The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Circulating Tumor Cell Biomarker Panel As an Individual-Level Surrogate for Survival in Metastatic Castration-Resistant Prostate Cancer

Scher, et al

DOI: 10.1200/JCO.2014.55.3487

Cougar Biotechnology, Inc

Redacted Clinical Protocol for Journal Use

A Phase 3, Randomized, Double-blind, Placebo-Controlled study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostrate Cancer Who Have Failed Docetaxel- Based Chemotherapy.

EudraCT No.: 2007-005837-13; Phase 3

AMENDMENT 3.0

CB7630 (Abiraterone Acetate)

Issued: 26 August 2010

Prepared by: Cougar Biotechnology, Inc

TABLE OF CONTENTS

1. OBJECTIVES 4

2. TREATMENT PLAN 4
2.1 Overall Study Design and Plan 4
2.2 Study Duration and Dates 5
2.3 Study Activities 5
2.4 Criteria For Cross Over Therapy with Abiraterone Acetate 6
2.5 Follow-up Period 7

3. SUBJECT SELECTION 7
3.1. General considerations 7
3.2. Inclusion criteria 7
3.3. Exclusion criteria 8

4. DOSAGE AND ADMINISTRATION 9
4.1 Description of the treatment(s) 9
4.1. Treatment administered 9
4.1.1 Abiraterone Acetate/Placebo (Study Treatment) 9
4.2.2 Prednisone 10
4.2. Selection and timing of dose 10
4.3. Dose Reductions 10
4.3.1 Dose reductions for Hypokalemia 10
4.3.2 Dose reductions for Hypertension Side Effects 11
4.3.3 Dose reductions for Edema, Fluid Retention 11
4.3.4 Dose reductions for Abnormal Liver Function Tests 11
4.3.5 Dose reductions for other Non-mineralocorticoid Based Side Effects 11

5. TREATMENT EFFECT 12
5.1 Efficacy Assessments 12
5.5.1 The Primary Endpoint Measure 12
5.5.2 Secondary Endpoint Measures 12
5.2 Other Measures 12
5.3 Adverse Events Assessments 13
5.3.1 Safety Measures 13
5.3.2 Definitions of an Adverse Event and Adverse Reaction 13
5.4 Time and Events Schedule 13

6. DISCONTINUATION OF TREATMENT 15

7. STATISTICAL METHODS 17
7.1 General Considerations 17
7.2 Determination of Sample Size 17
7.3 Analysis Populations 17
7.4 Demographics and Baseline Characteristics 17
7.5 Study Endpoint(s) 17
7.5.1 Efficacy Endpoint(s) 18
7.5.1.1 Primary Efficacy Endpoint(s) 18
7.5.1.2 Secondary Time to Event Endpoint 18
7.5.1.3 Other Efficacy Endpoints 18
7.5.2 Safety Evaluations 19
7.6 Pharmacokinetics Analysis 20
7.7 Circulating Tumor Cells (CTC) 20
7.8 Other Assessments or Analyses 20
7.9 Interim Analysis 20

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description of abbreviated term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
bid	Twice daily
BFI	Brief Fatigue Inventory
BPI-SF	Brief Pain Inventory Short Form
CBC	Complete blood count
CRF	Case Report Form
CRPC	Castration resistant prostate cancer
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
FACT-P	Functional Assessment of Cancer Therapy-Prostate
HRPC	Hormone refractory prostate cancer
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-treat
LHRH	Luteinizing hormone releasing hormone
LN	Lymph Node
MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical resource utilization
MUGA	Multiple Gated Acquisition Scan
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall survival
PFS	Progression Free Survival
PK	Pharmacokinetics
PO	Per Os (by mouth)
PSA	Prostate Specific Antigen
PSAWG	Prostate Specific Antigen Working Group
PT	preferred term
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SOC	system organ class
SRE	skeletal related event
TEAE	Treatment emergent adverse events
ULN	Upper limit of normal

1. OBJECTIVES

The primary objective of the study is to compare the clinical benefit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (CRPC) who have failed one or two chemotherapy regimens, one of which contains docetaxel.

The secondary objectives of this study are to evaluate the safety profile of abiraterone acetate plus prednisone, to characterize the PK of abiraterone acetate when administered concurrently with prednisone, to explore the potential utility of CTCs as a surrogate for clinical benefit and to evaluate the impact of abiraterone acetate plus prednisone on health related quality of life (QOL).

2. TREATMENT PLAN

This is a Phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled study with a randomization allocation ratio of 2:1 (abiraterone acetate: placebo). This study will be conducted at approximately 175 investigative sites and approximately 1158 patients will be enrolled.

2.1 Overall Study Design and Plan

2.1.1 The primary study endpoint is overall survival, defined as the time from randomization to death from any cause.

2.1.2 Secondary Efficacy Endpoints include

- Proportion of patients achieving a PSA decline ≥ 50% according to protocol-specific PSAWG criteria
- Time-to-PSA progression based on protocol-specific PSAWG criteria
- Progression-free survival (PFS) based on imaging studies.

2.1.3 Other Study Endpoints include

- Proportion of patients with objective tumor response by modified RECIST (baseline LN size must be ≥ 2 cm to be considered a target lesion)
- Proportion of patients experiencing pain palliation using BPI-SF and analgesic score
- Time to pain progression
- Time to first skeletal-related event
- Modified PFS based on criteria for discontinuation of study treatment
- Proportion of patients achieving a decline in CTCs/7.5ml to less than 5
- QOL total score and each subscale score as assessed by FACT-P.

2.1.4 Safety Assessments

- Medical history, vital sign measurements, physical examination, and body weight
- Concomitant therapy and procedures

- Adverse events (AEs) and serious adverse events (SAEs) including laboratory test AEs will be graded and summarized according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
- Blood chemistry, hematology, coagulation studies, serum lipids, and urinalysis

- Electrocardiograms (ECGs) and measurement of cardiac ejection fraction.

2.1.5 Other Assessments

- Quality of Life (QOL) using FACT-P Quality of Life questionnaire
- Fatigue evaluated in the Brief Fatigue Inventory (BFI) instrument
- Medical resource utilization (MRU) information
- PK measurements
- CTC enumerations.

2.2 Study Duration and Dates

The study period will consist of screening, treatment, and follow-up periods. In this study, patients will receive study treatment (abiraterone acetate or placebo) plus prednisone until progression of clinical disease. Follow-up will continue until patient dies, is lost to follow-up, or withdraws informed consent up to 60 months (5 years).

2.3 Study Activities

2.3.1 Screening Period

All patients must sign a written informed consent form before study specific screening procedures are performed. Informed consents may be obtained up to 30 days prior to Cycle 1 Day 1. Screening procedures to evaluate patient eligibility for the study will be conducted within 14 days prior to Cycle 1 Day 1. If the patient meets eligibility and screening requirements he will be randomized and will return to the site for the Cycle 1 Day 1 visit and dosing.

2.3.2 Randomization

Once eligibility is confirmed, patients will be randomized to a treatment group according to the randomization schedule. All patients must commence treatment within 72 hours (3 calendar days) of randomization.

2.3.3 Treatment Period

Randomized patients will have Cycle 1 Day 1 procedures and receive study treatment (abiraterone acetate or placebo) that will subsequently be administered orally once daily. Patients who participate in the pharmacokinetics testing will take their Day 1 dose on Cycles 1, 2 and 5 in the clinic. All patients will also take 5 mg of prednisone or prednisolone orally twice daily. In regions where prednisone is not marketed or available, prednisolone will be provided. If a patient has been receiving glucocorticoids other than prednisone or prednisolone, it will be necessary to switch the glucocorticoid to prednisone or prednisolone 5 mg bid prior to Cycle 1 Day 1.

No crossover will be permitted between the 2 treatment groups. Each cycle of treatment will be 28 days. Patients will return for Cycle 1 Day15 visit ± 3 days visit to evaluate safety and dosing compliance (a count of study drug tablets). From Cycle 2 to End-of-Study, Day 1 visits will occur every 28 days with a ± 2 day window. Study windows are to be calculated from Cycle 1 Day 1 date, and if utilized, every effort will be made for the patient to return to schedule. Patients may have additional imaging visits up to 8 days before Cycles requiring images (Cycle 4 Day 1,

Cycle 7 Day 1, and Cycle 10 Day 1 and every 3rdCycle and beyond Cycle 10) or at Treatment Discontinuation Visit.

2.3.4 Treatment Period Following Study Unblinding

Pursuant to the IDMC's recommendation on August 20, 2010, all patients will be unblinded and patients who have received placebo will be offered cross over therapy with abiraterone acetate. The study schedule for all patients is as follows:

- Patients who are currently receiving placebo or are in long term follow up after receiving placebo will follow the schedule entitled, "Starting Abiraterone Acetate AFTER Placebo".
- Patients who are currently receiving abiraterone acetate will follow the schedule entitled, "Continuing Abiraterone Acetate Treatment".

Treatment will be continued until patients have clinical progression as determined by the Investigator, or until they meet the following criteria for withdrawal in Section 6:

- Dosing compliance
- Sustained side effects
- Initiation of new anti-cancer treatments
- Administration of prohibited medications
- Patient withdraws consent
- Patients who are crossing over must meet all of the criteria for cross over therapy listed below.

2.4 Criteria For Cross Over Therapy with Abiraterone Acetate

1. Willing to provide written informed consent.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
3. Hemoglobin ≥ 8.0 g/dL independent of transfusion.
4. Platelet count ≥ 50,000/μL.
5. Serum albumin ≥ 2.5 g/dL .
6. Serum creatinine < 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min.
7. Serum potassium ≥ 3.5 mmol/L.
8. Able to swallow the study drug whole as a tablet.
9. No serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection.
10. Liver functions as follows:

- Serum bilirubin < 1.5 x ULN (except for patients with documented Gilbert's disease, where the upper limit of serum bilirubin is 3 mg/dL).
- AST or ALT < 2.5 x ULN (for patients with known liver metastasis, AST or ALT < 5 x ULN is allowed).

11. Blood pressure as follows: systolic BP ≤ 160 mmHg and diastolic BP ≤ 95 mmHg) Patients with a history of hypertension are allowed provided blood pressure is within these limits while receiving anti-hypertensive therapy.
12. No active or symptomatic viral hepatitis or chronic liver disease.

13. No clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III or IV heart disease or cardiac ejection fraction measurement of < 45 % at baseline.
14. Recovered from the acute toxicities due to prior chemotherapy or radiotherapy (resolved to a NCI CTCAE (version 3.0) grade of ≤ 1). Chemotherapy induced alopecia and grade 2 peripheral neuropathy are allowed.
15. At least 30 days since last treatment with an investigational drug or device (with the exception of abiraterone acetate/placebo).
16. No condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's participation in the study.
17. Willing to comply with the procedural requirements of this protocol.
18. Willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 13 weeks after last study drug administration.

2.5 Follow-up Period

During the Follow-up period, overall survival follow-up should be performed every 3 months for up to 60 months (5 years) and may be collected by telephone interview or chart review.

3. SUBJECT SELECTION

3.1. General considerations

Medically or surgically castrated male patients with metastatic CRPC who have failed docetaxel-based chemotherapy will be enrolled for the study.

3.2. Inclusion criteria

Each patient must meet the following criteria to be enrolled in this study.

- Willing and able to provide written informed consent.
- Written Authorization for Use and Release of Health and Research Study Information (US sites only) or Data Protection Consent (European sites only) has been obtained.
- Age ≥ 18 years and male.
- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology.
- At least one but not more than 2 cytotoxic chemotherapy regimens for metastatic castration-resistant prostate cancer. At least one regimen must have contained docetaxel. If docetaxel-containing chemotherapy is used more than once, this will be considered as one regimen.
- Documented prostate cancer progression as assessed by the investigator with one of the following:
    - PSA progression according to PSAWG criteria.
- Patients on systemic glucocorticoids for the treatment of prostate cancer or control of symptoms must have documented PSA progression by PSAWG criteria prior to Cycle 1 Day 1. Patients with confirmed PSA progression while on systemic glucocorticoids other

than prednisone or prednisolone are required to switch to prednisone or prednisolone 5 mg twice daily prior to Cycle 1 Day 1, but PSA progression does not have to be reconfirmed.
    - Radiographic progression in soft tissue or bone with or without PSA progression.
- Ongoing androgen deprivation with serum testosterone < 50 ng/dL (< 2.0nM).
- Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
- Hemoglobin ≥ 9.0 g/dL independent of transfusion.
- Platelet count ≥100,000/μL.
- Serum albumin ≥ 3.0 g/dL.
- Serum creatinine < 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min.
- Serum potassium ≥ 3.5 mmol/L.
- Able to swallow the study drug whole as a tablet.

3.3. Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

- Serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection.
- Abnormal liver functions consisting of any of the following:
    - Serum bilirubin ≥ 1.5 x ULN (except for patients with documented Gilbert's disease).
    - AST or ALT ≥ 2.5 x ULN, (for patients with known liver metastasis, AST or ALT ≤ 5 x ULN is allowed).
- Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg) Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy.
- Active or symptomatic viral hepatitis or chronic liver disease.
- History of pituitary or adrenal dysfunction.
- Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III or IV heart disease or cardiac ejection fraction measurement of < 50 % at baseline.
- Other malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 12 months.
- Known brain metastasis.
- History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.
- Prior therapy with abiraterone acetate or other CYP17 inhibitor(s), or investigational agent(s) targeting the androgen receptor for metastatic prostate cancer.
- Prior therapy with ketoconazole for prostate cancer.
- Surgery or local prostatic intervention within 30 days of the first dose. In addition, any clinically relevant sequelae from the surgery must have resolved prior to Cycle 1 Day 1.
- Radiotherapy, chemotherapy or immunotherapy within 30 days, or single fraction of palliative radiotherapy within 14 days of administration of Cycle 1 Day 1.

- Any acute toxicity due to prior chemotherapy and/or radiotherapy that have not resolved to a NCI CTCAE (version 3.0) grade of ≤ 1. Chemotherapy induced alopecia and Grade 2 peripheral neuropathy is allowed.
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days of Cycle 1 Day 1.
- Condition or situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with patient's participation in the study.
- Not willing to comply with the procedural requirements of this protocol.
- Patients who have partners of childbearing potential who are not willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 13 weeks after last study drug administration.

4. DOSAGE AND ADMINISTRATION

After unblinding at Interim Analysis, all patients will receive open label abiraterone acetate.

4.1 Description of the treatment(s)

4.1.1 Study Drug

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

4.1.2 Placebo

Placebo will be provided as a tablet formulation and will be matched in size, color (white to off-white), and shape (oval) to abiraterone acetate tablets in order to maintain the study blind.

4.1.3 Prednisone

Prednisone (5-mg tablets) will be prescribed or provided. In regions where prednisone is not marketed, prednisolone will be substituted.

Prednisone tablets are open label.

4.2 Treatments Administered

4.2.1 Abiraterone Acetate/Placebo (Study Treatment)

Patients will be instructed to take 4 tablets (abiraterone acetate or placebo) orally (PO) at least 1 hour before a meal or 2 hours after a meal any time up to 10 pm every day.

4.2.2 Prednisone

Patients will be instructed to take 5mg prednisone, twice daily.

4.3 Selection and Timing of Dose for Each Patient

Each treatment cycle consists of 28 consecutive days. Patients may take study treatment (abiraterone acetate or placebo) until disease progression. At the time of disease progression, study treatment will remain blinded. Study treatment will be discontinued and dose of prednisone will be gradually reduced if clinically indicated.

It is not required for the prednisone to be taken with study treatment (abiraterone acetate or placebo) at the same time. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. If a prednisone dose is missed, it should be omitted and will not be made up.

4.3 Dose reductions

In the event where dose-reduction is considered to be due to an adverse reaction, 2 dose reductions are allowed. At each dose reduction, one tablet will be removed, e.g., 4→3 tablets, and 3→2 tablets. Otherwise AEs, although anticipated in this study, are primarily related to underlying advanced prostate cancer and its management; therefore, approaches other than dose reduction are recommended to manage the AE. Any return to protocol dose level after dose reduction must follow documentation of AE resolution and a discussion with the Medical Monitor.

4.3.1 Dose reductions for Hypokalemia

If any patient experiences Grade 3 hypokalemia (serum potassium levels < 3.0 mM – 2.5 mM, NCI CTCAE v3.0) or life-threatening hypokalemia with potassium levels < 2.5 mM (NCI CTCAE v3.0 hypokalemia Grade 4), abiraterone acetate treatment will be withheld, and the patient hospitalized for intravenous potassium replacement and cardiac monitoring.
Re-initiation of abiraterone acetate treatment after normalization of potassium levels must be discussed with and approved by the Protocol Medical Monitor.

4.3.2 Dose reductions for Hypertension Side Effects

Grade 3-4 – Hold study medication. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor blocker, Eplerenone (Inspra). When hypertension resolves to ≤Grade 1, resume study medication at full dose.

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).

4.3.3 Dose reductions for Edema, Fluid Retention

Anasarca and/or Pulmonary edema requiring supplemental oxygen – Hold study medication. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor blocker, Eplerenone (Inspra). When toxicity resolves to ≤Grade 1, resume study medication at full dose.

- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).
- If toxicity recurs despite optimal medical management and two dose level reductions, discontinue study medication.

4.3.4 Dose reductions for Abnormal Liver Function Tests

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. 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 subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, and the Medical Monitor agrees, resume study treatment with the first dose level reduction (3 tablets, 750 mg of study treatment) 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, and the Medical Monitor agrees, resume study treatment with the second dose level reduction (2 tablets, 500 mg of study treatment) 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 rechallenged. They should be followed until resolution of abnormal liver function tests.

4.3.5 Dose reductions for other Non-mineralocorticoid Based Side Effects

If Grade 1-2 toxicities, give supportive care per institutional guidelines. No study medication 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 related to study treatment is observed where the patients safety is jeopardized, hold study medication.
When toxicity resolves to ≤ Grade 1, resume study medication at full dose.
If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity.
When resolved to ≤ Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity.
When resolved to ≤ Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).
If toxicity recurs despite aggressive medical management and two dose level reductions, discontinue study medication.

5. TREATMENT EFFECT

5.1 Efficacy Assessments

5.5.1 The Primary Endpoint Measure

The primary endpoint of overall survival will be measured from date of randomization to death from any cause.

5.5.2 Secondary Endpoint Measures

- Post-treatment PSA level will be used to measure PSA response rate and time to PSA progression.
- PFS based on imaging studies.

5.2 Other Measures

- Modified RECIST criteria will be used to assess objective tumor response.
- The Brief Pain Inventory-Short Form (BPI-SF) and analgesic usage score will be used to measure time to pain progression and proportion of patients experiencing pain palliation.
- Time to first skeletal-related events will be measured by the time to a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.
- Modified PFS based on criteria for discontinuation of treatment.
- CTC enumeration.
- Quality of Life questionnaire (FACT-P).
- Brief Fatigue Inventory (BFI).
- Medical resource utilization information.
- Hospital admission date.
- Hospital discharge date.
- Total number of days in the Intensive Care Unit.
- Principal reason for hospitalization.
- Pharmacokinetics.

5.3 Adverse Events Assessments

5.3.1 Safety Measures

All study patients who have received any dose of abiraterone acetate will be evaluable for safety. Adverse events including laboratory adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

- Electrocardiograms (ECGs) and measurement of cardiac ejection fraction
- Laboratory tests (CBC with differential, coagulation factors, platelets, chemistry, urinalysis, and serum lipids)
- Vital Signs (oral or aural temperature, upright blood pressure, heart rate, respiratory rate and weight)
- Physical exam
- ECOG performance status.

5.3.2 Definitions of an Adverse Event and Adverse Reaction

An adverse event (AE) is any reaction, side effect, or other untoward medical occurrence, regardless of relationship to study drug that occurs any time from the beginning of the first study dose administration in cycle 1 until the final study visit or early termination visit.

5.4 Time and events schedule

Table of Scheduled Events								
Treatment Phase	**Follow-Up Phase**							
Evaluation	**Screening Day -14 to 1**	**[1]Cycle 1 Day 1**	**Cycle 1 Day 15**	**[1]Cycle 2, 3, 5, 6, 8, 9, 11, 12 Day 1**	**Cycle 2 and 3 Day 15**	**[1]Cycle 4, 7, and 10 Day 1 & at Treatment Discontinuation[2]**	**End of Study Visit[3]**	**Q3 Months up to Month 60**
Procedures								
Signed consent form[4]	X							
Medical history prior to prostate therapy	X							
QOL - FACT-P		X				X[5]		
BPI-SF, analgesic usage	X	X	X	X		X		
BFI, Fatigue	X	X	X	X		X		
Physical exam and Weight[6]	X		X	X		X	X	
Vital signs[6]	X	X	X	X		X	X	
ECOG	X	X	X	X		X	X	
12 Lead ECG[7]	X					X	X	
MUGA Scan or Cardiac ECHO	X					X[8]	X	
Dosing compliance			X	X		X	X	
Concomitant medications	X	X	X	X		X	X	
Adverse events	X[9]	X	X	X		X	X[10]	
Laboratory Assessments								
CBC	X	X		X		X	X	
Coagulation Factors- PT/PTT (INR)	X	X	X	X		X	X	
Serum chemistry, electrolytes[18]	X	X	X	X	X	X	X	
Fasting Glucose[11]	X					X	X	
Serum Lipids	X					X	X	
PSA[12]	X	X				X	X	
Serum	X					X		

testosterone & other androgens								
Urinalysis (dipstick)	X							
CTC Assessments	X	X		X[13]		X[13]		
Tumor Assessments								
CT/MRI/other imaging procedure Chest x-ray[14]	X					X		
Bone Scan[14]	X					X[15]		
Disease progression assessment								
Overall survival								X[16]
PK[17] and Additional ECG Sampling at Select Study Centers								
Pre-dose PK		X		X[17]				
In Clinic Dosing of Study Treatment for PK[17]		X		X				
1st Post-dose PK		X		X[17]				
2 hr Post-dose ECG		X						
2nd Post-dose PK		X						

If patient's continues on study without disease progression or discontinuation of treatment beyond Cycle 12 they should continue visit assessments as indicated for every 3rd Cycle starting with Cycle 13 and restart to every 1st and 2nd Cycle visit assessments following.
2 Treatment Discontinuation Visit can occur at any scheduled or unscheduled visit when applicable. At this visit, documentation to confirm progressive disease is required.
3 End of Study Visit should be scheduled to collect safety assessments between 15 to 28 days after the patient stops treatment. Patients will enter Follow up Phase at that time.
4 Written informed consent must be obtained within 30 days prior to Cycle 1 Day 1.
5 After Cycle 10, QOL assessment will be collected every 6 cycles up to the Treatment Discontinuation Visit.
6 Weight will be recorded at every visit. Height will be measured at Screening visit only. Vitals Include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
7 An ECG should be obtained prior to Day 1 visit, every 3 cycles, and at End of Study visit except for patients in the PK sampling portion of the protocol who will also have ECGs collected at approximately 2 hrs post-dose on Cycle 1. ECGs should not be obtained when serum potassium is < 3.5mg/mL. Hypokalemia should be corrected prior to ECG collection.
8 A MUGA scan should be obtained at baseline and at End of Study visit in all patients. Patients who have had prior mitoxantrone should also have a MUGA scan at every 3 cycles. A cardiac ECHO can be used if MUGA is not available or when ECHO is standard of care at the study site.
9 Pre-Treatment SAEs should be reported from time patient signs a consent form up to Day 1 treatment administration.
10 Adverse event follow-up is required for 30 days following last dose to determine if any new or ongoing drug related AE or any SAE regardless of relationship to drug exists. Follow-up could be conducted by sites via telephone attempts and must be documented in source notes.
11 Fasting Glucose can be done as part of Chemistry Panel run by central laboratory when possible or as a pre-test run by site local laboratory to full chemistry panel if patient would be coming in not fasted. If local lab used results will be collected on the supplemental Lab CRF.
12 If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE
13 CTCs will be collected from select centers at screening, Cycle 1 Day 1, and then Cycle 2, 3, and 4 Day 1, and at time of disease progression. CTC enumeration will be run on all samples collected; molecular characterization will be performed on samples when patients provide a signed informed consent form for molecular testing.
14 *Scans (CT, MRI, and Bone) performed up to 28 days prior to Study Day 1 can be used for baseline assessments.* If a status of partial or complete response is made, 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. If a Chest CT or MRI is performed as part of the imaging evaluation, then the Chest x-ray is optional and may not be performed.
15 Bone scans after screening should be conducted as part of the response assessment
16 Overall survival may be collected by telephone interview or chart review
17 *Selected Study Centers Only:* PK blood samples collected pre and post dose on Cycle 1 Day 1 (2 post dose samples on Cycle 1), Cycle 2, and Cycle 5. Patients will be asked to withhold their daily dose and take study treatment following pre-sample PK collection. Additional ECG assessments at approximately 2-hour post dose on Cycle 1.
18 At C2D15 and C3D15 Chemistry is limited to Liver Function Tests: AST, ALT, alkaline phosphatase, and total bilirubin.

6. DISCONTINUATION OF TREATMENT

To discontinue study treatment, all three of the following criteria are required:

1) PSA progression as defined by PSAWG eligibility criteria (25% increase over baseline) with minimum PSA increase of 5 ng/mL

2) Radiographic progression defined by at least one of the following:

- Progression on bone scans with ≥ 2 new lesions not consistent with tumor flare, confirmed on a second bone scan ≥ 6 weeks later that shows ≥1 additional new lesion.
- Soft tissue disease progression by modified RECIST criteria (baseline LN size must be ≥ 2.0 cm to be considered target or evaluable lesion).

3) Symptomatic or clinical progression defined by one of the following:

- Pain progression - Worsening of pain due to metastatic bone disease defined as an increase of ≥ 30% in the worst pain over the past 24 hours on the BPI-SF numeric rating scale observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score ≥ 30% observed at 2 consecutive evaluations 4 weeks apart; to qualify as progression, the patient must have a BPI-SF score ≥ 4.
- Development of a skeletal related event (SRE) defined as pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.
- Any increase in prednisone or prednisolone dose or a change to a more potent glucocorticoid such as dexamethasone, to treat prostate cancer related signs and symptoms, such as fatigue and pain is considered a disease progression event.
- Treating physician decides to initiate new systemic anti-cancer therapy.

The investigator may withdraw a patient from study treatment phase for any of the following reasons.

- Discontinuation of treatment criteria as defined above.
- Dosing noncompliance: Study treatment administration and dosing compliance will be assessed on Cycle 1 Day 15 visit. A count of study treatment will be conducted during this visit and patient dosing compliance will be assessed. If dosing compliance is not 100% in the absence of toxicity, patient should be re-instructed regarding proper dosing procedures and continue in the protocol. Subsequent dosing compliance procedure will be conducted at each study visit. If a patient misses 14 or more doses within a single 28-day cycle, the patient should be discontinued from the study treatment Phase. All End-of-Study treatment procedures should be followed. The patient will be followed for survival.
- Sustained Side Effects: Patients who have sustained toxicities, such as hyperglycemia or hypertension that do not return to NCI CTCAE (version 3.0) Grade 1 or less with appropriate medical management, should be discontinued from the study treatment Phase. All End-of-Study treatment procedures should be conducted. The patient will be followed for survival.
- Initiation of new anticancer treatment: Patients will be discontinued from the protocol treatment when investigator, in his or her judgment, determines new treatment for prostate cancer is warranted. All End-of-Study treatment procedures should be conducted and the patient should be followed for survival.
- Administration of prohibited medications: The patient will be discontinued from the protocol treatment when prohibited drug is administered. All End-of-Study treatment procedures should be conducted and the patient should be followed for survival. Supportive care medications are permitted with their use following institutional guidelines. For patients who did not undergo orchiectomy, concurrent treatment with LHRH analogue is mandatory and must be recorded. The concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists), or immunotherapy is prohibited during study treatment Phase. Use of other investigational drug therapy for any reason is prohibited.
- Patient withdraws consent: In this event, the reason(s) for withdrawal must be documented and clarification if withdrawal of consent includes follow-up phase for overall survival data collection. A patient's decision to take part in the study is voluntary and he may choose not to take part in the study or to stop taking part at any time. If he chooses not to take part or to stop at anytime, it will not affect his future medical care or medical benefits.

7. STATISTICAL METHODS

7.1 General Considerations

All statistical analyses will be performed using SAS®. The resulting statistic will be evaluated using East® given the precise number of events observed at the time of interim analysis.

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of patients (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the date of first study treatment.

7.2 Determination of Sample Size

This is a group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method. One interim analysis and one final analysis are planned (East®). The interim and final analyses of data will be performed after the pre-specified number of death events are observed (see Sections 7.3 to 7.9 below). All statistical tests of treatment effects will be conducted at the two-sided 0.05 level of significance.

Patients will be randomized in a 2:1 ratio to receive abiraterone acetate plus prednisone or placebo plus prednisone. Patients with metastatic CRPC after failure of docetaxel-based chemotherapy are expected to have an estimated median overall survival of 12 months. It is assumed that failure will follow an exponential distribution with a constant hazard rate. The planned sample size of approximately 1158 patients (772 on abiraterone acetate and 386 on placebo) will provide 85% power to detect a difference between a median survival of 15 months in the abiraterone acetate group and a median survival of 12 months in the placebo group (hazard ratio=0.80) under the assumptions of a 2-tailed significance level of 0.05 and an enrollment of approximately 13 months over a total duration of approximately 30 months to obtain the required 797 total events.

7.3 Analysis Populations

Patient disposition and efficacy analyses will be performed on data from the intent-to-treat (ITT) population. All randomized patients will be included in the ITT analysis who will be classified according to their assigned treatment group, regardless of the actual treatment received. The primary efficacy analyses will be on the ITT basis.

All patients who receive at least one dose of study drug will be included in the analysis of safety (Safety Population).

7.4 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, height, and weight. Baseline disease characteristics will include time from diagnosis, time since initiating chemotherapy to study drug, prior chemotherapy, and etc (as documented in the CRF) will be presented.

7.5 Study Endpoint(s)

7.5.1 Efficacy Endpoint(s)

7.5.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is OS, and will be measured from the date of randomization to the date of death (whatever the cause). Survival time of living patients will be censored on the last date a patient is known to be alive or lost to follow-up.

7.5.1.2 Secondary Time to Event Endpoint

- PSA response is scored in patients achieving a post-treatment PSA decline of at least 50% according to the protocol-specific PSAWG criteria.
- Time to PSA progression will be measured from the time interval from the date of randomization to the date of the PSA progression as defined in the protocol-specific PSAWG criteria. The determination of PSA progression will require that the patient receive at least 3 cycles of therapy. A rise in PSA value alone, in the absence of radiographic progression, during the first 3 cycles will not be considered disease progression.
- Radiographic PFS will be measured from the date of randomization to the first occurrence of radiographic progression or death. Progression is defined as the time from randomization to the occurrence of either tumor progression in soft tissue according to modified RECIST criteria or by bone scan (≥ 2 new lesions confirmed ≥ 6 weeks later shows ≥ 1 additional new lesion). If no event exists, then PFS will be censored at the last scheduled disease assessment on study. PFS of living patients with no assessment on-study, and PFS of patients with no baseline assessment will be censored at randomization.

7.5.1.3 Other Efficacy Endpoints

- Objective response is achieved in patients with a complete or partial response by modified RECIST criteria.
- Proportion of patients experiencing pain palliation using BPI-SF worst pain intensity score and analgesic score.
- Time to pain progression will be measured from the date of randomization to the first observation of symptomatic pain progression.
- Time to first skeletal-related event will be measured from the date of randomization to the first observation of skeletal-related event, defined as pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. Patients with no such assessment on-study will be censored at randomization.
- Modified PFS based on criteria for discontinuation of study treatment criteria from the date of randomization to death or the first observation composed of:
  1. PSA progression,
  2. Radiographic progression,
  3. Pain progression, SRE, increase in glucocorticoid use, or initiation of a new systemic anti-cancer therapy.
- Proportion of patients achieving a decline in circulating tumor cells (CTCs)/7.5ml to less than 5.
- QOL total score and each subscale score as assessed by FACT-P.

Distribution of time-to-event variables will be estimated using the Kaplan-Meier product-limit method. The median times to event with two-sided 95% confidence intervals will be estimated, together with the estimate of event rates at 6 and 12 months. Stratified logrank test will be used

as the primary analysis for treatment comparison; the score statistic from the cox proportional hazards model will be used in the estimation of the hazard ratio and the associated 95% confidence interval will also be provided.

Response variables are the proportion of patients fulfilling the respective criteria for response. The relative risk (treatment: control) will be reported along with the associated 95% confidence interval. Statistical inference will be evaluated using Chi-square statistic; the Fisher's exact test may be used if the expected counts in some cells are small.

The total score and the subscale scores assessed by FACT-P for the QOL will be descriptively summarized and t-test will be used to compare the score at each time point with the baseline score. Repeated measures analysis may be carried out as appropriate. In addition, non-stratified analyses and cox proportional analyses will also be carried out for the primary endpoint of OS as supportive analysis. Sensitivity and subgroup analyses will also be carried out as appropriate.

7.5.2 Safety Evaluations

Safety analysis will be summarized using the Safety Population.

Extent of exposure to study drug will be summarized and details will be provided.

Treatment emergent adverse events (TEAEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be coded using the MedDRA coding system and all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI-CTCAE).

Incidence of AEs will be summarized by system organ class (SOC) and preferred term (PT), and will be presented by treatment groups and overall. Adverse events will be summarized by grade, according to the worst grade experienced. In addition, most frequently observed AEs will be summarized by treatment groups. In the summary of AE, an AE occurs more than once within a SOC and PT will be counted only once using the worst grade experienced.

Serious AE and deaths observed within 30 days of the last dose of study treatment will be provided in a listing.

All adverse events resulting in discontinuation, dose modification, dosing interruption, and/or treatment delay of study drug will also be listed and tabulated by preferred term.

Clinical laboratory test results will be collected pretreatment and through 30 days post last dose of study treatment. All laboratory test results will be classified according to the NCI CTCAE criteria. Standard reference ranges will be used for missing or discrepant normal ranges. Baseline laboratory test values are the results from the last blood samples drawn on or prior to the first day of study treatment. On-study laboratory test values are those results from blood samples drawn a day after the first study treatment up until 30 days after the last dose of study treatment.

Mean change from baseline in laboratory test values at each visit will be provided. On-study clinical laboratory test abnormalities will be summarized. Shifts in laboratory test values will also be summarized.

Electrocardiograms data will be descriptively summarized for QTc, PR interval, and QRS at each visit. Comparison between baseline and maximum on-study QTc will also be presented. Both Fredericia and Bazett corrections will be reported.

Multiple gated acquisition (MUGA)/echocardiogram (ECHO) scan data will be collected. Distribution of the results from MUGA and/or ECHO will be summarized in terms of number of patients and percentages of patients whose ejection fraction falls below 50%.

7.6 Pharmacokinetics Analysis

Approximately 150-200 patients are scheduled to be enrolled at selected sites for the PK assessment. Based on the 2:1 randomization this should yield approximately 100-133 patients on active treatment (abiraterone acetate).

Nonlinear mixed effects modeling will be used to develop a population PK model for abiraterone plasma concentrations in HRPC patients. A covariate analysis will be performed to investigate the influence of patient factors on the apparent clearance of abiraterone. Patient factors will include, but are not limited to, body weight, calculated creatinine clearance, liver function, sex, age, race, and time of meal relative to the time of dose administration. Patient factors on other disposition and absorption parameters will be tested in a secondary fashion. A separate report will be generated summarizing the results from the modeling.

7.7 Circulating Tumor Cells (CTC)

Change in CTC counts will be descriptively summarized. Analyses of proportion of CTC responder and its potential clinical benefit with respect to the primary endpoint will be carried out as described in Section 7.5.1.3. Analyses on CTC responders will also be presented by visit. Additional analyses to explore CTC enumeration as surrogate for clinical benefit will be provided in a separate report.

7.8 Other Assessments or Analyses

Other endpoints of the study are fatigue as evaluated in the Brief Fatigue Inventory (BFI) instrument, pain evaluated in the Brief Pain Inventory (BPI), and medical resource utilization (MRU) information. Descriptive statistics will be presented for each item collected.

In addition, analysis of pharmacoeconomic data and production of a final pharmacoeconomic report will be handled separately from the final clinical study report. Information obtained from the collection of medical resource utilization data may be combined with other data, such as cost data or other clinical parameters, in the production of final pharmacoeconomic report.

7.9 Interim Analysis

A group sequential design using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method was used in the planning of the study (East®). In this study, there will be one interim analysis after 534 death events are observed (67% of 797 total events) and a final analysis after observing the required 797 total events. Details of the interim analysis and final analysis are provided in the table given.

Variable	**Interim Analysis**	**Final Analysis**
Number of Patients Enrolled	1158	1158
Number of Events	534	797
Efficacy Boundary (HR)	0.7975	0.8628
Cumulative Power	0.4864	0.8500
Cumulative Alpha Spent (2-tailed)	0.0124	0.0500

These stopping boundaries were calculated assuming that the number of events available at the time of interim analysis is exactly as planned and as provided in the above table. The actual stopping boundaries will be determined at time of analysis based on the number of events included in the analysis.