In the last 3 months
    e. Never

17. Have you skipped or stopped taking abiraterone because it made you feel bad?
    a. In the last week
    b. In the last two weeks
    c. In the last month
    d. In the last 3 months
    e. Never

18. Have you skipped, stopped, not refilled, or taken less abiraterone because of cost?
    a. In the last week
    b. In the last two weeks
    c. In the last month
    d. In the last 3 months
    e. Never

19. How much do you have to pay out-of-pocket for your abiraterone monthly?

    $_____

20. Have you not had abiraterone with you when it was time to take it?
    a. In the last week

b. In the last two weeks
c. In the last month
d. In the last 3 months
e. Never

Section three: Beliefs

I would like to now ask you about your personal views about abiraterone prescribed for you as well as your prostate cancer. These are statements that other people have made about their medicines. Please indicate the extent to which you agree or disagree with each one of the following statements. You will be asked if STRONGLY AGREE, AGREE, UNCERTAIN, DISAGREE, OR STRONGLY DISAGREE. *There are no right or wrong answers. We are interested in your personal views.*

21. My health, at present, depends on my abiraterone.
    a. Strongly agree
    b. Agree
    c. Uncertain
    d. Disagree
    e. Strongly disagree

22. Having to take abiraterone worries me.
    a. Strongly agree
    b. Agree
    c. Uncertain
    d. Disagree
    e. Strongly disagree

23. My life would be impossible without my abiraterone.
    a. Strongly agree
    b. Agree
    c. Uncertain
    d. Disagree

e. Strongly disagree

24. Without my abiraterone I would be very ill.

a. Strongly agree
b. Agree
c. Uncertain
d. Disagree
e. Strongly disagree

25. I sometimes worry about long-term effects of my abiraterone.

a. Strongly agree
b. Agree
c. Uncertain
d. Disagree
e. Strongly disagree

26. My abiraterone is a mystery to me.

a. Strongly agree
b. Agree
c. Uncertain
d. Disagree
e. Strongly disagree

27. My health in the future will depend on my abiraterone.

a. Strongly agree
b. Agree
c. Uncertain
d. Disagree
e. Strongly disagree

28. My abiraterone disrupts my life.

a. Strongly agree

b. Agree
c. Uncertain
d. Disagree
e. Strongly disagree

29. I sometimes worry about becoming too dependent on my abiraterone.
    a. Strongly agree
    b. Agree
    c. Uncertain
    d. Disagree
    e. Strongly disagree

30. My abiraterone protects me from becoming worse.
    a. Strongly agree
    b. Agree
    c. Uncertain
    d. Disagree
    e. Strongly disagree

31. Do you believe that the abiraterone you are taking is chemotherapy?
    a. Yes
    b. No

32. If you are taking other medicines, do you believe that the abiraterone you are taking is more, less or as important as the other medicines you are taking?
    a. More
    b. Less
    c. As important
    d. I do not take other medications

33. Do you believe that your prostate cancer is a chronic disease like diabetes, heart disease or high cholesterol is for some people?

a. Yes
b. No

Section four: Communication and Barriers

Now, I would like to ask you a few more final questions about communication.

34. Have you received counseling about how and when to take your abiraterone?
    a. Yes
    b. No

35. If you received counseling, whom did you speak with?
    a. Physician
    b. Nurse
    c. Pharmacist
    d. Someone else

36. I have someone I can call with questions about my abiraterone
    a. Strongly agree
    b. Agree
    c. Neither agree nor disagree
    d. Disagree
    e. Strongly disagree

37. How satisfied are you with the communication you have had with your team about issues surrounding taking your abiraterone?
    a. Strongly satisfied
    b. Satisfied
    c. Neither satisfied or dissatisfied
    d. Dissatisfied
    e. Strongly Dissatisfied

38. We would be surprised if people took 100% of their medications. Below 0% means you have taken no abiraterone this past month, 50% means you have taken half of your abiraterone this past month and 100% means you have taken every single dose this past month. What percent of your abiraterone did you take?

0%	10	20	30	40	50%	60	70	80	90	100%

Is there anything else that you would like to share with me about taking your abiraterone? If not, I would like to thank you again for your time and information shared with me during this interview. Your feedback has been extremely important in trying to improve the care of future cancer patients.

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