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TITLE: Phase II Study of Abiraterone Acetate and Prednisone in Combination with Cabazitaxel Compared to Cabazitaxel Alone, in Patients with Metastatic Castrate Resistant Prostate Cancer.

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Phase II Study of Abiraterone Acetate and Prednisone in Combination with Cabazitaxel, Compared to Cabazitaxel Alone, in Patients with Metastatic Castration-Resistant Prostate Cancer.	
Primary Objective	To assess the anti-cancer efficacy of abiraterone acetate and cabazitaxel , compared with cabazitaxel alone, in patients with mCRPC, as determined by progression-free survival at 3 months.
Secondary Objectives	To assess the anti-cancer efficacy of abiraterone acetate and cabazitaxel, compared with cabazitaxel alone, in patients with mCRPC, as determined by PSA response, maximum PSA decline during study treatment, time to PSA and radiographic progression, radiographic objective response, median progression-free survival, and overall survival at two years. To assess ongoing safety and tolerability of the combination of abiraterone acetate and cabazitaxel.
Study Population	Metastatic castrate-resistant prostate cancer. Prior treatment with both docetaxel and abiraterone acetate.
STUDY DESIGN	
Arm A: Cabazitaxel monotherapy 1. Patients will receive cabazitaxel 25 mg/m2 intravenously every 3 weeks, until radiographic disease progression per RECIST 1.1, unacceptable toxicity, or patient withdrawal. 2. Patients will receive prednisone 5mg orally BID. **3.** Patients will continue on LHRH agonist or antagonist, unless surgically castrate. **4.** Patients will receive pegfilgrastim or filgrastim support with cabazitaxel dosing. **Arm B: Cabazitaxel + Abiraterone Acetate** 1. Patients will receive cabazitaxel 25 mg/m2 intravenously every 3 weeks, in combination with oral abiraterone acetate 1000 mg daily, until radiographic disease progression per RECIST 1.1, unacceptable toxicity, or patient withdrawal. 2. Patients will receive prednisone 5mg orally BID. 3. Patients will continue on LHRH agonist or antagonist, unless surgically castrate. 4. Patients will receive pegfilgrastim or filgrastim support with cabazitaxel dosing.	

Table 1: Arm A	Screen	C1D1	C1D2	C2D1	C2D2	C3D1	C3D2	CnD1	CnD2	EOS
Informed Consent	X									
Adverse events assessment	X	X		X		X		X		X
Review medication list	X	X		X		X		X		X
Physical exam and history	X	X		X		X		X		X
Vital signs	X	X		X		X		X		X
Performance Status	X	X		X		X		X		X
CBC, CMP	X	X		X		X		X		X
PSA[1]		X		X		X		X		X
Testosterone, HgbA1C	X									X
Electrocardiogram[2]	X			X						
CT [3]	X							X		
Nuclear Bone scan [3]	X							X		
Prednisone[4]		X	X	X	X	X	X	X	X	
Cabazitaxel infusion		X		X		X		X		
Neulasta injection[5]			X		X		X		X	

1 PSA every 3 weeks (on day 1 of each 21-day cycle).
2 ECG (electrocardiogram) performed at screening visit and C2D1 visit.
3 CT chest, abdomen, and pelvis and whole body bone scan will be performed at baseline (within 28 days of C1D1) and every 12 weeks.
4 Prednisone is given on a continuous daily basis (5mg orally BID) beginning with C1D1.
5 Pegfilgrastim is given on day 2 of each cycle. If pegfilgrastim is not covered by patient's insurance, or not tolerated, then substitution with filgrastim per institutional guidelines will be allowed.

Table 2: Arm B	Screen	C1D1	C1D2	C1D15	C2D1	C2D2	C2D15	C3D1	C3D2	C3D15	C4D1	C4D2	C4D15	CnD1	CnD2	EOS
Informed Consent	X															
Adverse events assessment	X	X			X			X			X			X		X
Review medication list	X	X			X			X			X			X		X
Physical exam and history	X	X			X			X			X			X		X
Vital signs	X	X			X			X			X			X		X
Performance Status	X	X			X			X			X			X		X
CBC, CMP	X	X		X[6]	X		X[6]	X		X[6]	X		X[6]	X		X
PSA[1]		X						X			X			X		X
Testosterone, HgbA1C	X															X
Electrocardiogram[2]	X				X											
CT [3]	X													X		
Nuclear Bone scan [3]	X													X		
Abiraterone acetate,[4] Prednisone[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cabazitaxel infusion		X			X			X			X			X		
Neulasta injection[5]			X			X			X			X			X	

1 PSA every 3 weeks (on day 1 of each 21-day cycle).
2 ECG (electrocardiogram) performed at screening visit and C2D1 visit.
3 CT chest, abdomen, and pelvis and whole body bone scan will be performed at baseline (within 28 days of C1D1) and every 12 weeks.
4 Abiraterone acetate and prednisone are given on a continuous daily basis. Prednisone and abiraterone acetate will start on C1D1.
5 Pegfilgrastim is given on day 2 of each cycle. If pegfilgrastim is not covered by patient's insurance, or not tolerated, then substitution with filgrastim per institutional guidelines will be allowed.
6 Liverfunction test analysis will be done at least every 2 weeks during first 3 months on abiraterone, Day 1 and Day 15 of cycles 1-4.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
$AUC_{0\text{-}48hr}$	Area under the plasma concentration versus time curve zero to 48 hours
$AUC_{0\text{-}\tau}$	Area under the plasma concentration versus time curve zero to next dose
CBC	Complete blood count
CI	Confidence interval
CL	Clearance
CL/F	Apparent oral clearance
C_{max}	Maximum plasma concentration
CR	Complete remission ***or*** complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CV	Cardiovascular
CYP	Cytochrome P_{450}
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GLP	Good Laboratory Practices
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IB	Investigator's Brochure
IC_{50}	Concentration producing 50% inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

Abbreviation	Term
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LHRH	Leutinizing hormone releasing hormone
mCRPC	Metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Objective response rate
PI	Principal investigator
PD	Pharmacodynamic(s)
PFS	Progression-free survival
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial remission ***or*** partial response
PSA	Prostate specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SD	Stable disease
STD	Severe Toxic Dosage
T_{max}	First time to maximum plasma concentration
ULN	Upper limit of the normal range
Vss	Volume at steady state
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Prostate Cancer

Prostate cancer is the most common non-cutaneous cancer in men in the United States, and the second leading cause of cancer death in US men (1). As many as three-quarters of prostate cancer patients present with localized disease yet a good proportion have recurrent or metastatic disease requiring systemic treatment with androgen deprivation therapy (ADT). This is our most effective form of systemic therapy; however, the majority of prostate cancer cases will become resistant to castrate levels of testosterone. We continue to learn that maximum suppression of androgen production or signaling may improve response even in castrate-resistant populations. Patients with castrate-resistant prostate cancer may have an overall survival of 12-25 months based on recent trial data (2-5). Currently, patients receive hormonal manipulation early on and are then offered chemotherapy as their disease progresses. In the last few years, we have seen the approval of several new agents for use in the post-chemotherapy setting. The present challenge is to evaluate how these drugs may be used in combination.

1.2 Cabazitaxel

Cabazitaxel is a novel semi-synthetic taxane which binds tubulin, inhibiting microtubule formation and thus cell division(6). Additionally, taxanes may also influence the androgen receptor by inhibiting nuclear translocation and signaling(7, 8). Cabazitaxel is currently FDA approved for the treatment of metastatic castrate-resistant prostatic adenocarcinoma that is refractory to docetaxel chemotherapy(9). Taxanes, such as docetaxel, are susceptible to the p-glycoprotein (p-gp) transporter that decreases the efficacy of the drug. However, cabazitaxel is less influenced by p-gp and able to overcome taxane resistance as evidenced in a phase III trial of patients that had progressed on previous docetaxel therapy. The TROPIC trial, which led to FDA approval, patients received cabazitaxel 25mg/m^2 and prednisone or mitoxantrone 12mg/m^2 and prednisone. The study showed a 2.6-month survival advantage for patients treated with cabazitaxel. The hazard ratio (HR) for death was 0.70 (95% CI, 0.59-0.83; $p<0.0001$) and other endpoints of progression free survival (PFS) and PSA response (39% v 17.8%) were also significantly improved in those receiving cabazitaxel. Additionally, a tumor response rate based on RECIST was reported at 14.4% in the cabazitaxel group as compared to 4.4% for those treated with mitoxantrone (9). The approved dose is 25mg/m2 intravenously every 21 days.

The most commonly reported toxicities associated with the clinical use of cabazitaxel include anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, asthenia, anorexia, peripheral neuropathy, hematuria, and back pain as reported in the full prescribing information(10). The above toxicities are the most common of all grades, while the most common grade 3/ 4 toxicities mainly included the hematologic effects of neutropenia, leukopenia, anemia, and febrile neutropenia. Additional grade 3/ 4 toxicities were fatigue and asthenia. The most common adverse reaction leading to drug discontinuation was neutropenia, with 5 patients experiencing related fatal infectious events. In fact, the FDA has issued a warning for febrile neutropenia and recommended that patients at high risk be prophylactically treated with colony stimulating factors.

1.2.1 Pegfilgrastim and filgrastim

Pegfilgrastim and filgrastim are synthetic forms of granulocyte colony stimulating factor administered in order to decrease the incidence of infection in patients receiving myelosuppressive anti-cancer therapy that carry a significant risk of febrile neutropenia. Pegfilgrastim is a subcutaneous injection commonly given once per cycle, 24-72 hours after chemotherapy infusion. Filgrastim is given daily for 5 days each cycle. Bone pain and pain in extremity occurred at a higher incidence in pegfilgrastim- and filgrastim-treated patients as compared with placebo-treated patients. Uncommon risks of pegfilgrastim and filgrastim use include splenic rupture, acute respiratory distress syndrome, allergic reactions, or sickle cell crisis.

1.3 Abiraterone acetate

Abiraterone acetate is a selective irreversible oral inhibitor of CYP17 that has shown a survival benefit in patients with metastatic castrate-resistant prostate cancer after progression on docetaxel(11). Abiraterone acetate is a pro drug that converted to abiraterone in vivo. Abiraterone is an inhibitor of 17 alpha-hydroxylase/C17, 20-lyase (CYP17), which is expressed in testicular, adrenal, and prostatic tumor tissues. The enzyme is required for androgen synthesis by catalyzing the formation of dehydroepiandrosterone (DHEA) and androstenedione, which are precursors of testosterone. By inhibiting the function of the CYP17 enzyme, steroid production downstream is inhibited, and a patient's testosterone level will drop considerably, with approximately ten-fold higher potency for CYP 17 than ketoconazole(12). Ryan *et al* included 19 patients previously treated with ketoconazole in the phase I trial, and 47% of them responded, supporting the strength of the therapy and the remaining sensitivity seen in these androgen-dependent pathways(13). The phase III COU-AA-301 trial looked at 1195 patients with docetaxel based chemotherapy-refractory metastatic CRPC and showed a median overall survival in the abiraterone acetate plus prednisone arm of 14.8 months compared to 10.9 months in the placebo with prednisone arm (HR 0.646; $p<0.0001$) (14). There was a significantly improved PSA response rate of 38% vs. 10% and a delayed PFS of 5.6 vs. 3.6 months. The response rate based on RECIST was 14% in comparison to 3% ($p<0.001$). The COU-AA-302 trial evaluated the use of abiraterone acetate prior to chemotherapy (15). This trial compared the clinical benefit of abiraterone acetate and prednisone to a placebo and prednisone in mCRPC patients without prior chemotherapy. Interim analysis over a median follow up time of 27.1 months has shown a statistically significant benefit in progression free survival (16.5 vs. 8.2 months, $p <0.0001$) and in overall survival (35.3 vs. 30.1 months, $p = 0.0151$) (16). Based on the results of these trials, abiraterone acetate (Zytiga®) is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. Adverse events of special interest throughout all phase of clinical trials were mineralocorticoid excess (edema, hypokalemia and hypertension), cardiac adverse reactions and liver toxicities. These symptoms were minimized, though not completely eradicated, with 5mg of prednisone twice daily. The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia (17).

1.3.1 Prednisone

Prednisone is a synthetic corticosteroid administered orally as replacement therapy in adrenocortical deficiency states. It is used in combination with abiraterone acetate in order to decrease the symptoms of mineralocorticoid excess. Prednisone is also regularly administered with cabazitaxel at a dose of 10mg daily. Common side effects of prednisone use include fluid retention, cataracts, increased risk of gastritis, Cushing syndrome, insomnia, and increased appetite. Additionally, steroid use will alter glucose metabolism. The approved dose of prednisone in combination with abiraterone acetate is 5mg orally twice daily and has been studied in the phase II and III trials.

1.4 Rationale for Combination of Abiraterone Acetate and Cabazitaxel

The combination of abiraterone acetate and cabazitaxel offers treatment of castrate resistant prostate cancer utilizing both hormone directed therapy and a cytotoxic approach. Traditionally, agents that block production of androgens from the testes have manipulated the androgen axis. Abiraterone

acetate offers blockade of androgen production of all sources of testosterone (testes, adrenals, tumor), thus accentuating the anti-proliferative effect on tumor cells. Both clinical and preclinical data support the importance of maximizing the decrease in androgen availability to inhibit disease progression(18). The combination of LHRH agonists and abiraterone acetate will decrease testosterone production from multiple sources. In practice, androgen blockade is commonly continued even beyond disease progression and once a patient's disease becomes castrate resistant, additional agents are added to the blockade. Abiraterone acetate has already shown promising efficacy in the pre-chemotherapy setting(15). Additionally, chemotherapy is often used to treat castrate resistant prostate cancer based on its different mechanism of action. The effectiveness of cabazitaxel in the castrate resistant setting has been proven, and there clearly exists rationale to continue maximal androgen blockade, thus the combination of abiraterone acetate and cabazitaxel is very clinically relevant. Using the combination of cabazitaxel and abiraterone acetate is rational in that each individual agent has shown a survival benefit through differing mechanisms, and understanding whether they will result in additive or synergistic efficacy is an important clinical question.

1.4.1 Drug Metabolism and Pharmacokinetics

Abiraterone acetate

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 1,000 mg dose of abiraterone acetate. At the dose of 1,000 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 1,000 mg. However, the exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC).

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone Cmax and AUC0-∞ 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 ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water.

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. 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.

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) (17).

Cabazitaxel

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. 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.

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 CYP3A4/5) is low. In addition, cabazitaxel did not induce CYP isozymes (-1A, -2C and -3A) in vitro. A drug interaction study in 11 patients with advanced cancers has shown that cabazitaxel (25 mg/m2 administered as a single 1-hour infusion) did not modify the plasma levels of midazolam, a probe substrate of CYP3A. Therefore, cabazitaxel is not an inhibitor of CYP3A in vivo.

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 α-, β-, and γ- half-lives of 4 minutes, 2 hours, and 95 hours, respectively (20).

1.4.2 Overlapping Toxicities

Phase III data on toxicities associated with each of these individual agents have been reported. Cabazitaxel associated AEs include significant hematologic toxicities as well as fatigue, neuropathy, nausea/vomiting and diarrhea. These toxicities are generally manageable with supportive care, although some treatment related deaths were associated with febrile neutropenia while on treatment with cabazitaxel. Therefore, colony stimulating factor use is also permissible. The reported AEs of abiraterone acetate involve the adreno-corticosteroid axis, consequently, patients experienced hypertension, fluid retention and hypokalemia. Liver function test abnormalities were also observed

Potential overlapping toxicities are expected to be limited to GI toxicities or abnormal liver function tests. A review of full safety information will be conducted throughout this trial.

The phase 2 data from this trial was presented at ASCO GU Symposium 2015. Twenty-seven patients were treated in the phase 2 part of the study. Main treatment-emergent adverse events (AE) Grade≥3 were neutropenia (15 pts; 55%; 1 pt [3.7%] had febrile neutropenia), fatigue (4 pts; 15%) and sepsis (3 pts; 11%). A 1-sided exact test was planned to test a null hypothesis of PSA-RR 25%, with a type 1 error of 0.05. With a sample size of 26, this test would have a power of 83% under the alternative hypothesis of PSA-RR 50%. Of 26 patients evaluable for the primary endpoint, 12 achieved a PSA response (PSA-RR 46.2%; 95% CI 26.6–66.4%) and therefore the null hypothesis was rejected (22).

1.4.3 Drug-Drug Interaction Risk Assessment

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

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA. Cabazitaxel has a narrow therapeutic index and was suggested by the FDA as an example for a possible drug-drug interaction with abiraterone acetate at the level of CYP2C8; therefore further testing of this combination is warranted.

Moreover, cabazitaxel is primarily metabolized through CYP3A. Co-administration with strong CYP3A inhibitors should be avoided and caution should be exercised with concomitant use of moderate CYP3A inhibitors. Abiraterone acetate inhibits CYP17A1 to block androgen production, however all CYP450 enzymes contain similar cofactors and thus abiraterone acetate has been found to inhibit CYP3A4/5. In preclinical studies, abiraterone acetate has been found to inhibit CYP3A4 at an IC_{50} ranging from 2.7 to 11μM(19). Therefore, the combination of these agents may alter plasma levels of cabazitaxel. While significant overlapping toxicity is not anticipated between these two agents, the known toxicities of cabazitaxel may be potentiated by this altered metabolism, including hematologic toxicities. Therefore it is imperative that we have a better understanding of the toxicities of the combination of these two agents. Additional details on drug-drug interactions and concomitant therapies will be addressed in section 7.3.3.

1.5 Rationale for Change in Current Study Design

We originally conceived and designed this trial as a phase I/II clinical trial to explore the maximum tolerated dose, safety and efficacy of the combination of abiraterone acetate and cabazitaxel. Massard and colleagues reported the MTD results of the combination with abiraterone acetate and cabazitaxel from their Phase I trial recently. The reported MTD doses were the currently approved doses of each drug individually, cabazitaxel 25 mg/m2 and abiraterone acetate 1000 mg/day(21). Daily abiraterone

acetate did not affect the clearance of cabazitaxel. Cabazitaxel did not affect the exposure of abiraterone acetate. In the phase I portion of the trial by Massard and colleagues, ten patients (median age 63) were treated in two cohorts with a median of 4 cycles. Grade 3 or 4 adverse effect of neutropenia was seen in 1 of 3 patients in cohort 1 and 1 of 7 patients in cohort 2. The phase II single arm study of this combination is ongoing (NCT01511536).

Given this new data and that the MTD of this combination was already established by the Massard study, we opted to change the orginal design of this trial in order not to duplicate the phase I that has already been established, and focus on evalutatation of the efficacy of the combination in a more clinically relevant manner. Therefore, this study is amended to 1) remove the phase I portion of the study; 2) change the phase II portion of the study to a randomized study comparing cabazitaxel alone to cabazitaxel in combination with abiraterone acetate at the MTD. This revised design would be informative in that Arm A would inform the response to cabazitaxel monotherapy after prior abiraterone acetate treatment (currently not known since the TROPIC study was done in era when abiraterone acetate was not approved); and Arm B would evaluate whether the combination of cabazitaxel and abiraterone acetate can improve upon chemotherapy alone.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the anti-cancer efficacy of abiraterone acetate and cabazitaxel, compared with cabazitaxel alone, in patients with CRPC, as determined by progression-free survival at 3 months.

2.2 Secondary Objectives

- To assess the anti-cancer activity of cabazitaxel vs. cabazitaxel with abiraterone acetate in patients with CRPC, after prior treatment with docetaxel and abiraterone acetate. Efficacy will be determined by PSA response, maximum PSA decline at anytime during study treatment, time to PSA and radiographic progression, radiographic objective response, median progression-free survival, and overall survival.

- To assess ongoing safety and tolerability of the combination of abiraterone acetate and cabazitaxel.

3. STUDY ENDPOINTS

3.1 Primary Endpoint

Progression-free survival at 3 months in patients treated with cabazitaxel alone vs the combination of cabazitaxel with abiraterone acetate. PFS is measured from the time of randomization until radiographic progression, clinical progression, or death due to any cause.

3.2 Secondary Endpoints

- Median progression-free survival. The duration of PFS is measured from the time of randomization until radiographic progression, clinical progression, or death due to any cause.
- Overall survival. Two year overall survival as defined as death due to any cause beginning with the time of randomization and continuing 2 years later based on assessment by telephone, email, or mail every 3 months.
- PSA response rate, defined as the proportion of patients achieving at least a 50% decline in PSA. Baseline PSA from screening or C1D1 will be used.

- Maximal PSA decline. Baseline PSA from screening or C1D1 will be used. PSA response will also be reported as the maximum PSA decline from baseline occurring at any time point on trial.
- Radiographic response rate. Radiographic response from the time of randomization until radiographic progression as defined per RECIST 1.1 and protocol specific bone scan evaluation.
- Time to PSA progression, as defined in endpoint analysis as an increase in >25% from nadir occurring at least 12 weeks after start of therapy.
- Time to radiographic progression as measured from the time of randomization until protocol specific progression occurs based on CT and bone scans obtained every 12 weeks.
- Safety and tolerability as assessed by regular recording of toxicities via physical exam and laboratory analysis using the CTCAE v4.1 guidelines.

4. STUDY DESIGN

4.1 Overview of Study Design

This study is an open-label, randomized phase II study of abiraterone acetate in combination with cabazitaxel, compared with cabazitaxel alone, in patients with metastatic castrate-resistant prostate cancer who have previously been treated with docetaxel and abiraterone acetate (separately). Thirty-five patients will be enrolled in each arm of the study.

Treatment will be administered over a 21-day cycle. In both Arm A and Arm B, the cabazitaxel infusion will be administered intravenously on day 1 of each 21-day cycle. In Arm B, abiraterone acetate will be taken orally daily on each day of the 21-day cycle. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.1.(27)

AEs will be assessed; and laboratory values, vital signs, and physical exam will be obtained in order to evaluate the safety and tolerability of cabazitaxel +/- abiraterone acetate. Patients will be evaluated with PSA every 3 weeks and radiographic imaging every 12 weeks. Patients with at least stable disease will continue on study treatment until radiographic disease progression, unacceptable toxicity, or withdrawal of consent.

4.2 Duration of Study

Patients will continue therapy until radiographic disease progression, development of unacceptable toxicities, non-compliance, intercurrent illness that prevents treatment continuation, withdrawal of consent, or change in subject condition that render the subject unacceptable for further treatment. If a patient develops unacceptable toxicity related to one drug, but the patient has at least stable disease and ongoing clinical benefit, then the patient may be allowed to continue dosing with a single agent after discussion with the PI. The End of Study (EOS) visit will occur within 30 days after the last dose of study drug, or prior to the start of subsequent anti-cancer therapy. It is anticipated that enrollment for study will be 24-35 months and study duration will be approximately 48 months..

4.3 Overview of Drug Administration

Table 3: Regimen Description

REGIMEN DESCRIPTION					
	Premedications;				***Cycle***

Agent	*Precautions*	*Dose*	*Route*	*Schedule*	*Length*
Cabazitaxel (Arm A and B)	*Premedicate with an antihistamine, steroid (8mg dexamethasone or equivalent steroid), and H2 antagonist. Administered at least 30 minutes prior to each dose of cabazitaxel.*	*25mg/m2 in 500 cc NS or D5W*	*IV over 1 hours*	*Day 1*	*21 days (3 weeks)*
Abiraterone acetate (Arm B)	*To be taken on an empty stomach**	*1000mg*	*Orally once daily*	*Day 1-21*	
Pegfilgrastim≠ (Arm A and B)		*6mg*	*subcutaneous*	*Day 2*	
Prednisone (Arm A and B)	*To be taken with food*	*5mg*	*Orally twice daily*	*Day 1-21*	
** To be taken on an empty stomach, at least two hours before the dose of abiraterone acetate and for at least one hour after the dose is taken* *≠ If pegfilgrastim is not covered by patient's insurance, or not tolerated, then substitution with filgrastim per institutional guidelines will be allowed.*					

4.4 Criteria for Dose Administration

4.4.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Cabazitaxel and abiraterone acetate will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

Cabazitaxel will be infused only after evaluation of blood chemistry and hematology results that must have been drawn within 24 hours prior to infusion.

Abiraterone acetate will be administered on an empty stomach. Patients should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose. Each dose of abiraterone acetate will be taken orally with at least 8 ounces of water.

Patients should be instructed to take their study medication at approximately the same time each day. In the event that a patient fails to take their abiraterone acetate doses within the time frame specified, or has an episode of emesis after study drug administration, the dose should be skipped and considered a missed dose. Patients should record any missed doses in their dosing diary and resume dosing at the next scheduled time with the prescribed dosage.

4.4.2 Clinical Benefit

Continuation on the trial is dependent on toxicities, as well as evidence of clinical benefit. Patients must not have evidence of radiographic disease progression per RECIST 1.1 and modified Prostate Cancer Working Group 2 (PCWG2) bone scan evaluation criteria. Efficacy assessments will be performed via imaging studies every 12 weeks. Patients with progressive disease per RECIST 1.1 in combination with stipulations described in section 7.1 will be ineligible to receive further study treatment.

4.5 Dose Modification Guidelines

Patients will be evaluated at the start of each cycle. Patients may be evaluated more frequently at the discretion of the treating provider. Toxicities are to be assessed according to the NCI CTCAE, version 4.1. Each AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction of one agent and not the other is appropriate if toxicity is attributable to just one of the agents. Further clarification can be obtained in consultation with the principal investigator. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines. The same dose modification guidelines will apply to maintenance cycles unless otherwise noted. Guidelines for dose adjustments for hematologic and non-hematologic toxicity are presented in Table 4.

4.5.1 Criteria for Toxicity Recovery Before Beginning the Next Cycle of Treatment

If a patient fails to meet the criteria below for beginning the next cycle of treatment, initiation of the next cycle should be delayed. At $\leq$ 7 day's time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. Should the start of the next cycle need to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, dose reduction should occur according to Table 4.

In Arm B, if the AE is thought to be secondary to one drug alone, the non-offending agent may be restarted at the resolution of its respective toxicities. The offending agent may then be resumed according to the appropriate dosage schedule at recovery of symptoms. Criteria for Start of New Cycle in the Hematologic and Non-hematologic Recovery

- ANC must be $\geq 1{,}500/mm^3$.
- Platelet count must be $\geq 100{,}000/mm^3$.
- All other non-hematologic toxicity (except for alopecia, fatigue) must have resolved to $\leq$ Grade 1, or to the patient's baseline condition.

4.5.2 Criteria for Dose Modification (Delays, Reductions, and Discontinuations)

Toxicities should be attributed to a specific study drug if possible so that dose modifications can be made rationally. If multiple toxicities are noted, the dose adjustments and/or delays should be made once per cycle according to the most severe toxicity guidelines.

4.5.3 Guidelines regarding monitoring of patients while on abiraterone acetate

The protocol design has incorporated the required monitoring parameters when treating patients on abiraterone acetate. Please refer to the following guidelines for monitoring patients on abiraterone acetate:

Hypertension

- Control hypertension before and during treatment with Abiraterone Acetate. Monitor blood pressure at least monthly.

Hypokalemia

- Correct hypokalemia before and during treatment with Abiraterone Acetate. Monitor serum potassium at least monthly.

Fluid Retention

- Monitor for symptoms of fluid retention at least monthly.

Adrenocortical Insufficiency

- Monitor for symptoms and signs of adrenocortical insufficiency.

- Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with Abiraterone Acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity

- Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with Abiraterone Acetate, every two weeks for the first three months of treatment and monthly thereafter.
- Promptly measure serum total bilirubin, AST, and ALT, if clinical symptoms or signs suggestive of hepatotoxicity develop.
- Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring.
- For subjects with baseline hepatic impairment or those that develop hepatotoxicity, please refer to Mandatory Dose Modification Guidelines.

4.5.4 Dose Adjustments for Hematologic and Non-Hematologic Toxicity:

A decision regarding which study drug requires dose reduction will be dependent upon the toxicity, its onset, and time course. Alternative dose modifications may be recommended after discussion with the investigator in order to maximize exposure of study treatment while protecting patient safety. Guidelines for dose adjustments for hematologic and non-hematologic toxicity are presented in Table 4.

Table 4: Dose Adjustment for Hematologic and Non-hematologic toxicity

Adverse Event NCI CTC Grade	**Immediate Action**	**Dose Adjustments**
THROMBOCYTOPENIA – Platelet count decreased		
Grade 3 with clinically significant bleeding or Grade 4 < 25,000/mm^3	• Hold treatment with cabazitaxel and continue abiraterone acetate	*1st occurrence*: Decrease cabazitaxel to 20 mg/m2 *2nd occurrence*: decrease

	Check CBC at least weekly	cabazitaxel to 15 mg/m2. *3rd occurrence*: Stop cabazitaxel. Withdraw from study if Arm A. After discussion with PI, Arm B patients may continue abiraterone acetate alone if no radiographic progression and clinically benefitting.
NEUTROPENIA - Neutrophil count (ANC) decreased		
Grade 3 or 4 or > Grade 3 with fever (temperature > 38.3°C)	• Hold cabazitaxel and continue abiraterone acetate • Follow CBC with differential at least weekly • Do not dose next cycle of cabazitaxel until neutropenia is resolved to grade ≤ 1	• *1st occurrence*: Decrease cabazitaxel to 20 mg/m2 • *2nd occurrence*: decrease cabazitaxel to 15 mg/m2. • *3rd occurrence*: Stop cabazitaxel. Withdraw from study if Arm A. After discussion with PI, Arm B patients may continue abiraterone acetate alone if no radiographic progression and clinically benefitting.
ANEMIA – Hemoglobin decreased		
Grade 3 or 4	• Hold cabazitaxel and transfuse as appropriate • Wait until recovery to grade ≤ 2 prior to retreatment with cabazitaxel.	• *1st occurrence*: Decrease cabazitaxel to 20 mg/m2 • *2nd occurrence*: decrease cabazitaxel to 15 mg/m2. • *3rd occurrence*: Stop cabazitaxel. Withdraw from study if Arm A. After discussion with PI, Arm B patients may continue abiraterone acetate alone if no radiographic progression and clinically benefitting.

HYPERTENSION – Blood pressure elevated		
Grade 3 and systolic blood pressure >20mm Hg higher than baseline OR diastolic blood pressure >10 mm Hg higher than baseline	• Add additional anti-hypertensives or increase dose of existing anti-hypertensives	• If not controlled to <140/90 mm Hg with maximum medications, hold treatment with abiraterone acetate until controlled and restart at 1 dose level reduction (decrease by 250mg/day)
Grade 4	• Discontinue treatment	• Do not continue treatment with abiraterone acetate
DIARRHEA		
Grade 2	• Begin treatment anti-diarrheal agents per local standard of care	• If Grade 2 diarrhea persists despite maximal supportive therapy, hold both drugs until resolution to grade $\leq$1 and reduce cabazitaxel by 1 dose level.
Grade 3	• Hospitalization may be indicated	• Hold both drugs until symptoms resolve to grade $\leq$1 and restart each at one dosage level reduction.
Grade 4	• Hospitalization likely indicated	• Stop cabazitaxel. Once symptoms resolve to grade $\leq$ 1 restart abiraterone acetate at 1 dose level reduction. At second occurrence, discontinue abiraterone acetate.
NAUSEA AND VOMITING		

Grade 3 (except): • > Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis		• Hold cabazitaxel and abiraterone acetate until resolution to Grade ≤ 1 or baseline.
HEPATOTOXICITY - Transaminase Elevation, Bilirubin Elevation) **Please note full text of dose alterations is following this chart**		
Grade 3	• Hold abiraterone acetate	• If recover to Grade ≤ 2 transaminitis, grade ≤1 hyperbilirubinemia, or baseline, restart at one dose level reduction of abiraterone acetate. For patients who resume treatment, monitor LFTs at least every 2 weeks for 3 months and monthly thereafter. • On second occurrence, if recovery to Grade ≤1, or baseline, restart at one dose level reduction of both medications. • On third occurrence, discontinue abiraterone.
Grade 4	• Hold both drugs	• If recovery to Grade ≤1 or baseline, restart both drugs at one dose level reduction. Patients will then need LFTs checked every 2 weeks for 3 months and monthly thereafter. The safety of abiraterone acetate re-treatment of patients who develop grade 4 toxicity is unknown.
HYPOKALEMIA		
Grade 2	• Begin oral potassium supplementation. Recheck at weekly intervals and adjust potassium dose as necessary	

Grade 3	• Hold abiraterone acetate. • Increase oral repletion. • Recheck at least weekly until replete. • Hospitalization may be indicated. •	• If unable to replete to grade ≤1 within 2 weeks, decrease dose of abiraterone acetate by 1 dose level. • If recurs, or again, unable to replete to grade ≤1 within 2 weeks decrease by an additional dose level. • If unable to fully replete to grade ≤1 after above adjustments, discontinue drug.
Grade 4	• Hold abiraterone acetate. • Hospitalization may be indicated. • Begin IV repletion in a monitored setting. Replete to at least grade ≤2 before resuming abiraterone acetate.	• If unable to replete to grade ≤1 within 2 weeks, decrease dose of abiraterone acetate by 1 dose level. • If recurs, or again, unable to replete to grade ≤1 within 2 weeks decrease by an additional dose level. • If unable to fully replete to grade ≤1 after above adjustments, discontinue drug.
CARDIOTOXICITY		

QTc Increase of 15ms-20ms from baseline	• Repeat EKG in one week	• If not increased, no change
Increase of >20ms from baseline	• Hold drug for 1 week, repeat EKG within 10 days	• If not decreased below 20ms change, patient must withdraw. If decreased, recheck in 1 week to confirm
Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count; G-CSF = granulocyte colony stimulating factor; NCI CTC = National Cancer Institute Common Terminology Criteria.		

Specific Instructions on Hepatotoxicity:

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of Abiraterone Acetate re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Table 5: Treatment of Cabazitaxel associated hypersensitivity reactions: A cabazitaxel associated hypersensitivity reaction will likely occur within minutes of the start of the infusion.

SYMPTOM SEVERITY	INTERVENTION RECOMMENDATION
Mild symptoms: cutaneous flushing, rash, pruritus	• Decrease rate of infusion until recovery • Once resolved, may increase to initial rate
Moderate: generalized flushing, rash, dyspnea, back pain during infusion, systolic hypotension	• Give diphenhydramine 50 mg IV and/or dexamethasone 10mg IV or equivalent. • Resume infusion within 3 hours of recovery of symptoms • Slow all future infusions to 2 hours
Severe: bronchospasm, urticaria, systolic blood pressure <80 mmHg	• Stop the infusion • Give diphenhydramine 50mg IV and/or dexamethasone 10mg IV (or equivalent) and or epinephrine

	• Wait at least 3 hours and for full recovery of symptoms prior to considering rechallenge. • If recurrent severe reaction at rechallenge, withdraw patient from study
Anaphylaxis	• Remove from protocol

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Written informed consent has been obtained.
- Adults over 18 years of age.
- Histologically or cytologically proven adenocarcinoma of the prostate.
- Stage IV disease as evidenced by soft tissue, visceral and/or bony metastasis must be RECIST evaluable on CT scan and/or bone scan
- Progressive disease while receiving hormonal therapy or after surgical castration documented by at least one of the following: (1) Increase in measurable disease per RECIST 1.1, (2) Appearance of new lesions on bone scan consistent with progressive prostate cancer ($\geq$2 new lesions on bone scans if this is the only measure of PD), (3) rising PSA defined as 2 sequential increases above a previous lowest reference value. Each value must be obtained at least 1 week apart.
- PSA at least 2 ng/mL
- Received prior docetaxel chemotherapy
- Received prior abiraterone acetate, but not within the 3 months prior to study drug dosing.
- Testosterone level <50 ng/dL. Patients receiving LHRH agonists or antagonists must be continued to maintain castrate levels of testosterone while on study.
- Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2.
- Adequate hematologic function (platelet $\geq$100, 000/uL; neutrophil count of >1500 cell/mm3; hemoglobin $\geq$9.0 g/dL)
- Adequate renal function (Creatinine < 1.5 X ULN or creatinine clearance $\geq$ 50 mL/min)
- Adequate potassium level > 3.5 mEq/dL
- Adequate hepatic function (bilirubin $\leq$ 1.5 X upper limit of normal (ULN), alanine aminotransferase (ALT) $\leq$ 1.5 X ULN, aspartate aminotransferase (AST) $\leq$1.5 X ULN. Have a serum albumin of $\geq$ 3.0 g/dL
- Controlled blood pressure, defined as blood pressure $\leq$ 140/90 on average (3 separate readings taken at screening visit in a relaxed clinical environment and averaged)
- Must be able to take oral medication without crushing, dissolving or chewing tablets
- Willing to take abiraterone acetate on empty stomach; no food should be consumed at least two hours before and for at least one hour after the dose of abiraterone acetate is taken

- Patients must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
- Written authorization for use and release of health and research study information has been obtained.
- Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection during the study and for 1 week after the last dose of abiraterone acetate.

5.2 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

- Surgery or radiation therapy within 2 weeks. Cytotoxic anti-cancer therapy within 3 weeks. Non-cytotoxic anti-cancer therapy within 2 weeks, or 5 half-lives (whichever is shorter) of Study Day 1.
- Prior radiotherapy to $\geq$ 40% of bone marrow.
- Use of an investigational therapeutic agent within 30 days
- Have a history of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents
- Prior treatment with cabazitaxel
- Known chronic infection with human immunodeficiency virus (HIV)
- Known active, or symptomatic, brain metastasis
- Blood pressure >140/90 mm/Hg on average (3 separate readings taken at screening visit in a relaxed clinical environment and averaged)
- Baseline peripheral edema $\geq$ grade 3
- Pre-existing diarrhea uncontrolled with supportive care; prior hemorrhagic diarrhea due to ulcerative colitis, inflammatory bowel disease or other cause; active, uncontrolled peptic ulcer disease even in the setting of proton-pump inhibitor or Histamine2-blocker use.
- Pre-existing peripheral neuropathy grade $\geq$ 2
- Documented hypersensitivity (CTCAE grade $\geq$ 2) to any drug containing polysorbate 80
- Have known allergies or hypersensitivity to abiraterone acetate or prednisone or their excipients
- Contraindications to steroid use
- Need for medications that strongly induce or inhibit CYP3A4 or CYP2D6 activity. See section 7.2.3 for details
- Serious infection requiring parenteral antibiotics within 14 days of enrollment
- Poorly controlled diabetes (Hgb A1C >9)
- Active or symptomatic viral hepatitis or chronic liver disease, including Child-Pugh Class B and C liver disease.
- History of pituitary or adrenal dysfunction

- Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class III-IV heart disease or cardiac ejection fraction measurement of <50% at baseline.
- Consumption of food or beverages containing grapefruit juice within 7 days of study drug dosing
- Use of a first-generation anti-androgen such as bicalutamide within 6 weeks of study drug dosing, or flutamide within 4 weeks of study dosing.
- Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements

6. STUDY PROCEDURES AND ASSESSMENTS

The schedule of assessments is summarized in **Table 1.**

6.1 Informed Consent

Enrollment in the study requires that all inclusion and exclusion criteria have been met. A patient may be enrolled into the study when the written informed consent has been obtained and the patient's eligibility per all inclusion and exclusion criteria has been confirmed.

6.2 Study Visits

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, and EOS. Evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of cabazitaxel and abiraterone acetate. Bone scan and CT scan evaluations performed within 6 weeks of Cycle 1 Day 1 are acceptable. Unless otherwise noted, evaluations during the Treatment period must occur before study drug administration. Tests and procedures should be performed on schedule for all visits. Occasional changes are allowable with permission for holidays, vacations, and other administrative reasons.

All EOS evaluations should occur within 30 days after the last dose of study drug, or prior to the start of subsequent anti-cancer therapy, whichever is earlier.

6.2.1 Physical Examination

A complete physical examination will be performed before dosing on Day 1 of each cycle and at the end of treatment. Vital signs (temperature, blood pressure, pulse rate, respiratory rate, and weight) will be performed at each visit. ECOG performance status will be evaluated at day 1 of each cycle and end of study. Clinically significant AEs will be captured as well.

6.2.2 Schedule of Events Arm A and Arm B

Screening/Baseline (Days -28 to 0)

- Informed consent and HIPAA
- Study eligibility per inclusion/exclusion criteria
- Medical history/baseline conditions
- Physical examination

- Vital signs, including height and weight
- ECOG performance status
- ECG
- Blood samples for hematology, comprehensive metabolic panel
- Serum PSA
- Serum Testosterone
- Blood sample for HA1C
- CT scan and assessment of tumor burden
- Bone scan
- Collection of concomitant medications
- Collection of adverse events

Day 1 of each cycle

- Physical examination and history
- Vital signs
- ECOG performance status
- ECG for cycle 2
- Blood samples for hematology, comprehensive metabolic panel
- Serum PSA
- CT and bone scan to be performed every 12 weeks
- Collection of concomitant medications
- Collection of adverse events

Cycle 1-4 Day 15 visits

Liver function test lab visit (Arm B only)

7. STUDY ASSESSMENTS

7.1 Efficacy Evaluations

The primary endpoint is progression-free survival at 3 months in patients treated with cabazitaxel alone vs the combination of cabazitaxel with abiraterone acetate. PFS is measured from the time of randomization until radiographic progression per RECIST 1.1, clinical progression, or death due to any cause.

The secondary endpoints include:

- Median progression-free survival. The duration of PFS is measured from the time of randomization until radiographic progression, clinical progression, or death due to any cause.
- Overall survival. Two year overall survival as defined as death due to any cause beginning with the time of randomization and continuing 2 years later based on assessment by telephone, email, or mail every 3 months.
- PSA response rate, defined as the proportion of patients achieving at least a 50% decline in PSA. Baseline PSA from screening or C1D1 will be used.
- Maximal PSA decline. Baseline PSA from screening or C1D1 will be used. PSA response will also be reported as the maximum PSA decline from baseline occurring at any time point on trial.
- Radiographic response rate. Radiographic response from the time of randomization until radiographic progression as defined per RECIST 1.1 and protocol specific bone scan evaluation.

- Time to PSA progression, as defined in endpoint analysis as an increase in >25% from nadir occurring at least 12 weeks after start of therapy.
- Time to radiographic progression as measured from the time of randomization until protocol specific progression occurs based on CT and bone scans obtained every 12 weeks.
- Safety and tolerability as assessed by regular recording of toxicities via physical exam and laboratory analysis using the CTCAE v4.1 guidelines.

Patients will be removed from study if they have evidence of radiographic disease progression as defined below. Radiographic analysis via CT scan and bone scan will occur at baseline and every 12 weeks after the initiation of study treatment. CT scans should be performed with cuts of 10mm or less in slice thickness contiguously. For the purposes of this study, investigators should utilize the protocol-specified tumor assessment criteria, defined as assessment of evaluable soft tissue disease sites according to RECIST (version 1.1), and/or assessment of bone disease. Bone disease progression will be defined as the development of one new lesion at the first imaging analysis that is confirmed with an additional lesion 6 weeks later. Subsequent to cycle 4, bone scan progression will constitute the appearance of two or more new bone lesions from baseline. Increase in intensity of known bone lesions will not constitute progression. The date of progression will be recorded as the date the first scan shows change. Soft tissue response will be evaluated as follows:

Target lesions	**Nontarget lesions**	**New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

PSA response will be evaluated for endpoint analysis, but will not be a contributor to the ongoing measurement of response or progression to determine treatment continuation throughout the study. Thus, PSA progression alone, in the absence of radiographic progression, does not necessitate removal from study treatment, and treatment in the setting of PSA rise is allowable at the discretion of the investigator. Progression-free survival is measured from the date of randomization to the date of radiographic progression, clinical progression, or until death from any cause.

7.2 Safety Evaluations

The investigator will oversee the care and safety of all subjects enrolled in the trial. Study visits occur every 21 days, more frequently at investigator discretion, and will include monitoring and recording all adverse events and serious adverse events; regular monitoring of hematology, blood chemistry,

hepatic function; ECG assessment for cycles 1-3; regular measurement of vital signs, physical examination including weight and performance status. Safety and tolerability will be assessed using the CTCAE v4.1 guidelines.

7.2.1 Adverse Events

Monitoring of AEs will be conducted throughout the study. AEs will be reported from the date written informed consent is obtained and through 30 days post-last dose of study drug. Serious pretreatment events will be reported to the Janssen Scientific Affairs designee from the time of the signing of the Informed Consent Form (ICF) up to first dose of study drug. SAEs will be reported to the Janssen Scientific Affairs designee from the date written informed consent is obtained through 30 days after administration of the last dose of study drug. All SAEs will be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

7.2.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Blood chemistry and hematology tests performed within 5 days of Cycle 1 Day 1 do not need to be repeated before dose 1 administration. For subsequent cycles, chemistry and hematology results must be drawn and reviewed within 24 hours prior to all cabazitaxel infusions.

7.2.3 Concomitant Medication and Therapies

Abiraterone acetate is a strong inhibitor of CYP2D6, CYP1A2, and CYP2C8. It is a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5 and thus may influence the metabolism of other CYP2D6 substrates. Additionally, abiraterone acetate is a substrate of CYP2A4 and thus medications which inhibit or induce this enzyme may influence the metabolism of abiraterone acetate.

Effects of Abiraterone on Drug Metabolizing Enzymes

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

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA.

Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, Abiraterone Acetate 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*.

The following medications and procedures are PROHIBITED during the study:

- Any anti-cancer therapies other than abiraterone acetate and cabazitaxel
- Any investigational therapies other than abiraterone acetate and cabazitaxel
- Strong inducers/inhibitors of CYP3A4 or CYP2D6: dextromethorphan, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycine, ritonavir, indinavir, neflinavir, voriconazole, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital.
- In addition to the above medications, grapefruit juice or grapefruit juice products should be avoided.

The following medications and procedures are ALLOWED during the study:

- LHRH agonists or antagonists are acceptable while on trial
- Bisphosphonates or denosumab are allowed
- 5- alpha- reductase inhibitors are allowable for patients treated > 2 months prior to study enrollment, with continued PSA rise through this treatment
- Use of colony-stimulating factors are allowed
- Palliative radiotherapy to a bone lesion that was present at baseline.

7.2.4 Completion of Study

Patients will be considered to have completed the study if they (1) have received at least 1 cycle of treatment, AND (2) experienced progressive disease, OR (3) experienced unacceptable toxicity. In the absence of progressive disease radiographically or unacceptable toxicity, and in the setting of continued clinical benefit, patients may be permitted to remain on therapy upon discussion with the PI.

7.2.5 Withdrawal of Patients from Study

Patients will be informed that they have the right to withdraw from study treatment at any time for any reason, without prejudice to their medical care. A patient may be withdrawn from study treatment for any of the following reasons:

- Adverse Event
- Protocol Violation
- Radiographic Progressive Disease as defined in section 7.1
- Symptomatic Deterioration
- Study Terminated by the University of Colorado Cancer Center
- Withdrawal by Subject
- Lost to Follow-up
- Other

At the time of study drug discontinuation, all study procedures outlined for the EOS visit should be completed within 30 days after the last dose of study drug. The primary reason for a patient's withdrawal from the study is to be recorded.

The consequence of withdrawal of consent by a patient will be that no new information will be collected from that patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

7.3 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing, including the following: applicable lot numbers and total drug administered in milligrams (mg). Any discrepancy regarding the dose administered and the reason for the discrepancy will be noted.

Patients will receive a sufficient quantity of abiraterone acetate for each treatment cycle. The study center staff will check the patient's diary versus the patient's supply of remaining abiraterone acetate tablets at each study visit to ensure proper compliance with dosing. At the discretion of the treating physician, patients who are not compliant with the dosing schedule (e.g. miss more than 50% of the study medication dosing) may be withdrawn from the study.

8. INVESTIGATIONAL AGENTS

8.1 Precautions and Restrictions

In general, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored, as potential drug-drug interactions between the combination of cabazitaxel, abiraterone acetate, and other drugs have not been studied in humans. Patients should be instructed to consult with the investigator before taking any new medications, including over-the-counter and herbal products. Patients should be instructed to limit the use of alcohol while enrolled in this study.

8.2 Description of Investigational Agents

8.2.1 Abiraterone acetate

The drug product is labeled abiraterone acetate. Each tablet contains 250 mg of active abiraterone acetate. Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide. Please refer to the package insert for further details.

8.2.2 Cabazitaxel

Cabazitaxel injection 60 mg/1.5 mL is a sterile, non-pyrogenic, clear yellow to brownish-yellow viscous solution and is available in single-use vials containing 60 mg cabazitaxel (anhydrous and solvent free) and 1.56 g polysorbate 80. Cabazitaxel is to be mixed with a diluent that is a clear, colorless, sterile, and non-pyrogenic solution containing 13% ethanol in water for injection, approximately 5.7 mL. Cabazitaxel requires two dilutions prior to intravenous infusion and should only be diluted with the supplied diluent with the second dilution in 0.9% sodium chloride solution or 5% dextrose solution. Both items are in a blister pack in one carton. Please refer to the package insert for further details.

8.2.3 Prednisone

Please refer to post-marketing product information on prednisone.

8.2.4 Pegfilgrastim

Please refer to post-marketing product information on pegfilgrastim.

8.2.5 Filgrastim

Please refer to post-marketing product information on filgrastim.

8.3 Preparation, Reconstitution, and Dispensation

The University of Colorado Cancer Center clinical trials team and the PI will assign each patient who signs a consent form a patient number. Patients will be randomized by the statistician involved with this study to either Arm A or Arm B. Patients in Arm B will be dispensed bottles of study drug containing an appropriate number of tablets.Preparation and reconstitution of cabazitaxel will be performed according to section 8.2.2 above.

All unused study drug and the amount of study drug returned will be recorded on the drug accountability form. Patients will be instructed to store the abiraterone acetate tablets only in the bottles dispensed. Patients will be given a diary with instructions to record each study drug dose whether taken or missed.

8.4 Storage, Handling, Accountability

8.4.1 Cabazitaxel

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). Do not refrigerate. For additional details please consult the full prescribing information.

8.4.2 Abiraterone acetate

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). For additional details please consult the full prescribing information.

8.4.3 Handling and Accountability

This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

All clinical drug supplies must be kept in an appropriate, limited-access, secure place until used or destroyed. The investigator must maintain 100% accountability for all study medication received and dispensed. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the PI must be notified immediately.

The investigator must maintain a current inventory of all study medication delivered to the site, inventory at the site, and records of patient use. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of study medication, expiration date, date and amount dispensed, and the date and amount returned to the site by the patient, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Before site closure, or at appropriate intervals, a representative from the PI or its designee will perform clinical study material accountability and reconciliation before clinical study materials are destroyed.

The investigator will retain the original documentation regarding clinical study material accountability and destruction.

The investigational pharmacy will monitor any expiration date and subsequently segregate and destroy expired clinical study drug.

9. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.2 Treatment Group Assignments

Stratified randomization (bone metastasis only vs bone and soft tissue metastasis, presence/absence of visceral disease) will be performed by the statistician for this trial.

10. STATISTICAL AND QUANTITATIVE ANALYSES

10.1 Statistical Methods

A University of Colorado Anschutz Campus statistician will perform the data analysis for this trial. Janssen Scientific Affairs will not have a decisional role in the analysis or writing of any resultant manuscripts.

This is a randomized 2 arm study. Arm A will be the standard of care arm of cabazitaxel alone. Arm B will be the investigational arm combining cabazitaxel and abiraterone. All patients will have received prior docetaxel and prior abiraterone acetate. The primary endpoint will be proportion that is progression free at 3 months. From the registration trial of cabazitaxel vs. mitoxantrone (TROPIC), the median PFS was 2.8 months, and PFS at 3 month for the cabazitaxel arm was 47.6%.

10.1.1 Sample Size

The goal of this trial is to estimate the proportion that is progression free at 3 months for each of the two arms with a pre-specified precision (80% confidence limits are within 12% of the rate). Given that all the subjects in this trial will have had prior exposure to abiraterone acetate, whereas patients in the TROPIC trial were not pretreated with abiraterone acetate, we would assume that the median PFS is at least 2.8 months in either arm. The table below summarizes the 80% confidence limits for the proportion of proportion that is progression free at 3 months with several potential median PFS values.

Median PFS (months)	Percentage (%) increase from 2.8 months	Proportion that is progression free at 3 months (%)	80% CI With 35 subjects per arm
2.8	-	0.48	0.37, 0.61
3.1	10	0.51	0.39, 0.63
3.36	20	0.54	0.42, 0.66
3.64	30	0.57	0.45, 0.69
3.92	40	0.59	0.48, 0.71
4.2	50	0.61	0.49, 0.73

10.1.2 Aim Analysis

Primary Aim

The primary endpoint is progression-free survival at 3 months in patients treated with cabazitaxel alone vs the combination of cabazitaxel with abiraterone acetate. PFS is measured from the time of randomization until radiographic progression, clinical progression, or death due to any cause. The probability distributions for PFS will be calculated using the Kaplan-Meier method, all measured from the time of randomization. The 3 month PFS estimates will be obtained from the probability distributions.

Secondary Aims

The secondary endpoints include median progression-free survival, duration of PFS, overall survival, PSA response rate, maximal PSA decline, radiographic response rate, time to PSA progression, time to radiographic progression, and safety and tolerability. See section 7.1 for definitions of each outcome. The probability distributions for the PFS and OS outcomes will be calculated using the Kaplan-Meier method, all measured from the time of randomization. The median point estimates will be obtained from these probability distributions and presented with 95% confidence intervals. PSA and radiographic endpoints will be presented graphically using a waterfall plot or in tabular form. Adverse events data will be analyzed using tables and descriptive statistics.

10.1.3 Accrual

The study center treats approximately 4-5 patients monthly who would be eligible for enrollment in the trial. We estimate that 2-3 patients will enroll a month.

10.2 Safety Population

The safety population is defined as all patients who receive at least 1 dose of either abiraterone acetate OR cabazitaxel. This population will be used for all safety analyses as well as efficacy analyses.

10.3 PSA Response Evaluable Population

The PSA response-evaluable population is defined as all patients who receive at least 1 dose of either study drug, have a baseline PSA measurement, and have 1 post-baseline PSA assessment. This population will be used for analyses of response.

10.4 Tumor-Response Evaluable Population

The response-evaluable population is defined as all patients who receive at least 1 dose of either study drug, have RECIST 1.1 evaluable bone metastasis or RECIST 1.1 evaluable soft tissue metastasis at baseline, and have 1 post-baseline disease assessment. This population will be used for analyses of response.

11. SAFETY ANALYSIS

11.1

The safety population will be used for the analysis of the toxicities and AEs in the study. In addition, to assess the relationship between toxicities and cabazitaxel in combination with abiraterone acetate, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment related AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Drug-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher drug-related AEs
- The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥ 10% of all patients)
- SAEs

A listing of AEs resulting in study discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of cabazitaxel with abiraterone acetate.

12. ADVERSE EVENTS

12.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this

treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Events of Special Interest

Events that Janssen Scientific Affairs are actively monitoring, as a result of a previously identified signal (even if non-serious) and are typically defined in the Protocol.

- Events of special interest include:
- Mineralocorticoid excess (Hypertension, Hypokalemia, Fluid retention)
- Hepatotoxicity
- Cardiac disorders
- Osteoporosis including osteoporosis-related fractures
- Increased exposure with food
- Rhabdomyolysis/myopathy
- Drug-drug interaction (CYP2D6)
- Allergic alveolitis

Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

J&J Medicinal Product

The specific Johnson & Johnson drug under study and any other J&J medicinal product,

Product Quality Complaint (PQC)

Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy, or intended performance of a drug product.

A complaint may allege an injury or malfunction associated with the use of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product.

Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered ''serious'' if, in the view of either the Institution or principle investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
    - *Life-threatening adverse event or life-threatening suspected adverse reaction*.
        - An adverse event or suspected adverse reaction is considered ''life-threatening'' if, in the view of the principle investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.
- Is a suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Special Reporting Situations

When a report contains a Johnson &Johnson medicinal product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of Johnson & Johnson medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal Johnson & Johnson product
- inadvertent or accidental exposure to a medicinal Johnson & Johnson product
- medication error involving a medicinal Johnson & Johnson product (with or without patient exposure to the medicinal Johnson & Johnson product, e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal product.
- Any failure of expected pharmacological action (i.e. lack of effect) of a Johnson & Johnson medicinal product
- Unexpected therapeutic or clinical benefit from use of a Johnson & Johnson medicinal product

12.2 Management of Adverse Events, Serious Adverse Events and Special Reporting Situations

In general, the study clinical staff must immediately report to Janssen Scientific Affairs any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Janssen Scientific Affairs. All other non-serious adverse events must be reported to Janssen Scientific Affairs according to the timetable for reporting as specified either in the protocol or to fulfill regulatory reporting requirements.

For each subject, AEs, SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse event or Special Reporting Situations must be reported if it occurs during a subject's participation in the Study (whether receiving Study Product or not) and within 30 days of receiving the last dose of Study Product.

Any serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- the event resolves or stabilizes;
- the event returns to baseline condition or value (if a baseline value is available);
- the event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

12.3 Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations

Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are a planned surgery or procedure prior to entry into the study or not related to study drug.

If, in the PI's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event whenever possible. However, a complete description of the signs, symptoms and investigations that led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

12.4 Maintenance of Safety Information

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of the Study, the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e/g/ to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Service's request.

12.5 Reporting Timelines

All safety information covered in Exhibit B (SAEs, Adverse Events of Special Interest, Special Reporting Situations, and PQCs) should be reported within **24 hours** of becoming aware of the event(s).

All non-serious AEs should be reported according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

12.6 Transmission Methods:

SAEs should be recorded on the Medwatch form and sent to JANSSEN SCIENTIFIC AFFAIRS, LLC, SAE Secure! email address: IIS-BIO/VIRO-GCO Central Email. RA-OMPUS-COBS_Cen_E@its.jnj.com

The subject line for Initial SAE Reports should be named: Lam MD_Pt <No> Secure! SAE Initial Report

The subject line for Follow Up SAE Reports should be named: Lam MD_Pt <No> Secure! SAE Follow up Report.

12.7 Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Special Reporting Situation, and Product Quality Complaints (PQCs) to Janssen Scientific Affairs.

12.7.1 Serious Adverse Events (SAE), Adverse Events of Special Interest, and Special Reporting Situations

The principle investigator will transmit these reports in a form to be provided (or a form substantially similar to the form provided and approved for use by Janssen Scientific Affairs in writing) in accordance with Section 12.6, in English **within 24 hours** of becoming aware of the event(s) along with their determination of whether the event was caused by a J&J product.

All available clinical information relevant to the evaluation of an SAE, Adverse Events of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE) including paternal exposure are required.

- The Principal Investigator is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the Principal Investigator and that follow-up information is summarized e.g. hospital records, coroner's reports, autopsy results and recorded on the appropriate forms.
- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Study Drug in the course of the Study, by facsimile within 24 hours of such report or correspondence being sent to applicable health authorities.

12.7.2 Product Quality Complaints

Any PQC, with or without an AE, (including reports of suspicion of counterfeiting, diversion, or tampering, and suspected transmission of pathogens) will be transmitted by the Principal Investigator

in the form provided by Janssen Scientific Affairs in accordance with Section 12.6, in English, within **24 hours** of becoming aware of the event(s).

12.7.3 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Principal Investigator, a listing of all SAEs reported to Janssen Scientific Affairs. The PI will review this listing and provide any discrepancies to Janssen Scientific Affairs.
Upon request, the Principal Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

12.8 Reporting of Serious Adverse Events to the FDA

Investigators and other site personnel must inform Janssen Scientific Affairsvia a MedWatch form, of any serious or unexpected adverse events that occur from the time of informed consent from the time of consent through 30 days after administration of the last dose of study drug. A copy of the MedWatch report will be faxed to Janssen Scientific Affairs. Because this study has an FDA IND exemption, all reportable events fall under the voluntary reporting requirements. Janssen Scientific Affairs will decide if it is reportable under the post-marketing regulations. Janssen Scientific Affairs is then required to submit postmarketing expedited safety reports to the FDA.
A cover page should accompany the MedWatch form indicating:

- Investigator's name and address
- The trial name/title and reference number

The site must also indicate the causality of events in relation to all study medications as determined by the principal investigator.

12.9 Dissemination of Safety Information from Janssen Scientific Affairs to Principal Investigator

Janssen Scientific Affairs will provide to the Principal Investigator IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by the Janssen Scientific Affairs for the Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

12.10 Monitoring of Adverse Events and Period of Observation

AEs, both non-serious and serious (which include all deaths), will be monitored throughout the study as follows:

- AEs will be reported from the time of consent through 30 days after administration of the last dose of study drug and recorded.
- Serious pretreatment events will be reported to Janssen from the time of the signing of the ICF up to first dose of study drug.
- SAEs will be reported to Janssen Scientific Affairs from the time of consent through 30 days after administration of the last dose of study drug and recorded. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). If an SAE occurs in the follow-up period and is thought to be possibly related to study drug, it must be reported.

12.11 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the PI, or representative, must be contacted immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

12.12 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Jansen will provide to the University of Colorado and/or Dr. Elaine Lam, a listing of all SAEs reported to the Janssen Scientific Affairs. Janssen Scientific Affairs and/or Dr. Elaine Lam will review this listing and provide any discrepancies to Janssen Scientific Affairs.

Upon request, the University of Colorado and Dr. Elaine Lam shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

13. ADMINISTRATIVE REQUIREMENTS

This is an investigator-initiated trial and thus major trial decisions and document design will occur with the PI and supporting institution, the University of Colorado Cancer Center. Janssen Scientific Affairs is providing study support and thus will have access to trial data and patient safety information.

13.1 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be monitored via an audit trail.

13.2 Study Monitoring

Monitoring and Oversight

The Principal Investigator (PI) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are

reported to the DSMC, IRB and the sponsor per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The PI will provide a DSM report to the CU Cancer Center DSMC on a six-month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six-month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

Janssen Scientific Affairs will not be monitoring this study.

13.3 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well being of the patients. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator, as allowed by local regulations.

13.4 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

13.5 Patient Confidentiality

To maintain patient privacy, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.6 Investigator Compliance

Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Janssen Scientific Affairs, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

13.7 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Janssen Scientific Affairs may request access to all source documents, and any study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

13.8 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Please see section 8.4.3 for details.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

13.9 Closure of the Study

Study participation may be prematurely terminated if, in the opinion of the investigator or Janssen Scientific Affairs, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data

13.10 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 3 years after the last patient is removed from trial or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.

14. USE OF INFORMATION

The information obtained from the clinical study will be used toward the development of cabazitaxel in combination with abiraterone acetate and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required. Additionally, Janssen Scientific Affairs will also have access to complete data obtained during the study as the provider of an investigational agent.

Upon completion of the clinical study and evaluation of results by the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

Printed Name of Investigator

_____ _____

Signature of Investigator Date

15. REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012 Jan-Feb;62(1):10-29.

2. Sonpavde G. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 Aug 25;365(8):766-7; author reply 7-8.

3. Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jr., Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1513-20.

4. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1502-12.

5. Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone FH, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006 Jul 1;24(19):3089-94.

6. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. Nat Rev Cancer. 2004 Apr;4(4):253-65.

7. Gan L, Chen S, Wang Y, Watahiki A, Bohrer L, Sun Z, et al. Inhibition of the androgen receptor as a novel mechanism of taxol chemotherapy in prostate cancer. Cancer Res. 2009 Nov 1;69(21):8386-94.

8. Jiang J, Huang H. Targeting the Androgen Receptor by Taxol in Castration-Resistant Prostate Cancer. Mol Cell Pharmacol. 2010 Jan 1;2(1):1-5.

9. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010 Oct 2;376(9747):1147-54.

10. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201023lbl.pdf SpJFpiAa.

11. Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settatree S, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol. 2008 Oct 1;26(28):4563-71.

12. Haidar S, Ehmer PB, Barassin S, Batzl-Hartmann C, Hartmann RW. Effects of novel 17alpha-hydroxylase/C17, 20-lyase (P450 17, CYP 17) inhibitors on androgen biosynthesis in vitro and in vivo. J Steroid Biochem Mol Biol. 2003 Apr;84(5):555-62.

13. Ryan CJ, Smith MR, Fong L, Rosenberg JE, Kantoff P, Raynaud F, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol. 2010 Mar 20;28(9):1481-8.

14. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005.

15. Ryan CJ, Smith R, de Bono J, Molina A, Logothetis CJ, De Souza P, et al. Interim analysis (IA) results of COU-AA-302, a randomized, phase III study of abiraterone acetate (AA) in chemotherapy-naive patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2012(30):suppl Abstr LBA4518.

16. Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302). Eur Urol. 2014 Mar 6.

17. Zytiga (abiraterone acetate) Prescribing Information. 2013 9/2013.

18. Mostaghel EA, Nelson P, Lange PH, Lin DW, Taplin M, Balk SP, et al. Neoadjuvant androgen pathway suppression prior to prostatectomy. J Clin Oncol. 2012;30:suppl, abstr 4520.

19. Pinto-Bazurco Mendieta MA, Negri M, Jagusch C, Muller-Vieira U, Lauterbach T, Hartmann RW. Synthesis, biological evaluation, and molecular modeling of abiraterone analogues: novel CYP17 inhibitors for the treatment of prostate cancer. J Med Chem. 2008 Aug 28;51(16):5009-18.

20. Jevtana (Cabazitaxel) Prescribing Information. In: LLC s-aUS, editor.2010.

21. Massard C, Pezaro C, Bobilev D, Omlin AG, Bianchini D, Estelles DL, et al. A phase I/II study of cabazitaxel (Cbz) combined with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed after docetaxel (D) chemotherapy: Preliminary results. J Clin Oncol. 2013;31(abstr 5049).

22. Mateo J, Fizazi K, Pezaro CJ, Loriot Y, Mehra N, Albiges L, et al. Phase 1/2 trial of cabazitaxel with abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel and abiraterone acetate: Phase 2 results. J Clin Oncol 33, 2015 (suppl 7; abstr 268).

23. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med 2015, published on August 5, 2015, at NEJM.org; DOI: 10.1056/NEJMoa1503747.

24. Common Terminology Criteria for Adverse Events (CTCAE). 2010.

16. APPENDICES

16.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
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)
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.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.(28)