AN EXPLORATORY RANDOMIZED PHASE II MULTICENTER TRIAL OF ABIRATERONE ACETATE WITH OR WITHOUT CABAZITAXEL IN TREATMENT OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Prostate Cancer Clinical Trials Consortium, LLC (PCCTC)
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Sponsor: Memorial Sloan Kettering Cancer Center

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CONFIDENTIALITY STATEMENT

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: AN EXPLORATORY RANDOMIZED PHASE II MULTICENTER TRIAL OFABIRATERONEACETATE WITH OR WITHOUTCABAZITAXEL IN TREATMENT OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Principal Investigator Signature: _____

Principal Investigator Print: _____

Date: _____

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1. INTRODUCTION, BACKGROUND AND RATIONALE

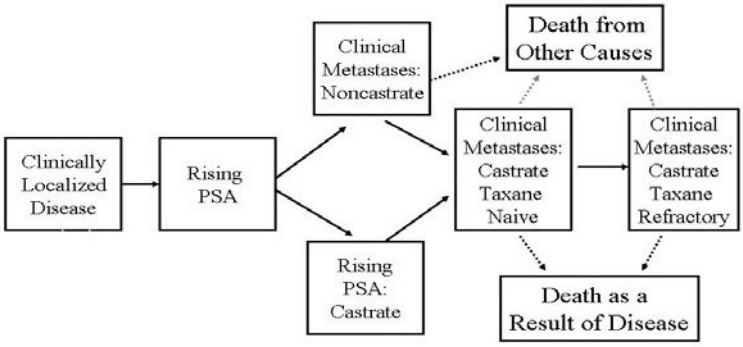
1.1 Disease Background

Every year in the United States 28,000 men die of metastatic prostate cancer.[8] Since the introduction of hormonal therapy sixty years ago,[9] progress in developing new treatments has been poor.[10] The biological revolution of the past two decades has produced few useful targeted agents against prostate cancer. In 2012, metastatic prostate cancer remains a uniformly fatal disease. It is striking that while molecular subtyping has afforded therapeutic benefit and improved patient survival in other tumor types,[11-14] no comparative advances have been gained in the context of prostate cancer. At present, all patients with metastatic prostate cancer are treated identically, and there are no means with which to select appropriate therapeutic regimens based on tumor profiling.

The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states (Figure 1). These clinical states involve the complex interplay of a network of signaling molecules that collectively promote net cell proliferation relative to cell death.

Treatment options for patients with castrate resistant prostate cancer (CRPC) are limited and until recently only docetaxel was shown to improve survival. In the last year we had 4 new agents; abiraterone acetate, cabazitaxel, enzalutamide and Sipuleucel-T approved for use in this clinical state. However the optimal sequencing of these agents is unknown. Moreover all patients with CRPC are treated identically and there is no means of identifying which patient population would benefit from a particular agent.

Figure 1. Clinical states of prostate cancer



1.2 Background

This study is based on robust *in vitro, in vivo,* and clinical findings that have been reported. *First,* loss of retinoblastoma tumor suppressor (RB) function was recently identified as a major means by which castration-resistant tumors develop. Up to 60% of CRPC tumors examined to date show loss of RB function. *Second,* modeling this event in human xenografts demonstrated that loss of RB is sufficient to drive the transition to castration resistance. The underlying mechanisms by which RB loss promotes CRPC were illuminated, whereupon it was revealed that expression of the androgen receptor (AR) is under stringent RB control. Consonantly, loss of RB results in AR deregulation and bypass of androgen deprivation therapy, and investigation of human CRPC revealed that this occurrence is frequent in the clinical setting. *Third,* while RB-deficient tumors are resistant to androgen deprivation therapy, tumors lacking RB are compromised for DNA damage checkpoints that normally allow for repair after genomic insult. As a result, tumors devoid of RB function are

hypersensitive to treatment with agents that induce genotoxic stress. ***These collective findings strongly support the novel hypothesis that leveraging RB status to tailor treatment for CRPC will improve outcomes for advanced disease.***

Loss of RB function is a major effector of the transition to advanced prostate cancer: The RB tumor suppressor protects against tumor development in a large number of tissues; accordingly, RB function is ablated in early stages as a function of tumorigenesis in several human malignancies *(e.g.* breast, cervical and small cell lung cancer).[15,16]

The function of RB in protecting against tumor development is manifest through the ability of this protein to act as a transcriptional repressor, binding to the regulatory region of genes whose functions are important for cell cycle progression and DNA replication. Recent interrogation of RB function in human prostate cancer does not fit this paradigm, and deep investigation illuminated five key features of RB action that have a significant impact on disease progression and therapeutic intervention:

1.2.1 *Knudsen and colleagues at Thomas Jefferson University observed in clinical specimens that RB expression (mRNA or protein) is retained in primary disease.*[1]
This premise was further validated by analyses of RB function and they have developed a unique mRNA "signature" using genetically modified tissues that accurately assesses RB function in any cell type.1,2

Such analyses are critical, as tumors retaining RB expression can be devoid of RB function, as occurs through mutation of RB and or factors that induce excessive RB phosphorylation (thus suppressing RB tumor suppressor activity). They have further refined this gene signature (unpublished data), and recently developed a high density microarray chip that provides a robust measure of RB function built off of an FDA approved Affymetrix platform in accordance with GMP/GLP (Figure 2). For this proposal, RB status will be determined using immunohistochemistry but an accompanying, exploratory endpoint will be to assess clinically whether the RB chip can be used to assign RB functional status from tissue and circulating tumor cells.

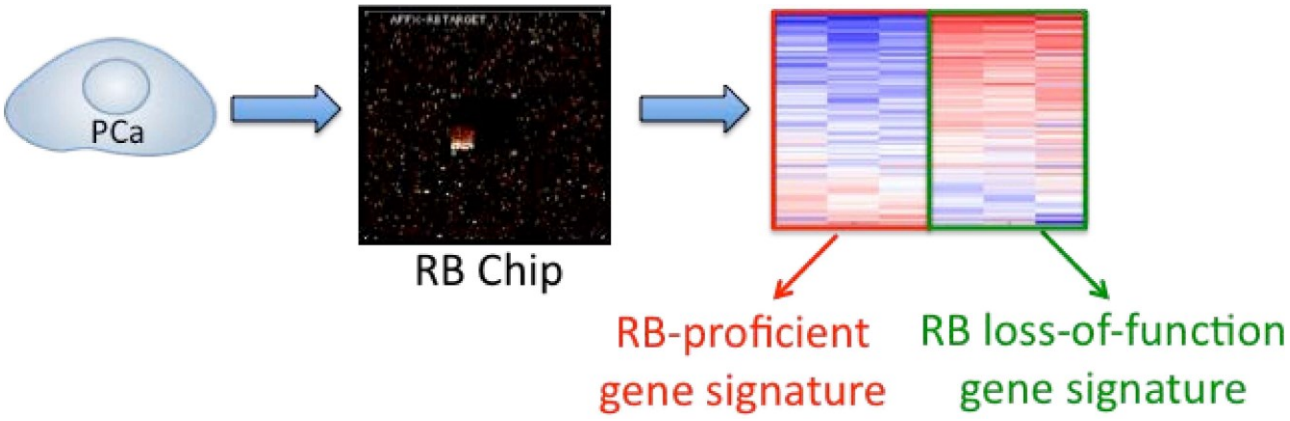


Figure 2. Development of the RB loss signature microarray chip. A refined version of the published RB loss-of-function gene expression signature was recently developed into a proprietary high density microarray chip (middle panel) that provides faithful measure of RB function. The right panel provides examples of data obtained from 3 samples that retain RB function vs. 3 from tumors wherein RB function has been suppressed.

1.2.2 *Using multiple methods to assess RB expression and activity, it was noted that RB loss of Junction* is *highly overrepresented in CRPC.*
A representative example of the data are shown in Figure 3 and in the study by Sharma et al. [1]

Using the combined analyses of RB expression and the RB signature, up to 60% of CRPCs show loss of RB activity. While the initial study examined over 150 CRPC specimens, enrichment of RB loss in the CRPC setting has been further confirmed by the work of Gerald and Sawyers,[17] and in subsequent analyses of cohorts from Dr. Tapio Visakorpi (data not shown). Moreover, recent mouse models confirm the importance of RB in prostate cancer.1[8]

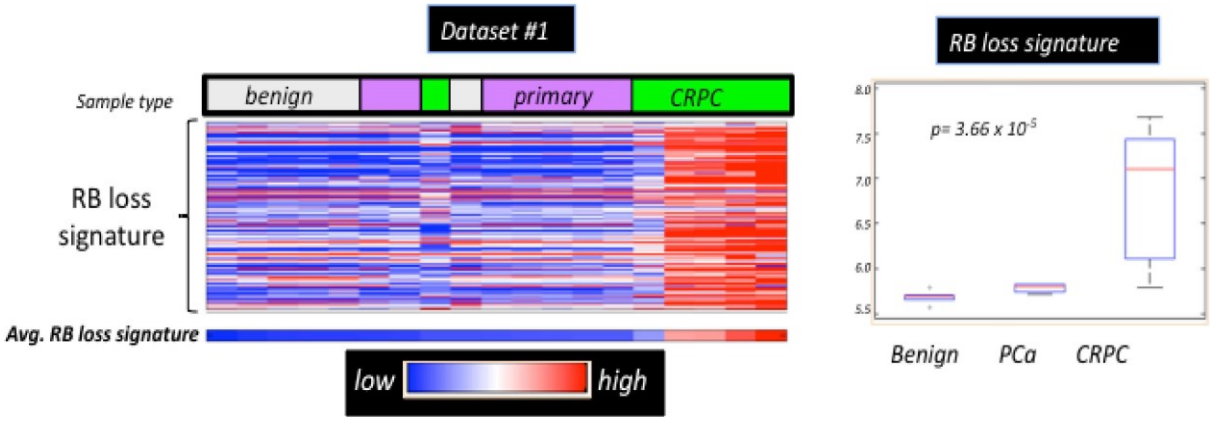


Figure 3. RB function is perturbed in the transition to CRPC. These data are taken from a recent comprehensive study (Sharma et al., J Clin Invest 2010) which assesses RB functional status in multiple tumor sets. As shown, the RB loss signature is highly overrepresented in CRPC (left). Quantification and statistical analyses (right) demonstrate that there is little evidence for loss of RB function in primary disease, whereas this event is frequent in CRPC. Based on this published (Sharma et al., 2010) and new preliminary data, analyses of over 150 CRPCs demonstrate that RB loss of function occurs in up to 60% of CRPCs.

1.2.3 *Modeling of RB loss in multiple human xenografts unexpectedly revealed that ablation of RB function does not induce a significant tumor growth advantage prior to hormone therapy,[1] thus indicating that in this tumor type, RB plays a role distinct from that in other tissues.*
Strikingly, *in vivo* castration challenge revealed that RB-deficient tumors are exquisitely resistant to castration therapy. *A* representative example of these data are shown in Figure 4 and in the article by Sharma et al. [1]

These observations were the first to suggest that in prostate cancer, RB serves a unique role to protect against the transition to lethal disease.

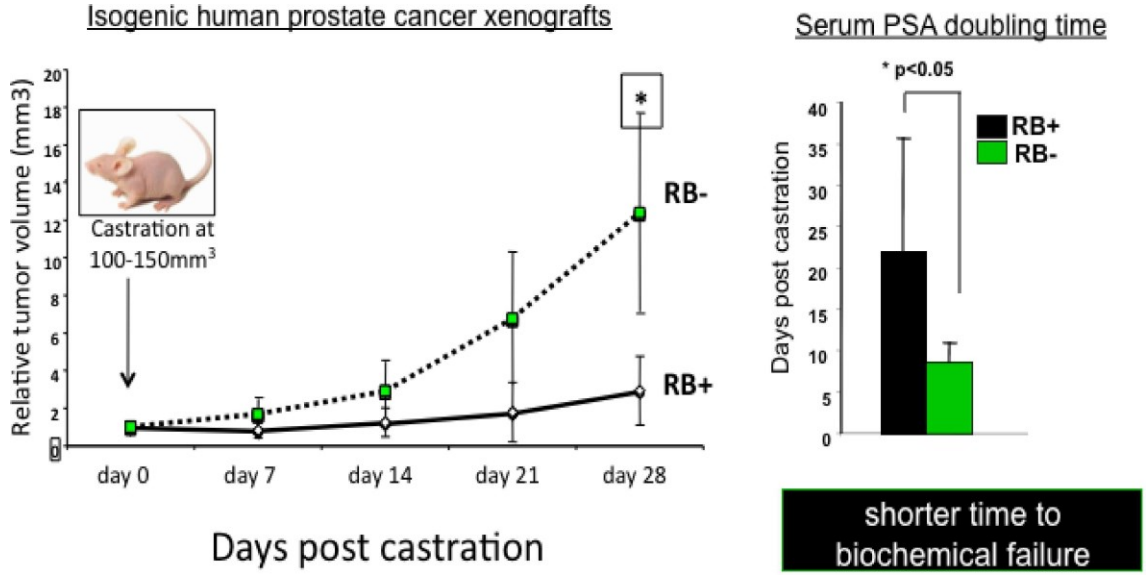


Figure 4. RB loss is *sufficient to drive the transition to CRPC.* Ablation of RB in human prostate cancer xenografts is sufficient to render castration resistance. An example is provided here, wherein isogenic pairs of human xenografts were examined +/- sh RNA directed against RB. RB ablation alone had no effect on tumor growth in the pre-castration setting (not shown but provided in[1]), whereas RB depletion strongly promoted castration-resistant growth (left) and a shorter time to biochemical failure serum PSA (right).

1.2.4. *The underlying mechanisms of RB Junction were further explored, whereupon it was discovered that expression of the gene encoding the AR* is *under RB control.*
These data are extensive and not shown herein due to space limitations. Please see the recent study inf. *Clin. Invest.,[1]and* resulting commentary article inf *Clin Invest.*[19]

In brief, loss of RB caused de-repression of the AR locus, excessive AR production, and castration-resistant (ligand independent) AR activity that proved sufficient to bypass hormone therapy. Thus, means to restore RB function would be of a significant therapeutic benefit.

1.2.5. *Finally, RB status proved strongly predictive of surviva/,1as was confirmed using multiple cohorts.*
An example of these data is shown in Figure 5.

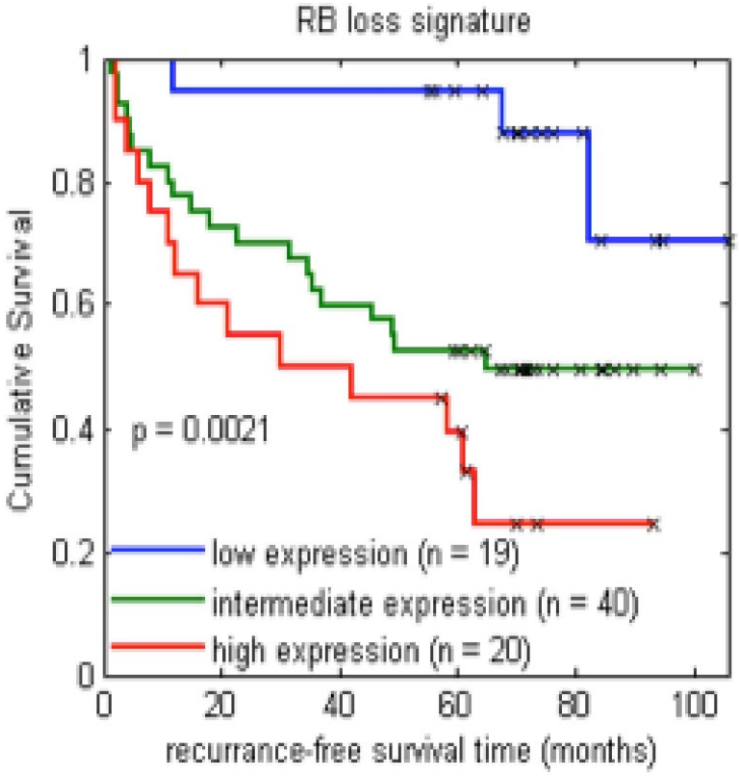


Figure 5. RB loss of function is associated with poor outcome. As was shown and described in detail the RB loss signature is associated with poor outcome, including a shorter time to recurrence free survival.

Combined, these data identify RB tumor suppressor activity is critical to determine the outcome and possible treatments for patients with castrate resistant prostate cancer.

1.2.6. *Treatment of RB-deficient tumors: leveraging the loss of DNA damage checkpoints for clinical benefit*

Studies demonstrate that RB-deficient tumors acquire hyperactive AR activity and bypass first line hormone therapy. By contrast, it has been shown in multiple models of disease that RB-deficient cells lack cell cycle checkpoints that induce cell cycle arrest after genomic insult.[1-3]

Thus, in model systems, RB-deficient tumor cells are hypersensitive to agents that induce genotoxic stress (including etoposide, radiation, and taxanes). Examples in fibroblasts and prostate cancer cells are shown in Figure 6. Furthermore, it was recently observed in breast cancer that patients harboring RB-deficient tumors showed improved survival upon treatment with chemotherapy.[20]

Based on these findings, it is anticipated that stratification of patients with RB-deficient tumors into chemotherapy containing regimens will afford significant clinical benefit.

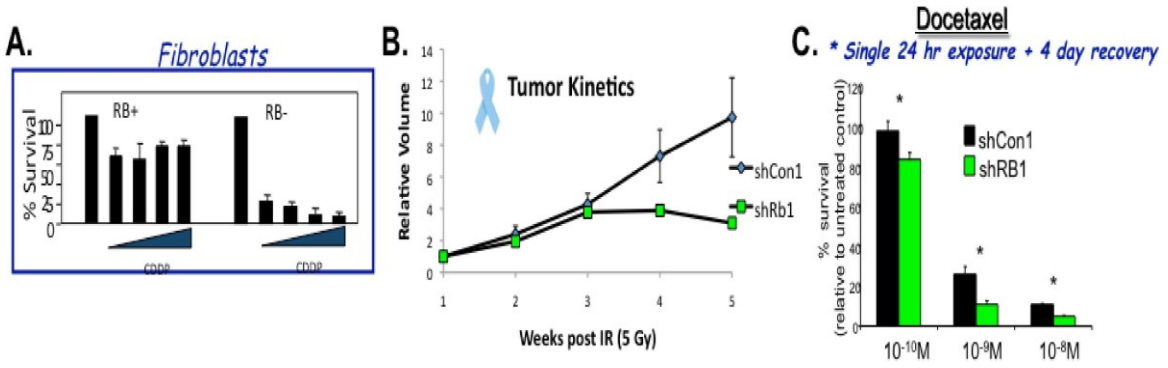


Figure 6. RB deficient tumors are hypersensitive to a subset of DNA damaging and chemotherapeutic agents. **A.** Early studies in fibroblasts revealed that RB-deficient cells are compromised for a subset of DNA damaging checkpoints and become hypersensitive to treatment with agents that induce genotoxic stress.[21] For example, fibroblasts deficient in RB are hypersensitive to cisplatin. Subsequent analyses revealed that the hypersensitization events are tissue specific. **B.** In vivo analyses show that RB deficient human prostate cancer cells are hypersensitive to ionizing radiation. **C.** Initial screening agents, wherein isogenic pairs of RB+ and RB- cells were treated with chemotherapeutics revealed that RB-deficient cells are also hypersensitive to microtubule poisons. These preliminary studies entailed only a brief exposure to low dose chemotherapy, so as to identify meaningful changes in survival that could be refined through multiple dosing.

1.3 Rationale

The clinical dilemma that faces physicians once a patient relapses from primary hormonal therapy is whether to initiate secondary endocrine therapies such as anti-androgens/androgen biosynthesis inhibitors or move directly to chemotherapy. Currently, there are no biomarkers to help us identify patients that may still be androgen receptor sensitive and many clinicians will use a trial and error approach to patients thus delaying patients from receiving chemotherapy in a timely manner. Methods to distinguish androgen receptor sensitive vs. insensitive patients would greatly personalize the approach of CRPC and is an unmet clinical need.

Recently, the drug abiraterone acetate, a 17 lyase inhibitor, has shown to improve the survival of CRPC patients that have failed docetaxel based chemotherapy.[4] While abiraterone acetate has recently received FDA approval for CRPC that have failed prior docetaxel chemotherapy, more recently abiraterone acetate has shown clinical benefit in the pre-chemotherapy setting (RB+ and RB- tumors). Abiraterone acetate improved radiographic progression-free survival (16.5 vs. 8.3 months, hazard ratio 0.53, $p<0.001$) showed a trend toward improved overall survival, and significantly delayed initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer. Based on the cumulative data on abiraterone acetate, the FDA has approved the use in pre-chemotherapy setting.s

Abiraterone acetate is a safe drug and the most common side effects of the medication appear to be hypertension, hypokalemia and fluid retention which are likely from excess mineralocorticoid secretion, which are mostly corrected with the concomitant use of prednisone. Most other adverse events (AEs) were Grade 1 or 2 toxicities in prior studies. Due to the ease of administration, the recent results showing clinical benefit in CRPC prior to chemotherapy along with its favorable safety profile, it is expected that abiraterone acetate will be used extensively prior to chemotherapy. However, there is still a substantial

proportion of patients that do not clinically respond to abiraterone acetate treatment and pre-clinical studies suggest that these tumors may have a RB deficient phenotype as described above. Thus, these patients may benefit from earlier chemotherapy.

Docetaxel is the standard chemotherapy in the first line setting for CRPC.[22] Cabazitaxel is a more potent micro-tubule inhibitor that has improved overall survival in CRPC patients that have failed docetaxel chemotherapy when compared to mitoxantrone.[6] Cabazitaxel's most common side effects are hematological with the dose limiting side effect being neutropenia. Other Grade 3 toxicities noted were diarrhea, fatigue, asthenia and back pain. Febrile neutropenia was observed **in** 8% of patients in the second line setting. *A* head to head comparison of docetaxel and cabazitaxel is ongoing; but it is generally considered that cabazitaxel will be equivalent or better than docetaxel **in** the first line setting. Therefore, it would be reasonable to consider a combination of abiraterone acetate and cabazitaxel in this setting given the non- overlapping toxicities. There is a phase I\II trial of cabazitaxel and abiraterone acetate in patients that have progressed after treatment with docetaxel (Sanofi sponsored study, NCT01511536). This study has completed dose escalation part of the study where 2 dose levels of cabazitaxel, 20 and 25 mg/m^2 IV every 3 weeks, were administered with abiraterone acetate 1000 mg daily and prednisone 5 mg po BID. The maximal tolerated dose was established at cabazitaxel 25 mg/m^2 dose level without dose limiting toxicities in 6 evaluable patients (personal communication Massard et al.; abstract submitted ASCO 2013).

This is an exploratory randomized phase II trial of abiraterone acetate\prednisone (AA) alone followed by cabazitaxel on progression of disease versus the combination of abiraterone acetate and cabazitaxel (AA+C) upfront in patients with chemotherapy nai've CRPC. Since little is known about the RB status in patients treated on prior trials with abiraterone acetate or chemotherapy, the RB status of all patients will be determined prior to treatment at study entry to help develop a possible marker that may help select treatment in the future. In this study, the RB status will not be used to determine treatment but to determine the feasibility in assessing the RB status in patients and to predict the prevalence of the RB positive and negative tumors **in** patients treated with abiraterone acetate\prednisone or abiraterone acetate\prednisone + cabazitaxel. This will allow us to understand the effects of treatment in these populations and in the future could identify patients that may benefit from chemotherapy earlier. While, this technology for RB profiling has shown robust results **in** the laboratory, this will be the first trial to determine RB profiles prospectively in patients and data from this trail will help guide future randomized trials that can be designed to evaluate the utility of RB status in patients with CRPC.

In summary, this study is a non-comparative randomized trial to 1) extend the pre-clinical work on RB status in prostate cancer to patients, 2) explore the feasibility of determine RB status in patients tumors and circulating tumor cells, 3) to determine the prevalence of RB status in prostate tumors that are chemotherapy nai've, 4) to determine the safety and clinical outcomes in chemotherapy nai've prostate cancer with the combination of *AA* + C, and 5) correlate the clinical outcomes based on RB status and treatment in patients. The information derived from this study is critical for the development of RB as biomarker and designing\powering future studies that will help select those patients that will need chemotherapy in their disease course.

2. OBJECTIVES

2.1 Primary Objective

1. To determine the radiographic progression free survival (rPFS) of abiraterone acetate\prednisone with and without cabazitaxel in patients with chemotherapy naive CRPC.

2.2 Secondary Objectives

1. To determine PSA progression free survival (PSA PFS) in patients treated with abiraterone acetate\prednisone with and without cabazitaxel in patients with chemotherapy naive CRPC

2. To determine the proportion of chemotherapy naive CRPC patients with measurable disease regression based on RECIST treated with abiraterone acetate with and without cabazitaxel.

3. To determine the overall toxicity and survival of abiraterone acetate with and without cabazitaxel **in** patients with chemotherapy naive CRPC.

4. To determine the proportion of patients that have an objective response by RECIST and post-therapy PSA decline using a waterfall plot in patients that are treated cabazitaxel after progression on the abiraterone\prednisone alone arm

2.3 Correlative Studies

1. To prospectively estimate the proportion of patients that have tumors that are RB negative\positive based on immunohistochemistry and RB gene signature from the baseline tumor biopsy samples.
2. To determine the feasibility of obtaining the RB status for prostate cancer on circulating tumor cells at baseline.

3. PATIENT SELECTION

3.1 Inclusion Criteria

Patient needs to have a histologic or cytologic diagnosis of prostate cancer

3.1.1 Documented progressive metastatic CRPC based on <u>at least one</u> of the following criteria:

a) PSA progression defined as 25% increase over baseline value with an increase in the absolute value of at least 2 ng/mL that is confirmed by another PSA level with a minimum of a 1 week interval and a minimum PSA of 2 ng/mL.
b) Soft-tissue progression defined as an increase 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions.
c) Progression of bone disease (evaluable disease) or (new bone lesion(s)) by bone scan.

3.1.2 Agree to undergo a biopsy of at least one metastatic site or primary prostate for determination of the RB status. Adequate archival metastatic tissue can be used if

available in lieu of a biopsy if done when patient had CRPC (within 6 months of *treatment start).*

3.1.3 ECOG performance status of0-2.

3.1.4 Age 18years.

3.1.5 Have testosterone < 50 ng/dL. Patients must continue primary androgen deprivation with an *LHRH/GnRH* analogue (agonist or antagonist) if they have not undergone orchiectomy.

3.1.6 Patients on long term (>6 months) anti-androgen therapy (e.g. flutamide, bicalutamide, nilutamide) will need to be off anti-androgen for 4 weeks (wash out period) and show evidence of disease progression off the anti-androgen. Patients that have been on an anti-androgen 6 months or less will need to discontinue anti-androgen therapy prior to *treatment start* (no wash out period required).

3.1.7 Patients must have adequate organ and marrow function as defined below obtained within 14 days prior to *treatment start:*

ANC	1,500/µl
Hemoglobin	9g/dL
Platelet count	100,000/µl
Creatinine	s; 1.5 x the institutional upper limit of normal (ULN)
Potassium	within institutional range
Bilirubin	s; ULN (unless documented Gilbert's disease)
SGOT (AST)	:-:::; 2.5 x ULN
SGPT (ALT)	:-:::; 2.5 xULN

3.1.8 The effects of cabazitaxel and abiraterone acetate on the developing human fetus at the recommended therapeutic dose are unknown. Men must agree to use adequate contraception prior to study entry, for the duration of study participation and for at least 3 months thereafter.

3.1.9 Patients must be able to take oral medication without crushing, dissolving or chewing tablets.

3.1.10 Patients may have received prior radiation therapy or *major* surgery. However, at least 21 days *prior to treatment start* must have elapsed since completion of radiation therapy or *major* surgery and patient must have recovered from all side effects at the time of randomization.

3.1.11 Ability to understand and the willingness to sign a written informed consent document that is approved by the local institutional review board.

3.2 Exclusion Criteria

3.2.1 Patients may not be rece1vmg any other investigational agents. Any prior investigational *therapeutic* products must be stopped at least 28 days (4 week washout) prior to *treatment start.*

3.2.2 No prior exposure to abiraterone acetate or other specific CYP-17 inhibitors.

3.2.3 No prior chemotherapy regimen. Prior isotope therapy with Strontium-89, Samarium or RAD223 should be completed at least three months (12 weeks) prior to *treatment start.*

3.2.4 No ;:: grade 2 peripheral neuropathy

3.2.5 Patients who have had antifungal agents (itraconazole, fluconazole) within 4 weeks prior to *treatment start* or those who have not recovered from AEs due to *these* agents administered more than 4 weeks earlier.

3.2.6 Patients with a history of pituitary or adrenal dysfunction, active or symptomatic viral hepatitis or chronic liver disease are not eligible.

3.2.7 Patients with known symptomatic brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other AEs.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cabazitaxel or other drugs formulated with polysorbate 80; or abiraterone acetate.

3.2.9 Patients may continue on a daily Multi-Vitamin, calcium and Vitamin D, but all other herbal, alternative and food supplements (i.e. PC-Spes, Saw Palmetto, St John Wort, etc.) must be discontinued before *treatment start.* Patients must not be planning to receive any concurrent cytotoxic chemotherapy, surgery *for their prostate cancer,* or radiation therapy during protocol treatment.

3.2.10 Patients on stable doses of bisphosphonates or the RANK-L inhibitor, Denosumab, which have been started no less than 4 weeks prior to *treatment start,* may continue on this medication, however patients are not allowed to initiate bisphosphonate/Denosumab therapy during the study.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III and IV heart failure), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, *in the opinion of the investigator,* would limit compliance with study requirements or concurrent medications that alter cardiac conduction.

3.2.12 Patients with a "currently active" second malignancy other than non-melanoma skin or superficial urothelial cancers are not eligible. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are now considered without evidence of disease for 2 years.

3.3 Prohibited Concomitant Medications

- Chemotherapy
- Immunotherapy
- Radiopharmaceuticals like Strontium or Samarium or Radium-223
- S alpha reductase inhibitors
- Spironolactone
- Diethy-Stilbestrol
- Ketoconazole
- Newer medications targeting androgen receptors.

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be documented on the case report form (CRF). The principal investigator should be alerted if the patient is taking any agent which interacts with CYP450 system as found in Appendix B (a listing of medications with the potential for drug-drug interactions).

4. ENROLLMENT PLAN AND SUBJECT REGISTRATION

4.1 Enrollment Plan

4.1.1 Participating Study Centers

This study is anticipated to be conducted in S site(s).

4.1.2 Recruitment

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at participating centers from Medical Oncology, Radiation Oncology and Urology offices. Investigators will screen the patient's medical records for suitable research study subjects and discuss the study and their potential for enrolling in the research study.

4.2 Registration Procedure

After eligibility screening and confirmation that a patient is eligible, patients who are selected to participate will be registered with the PCCTC Caisis EDC, the PCCTC's Clinical Data Management System (CDMS). *A* record of patients who fail to meet eligibility criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning any treatment or study activities. *A* complete, signed study consent and HIPAA authorization are required for registration.

4.2.1 Registration

- Confirm eligibility as defined in Section 3 Patient Selection.
- Obtain informed consent, by following procedures in Section 12.6 Written Informed Consent.
- Obtain completed or partially completed protocol specific Eligibility Checklist.
- All participants will be registered through PCCTC Caisis EDC, the PCCTC's CDMS.

Central registration for this study will take place at MSKCC. To complete registration and enroll a participant, the study staff at that site must contact the designated research staff at the PCCTC to notify him/her of the participant registration. The site staff then needs to email registration/ eligibility checklist and source documents to the PCCTC at PCCTC@mskcc.org. **(Note: Source documentation of eligibility is not required for MSKCC participants.)**

These documents must be sent for each enrollment within 24 hours of the informed consent form being signed.

Upon receipt, the research staff at the PCCTC will conduct an interim review of all documents for all non-MSKCC participants. If the eligibility checklist is not complete or source documentation is missing, the patient will be registered pending enrollment and the site is responsible for sending the completed registration documents within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site has been activated by MSKCC, the PCCTC will register the participant non-MSKCC participants. MSKCC participants will be fully registered by MSKCC.

Once the participant is registered, the participant will be assigned a PCCTC Caisis Subject ID. This number is unique to the participant and must be written on all data and correspondence for the participant. This PCCTC Caisis Subject ID will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation. This number is unique to the participant and must be written on all data and correspondence for the participant.

Participating sites will register subjects locally per their Institutional guidelines and the PCCTC will register all non-MSKCC participants with MSKCC's Protocol

Participant Registration (PPR) Office per MSKCC's guidelines. MSKCC participants will be fully registered by MSKCC with PPR.

4.2.2 Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Patients must be registered with the PCCTC, MSKCC and their local site/institution before beginning any treatment or study activities.

At MSKCC, all participants must be pended with MSKCC's Protocol Participant Registration (PPR) Office prior to submitting registrations to the PCCTC.

The PCCTC will register all non-MSKCC participants with MSKCC's Protocol Participant Registration (PPR) Office per MSKCC's guidelines.

MSKCC will register all MSKCC participants with MSKCC's Protocol Participant Registration Office (PPR) per MSKCC's guidelines.

5. RANDOMIZATION

This is a randomized phase II trial in which 80 patients will be randomized with equal probability to one of two possible treatment regimens: abiraterone acetate\prednisone (AA) or *AA* plus cabazitaxel (AA+C). The randomization will be stratified by Halabi nomogram (Appendix L) based on low (defined as (166.6 points in the nomogram) or high risk(>166.6 total points)7. Patients will be randomized after the investigator has verified that all eligibility criteria have been met and the patient is registered to the study. Patients will be randomized to receive abiraterone acetate\prednisone (AA) (Arm 1) or *AA* plus cabazitaxel (AA+C) (Arm 2) in a 1:1 ratio.

Accrual is expected to be completed within 2 years after trial activation at participating sites.

6. STUDY ASSESSMENTS BY VISITS

Arm1 Abiraterone acetate 1000 mg po daily+ prednisone 5 mg po BID	Screening		One Cycle= 3 Weeks (21 days)A				EQSK
	Within 28 days of treatment start	Within 14 days of treatment start	Cycle 1 Dayl	Cycle 2 Dayl	Cycle 3 **Dayl**	Cycle 4, 7, 10 and etc	
Tests and Observations							
Informed consent and research authorization/ HIPAA form	X						
Demographics, medical history, histologic and radiologic confirmation of disease	X						
Physical examination, vitals, weight, blood pressure[8]		X	X	X	X	X	X
Height		X					
Karnofsky or ECOG performance status		X	X	X	X	X	X
Halabi Nomogram Risk		X					
EKG		X					
Concomitant medications	X		X	X	X	X	X
Toxicity/Adverse Event assessments			X	X	X	X	X
Imaging							
CT\MRI of the chest or CXR, abdomen and pelvis, and radionuclide bone scanc	X					X	X
Tumor Measurementc	X					X	X
Laboratory Studies							
CBC, differential, Platelets[0]		X	X	X	X	X	X
Serum Chemistry (see Lab/ Correlatives Studies Manual)		X	X	X	X	X	X
Liver Function Tests E		X	XE	XE	XE	XE	X
PSA		X	X	X	X	X	X
Serum Testosterone		X					X
Serum Triglycerides		X				X	
Correlative Studies							
Tumor BiopsyF	X					XH	
Circulating Tumor Cells by EPICG		X		X			X
Androgen PanelM		X		X			X

Plasma for cDNA		X	X				X
Treatment Administration[L]							
Abiraterone/Prednisone			X ----------				X
CabazitaxelI						X'	

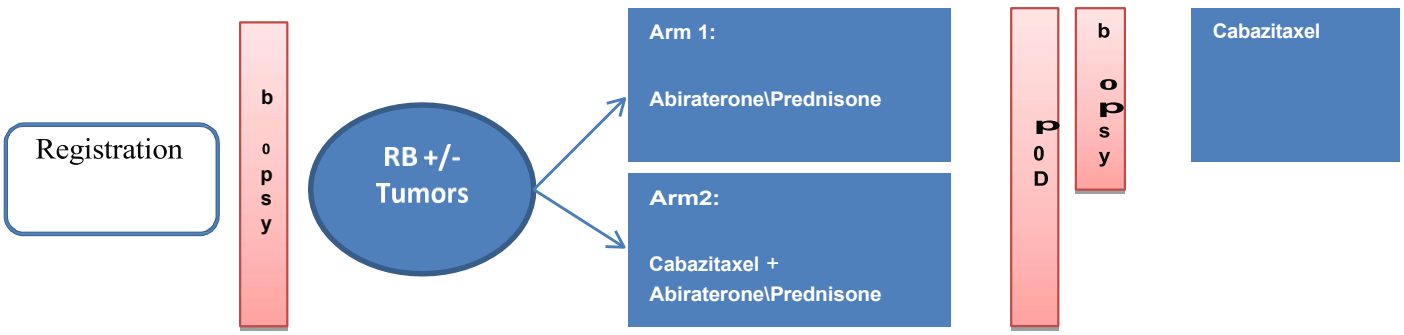
Arm 2: Cabazitaxel 25 mg/m2 IV every 3 weeks + abiraterone acetate 1000 mg po daily + prednisone 5 mg po BID	Screening		One Cycle= 3 Weeks (21 days)A				
	Within 28 days of treatment start	Within 14 days of treatment start	Cycle 1 Dayl	Cycle 2 Day 1	Cycle 3-9	Cycle 10, 13,	EOSK
Tests and Observations							
Informed consent and research authorization/ HIPAA form	X						
Demographics, medical history, histologic and radiologic confirmation of disease	X						
Physical examination, vitals, weight, blood pressure[8]		X	X	X	X	X	X
Height		X					
Karnofsky or ECOG performance status		X	X	X	X	X	X
Halabi Nomogram Risk		X					
EKG		X					
Concomitant medications	X		X	X	X	X	X
Toxicity/Adverse Event assessments			X	X	X		
Imaging							
CT\MRI of the chest or CXR, abdomen and pelvis, and radionuclide bone scanc	X				C4,C7	X	X
Tumor Measurementc	X				C4,C7	X	X
Laboratory Studies							
CBC, differential, Platelets[0]		xo	X	X	X	X	X
Serum Chemistry (see Lab / Correlative Studies Manual)		X	X	X	X	X	X
Liver Function Tests E		X	XE	XE	XE	X	X
PSA		X	X	X	X	X	X
Serum Testosterone		X					X
Serum Triglycerides		X			C4,C7	X	

Correlative Studies							
Tumor BiopsyF	X						
Circulating Tumor Cells by EPICG		X		X			X
Androgen Panel		X		X			X
Plasma for cDNA		X		X			X
Treatment Administration[L]							
Abiraterone /Prednisonel			X ---------- Xl				
Cabazitaxell			X ---------- X				

A: All visits have a window of± 7 days
B: Patients are to be encouraged to measure blood pressure weekly.
C: CT scans/MRI (to follow measurable disease) and bone scans (to follow bone disease) are required every 3 cycles beginning on Cycle 4 until evidence of progression or relapse. Patients who have received a chest CT (or MRI) need not have a chest x-ray. Scans may be done up to ±7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response. End of Study scans can be performed± 30 days from End of Study Visit
D: During the first cycle of cabazitaxel therapy, CBC will be obtained weekly. CBC: White blood cells count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT),, platelet count (UNVPLT), neutrophils (NEUTP), lymphocytes (LYMP).
E: Additional liver function tests (aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBILI)) measured every 2 weeks for the first 4 cycles of treatment. These labs may be done locally.
F: Adequate archival metastatic tissue can be used lieu of the baseline biopsy if done when patient had CRPC (within 6 months of treatment start).
G: Will be performed at baseline, Cycle 2, and End of Study.
H: A second optional tumor biopsy will be requested in patients with confirmed radiographic progression of disease on abiraterone acetate\prednisone alone arm. Biopsy will take place prior to starting cabazitaxel
I: For Arm 1: On confirmed radiographic progression of disease, the abiraterone acetate will be discontinued and patients will be treated with cabazitaxel 25mg/m2 IV every 3 weeks for a maximum of 9 cycles at the discretion of the treating physician. CT scans/MRI and bone scans are required every 3 cycles of cabazitaxel treatment beginning on Cycle 4. End of Study scans can be performed ± 30 days from End of Study Visit. Patients will continue to have procedures performed as outline in section 6.2 and 6.3. Please see section 6.4 for additional Progression on Arm 1 details.
J: For Arm 2: Patients will get a maximum of 9 cycles of cabazitaxel and if the patients have not shown evidence of confirmed radiographic progression after 9 cycles of cabazitaxel, patients will continue on the abiraterone acetate and prednisone until disease progression or until the therapy is not tolerated. Patients will continue to have procedures perform as outline in section 6.2 and 6.3
K: End of study visit must occur within 30 days of stopping study treatments. Patients withdrawn from the study because of AEs will be followed until the AE has either resolved or stabilized (minimum of every 4 weeks).
L: Study treatments must occur within 7 days of randomization
M: Testosterone, androstenedione, DHEAS

Treatment/Intervention/Dose-modification schema

Figure 7. Treatment schema



All patients will have a tumor biopsy performed on an assessable metastatic tumor or primary prostate. Adequate archival metastatic tissue can be used lieu of the baseline biopsy if done when patient had CRPC (within 6 months of treatment start). RB status will

be determined by the IHC stains (RB positive or negative) at Thomas Jefferson University. All patients will also have circulating tumors cells collected as part of the correlative studies.

1. **Arm 1: Abiraterone acetate 1000 mg po daily + prednisone 5 mg po BID**
   On confirmed radiographic progression of disease the abiraterone acetate will be discontinued and patient will be treated with cabazitaxel 25 mg/m² IV every three weeks for a maximum of 9 cycles at the discretion of the treating physician. *A* second tumor biopsy may be performed prior to starting cabazitaxel. Premedications should be given as per outlined below.
2. **Arm 2: CabazitaxeI 25 mg/m² IV+ abiraterone acetate 1000 mg po daily+ prednisone 5 mgpo BID**
   Patient will get a maximum of 9 cycles of cabazitaxel and if the patients have not shown evidence of confirmed radiographic progression after 9 cycles of cabazitaxel, patients will continue on the abiraterone acetate and prednisone until disease progression or until the therapy is not tolerated.

Abiraterone acetate 1000 mg po daily+ prednisone 5 mg po BID. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

IV cabazitaxel 25 mg/m² IV every 3 weeks with premedications according to institutional standards

The use of G-CSF support is allowed after cycle 1 of therapy at the investigators discretion according to the ASCO guidelines. G-CSF may be administered to reduce the risks of neutropenia complications associated with cabazitaxel use. Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious co-morbidities) that predispose them to increased complications from prolonged neutropenia. Therapeutic use of G-CSF and secondary prophylaxis should be considered in all patients considered to be at increased risk for neutropenia complications.

6.1 Screening/Pretreatment Assessment

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a Notice of Privacy Practice research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50).

The screening visit will determine patient eligibility according to the inclusion and exclusion criteria (Sections 3.1 and 3.2). Patients will complete screening/baseline

assessments prior to treatment start. The following assessments will be performed at this visit.

Within 28 days prior to treatment start:

- Informed consent and research authorization/ HIPAA form
- Demographics, medical history, histologic and radiologic confirmation of disease
- Discuss concurrent medications (see Appendix B for a listing of medications with the potential for drug interactions)
- Correlative studies:
    - Tumor biopsy (Note: Adequate archival metastatic tissue can be used in lieu of the baseline biopsy if done when the patient had CRPC, within 6 months of treatment start)
- Imaging (If imaging is being used to document progression of disease for study eligibility, assessments must be performed within 28 days prior to treatment start. Any other assessments not utilized for documentation of disease progression but are required for study entry can be performed within 42 days prior to treatment start)
    - Contrast-enhanced CT of the chest and contrast-enhanced CT of the abdomen and pelvis. For patients unable to receive contrast-enhanced CT of the chest abdomen and pelvis, a chest X-ray and MRI of the abdomen and pelvis will be allowed.
    - Radionuclide bone scan

Within 14 days prior to treatment start:

- Physical exam including vital signs, weight, height and EKG
- Karnofsky or ECOG performance status (Appendix A)
- Halabi Nomogram Risk (Appendix L)
- Laboratory studies
    - CBC
    - Serum Chemistry
    - Liver Function Tests
    - PSA
    - Serum Testosterone
    - Serum Triglycerides
- Correlative studies
    - Circulating Tumor Cells by EPIC
    - Androgen Panel
    - Plasma for cDNA

Relevant information should be documented. The institutional registration should be finalized, and appropriate documents (i.e., signed informed consent, research authorization/HIPAA form, eligibility checklist, and supporting source documentation for eligibility questions) emailed to the PCCTC. Information for patients who do not meet the eligibility criteria to participate in this study (i.e., screening failures) should be captured in Caisis at the pretreatment assessment.

6.2 Day 1 of Each Cycle(± 7 days)

On each visit, the following assessments will be performed:

- Physical examination, vitals, weight, blood pressure
- Karnofsky or ECOG performance status (Appendix A)
- Discuss concurrent medications
- Toxicity/ Adverse Event assessments
- CBC (additional weekly CBCs drawn during first cycle of cabazitaxel treatment)
- Serum Chemistry
- Liver Function Tests (Additional liver function: aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBILI) measured every 2 weeks for the first 4 cycles of treatment. These labs may be done locally)
- PSA
- Circulating Tumor Cells by EPIC, Androgen Panel, cDNA (Cycle 2 only)

Note:

Arm 1 patients are required to receive the above assessments for Cycles 1-3 and every 3 cycles± 7 days starting from Cycle 4 (Cycle 4, 7, 10, etc.). On confirmed radiographic progression of disease on abiraterone acetate, the patients will receive the assessments listed in section 6.2 on Day 1 of each cycle of cabazitaxel and will follow the Arm 2 treatment schedule from C1D1 including imaging.

Arm 2 patients are required to receive the above assessments for Cycles 1-9. Patients continuing abiraterone acetate after completing 9 cycles of cabazitaxel will receive the above assessments every 3 cycles starting with Cycle 10 (Cycle 13, 16, 19, etc.)

6.3 Every 3 Cycles (Cycle 4, 7,10, ETC.,± 7 days)

- Imaging
  - Contrast-enhanced CT of the chest and contrast-enhanced CT of the abdomen and pelvis. For patients unable to receive contrast-enhanced CT of the chest abdomen and pelvis, a chest X-ray and MRI of the abdomen and pelvis will be allowed.
  - Radionuclide bone scan
- Tumor Measurement
- Serum Triglycerides

6.4 Progression on Arm 1

On confirmed radiographic progression of disease, the abiraterone acetate will be discontinued.

Cabazitaxel treatment must be initiated within **28 days** of discontinuing abiraterone acetate.

Patients will have a new baseline CTC, cDNA, and androgen panel drawn within 14 days of starting therapy with cabazitaxel.

6.5 End of Study (30 days of stopping protocol study treatments)

A patient may be discontinued from study treatment at any time if the patient or the Investigator feels that it is not in the patient's best interest to continue on study. The following is a list of possible reasons for early discontinuation of study treatment

- Disease progression per protocol
- Patient is not compliant with study procedures
- Lost to follow-up
- Patient withdrawal of consent
- Treatment-limiting adverse event

A treatment-limiting adverse event is any AE related to protocol therapy experienced during the study resulting in treatment termination. Patients withdrawn from the study because of AEs will be followed until the AE has either resolved or stabilized (minimum of every 4 weeks). Reasons for premature withdrawal should be determined and noted.

The following study activities will occur at End of Study Visit:

- Physical exam including vital signs, weight, blood pressure
- Karnofsky or ECOG performance status (Appendix A)
- Discuss concurrent medications
- Toxicity/Adverse Event assessments
- Imaging (Can be performed± 30 days from End of Study Visit)
    - Contrast-enhanced CT of the chest and contrast-enhanced CT of the abdomen and pelvis. For patients unable to receive contrast-enhanced CT of the chest abdomen and pelvis, a chest X-ray and MRI of the abdomen and pelvis will be allowed. Radionuclide bone scan
- Tumor Measurement
- CBC
- Serum chemistry
- Liver Function Tests
- PSA
- Serum Testosterone
- Circulating Tumor Cells
- Androgen Panel
- Plasma for cDNA

6.6 Correlative/Special Studies

Each patient will have the following specimens obtained at the study site as described below:

a) *A* paraffin embedded tumor sample (block or 5-10 unstained slides; S micron thickness) from a new biopsy of a metastatic site of disease or prostate primary within 4 weeks prior to treatment start. Adequate archival metastatic tissue can be used lieu of the baseline biopsy if done when patient had CRPC (within 6 months of treatment start).

b) In a patient undergoing a soft tissue biopsy to determine RB status, an additional tumor sample will be collected to be placed in media/serum for explant culture in sites participating in the explant protocol.
c) Blood for circulating tumor cells by EPIC: screening (baseline), Cycle 2, and End of Study - total of 3 tubes (1 Streck and 2 PAXgene)
d) Blood for androgen panel by HPLC (pre-treatment and End of Study, 1 red top tube).
e) Plasma collected for circulating DNA (pre-treatment and End of Study, Streck™ Cell-Free DNA BCT tube (Streck Inc.)

The rationale, and a brief overview, for collection and handling of these specimens are described below. Further technical details regarding biopsies of metastatic sites, handling and shipping of these biopsy specimens can be found in the Lab/Correlative Studies Manual.

6.6.1. Collection and Handling of Biopsy Specimens

Patients will be scheduled for a CT or ultrasound-guided biopsy of a bone or soft tissue abnormality consistent with prostate metastasis or transrectal ultrasound guided biopsy of a recurrent tumor in the prostate. PET or **MRI** guided biopsies are acceptable. Alternatively, a standard bone marrow biopsy of the posterior iliac bone may be obtained. The site of biopsy will be determined after review of available radiographs, CT, MRI, ultrasound and/or bone scan, and will be selected based whatever site is expected to result in the best access, best yield and is safe for the patient. Verbal and written informed consent will be obtained per institutional standards. While the exact number of specimens obtained depends on the size of the target, the difficulty of the procedure, and risk of complications, the goal is to obtain 2-3 samples.

The soft or bone tissue samples will be sent to pathology for analysis to confirm the diagnosis of prostate cancer (at the Institution of participant registration). *A* portion of the confirmed paraffin tumor embedded block will be sent to Thomas Jefferson University for RB analysis as described below in Section 6.6.5. *Shipping of specimens after collection.*

If patient undergoes a soft tissue biopsy to determine RB status, an additional tumor sample will be collected in media/serum for explant culturing in sites participating in the explant protocol.

All tissue samples will be labeled with the clinical protocol number, the patient's study registration number, and specimen ID. In addition, a separate information sheet accompanying each specimen will be filled out (Please see Lab/Correlative Studies Manual).

Following biopsy, samples from metastatic sites or recurrent disease in the prostate need to be shipped to Thomas Jefferson University per shipping directions described below. Samples may be shipped Monday through Thursday. Samples will not be accepted on the weekends.

6.6.2. Circulating tumor cells (CTC): sample collection procedure

Blood will be collected at screening (baseline), Cycle 2, every 3 cycles beginning on Cycle 4 and End of Study. At each of these time point, blood samples will be drawn

into one 10-mL evacuated blood draw tubes (Cell-Free DNA BCT Streck tube; EPIC) and two 2.5 ml PAXgene tubes. These blood samples can be maintained at room temperature. The Streck tube will be shipped to EPIC SCIENCES for overnight delivery. The PAXgene tubes can be shipped overnight at ambient temperatures or frozen and batch shipped to Memorial Sloan Kettering Cancer Center. See the study-specific laboratory manual for further details on CTC sample collection, processing and shipping (Laboratory/Correlatives Studies Manual). These samples will be used to give cell count of CTC and the tumor cells and the DNA\RNA will be isolated to perform genomic analysis for RB function.

6.6.3. Procedures for processing tumor samples, plasma and serum samples

RB IHC from paraffin blocks

Formalin-fixed paraffin-embedded tissue from 400 archived specimens with prostate cancer will be placed in a tissue microarray (TMA) using the Veridiam ® tissue arrayer with Institutional IRB approval. 40 cancer cases will be placed in a single TMA block with control cases. Immunohistochemical (IHC) staining with the RB monoclonal antibody from Cell Signaling Technology ® will be applied [RB (4H1) Mouse mAb #9309L]. An automated IHC staining protocol (ultra View DAB vl.02.0018) will be used on the Ventana automated stainer (Benchmark XT, Ventana Medical Systems, Inc., Tucson, AZ). The stained slides will be evaluated by two pathologists (RD and RB) without clinical data to obtain a consensus result. The IHC stained TMA slides will then be scanned and analyzed digitally using the Aperio ® computer assisted image analysis system. A standardized nuclear analysis protocol will be used for scoring a minimum of 1,000 cells. The digital scoring will be reported as percentage and absolute number of nuclear staining with nuclear scores from 0 to 3+ intensity. Endothelial nuclear staining will be used as internal control. The Aperio ® results will be compared to the pathologists' consensus results and the discrepant cases will be excluded. RB will be consider positive when 25% or more of the nuclei have a combination of 2+ and 3+ score. Weak positive with 10% to 24% of the cells have a combination of 2+ and 3+ score; and negative when less than 10% of the cells have a combination of 2+ and 3+ score.

RB functional analyses via custom array[1]

cDNA generated from the tumor biopsy and collected CTCs will be used to assess functional status of the RB pathway. Probeset intensities for transcripts assayed on the RBTARGET will be assessed using robust multichip average (RMA) algorithm in Affymetrix Expression Console software. Additional analysis will be performed on the processed dataset using high-level programming languages for statistical computing, including Rand Matlab. Twenty distinct gene groups represented on the RBTARGET array, where genes within each group are highly correlated, will be assessed using an Affymetrix U133A Prostate Cancer training dataset. The RBTARGET expression profiles for genes in each group will be averaged together, resulting in twenty independent feature variables. These twenty feature variables will be used in supervised multivariate analysis to determine a linear equation that is best able to classify distinct characteristics of prostate cancer and inform diagnosis/prognosis.

Serum Samples for Androgen panel (testosterone, androstenedione, DHEAS)

In an analysis of patients receiving abiraterone after prior ketoconazole therapy it was observed that a high proportion of patients had undetectable androgen levels and that there was an association between lack of response to abiraterone and an undetectable level of DHEAS.(Ryan et al Proc ASCO 2011) Further, in the COU-301 study patients with above median baseline serum androgens were associated with a higher PSA response rate after adjusting for treatment and other laboratory parameters (i.e., LDH, hemoglobin, ALP; all $P < .0001$). Thus knowing the androgen levels may also be a major factor to the response to abiraterone acetate.

Serum for androgen profile will be collected prior to the initiation of treatment and at end of study. Collect 10 mL of whole blood in a serum separator tube (SST) (red/gray top). The tube should be inverted several times to mix clot activator with the blood. Allow the blood to clot for a minimum of 30 minutes in a vertical position. Observe a dense clot. Centrifuge clotted blood for 15 minutes at 1600 x g, 4°C (or in accordance with manufacturer's instructions). The serum should be separated and frozen in cyrotubes and stored in -80°C. The samples will be shipped on dry ice and shipped overnight mail to the Knudsen lab. Please note the samples can be batched shipped but do not ship on Fridays.

The assay to be used for determining the androgen panel (testosterone, androstenedione, DHEAS and other androgen derivatives) will be performed in the laboratory of Dr. Trevor Penning at the University of Pennsylvania and/or a CLIA certified laboratory that specializes in ultrasensitive endocrine analyses.

Plasma collected for circulating DNA

Plasma collected for circulating DNA_will be collected prior to the initiation of treatment and at End of Study visit. Please see the study-specific laboratory manual for further details on plasma sample collection, processing and shipping (Laboratory /Correlative Studies Manual).

6.6.5. Shipping of specimens after collection

Tumor, plasma and blood (serum) samples

All samples will be shipped to Thomas Jefferson University at the following address:

Renee de Leeuw
215-503-8579
Thomas Jefferson University
233 South 10th Street, BLSB 1006
Dr. Karen Knudsen Lab
Philadelphia, PA 19107
E-mail: Karen.Knudsen@jefferson.edu
Adam.Hawkins@jefferson.edu
renee.deleeuw@jefferson.edu

Note: Tissue collected for explant protocol at MSKCC may be shipped to Dr. Slovin's laboratory for processing and analysis.

- Paraffin embedded tumor samples: The paraffin embedded tumor samples can be shipped via standard mail, at room temperature. It is requested that efforts be made to ship the tumor samples within 30 days of patient enrollment onto the trial.
- Serum and plasma samples for the androgen panel and circulating DNA will be shipped frozen on dry ice

Shipping must occur only Monday-Thursday, and an e-mail or phone call to the contact listed on the laboratory contact sheet, alerting her to the shipment, is required. *A* copy of the sample requisition form should also be emailed to the PCCTC at pcctc@mskcc.org.

For further details regarding shipping, please refer to the Laboratory/Correlative Studies Manual.

1. PAXgene tubes will be shipped overnight to:
MSKCC Laboratory Medicine
Attn. CTC samples for AA ± Cabazi
411 E. 67th Street, S-359
New York, NY 10065
Tel (212) 639-5969

Please note, PAXgene tubes can be frozen and batch shipped on dry ice if processed per instructions in the Laboratory/Correlatives Studies Manual. Shipping reservations must be made to allow delivery within 24 hr of specimen collection, and prior to 2:00 PM the next day. Samples must not be drawn or shipped on Friday.

2. EPIC: Tube will be shipped overnight to:

Epic Sciences
Attn. EPIC samples for AA ± Cabazi
9381 Judicial Drive, Suite 200 San Diego, CA 9221, USA

Samples should be kept at room temperature at all times. Shipping reservations must be made to allow delivery within 24 hr of specimen collection, and prior to 2:00 PM the next day.

7. THERAPEUTIC MODALITIES

7.1 Pharmacokinetics

7.1.1 Cabazitaxe/23,24

A population pharmacokinetic analysis was conducted in 170 patients with solid tumors at doses ranging from 10 to 30 mg/m² weekly or every three weeks.

Absorption

Based on the population pharmacokinetic analysis, after an intravenous dose of cabazitaxel 25 mg/m2 every three weeks, the mean Cmax in patients with metastatic prostate cancer was 226 ng/mL (CV 107%) and was reached at the end of the one-hour infusion (Tmax). The mean AUC **in** patients with metastatic prostate cancer was 991 ng·h/mL (CV 34%).

No major deviation from the dose proportionality was observed from 10 to 30 mg/m2 **in** patients with advanced solid tumors.

Distribution

The volume of distribution (Vss) was 4,864 L (2,643 L/m2 for a patient with a median BSA of 1.84 m2) at steady state.

In vitro, the binding of cabazitaxel to human serum proteins was 89 to 92% and was not saturable up to 50,000 ng/mL, which covers the maximum concentration observed in clinical trials. Cabazitaxel is mainly bound to human serum albumin (82%) and lipoproteins (88% for HDL, 70% for LDL, and 56% for VLDL). The in vitro blood-to-plasma concentration ratio in human blood ranged from 0.90 to 0.99, indicating that cabazitaxel was equally distributed between blood and plasma.

Metabolism

Cabazitaxel is extensively metabolized in the liver(> 95%), mainly by the CYP3A4/5 isoenzyme (80% to 90%), and to a lesser extent by CYP2C8. Cabazitaxel is the main circulating moiety **in** human plasma. Seven metabolites were detected **in** plasma (including the 3 active metabolites issued from O-demethylation), with the main one accounting for 5% of cabazitaxel exposure. Around 20 metabolites of cabazitaxel are excreted into human urine and feces.

Based on in vitro studies, the potential for cabazitaxel to inhibit drugs that are substrates of other CYP isoenzymes (1A2,-2B6,-2C9, -2C8, -2C19, -2E1, -2D6, and 3A4/5) is low. In addition, cabazitaxel did not induce CYP isozymes in vitro.

Elimination

After a one-hour intravenous infusion [14C]-cabazitaxel 25 mg/m2, approximately 80% of the administered dose was eliminated within 2 weeks. Cabazitaxel is mainly excreted in the feces as numerous metabolites (76% of the dose); while renal excretion of cabazitaxel and metabolites account for 3.7% of the dose (2.3% as unchanged drug in urine).

Based on the population pharmacokinetic analysis, cabazitaxel has a plasma clearance of 48.5 L/h (CV 39%; 26.4 L/h/m2 for a patient with a median BSA of 1.84 m2) in patients with metastatic prostate cancer. Following a one-hour intravenous infusion, plasma concentrations of cabazitaxel can be described by a three-compartment pharmacokinetic model with *a-,* -, and y- half-lives of 4 minutes, 2 hours, and 95 hours, respectively.

Renal Impairment

Cabazitaxel is minimally excreted via the kidney. No formal pharmacokinetic trials have been conducted with cabazitaxel in patients with renal impairment. The population pharmacokinetic analysis carried out in 170 patients including 14 patients with moderate renal impairment (30 mL/min:,; CLcr < SO mL/min) and 59 patients with mild renal impairment (SO mL/min:,; CLcr < 80 mL/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. No data are available for patients with severe renal impairment or end-stage renal disease

Hepatic Impairment

No formal trials in patients with hepatic impairment have been conducted. As cabazitaxel is extensively metabolized in the liver, hepatic impairment is likely to increase the cabazitaxel concentrations.

Drug Interactions

As cabazitaxel is mainly metabolized by CYP3A in vitro, strong CYP3A inducers or inhibitors are expected to affect the pharmacokinetics of cabazitaxel. Prednisone or prednisolone administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel.

Adverse Events

The most common (:::: 10%) Grade 1-4 adverse reactions with cabazitaxel were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

The most common (:::: 5%) Grade 3-4 adverse reactions in patients who received cabazitaxel were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia

7.1.2 Abiraterone acetate[25]

Following oral administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic CRPC. *In vivo,* abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1000 mg dose of abiraterone acetate.

At the dose of 1000 mg daily in patients with metastatic CRPC, steady-state values (mean± SD) of Cmax were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL.

No major deviation from dose proportionality was observed in the dose range of 250 mg to 1000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone Cmax and AUC0-oo were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking abiraterone with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at 1least two hours before the dose of abiraterone is taken and for at least one hour after the dose of abiraterone is taken. The tablets should be swallowed whole with water.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

Following oral administration of 14C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of 14C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class *A* and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with

mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. Abiraterone has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C)

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1000 mg abiraterone acetate dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function.

Phase I pharmacokinetic (PK) studies showed increased systemic drug exposure at higher doses but antitumor activity was present at all doses tested. Adrenal metabolite analysis showed inhibition of CPYl 7 even at low doses of abiraterone acetate and a compensatory increase of corticosterone and deoxycorticosterone. Data from dose-finding studies indicated that when PK, adrenal CYPl 7 inhibition, and efficacy signals are taken into consideration, the 1000-mg dose offered consistent pharmacological effects without additional side effects. Therefore, the 1000-mg dose has been chosen for further efficacy and safety evaluation in this Phase II trial.

Adverse Events

The most common adverse drug reactions (::::5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.

The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patients taking abiraterone).

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly **in** patients treated with abiraterone than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively. In patients treated with abiraterone, Grades 3 to 4 hypokalemia occurred in 5% of patients and Grades 3 to 4 hypertension was reported in 1% of patients.

7.2 Dosage Selected, Preparation, and Schedule of Administration

Cabazitaxel (Jevtana) will be administered at 25 mg/m² IV every 3 weeks. The dose of cabazitaxel will be calculated as per institutional guidelines. Abiraterone acetate will be

taken daily at 1000mg PO daily in a fasting state along with prednisone 5mg PO BID to minimize mineralocorticoid side effects. Cabazitaxel will be supplied by Sanofi S.A. but distributed through the vendor Biologics. Abiraterone will be commercially supplied through patient's insurance.

7.2.1 Supply and Packaging

How Supplied

Cabazitaxel is supplied as a kit containing one single-use vial of Jevtana (cabazitaxel) Injection (clear glass vial with a grey rubber closure, aluminum cap and light green plastic flip-off cap) and one vial of Diluent for Jevtana Injection (13% (w/w) ethanol in water for injection) in a clear glass vial with a grey rubber closure, gold-color aluminum cap and colorless plastic flip-off cap. Both items are in a blister pack in one carton.

Injection 60 mg/1.5 mL (NDC 0024-5824-11) is supplied as a kit consisting of the following:

-Jevtana Injection 60 mg/1.5 mL: contains 60 mg cabazitaxel in 1.5 mL polysorbate 80,

- Diluent for Jevtana Injection 60 mg/1.5 mL: contains approximately 5.7 mL of 13% (w/w) ethanol in water for injection.

Administration Precautions

Jevtana is a cytotoxic anticancer drug and caution should be exercised when handling and preparing Jevtana solutions, taking into account the use of containment devices, personal protective equipment (e.g., gloves), and preparation procedures.

Instructions for Preparation

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of Jevtana infusion solution.

Read this entire section carefully before mixing and diluting. Jevtana requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the Jevtana Injection and the diluent vials contain an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL Jevtana.

The following two-step dilution process must be carried out under aseptic conditions to prepare the second (final) infusion solution.

Set aside the Jevtana Injection and supplied diluent vials. The Jevtana Injection is a clear yellow to brownish-yellow viscous solution, if appropriately stored.

- **Step 1 - First Dilution**

Each vial of Jevtana 60 mg/1.5 mL must first be mixed with the entire contents of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of Jevtana.

When transferring the diluent, direct the needle onto the inside wall of Jevtana vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam to dissipate prior to continuing the preparation process.

The resulting initial diluted Jevtana solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2.

- **Step 2 - Second (Final) Dilution**

  Withdraw the recommended dose from the Jevtana solution containing 10 mg/mL as prepared in Step 1 using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of Jevtana is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL Jevtana is not exceeded. The concentration of the Jevtana final infusion solution should be between 0.10 mg/mL and 0.26 mg/mL.

  Jevtana should not be mixed with any other drugs.

  Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

  Jevtana final infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion) or within a total of 24 hours if refrigerated (including the one-hour infusion).

  As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

  Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the Jevtana first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

  Discard any unused portion.

7.2.2 Administration

Cabazitaxel

The final Jevtana infusion solution should be administered intravenously as an approximately one-hour infusion at room temperature.

Use an in-line filter of 0.22 micrometer nominal pore size during administration.

The final Jevtana infusion solution should be used immediately. However, in-use storage time can be longer under specific conditions, i.e. 8 hours under ambient conditions (including the one-hour infusion) or for a total of 24 hours if refrigerated (including the one-hour infusion).

Abiraterone acetate

Abiraterone acetate 250 mg, immediate release, uncoated tablets are white to off-white, oval-shaped, debossed with AA250 on one side. **In** addition to 250 mg abiraterone acetate, each tablet contains the following compendia! inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide. Abiraterone acetate 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

7.2.3 Storage requirements

Cabazitaxel
Jevtana Injection and Diluent for Jevtana:

Store at 25°C (77°F); excursions permitted between 15°-30°((59°-86°F).

Do not refrigerate.

Stability of the First Diluted Solution in the Vial: First diluted solution of Jevtana should be used immediately (within 30 minutes). Discard any unused portion.

Stability of the Second (Final) Dilution Solution **in** the Infusion Bag: Fully prepared Jevtana infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the approximately one-hour infusion), or for a total of 24 hours (including the approximately one-hour infusion) under the refrigerated conditions.

In addition, chemical and physical stability of the infusion solution has been demonstrated for 24 hours under refrigerated conditions. As both the first diluted solution and the second (final) infusion solution are supersaturated, the solutions may crystallize over time. If crystals and/or particulates appear, the solutions must not be used and should be discarded.

Abiraterone acetate
Store tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

7.2.4 Special handling and disposal

Cabazitaxel
Procedures for proper handling and disposal of antineoplastic drugs should be followed. Several guidelines on this subject have been published [see References]. Any unused product or waste material should be disposed of in accordance with local requirements.

If Jevtana Injection, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Jevtana Injection, first diluted solution, or second (final) dilution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water.

References:

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
3. American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm 2006; 63:1172-1193.
4. Polovich, M., White, **J.** M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

Abiraterone acetate

Based on its mechanism of action, abiraterone may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle abiraterone without protection, e.g., gloves.

7.2.5 Handling and Dispensing

Abiraterone and prednisone will be commercially supplied and dispensed. Patients will be provided with a diary in which to record their intake of study drug (Appendix G).

Cabazitaxel will be supplied by Sanofi-Aventis and dispensed at the institution of registration. Study site personnel will record cabazitaxel administered during this trial on a drug dispensation log as per institutional policy at each site. The drug dispensation log will contain the following information:

- patient study identification number
- date(s) of cabazitaxel administered
- quantities of cabazitaxel administered

7.3 Dose Modifications and Dose Delay

At each study visit for the duration of their participation in the study, patients will be evaluated for adverse events (AEs, all grades), serious adverse events (SAEs), and AEs that require study drug interruption or discontinuation.

If a patient has a greater than 2 week delay in receiving cabazitaxel due to a drug-related AE, then cabazitaxel should be discontinued. If a patient has a greater than 2 week delay in

receiving abiraterone due to a drug-related AE, then abiraterone should be discontinued. *A* delay greater than 2 weeks and no more than 6 weeks of cabazitaxel due to an event that is not related to protocol therapy or after a patient receives limited field palliative radiation is acceptable. *A* delay greater than 2 weeks and no more than 6 weeks of abiraterone due to an event that is not related to protocol therapy or after a patient receives palliative radiation is acceptable.

Arm 2 patients who either require that the study drug to be discontinued because of a treatment-related AE (as described below) or have a treatment interruption of greater than 2 weeks for abiraterone acetate or 2 weeks for cabazitaxel due to a treatment-related AE, at the investigator's discretion, may continue on the other agent alone until progression as long as they have completed 2 cycles of combination therapy. Further details on the dose modifications for study drugs are in section 7.3.

Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 30 days after the last dose of the study drug. Any patient hospitalized during the study will be evaluated and treated as per supervising physician and appropriate communication reports to the PCCTC will be completed in a timely manner as per the FDA guidance for Industry.

General Rules

Every effort will be made to administer the full dose regimen to maximize dose-intensity. If possible, toxicities should be managed symptomatically. If toxicity occurs, the appropriate treatment will be used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, anti-diarrheals for diarrhea, and antipyretics, and/or antihistamines for drug fever.

Toxicity will be assessed using the most recent NCICTCAE, v4.0.

7.3.1 Dose modification for abiraterone acetate

Dose Level	Abiraterone acetate	Prednisone
0	1000 mg daily	5 mg twice daily
-1	750 mg daily	5 mg twice daily
-2	500 mg daily	5 mg twice daily

For any grade 2 or greater toxicity thought to be related to the abiraterone acetate, the dose will be held until grade 1 toxicity. The dose of may be restarted at one lower dose level. The dose of abiraterone acetate will not be re-escalated once a dose reduction has occurred. Patients may have a maximum of two dose reductions of abiraterone acetate. If patient after two dose reductions still has intolerance to the abiraterone acetate then the drug should be discontinued. The patient may continue on with the cabazitaxel or prednisone without the abiraterone acetate at the investigators discretion.

Asymptomatic laboratory abnormalities would not be considered a SAE unless the investigator believes it may potentially impact the participant's safety or unless it is specifically addressed separately in the protocol (e.g., hypokalemia and liver test abnormalities).

Due to the known side effect of hypokalemia, oral replacement of potassium is to be started with Grade 1 hypokalemia. With Grade 3 or 4 hypokalemia, abiraterone acetate is to be held until it resolves to :s; Grade 1 and IV potassium replacement is to be given with appropriate monitoring. The dose of abiraterone acetate should be restarted at one reduced dose level as described above.

If Grade 2 or higher liver function test abnormalities (AST, ALT or bilirubin) develop, the liver function tests should be followed at least weekly until they resolve to :5 Grade 1. If Grade 3 liver test abnormalities (AST, ALT or bilirubin) develop, abiraterone acetate and any other hepatotoxic drugs should be held until they resolve to :s; Grade 1. In the specific case of Grade 3 AST, ALT or bilirubin abnormalities, a mandatory dose reduction of abiraterone acetate to 500 mg daily must be undertaken, with every 2 week assessments of the liver function tests for at least 3 months. If Grade 4 liver test abnormalities (AST, ALT or bilirubin) occur, the drug should be permanently discontinued. The PCCTC should also be notified with any Grade 3 or 4 liver function test abnormality. If a dose reduction of abiraterone acetate below 500 mg daily is required, the abiraterone acetate will be discontinued and the cabazitaxel may be continued at the discretion of the investigator.

Prednisone is included in this regimen primarily as a safety medication to reduce the potential incidence of mineralocorticoid excess from abiraterone acetate. For this reason, the prednisone cannot be dose reduced or held without holding the abiraterone acetate. If Grade 3 or Grade 4 toxicity develops which is known to be related to prednisone (e.g. hyperglycemia) and this is believed to potentially impact the safety of participation, prednisone must be tapered down and abiraterone acetate should be held until the AE resolves to :5 Grade 1.

7.3.2 Dose modification for cabazitaxel

Dose Level	Cabazitaxel
0	25 mg/m^2
-1	20 mg/m^2
-2	15 mg/m^2

Patients may have a maximum of two dose reductions and the minimal dose of cabazitaxel to be administered is 15 mg/m^2 every 3 weeks. The dose, which has been reduced for toxicity, must not be re-escalated. Only two dose reductions will be allowed per patient. If more than two dose reductions are required per the modifications below, the patient should be removed from the study.

Patients may use G-CSF support at the discretion of the treating physician after cycle 1 of therapy. If a patient has a greater than 2 weeks delay in receiving cabazitaxel, then cabazitaxel should be discontinued. If the cabazitaxel is discontinued for intolerable toxicities, patients may continue on the abiraterone acetate and prednisone alone until POD or intolerable AEs from the abiraterone acetate.

Hematologic toxicity

The dose cabazitaxel depending on the treatment arm will be modified in case of hematological toxicity. Dose modifications are summarized in Table 1.

Table 1. Dose modifications for hematological toxicity

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia	If not recovered on D21, delay** next infusion until recovery to Grade ::;1 (neutrophil ;,;1.5 x 10^9/L). - 1st episode: No dose reduction required. - 2nd episode; reduce by 1 dose level	No dose reduction if isolated and duration :,;7 days. If duration more than 7 days or not recovered on D21 Delay** next infusion until ANC ;,;1.5 x 10^9/Land: - 1st episode: reduce the dose 1 dose level and in addition administer prophylactic G-CSF treatment in subsequent cycles if patient did not received G-CSF. - 2nd episode or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level. - 3rd episode or 2nd episode despite prophylactic G-CSF: Withdraw from study treatment	
Febrile neutropenia or neutropenic infection	Not applicable	Delay** next infusion until recovery and ANC ;,;1.5 x 10^9/L and: - 1st episode: reduce the dose 1 dose level and administer prophylactic G-CSF treatment in subsequent cycles. - 2nd episode: Withdraw from study treatment	
Thrombocytopenia	Delay** next infusion until recovery to Grade ::; 1 (platelets ;,;75 x 10^9/L). No dose reduction required.	Delay** infusion until platelets ;,;75 x 10^9/L If Grade 3 without delay, no dose reduction required. If Grade 4 with or without delay, or Grade 3 with delay - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Withdraw from study treatment in case of recurrence	

** maximum of 2 weeks delay, otherwise the patient will discontinue cabazitaxel

Blood counts will be performed in case of fever or infection. Blood count should be monitored weekly for the first cycle to determine if G-CSF or dosage modification is needed. Study treatment should not be given to patients with neutrophil counts <1,500 cells/mm^3.

Deaths due to sepsis following severe neutropenia have been reported in patients treated with cabazitaxel. Neutropenic complications should be managed promptly with antibiotic support and use of G-CSF should be considered according to ASCO guidelines. Infections concomitant with Grade 3-4 neutropenia should be reported with the term "neutropenic infection" in the eCRF.

No dose modification will be made for anemia; patients will be supported appropriately by the treating physician (the investigator can refer to ASCO guidelines).

Allergy (Anaphylactic and Hypersensitivity reactions))

Hypersensitivity reactions that occur despite premedication are very likely to occur within a few minutes of start of the first or of the second infusion of cabazitaxel.

Therefore, during the 1st and the 2nd infusions, careful evaluation of general sense of well being and of blood pressure and heart rate will be performed for at least the first 10 minutes, so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation along with the medications (i.e., antihistamine, corticosteroids, aminophylline, and epinephrine) must be immediately available. If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g., epinephrine in case of anaphylactic shock, aminophylline **in** case of bronchospasm, etc)) will be instituted. In addition, it is recommended to take the measures listed below:

Mild: localized cutaneous reaction, such as: pruritus, flushing, rash.	o Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside o Complete cabazitaxel infusion at the initial planned rate.
Moderate: Generalized pruritus, more severe flushing or rash, mild dyspnea, hypotension with systolic B8.P. >80 mmHg	o Stop cabazitaxel infusion o Give IV diphenhydramine 50 mg and/or !VIV dexamethasone 10mg o Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible. o Re-administer premedication regimen as described in Section 7.2 when cabazitaxel is reinfused more than 3 hours after the interruption o Administer cabazitaxel over 2 hours for all subsequent infusions
Severe:bronchospasm, generalized urticaria, hypotension with systolic B8.P.:::;80 mmHg, angioedema.	o Stop cabazitaxel infusion o Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg o Add epinephrine** or bronchodilators and/or IV plasma expanders if indicated o Once all signs and/or symptoms of hypersensitivity reaction disappear, cabazitaxel may be reinfused within 24 hours from the interruption, if medically appropriate, and whenever possible o Re-administer premedication regimen as described in Section 7.2 when cabazitaxel is reinfused more than 3 hours after the interruption o Administer cabazitaxel over 2 hours for all subsequent infusions o If a severe reaction recurs, patient will go off protocol therapy
Anaphylaxis (Grade 4 reaction)	Withdraw treatment

Nausea/Vomiting

A prophylactic anti-emetic treatment should be given to the patients in all cycles. The use of metoclopramide is recommended. More aggressive anti-emetic prophylaxis (i.e., ondansetron, etc.) should be given to the patient who has experienced Grade ::::3 nausea/vomiting in a preceding cycle. If despite the appropriate medication, Grade ::::3 nausea/vomiting still occur, reduce the dose of

cabazitaxel. If despite dose reduction and prophylaxis, nausea/vomiting still occur at Grade 3, the patient should be withdrawn from treatment with cabazitaxel.

Stomatitis

If Grade 3 stomatitis occurs, cabazitaxel should be withheld until resolution to Grade :51. Treatment may then be resumed, but the dose of cabazitaxel should be reduced by 1 dose level for all subsequent doses. In case of Grade 4 stomatitis, the patient will be withdrawn from treatment with cabazitaxel.

Diarrhea

No prophylactic treatment for diarrhea is recommended in Cycle 1. However, following the first episode of diarrhea, the patient should be treated with rehydration or antidiarrheal medications as needed. In case of Grade 3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement, delay treatment until improvement or resolution, then reduce the dose by 1 dose level. If despite dose reduction, diarrhea still occurs at Grade 3, the patient will be withdrawn from treatment with cabazitaxel.

Renal function

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage disease (creatinine clearance CLrn<15mL/min/1.73m^2), should be monitored carefully during treatment *[see* Clinical Pharmacology (12.3].

Hematuria

An imbalance in the incidence of hematuria was observed in the Phase III study in second line mCRPC (EFC6193). More hematuria was reported in cabazitaxel arm versus mitoxantrone arm (62 patients/16.7% versus 14 patients/3.8%). In cabazitaxel arm, no clear possible explanation such as local infection/obstruction/progression, or anticoagulation/aspirin therapy, or thrombocytopenia was found for 21 patients. In addition, in prior studies conducted in metastatic breast cancer, a total of 6 patients (2 in the ARD6191 and 4 in the TCD6945) experienced cystitis without local infection including 5 hemorrhagic cystitis (3 cystitis were documented with biopsy).

Therefore, in case of hematuria with no clear possible explanation every efforts should be undertaken to document the cause (e.g., urine cultures, urinary tract ultrasound, and if no cause identified cystoscopy with or without biopsy).

Peripheral neuropathy

Dose modification should be performed as follows:

- Grade :51: No change
- Grade 2: Retreat with reduced dose (reduce by 1 dose level)
- Grade 3: Patient will be withdrawn from treatment with cabazitaxel

Liver toxicity

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin > 1 to :5 1.5 x ULN or AST > 1.5 x ULN) should have cabazitaxel dose reduced to 20mg/m^2. Patients with moderate hepatic impairment

(total bilirubin > 1.5 to :,; 3.0 ULN and AST = any) should have cabazitaxel dose reduced to 15 mg/m^2. Administration of cabazitaxel to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety *[see Clinical Pharmacology (12.3)]*. Cabazitaxel is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN).

Other Toxic Effects

For <! Grade 3 toxicities except fatigue, local reaction, fluid retention, anemia and other toxicities that merely are uncomfortable but do not cause serious morbidity to patients, chemotherapy should be held for a maximum of 2 weeks from the planned date of reinfusion until resolution to :,; Grade 1, then reinstituted, if medically appropriate. *A* dose reduction of subsequent doses (1 dose level) will be left to the investigator's judgment. These patients will be withdrawn from study treatment if >2 dose reductions are needed. Any measures such as frozen gloves or socks or scalp cooling cap to prevent nail toxicity or alopecia are left to the investigator's judgment.

7.4 Removing Patients from the Protocol

In the absence of treatment delays because of AEs, treatment will continue until one of the following criteria applies:

- patient decides to withdraw from the study
- disease progression
- study closure
- symptomatic disease progression at any time
- objective clinical disease progression
- intercurrent illness that prevents further administration of treatment
- unacceptable AE(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the patient to be retreated
- general or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator

Because an excessive rate of withdrawals can render the study not interpretable, unnecessary withdrawal of patients should be avoided. When a patient discontinues treatment early, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

7.5 Concomitant Medications and Supportive Care

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented on the CRF. The principal investigator should be alerted if the patient is taking any agent found in Appendix B (a listing of medications with the potential for drug-drug interactions).

7.5.1 CYP450 system

Abiraterone causes inhibition of P450 CYPs 2C19, 2D6 and 1A2. So any medications known to be metabolized by the P 450 system should be used with caution. Abiraterone is thought to be a weak inhibitor of these enzymes.

7.5.2 Anticoagulants
Anticoagulants should be held prior to biopsy to obtain tumor to check the RB status of the tumor.

7.5.3 Supportive care
Use of growth factors will be should be utilized as needed to reduce complications from cabazitaxel after first cycle of therapy as per ASCO guidelines.

8. SAFETY EVALUATION AND REPORTING

8.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a research patient during a clinical study or within 30 days post-treatment, regardless of causality. This includes adverse clinical or laboratory findings, any adverse drug reaction (ADR), an illness with onset during the study, or an exacerbation of preexisting illness or condition.

8.2 Recording and Grading

8.2.1 Recording

All observed or volunteered AEs, regardless of treatment group, severity, suspected causal relationship, expectedness, or seriousness will be recorded. The NCI CTCAE v4.0 will be used for recording and grading AEs.

Follow-up of AEs should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator and the lead site/sponsor or medical monitor.

A clinically significant change in a physical examination finding or an abnormal test result (i.e., laboratory, x-ray, EKG) should be recorded as an AE, if it:

- is associated with accompanying symptoms
- requires additional diagnostic testing or medical or surgical intervention
- leads to a change in study dosing or discontinuation from the study
- requires additional concomitant drug treatment or other therapy, or
- is considered clinically significant by the investigator or sponsor.

An abnormal test result that is subsequently determined to be in error does not require recording as an AE, even if it originally met one or more of the above criteria.

8.2.2 Grading severity

All AEs will be graded for intensity on a scale of 0 to 5. Severity grades will be recorded and based on the CTCAE version 4.0.

8.2.3 Attributing causality

After grading for severity, the investigator must evaluate all clinical AEs and abnormal laboratory values for possible causal relationship to the study drugs. Causality attribution will be classified as either "related" or "non-related".

Abnormal laboratory values of clinical significance that were present at baseline and did not change in severity or frequency during experimental therapy or intervention and those that can obviously be attributed to underlying disease will be recorded as unrelated and will not be considered when evaluating the maximum tolerated dose (MTD).

8.3 Unexpected Adverse Events

An unexpected AE is any event not associated by nature or intensity with the investigational agent under study. The Comprehensive Adverse Event and Potential Risks (CAEPR) list provides a single, complete list of reported and potential AEs associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), contains events that are considered expected for expedited reporting purposes only. *A* listing of expected and unexpected events for the agent(s) under investigation for cabazitaxel and abiraterone acetate in this study may be found in Appendix E.

8.4 Serious Adverse Events and Serious Adverse Drug Reactions

Serious adverse event (SAE): any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening, (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or results in prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Related Adverse Event, i.e. Adverse Drug Reaction (ADR): There is a reasonable possibility according to the sponsor that the product may have caused the event.

Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the ADR might be associated with a fatal outcome.

All SAEs that occur any time a patient is on study (i.e., as soon as the informed consent has been signed) or within 30 days of the last dose of cabazitaxel or abiraterone acetate must be recorded, regardless of the suspected relationship to the drugs. Any SAE occurring more than 30 days after the last dose of the study drugs must be recorded if a causal relationship to them is suspected.

8.4.1 Progression of malignancy

Progression of a patient's malignancy should not be considered an AE, unless in the investigator's opinion, study treatment resulted in an exacerbation of the patient's condition. If disease progression results in death or hospitalization while on study or within 30 days of the last dose, progressive disease will be considered an SAE.

8.4.2 Life-threatening events

A life-threatening event is any AE that places the patient at immediate risk of death from the reaction as it occurs. It is not a reaction that, had it occurred in a more severe form, might have caused death.

8.4.3 Hospitalization or prolongation of hospitalization

Hospitalization encompasses any inpatient admission (greater than 24 hours) resulting from a precipitating, treatment-emergent AE. For chronic or long-term patients, inpatient admission also includes transfer within the hospital to an acute or intensive care inpatient unit. Hospitalizations for administrative reasons or a non-worsening preexisting condition should not be considered AEs (e.g., admission for workup of a persistent pretreatment laboratory abnormality, yearly physical exam, protocol-specified admission, elective surgery). Preplanned treatments or surgical procedures should be noted in the baseline documentation. Hospitalization because of an unplanned event will be deemed an SAE.

Prolongation of hospitalization is any extension of an inpatient hospitalization beyond the stay anticipated or required for the original reason for admission.

8.4.4 Significant disability

Disability is a substantial disruption of the patient's ability to conduct normal life functions.

8.4.5 Congenital anomaly

If the female partner of a male patient becomes pregnant during the course of the study, the treating physician must be notified immediately. All confirmed pregnancies must be immediately reported to the lead investigator and sponsor and recorded in the consortium database. All pregnancies will be followed until resolution (i.e., voluntary or spontaneous termination or birth) and assessed for congenital anomalies and birth defects.

8.4.6 Medically significant event

An event that is not fatal or life-threatening and that does not necessitate hospitalization may be considered serious if, in the opinion of the investigator, it jeopardizes the patient's status and might lead to medical or surgical intervention to prevent any of the above outcomes. Such medically significant events could include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, vasculitis, "generalized edema", or the development of drug dependency or abuse.

8.5 Reporting Serious Adverse Events

8.5.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to the lead site/sponsor and the PCCTC within 24 hours of knowledge of the event using the contact information below. The PCCTC will provide an initial notification of SAEs to Sanofi within 1 business day of PCCTC awareness or identification of the event.

The initial report for each SAE or death should include the following information:

- protocol# and title
- study identification number, sex, age
- date the event occurred
- description of the SAE
- causal relationship to the study drug

The PCCTC SAE Report Form (Appendix J) will be used for reporting each SAE and should be submitted to the PCCTC within 3 calendar days oflearning of the event. When a life-threatening event or death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify PCCTC as soon as possible but within 24 hours of the time the participating site becomes aware of the event. Severity, causality, action taken, concomitant medications, outcome, etc should be reported to the PCCTC as soon as possible.

Follow-up of adverse events should continue until the event and any sequela resolve or stabilize at a level acceptable to the investigator.

The PCCTC will facilitate all SAE reporting to the MSKCC IRB/PB and Sanofi within 5 calendar days. PCCTC is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE report from the MSK IRB/PB. PCCTC is responsible for informing all participating sites within 24 hours or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

SAE contact information for the PCCTC, lead site/sponsor is listed below:

Lead Site Study Pl:

Susan Slovin, MD, PhD
Memorial Sloan Kettering Cancer Center
Genitourinary Oncology Service
1275 York Avenue
New York, NY 10065
slovins@mskcc.org

PCCTC:
Prostate Cancer Clinical Trials Consortium
Phone: 646-888-0434/646-422-4383
Email: PCCTC@mskcc.org

Sanofi Pharmacovigilance Contact:
Fax: 908-547-8000
E-mail: CL-CPV-Receipt@sanofi.com

8.6 Safety Reports

The PCCTC will distribute outside safety reports to the participating sites immediately upon receipt. Participating sites are responsible for submitting safety reports to their local IRB/PB as per their local IRB guidelines. All local IRB approvals/acknowledgments of safety reports must be sent to the PCCTC upon receipt.

8.7 Unanticipated Problems

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); **and**
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to PCCTC as soon as possible but within 3 calendar days oflearning of the event. UPs that are SAEs should be reported to PCCTC via SAE Report form as per Appendix D. All other UPs should be reported to PCCTC in a memo signed by the site PI.

PCCTC is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, PCCTC is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

9. CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

9.1 Outcome Assessment

All baseline evaluations will be performed as closely as possible to the beginning of treatment. For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

9.1.1 Primary Objective

9.1.1.1 To determine the radiographic progression free survival (rPFS) in patients treated with abiraterone acetate\prednisone with and without cabazitaxel in patients with chemotherapy nai:ve CRPC.

9.1.1.2 Secondary Objectives

9.1.1.2.1 To determine PSA progression free survival (PSA PFS) in patients treated with abiraterone acetate\prednisone with and without cabazitaxel in patients with chemotherapy nai:ve CRPC

9.1.1.2.2 To determine the proportion of patients with measurable disease regression based on the RECIST treated with abiraterone acetate with and without cabazitaxel **in** patients with chemotherapy nai:ve CRPC.

9.1.1.2.3 To determine the overall toxicity and survival for patients treated with abiraterone acetate with and without cabazitaxel in patients with chemotherapy nai:ve CRPC.

9.1.1.2.4 To determine the proportion of patients that have an objective response using the RECIST and post-therapy PSA decline using a waterfall plot in patients that are treated with cabazitaxel after progression on the abiraterone/prednisone alone arm.

9.2 Therapeutic Response

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Table 4) and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG2, Table 5).[26]

Patients will need to be reevaluated for response every cycle according to the guidelines below.

9.2.1 PSA

Perform PSA testing at a minimum of 1-week intervals with the threshold PSA level at 2.0 ng/mL. To report PSA-based outcomes, PCWG2 recommends that the percent of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment be reported for each patient using a waterfall plot. Because the rate of rise has shown prognostic significance, estimate a pretreatment PSA doubling time (PSA-DT) if at least 3 values are available, but do not delay either treatment or enrollment

onto a trial simply to estimate PSA-DT. Because declines in serum PSA, if they occur, may not do so for several weeks, PSA measurements obtained during the first 12 weeks should not be used as the sole criterion for clinical decision making.zs

9.2.2 Measurable disease

According to RECIST, measurable disease is defined as at least 1 lesion> 20 mm in its longest diameter as measured with conventional techniques (i.e., CT [nonspiral or non-helical], MRI, physical exam) or> 10 mm as measured with spiral CT scan. All tumor measurements will be taken using a ruler or calipers and recorded in millimeters (or decimal fractions of centimeters).

9.2.3 Non-measurable disease

Following RECIST, all other lesions (or sites of disease) will be considered non-measurable disease. This includes small lesions (longest diameter< 20 mm with conventional techniques or< 10 mm using spiral CT scan) and any of the following:

- bone lesions
- ascites
- pleural or pericardia! effusion
- lymphangitis cutis or pulmonitis
- abdominal masses that are not confirmed and followed by imaging techniques
- cystic lesions
- lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

> ***Note:*** If only a single, asymptomatic bone lesion is present at baseline, and will be irradiated, the metastatic nature of this lesion must be confirmed by x-ray, CT, or MRI.

9.2.4 Target (nodal and visceral) lesions

Following RECIST, progression in a nodal or visceral site (i.e., liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 5 lesions per organ and 10 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected on the basis of size (i.e., the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). The sum of the longest diameter (LD) of all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Because small lymph nodes are difficult to measure accurately and may not be malignant, the greatest diameter of a lymph node must measure at least 2 cm by spiral CT to be considered a target lesion.zs

9.2.5 Bone lesions

When the bone scan is the sole indicator of progression, disease progression in bone is defined as 2 or more new lesions seen on bone scan compared with a prior scan for used trial entry.zs

In situations where scan findings suggest a flare reaction or where new lesion(s) may represent trauma, confirm these results with other imaging modalities (e.g., MRI or fine-cut CT). If many new areas of uptake are observed, confirmation is generally not necessary.

9.2.6 Non-target lesions

All other lesions (or sites of disease) will be identified as nontarget lesions and recorded at baseline. Nontarget lesions will include measurable lesions that exceed the maximum number per organ (5) or total of all involved organs (10), as well as nonmeasurable lesions. The presence or absence of these lesions will be recorded on the CRF and should be evaluated at the same assessment time points as all target lesions.

9.2.7 New lesions

The appearance of up to 10 new measurable lesions should be recorded. Each new lesion should be reassessed using the same imaging modality at each time point. If measurable, the LD of each new lesion should be recorded in the CRF and the sum LD of new and old lesions should be calculated. See Table 4 for a description of the determination of progression based on the presence of new lesions.

Note: The appearance of a new lesion does not by itself satisfy the criteria for confirmed progressive disease. Rather, the tumor burden imposed by the new lesions must be evaluated within the context of the total tumor burden (i.e., preexisting plus new lesions). Confirming progression in target lesions, non-target (i.e., other than bone) lesions, and bone lesions requires 2 assessment time points. The first must occur at Week 9 (or later) and the second occurring at least 6 weeks after the first. Progression declared at the first time point remains unconfirmed unless assessments at the second time point demonstrate continuing or worsening progression, as described in Section 9.4.

9.3 Response Criteria for Control/Relieve/Eliminate Endpoints

9.3.1. Measurable soft-tissue lesions

When evaluating soft-tissue lesions, the definitions in Table 2 apply.

Table 2. REC/ST response criteria for target (soft-tissue) lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	the disappearance of clinical and radiological evidence of all target lesions and normalization of tumor marker levels
Partial response (PR)	a decrease from baseline<'= 30% in the sum of the LD of all target lesions
Progressive disease (PD)	an increase <'= 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions or the appearance of new lesions
Stable disease (SD)	neither sufficient shrinkage to qualify for PR nor sufficient increase

	to qualify for PD based on the smallest sum LD recorded since treatment started

Abbreviations: LD, longest diameter.

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 (e.g., fine needle aspirate or biopsy) before confirming the complete response status.

Changes in nodal and visceral sites should be recorded and reported separately, and lymph nodes in the pelvis must measure at least 2 cm in greatest diameter to be considered target lesions. Complete elimination of disease at a particular site should be recorded separately. Any favorable change should be confirmed using a second follow-up scan.

9.3.2 *PSA*

As long as patient safety is the primary concern, in the absence of other indicators of disease progression, therapy should not be discontinued solely on the basis of a rise in PSA.

For each patient, use a waterfall plot to report the percent change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy) and the maximum decline in PSA that occurs at any point after treatment.

9.3.3 *Bone*

Record post-treatment changes as either "no new lesions" or "new lesions" as indicated on the forms in appendix K.

In the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later. In the rare case where visible lesions disappear, this too should be confirmed.

9.3.4 *Non-target lesions*

When assessing non-target lesions, the definitions in Table 3 will apply.

Table 3. RECIST response criteria for non-target lesions

Response	Evaluation of Non-target Lesions
Complete response (CR)	the disappearance of all non-target lesions and normalization of tumor marker levels
Incomplete response/ stable disease (SD)	the persistence of one or more non-target lesions and/or maintenance of tumor marker *levels above* the normal limits
Progressive disease (PD)	the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

A clear progression of non-target lesions only is exceptional. In such circumstances, the progression status, as assigned by the investigator, may be reviewed by a PCCTC panel.

9.3.5 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until either disease progression or recurrence. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessment performed 4-6 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet SD criteria at a minimum interval of 4 weeks after SD was first documented. Table 4 can be used as an assessment tool.

Table 4. Assessing Overall Response

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

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Patients with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered non-responders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- death attributed to disease progression
- early discontinuation attributed to disease progression
- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

Note: If a patient receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response

9.4 Confirmatory Measures/Duration of Response

9.4.1 Confirming time-to-event outcomes

Any post-treatment change in disease status, be it favorable or unfavorable should be confirmed using a second assessment.

9.4.2 Duration of overall response

Duration of overall response is measured from the time when partial response or complete response is first noted until the date when recurrent or progressive disease is objectively documented. Duration of overall complete response is measured from the time the criteria for complete response are first met until the first date that recurrent disease is objectively documented. Duration of stable disease is measured from the start of treatment until the criteria for progression are met.

9.4.3 Radiographic Progression-free survival

Radiographic progression-free survival (rPFS) is a composite endpoint defined as the time from treatment start to disease progression in bone or soft-tissue, or death, whichever occurs first. All assessments of disease should be collected at the same time interval (e.g., bone scan, CT scan, and PSA). In addition to PSA, confirm post-treatment changes in measurable target lesions, radionuclide bone scans, and symptoms.

Table 5. Prostate Cancer Clinical Trials Working Group Outcome Measures[26]

Variable	Control/Relieve/Eliminate Endpoints	Prevent/Delay Endpoints
PSA	Record the percent change from baseline (rise or fall) at 12 weeks and, separately, the maximal change (rise or fall) at any time using a waterfall plot	**Decline from baseline:** record time from start of therapy to first PSA increase that is ~25% and ~2 ng/mL *above* the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)t Recording the duration of PSA decline of little value **No decline from baseline:** PSA progression ~25% and ~2 ng/mL after 12 weeks
Soft-tissue lesions	Use RECIST with caveats: Only report changes in lymph nodes that were ~ 2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot	Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later Note that for some treatments, a lesion may increase in size before it decreases
Bone	Record outcome as either *new lesions* or *no new lesions* First scheduled reassessment: No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: No new lesions: continue therapy Additional new lesions: progression Subsequent scheduled reassessments: No new lesions: continue New lesions: progression	The appearance of~ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows at least 2 or more additional new lesions The date of progression is the date of the first scan that shows the change
Symptoms	Consider independently of other outcome measures Document pain and analgesia at entry with a lead-in period and measure repeatedly at 3- to 4-week intervals Perform serial assessments of global changes in HRQOL, urinary or bowel compromise, pain management, additional anticancer therapy Ignore early changes (~12 weeks) in pain or HRQOL in absence of compelling evidence of disease progression Confirm response or progression of pain or HRQOL endpoints ~3 weeks later	

Abbreviations: PSA, prostate-specific antigen; HRQOL, health-related quality of life.tParticularly important when anticipated effect on PSA is delayed or for biologic therapies.

10. DATA REPORTING AND REGULATORY REQUIREMENTS

10.1 Data Collection and Management

Data collected during this study will be entered into a secure database.

10.1.1 Electronic case report forms (eCRFs)

The participating sites will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based PCCTC Caisis Electronic Data Capture (EDC) system. Completion guidelines will be created by the PCCTC for the collection of all study data. Access and training for PCCTC Caisis EDC will be made available to participating sites upon local regulatory approval. The participating site PI is responsible for ensuring eCRFs are completed accurately and in a timely manner.

10.1.2 Source documents

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation will be made available to support the subject's research record. Source documentation must include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

10.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The investigator will ensure that all regulatory documents and participating site IRB correspondences are maintained in an onsite regulatory binder. After study closure, the investigator will maintain all source documents and study-related documents.. Records are to be retained and securely stored until the later of: (a) two (2) years following the date a New Drug Application is approved for the Study Drug that is the subject of the Clinical Trial; or (b) two (2) years after the Investigational New Drug Application for such Study Drug is terminated or withdrawn, or such longer period of time as may be required by Participant policies, applicable laws, rules or regulations.

10.1.4 Source Documentation Submission for Registration at Participating Sites

Participating sites should email any source documentation that corresponds to data entered at registration to the PCCTC at PCCTC@mskcc.org within 24 hours (see Section 4.2.1).

10.1.5 Data Submission Timelines

All study data should be transmitted to the PCCTC within 14 days of visit except for SAE submission (see section 8.5) as described in the Data Management Plan.

10.1.6 Data Review and Queries

The PCCTC will review data and source documentation as it is submitted. Data will be monitored and source verified as necessary and discrepancies will be sent as queries to the participating sites. In addition, the PCCTC will review data for logic,

consistency, and obvious anomalies. Queries will be sent by the PCCTC to participating sites as needed.

Participating sites should respond to data queries within 14 days ofreceipt.

10.2 Study Monitoring and Quality Assurance

10.2.1 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSMP) at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/pagel*. The DSMPs at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSMPs can be found on the MSKCC Intranet at:
http://inside2/ clinresearch/Documents/MSKCC%2 0Data%20and%2 0Safety%2 0Monitoring%20Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance **and** data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. There are several committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the MSKCC Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twice per year.

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology and additional lab reports will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.

10.2.2 Data Monitoring and Quality Assurance

In addition to review by DSMC, the PCCTC will conduct regularly scheduled monitoring visits.

Registration reports will be generated by the PCCTC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

Each site participating in the accrual of participants to this protocol will be monitored at a minimum of 10% of all subjects, but at least 2 from each site, will be 100% source data verified by the PCCTC. Monitoring will occur once shortly after initiation of subject recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial, for protocol and regulatory compliance, data verification and source documentation. Monitoring visits may be accomplished in one of two ways: (1) sending source documents and research records for selected patients from participating sites to the PCCTC for audit, or (2) on-site monitoring of selected patient records at participating sites.

The monitoring visit will include a review of source documentation to evaluate compliance for:

1. Regulatory /IRB compliance (review of current protocol and amendments, Informed consent documents and procedures, annual continuing review reports, AEs/SAEs)
2. Protocol defined treatment compliance
3. Subject records
   - Each subject is audited to reviewed to determine that there is a signed and dated consent form
   - Adherence to eligibility criteria
   - Baseline, on study and follow-up protocol testing
   - eCRF completion

Monitoring visit findings will be reviewed and disseminated to the site Pis and staff.

In addition, each participating site accruing participants to this protocol will be audited by MSKCC for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Audits will be conducted annually at minimum, and more often if significant and/or repeated findings are identified during monitoring visits. The number of participants audited will be determined by the outcome of monitoring visits and complexity of the protocol.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

11. STATISTICAL CONSIDERATIONS

11.1 Endpoints

The primary endpoint is radiographic progression-free survival (rPFS) defined as the time from randomization to minimum of radiographic progression or death, whichever occurs first.

Secondary endpoints include post-therapy changes in PSA, objective response rate (ORR) per RECIST criteria, PSA progression-free survival (PSA PFS), and toxicity.

11.2 Sample Size

This is a randomized phase II trial in which 80 patients will be randomized with equal probability to one of two possible treatment regimens: abiraterone acetate\prednisone (AA) or *AA* plus cabazitaxel (AA+C). The randomization will be stratified by Halabi nomogram[7] based on low (defined as (166.6 points in the nomogram) or high risk (>166.6 total points).

Based on Ryan et al. the median time to radiographic progression free survival (rPFS) is 16.5 months. This trial is non-comparative. Forty (40) patients will be enrolled in each arm. With an accrual rate of 40 patients/arm over 24-month accrual period, and assuming that rPFS follows an exponential distribution, based on 5,000 simulations the average width of a two-sided 95% confidence interval for the median rPFS is 16.

In addition, this trial will estimate the rPFS in patients who are RB negative and treated with either *AA* or AA+C. It is expected that 60% (48) patients will be RB negative and 40% (32 patients) will be RB positive. The radiographic PFS distribution by RB status and treatment arm will not be estimated with high precision. Nevertheless, the data from this study will be valuable for testing feasibility as well as providing pilot data for use in planning a larger randomized phase II/III trial.

Dr. Susan Halabi from Duke University will perform statistical analysis of this trial. Data will be de-identified from all sites prior to sending to Dr. Halabi for analysis.

11.3 Toxicity Monitoring

While the combination of *AA* + C has been safely administered in patients that had prior Docetaxel therapy, it is expected that this will also be well tolerated in the pre-chemotherapy population. However since it has not been used in the pre-chemotherapy population, close toxicity monitoring will occur. An unacceptable toxicity will be defined as death or grade 4 febrile neutropenia that is treatment related (probably or definitely related to treatment). If at any time during the accrual the observed proportion of unacceptable toxicity exceeds 15% by at least one standard error accrual to the trial will be immediately suspended and the trial re-evaluated.

11.4 Data Analysis

The trial is non-comparative and the analysis will be performed within each arm. The Kaplan-Meier product-limit estimator will be used to estimate rPFS, overall survival, and PFS distributions. In addition, the proportion of patients who are RB positive or RB negative with exact 95% confidence interval (CI) based on the binomial distribution will be computed. RB status will be performed at centralized laboratory at Thomas Jefferson University and RB immunohistochemistry status\genomic profile will be performed as previously described by Sharma et al.1

The rPFS distribution will be estimated in subgroups of patients who are RB positive or RB negative treated with either *AA* or AA+C. The rPFS distribution within each arm and RB status will not be estimated with high precision. Nevertheless, the data from this study will

be valuable for testing feasibility as well as providing pilot data for use in planning a larger phase 11\III trial.

Furthermore, post therapy changes in PSA (50%) and response rates using the RECIST criteria (complete+ partial) with exact 95% Cls based on the binomial distribution will be computed. Exploratory analysis will be performed to correlate the RB status with PFS and other clinical outcomes.

12. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

12.1 Roles and Responsibilities

12.1.1 lead Site/Sponsor Principal Investigator

The Sponsor Principal Investigator at the lead site is responsible for performing the following tasks:

- Responsibility for the overall conduct of the study at all participating sites and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all participating sites

12.1.2 PCCTC

The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AE's and SAE's to the PCCTC.
- Reviewing Serious Adverse Events (SAEs)
- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

12.1.3 Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, the guidelines of Good Clinical Practice (GCP), and applicable Standard Operating Procedures (SOPs).Registering all patients with the PCCTC by submitting the eligibility checklist, supporting source documentation, and signed informed consent promptly
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol
- Maintaining regulatory binders on site and providing copies of all required documents to the PCCTC
- Collecting and submitting data according to the schedule specified by the protocol

- Responding to queries in a timely manner

12.2 Ethical Considerations

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

12.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to the PCCTC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical licenses for each investigator and consenting professional
- Curriculum vitae for each lab director
- Consenting Professionals Lists (consenting professionals at each participating site that may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines)
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site
- Documentation of Good Clinical Practice (GCP) training for the Pl and co-Pl at the participating site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, the PCCTC will submit a participating site activation request to MSKCC. Once approved, MSKCC will formally contact the PCCTC and grant the site permission to proceed with enrollment.

12.4 Protocol Amendments

Before starting the study, the protocol must be approved by each institution's IRB or Independent Ethics Committee (IEC). Each change to the protocol document must be organized and documented by the PCCTC, reviewed and approved by Sanofi and approved by the MSKCC IRB/PB. Protocol amendments that affect MSKCC only (e.g. change in MSKCC Co-Investigator, MSKCC translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSKCC IRB/PB approval.

Each participating site must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval of the revised protocol

document is granted and submitted to the PCCTC, who will in turn submit the approval documentation to MSKCC.

The following documents must be provided to the PCCTC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

The PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSKCC upon receipt.

12.5 Additional IRB Correspondences

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to PCCTC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment. The PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSKCC upon receipt.

Deviations
A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections 8.5.1 and 8.7 of the protocol.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSKCC IRB/PB. However, they must be clearly documented in the patient's medical record.

Prospective Deviations
Deviations to the research protocol that involve an informed consent procedure change and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSKCC IRB/PB prior to the change being carried out. Participating sites should contact the PCCTC who will in turn seek approval from the MSK IRB/PB. Deviations to the research protocol that involve patient eligibility will not be permitted.

Retrospective Deviations
Deviations that include a change or departure from the research protocol without prior approval from the MSKCC IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the PCCTC as soon as possible, who will in turn report the deviation to the MSKCC IRB/PB as per MSKCC guidelines.

Participating Site !RB Reporting
Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to the PCCTC upon receipt. The PCCTC is responsible for submitting all participating site local IRB approvals and/or acknowledgments to MSKCC upon receipt.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to the PCCTC. The PCCTC is responsible for submitting all participating site local IRB correspondences to MSKCC upon receipt

12.6 Document Maintenance

The MSKCC PI and participating site PI will maintain adequate and accurate records to fully document protocol implementation and allow data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondence are maintained in an on-site regulatory binder and sent to the PCCTC as outlined within the protocol. The on-site regulatory binder will be reviewed by the designated study monitor at monitoring visits. *A* regulatory binder for each participating site will also be maintained at the PCCTC; this binder may be paper or electronic.

After study closure, the participating sites must maintain all source documents, study related documents and eCRFs for 7 years.

12.7 Written Informed Consent

Before obtaining consent, members of the study team will review the rationale for the treatment program with the patient. The discussion will review the alternatives available (including hormonal therapy, chemotherapy, or supportive care as appropriate), the potential benefits of this program, the risks and the probability of their occurrence, and the procedures to minimize these risks. Should an AE occur, the provisions available to ensure medical intervention will also be reviewed. Why the risks are reasonable in relation to the anticipated benefits, incentives, or costs that will or may be incurred as a result of participating in the study, as well as the efforts to maintain confidentiality, will also be discussed with the patient.

Patients will be required to sign and date a statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the lead site/sponsor pursuant to sponsor registration and to the PCCTC and a copy will be sent home with each patient.

The consent form will include the following:

- the nature and objectives, potential toxicities, and benefits of the intended study
- the length of therapy and likely follow-up required
- alternatives to the proposed therapy (including available standard and investigational therapies)
- the name of the investigator(s) responsible for the protocol
- the right of the patient to accept or refuse treatment and to withdraw from participation in this study

  Text regarding the PCCTC should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., "Prostate Cancer Clinical Trials Consortium")

12.8 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. After this discussion, they will be asked to sign a Notice of Privacy Practice research authorization/HIPAA form. The original signed documents will become part of the patient's medical records, and each patient will receive a copy of the signed documents. The use and disclosure of protected health information will be limited to the individuals described in the research authorization form. The research authorization form must be completed by the principal investigator and approved by the IRB.

12.9 Terminating or Modifying the Study

AE and laboratory data from this trial will be assessed by the lead site or the sponsor's medical monitor on an ongoing basis. SAEs will be reviewed as they are reported to the lead site/sponsor and the PCCTC, and the medical monitor will make an assessment regarding the safety of continuing or modifying the study. This assessment will be shared with the investigators either in writing or as part of a teleconference. Should the assessment of either the lead site/sponsor or the principal investigator be that the study should be terminated, the study will be closed to further accrual. Patients who are receiving cabazitaxel or abiraterone acetate will be assessed individually by the investigator to see if it is in the patients' best interest to continue, which might be the case for a patient that is responding to the intervention. Follow-up safety assessments will be performed for all patients who are terminated from the study prematurely.

12.10 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	%	**Description**
0	Normal activity. Fully active, able to continue 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 needs
		SO	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 >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: MEDICATIONS WITH THE POTENTIAL FOR DRUG-DRUG INTERACTIONS

CABAZITAZEL

No formal clinical drug-drug interaction trials have been conducted with cabazitaxel.

Prednisone or prednisolone administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel.

Drugs That May Increase Cabazitaxel Plasma Concentrations

CYP3A4 Inhibitors: Cabazitaxel is primarily metabolized through CYP3A. Though no formal drug interaction trials have been conducted for cabazitaxel, concomitant administration of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) is expected to increase concentrations of cabazitaxel. Therefore, co-administration with strong CYP3A inhibitors should be avoided. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

Drugs That May Decrease Cabazitaxel Plasma Concentrations

CYP3A4 Inducers: Though no formal drug interaction trials have been conducted for cabazitaxel, the concomitant administration of strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) is expected to decrease cabazitaxel concentrations. Therefore, co-administration with strong CYP3A inducers should be avoided. In addition, patients should also refrain from taking St. John's Wort.

ABIRATERONE

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

APPENDIX C: LABORATORY MANUAL\CORRELATIVE STUDIES

Please see the Laboratory & Correlative Studies Manual

APPENDIX D: STANDARD OPERATING PROCEDURES FOR ULTRASOUND\CT-GUIDED BIOPSY OF METASTATIC PROSTATE CANCER LESION

Please see the Laboratory & Correlative Studies Manual

APPENDIX E: LISTING OF EXPECTED/UNEXPECTED ADVERSE EVENTS

Comprehensive Adverse Events and Potential Risks (CAEPR) List for Cabazitaxel and Abiraterone.

The Comprehensive Adverse Event and Potential Risks (CAEPR) list provides a single, complete list of reported and potential adverse events associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column. The ASAEL contains events that are considered expected for expedited reporting purposes only. Refer to the NCI/CTEP Guidelines: Adverse Event Reporting Requirements available athttp://ctep.cancer.gov/reporting/adeers.html for further clarification.

Adverse Events in .::5% of patients receiving cabazitaxel plus prednisone

	Cabazitaxel plus prednisone N=371	
Adverse Reaction	**All Grades** %	**Grades 3-4** %
Blood and lymph		
Neutropenia	94	82
Febrile neutropenia	7	7
Anemia	98	11
Leukopenia	96	69
Thrombocytopenia	48	4
Cardiac		
Arrhythmia	5	1
GI Disorders		
Diarrhea	47	6
Nausea	34	2
Vomiting	22	2
Constipation	20	1
Abdominal pain	17	2
Dyspepsia	10	0
General		
Fatigue	37	5
Asthenia	20	5
Pyrexia	12	1
Peripheral edema	9	<1
Mucosal inflammation	6	<1
Pain	5	1
Infections		
Urinary tract infection	8	2
Weight decreased	9	0
Metabolism and nutrition		

Anorexia	16	<1
Dehydration	5	2
Musculoskeletal		
Back pain	16	4
Arthralgia	11	1
Muscle spasms	7	0
Nervous system		
Peripheral neuropathy	13	<1
Dysgeusia	11	0
Dizziness	8	0
Headache	8	0
Renal and Urinary		
Hematuria	17	2
Dysuria	7	0
Respiratory		
Dyspnea	12	1
Cough	11	0
Skin		
Alopecia	10	0
Vascular		
Hypotension	5	<1

Adverse reactions due to abiraterone acetate

	Abiraterone with Prednisone (N=791)		Placebo with Prednisone (N=394)	
	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Cardiac disorders				
Arrhythmias	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[6]	3.8	0.5	2.8	0
Cardiac failure[7]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 4.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness,
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalised edema
[5] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia.
[6] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[7] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

APPENDIX F: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

AdEERS	Adverse Event Expedited Reporting System
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
Bid	bis in die (twice a day)
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
BSA	Body Surface Area
BUN	blood urea nitrogen
C	Celsius
cDNA	Circulating DNA
Ca++	calcium
CAEPR	Comprehensive Adverse Event and Potential Risks
CBC	complete blood count
CDUS	Clinical Data Update System
CFR	Code of Federal Regulations
CI	confidence interval
Cl-	chloride
Cler	creatinine clearance
Cm	centimeter
Cmax	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell

CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	coefficient of variation
CYP	cytochrome p-450
dL	deciliter
DHEA	dehydroepiandrosterone
DLT	dose-limiting toxicity
DNA	Deoxyribo Nucleic Acid
DSM	data and safety monitoring
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
F	bioavailability
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunochemical
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
LC	liquid chromatography
LDH	lactate dehydrogenase
Ln	natural logarithm
LOCF	last observation carried forward
LOI	letter of intent
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MS	mass spectrometry
MTD	maximum tolerated dose
N	number of subjects or observations

NA	not applicable
NCI	National Cancer Institute
NIH	National Institutes of Health
PCCTC	Prostate Cancer Clinical Trials Consortium
PCRP	Department of Defense Prostate Cancer Research Program
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PCa	Prostate Cancer
PO	per os (by mouth)
POD	Progression of Disease
PR	partial response
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PT	prothrombin time
PTT	partial thromboplastin time
Qd	quaque die (every day)
QOL	quality of life
RBC	red blood cell
RB+	Retinoblastoma tumor suppressor+
RB-	Retinoblastoma tumor suppressor -
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
RSA	Research Study Assistant
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SD	stable disease
SOP	Standard Operating Procedures
T	temperature
t1/2	terminal half-life
T	time
Tid	ter in die (3 times a day)
TX	treatment
ULN	upper limit of normal
Vss	volume of distribution at steady-state

WBC	white blood cell
WHO	World Health Organization

APPENDIX G. PILL DIARY

Please see the attached patient pill diary.

APPENDIX H: STANDARD OPERATING PROCEDURE FOR SHIPMENT OF CLINICAL SAMPLES

Please see the Laboratory & Correlative Studies Manual

APPENDIX I: 1ST SAE REPORT

Sanofi ISS Serious Adverse Event Cover Page

Fax: Investigator Sponsored Studies (ISS) SAE Report
To: US Pharmacovigilance

Fax: 908-203-7783 or Email to: USPVmailbox@sanofi.com

Date: Pages:

From: Phone:

VisionTracker # / ClubNet#:	**CABAZL06066**
Study Title:	**An Exploratory Randomized Phase II Multicenter Trial of Abiraterone Acetate with or without Cabazitaxel in Treatment of Metastatic Castration Resistant Prostate Cancer**
PI Name:	**Susan Slovin, MD**
Causality:	All serious, related adverse events will be reported and documented on MedWatch Form FDA 3500A (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pd_f) and forwarded directly to sanofi-aventis Pharmaceuticals. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. **For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer.**
Check one:	
	Unrelated: The adverse event is clearly NOT related.
	Unlikely to be related: The adverse event is doubtfully related.
	Possibly related: The adverse event may be related.
	Probably related: The adverse event is likely related.
	Definitely related: The adverse event is clearly related.

APPENDIX J: PCCTC SERIOUS ADVERSE EVENT REPORT FORM

Please see the supplemental PCCTC Serious Adverse Event Form

APPENDIX K: PCCTC BONESCAN ASSESSMENT TOOL

Use the attached Appendix Bone Scan PCCTC Tool.

APPENDIX L: HALABI NOMOGRAM RISK

Use the following link for the Halabi Nomogram and see instructions below for completion:

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

1. Accept terms of the Disclaimer
2. For Display Output, select "Yes"
3. For Risk Group Classification, select "2 Groups"
4. Complete the remaining questions as according to the patient's source documentation
5. DO NOT provide patient ID.
6. Click "Validate" once complete
7. Click "PDF Results File".
8. Print the results and write in the patient's MRN as the patient ID for submission to the patient's EMR, for source documentation