A phase 2, randomized, 3-arm study of abiraterone acetate alone, abiraterone acetate plus degarelix, a GnRH antagonist, and degarelix alone for patients with prostate cancer with a rising PSA or a rising PSA and nodal disease following definitive radical prostatectomy

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Lead Site: Memorial Sloan-Kettering Cancer Center

Sponsor: Memorial Sloan-Kettering Cancer Center

Principal Investigator
Howard I. Scher, MD
Service Chief, Genitourinary Oncology Service
email: scherh@mskcc.org

Statistician
Glenn Heller, PhD
Memorial Sloan-Kettering Cancer Center
email: hellerg@mskcc.org

Co-investigator
Michael Morris, MD
Associate Attending, Genitourinary Oncology Service
email: morrism@mskcc.org

Protocol Manager
Ahkeem Simmons
Prostate Cancer Clinical Trials Consortium
email: simmona1@mskcc.org

Participating Sites	Principal Investigator	Site's Role
Oregon Health and Science University, Knight Cancer Institute	Julie Graff, MD	Data Collection
Rutgers Cancer Institute of New Jersey	Tina Mayer, MD	Data Collection
North Shore University Health System	Daniel Shevrin, MD	Data Collection
Duke University Medical Center	Michael Harrison, MD	Data Collection
Northwestern University, Feinberg School of Medicine	Timothy Kuzel, MD	Data Collection
Johns Hopkins University, The Sidney Kimmel Comprehensive Cancer Center	Emmanuel Antonarakis, MD	Data Collection
University of North Carolina	Matthew I. Milowsky, MD	Data Collection
Karmanos Cancer Institute, Wayne	Ulka Vaishampayan, MD	Data Collection

State University		
Perlmutter New York University Cancer Center	Arjun Balar, MD	Data Collection
Weill Cornell Medical Center	Scott Tagawa, MD	Data Collection
GU Research Network	Luke Nordquist, MD	Data Collection

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: *A phase 2, randomized, 3-arm study of abiraterone acetate alone, abiraterone acetate plus degarelix, a GnRH antagonist, and degarelix alone for patients with prostate cancer with a rising PSA or a rising PSA and nodal disease following definitive radical prostatectomy*

Principal Investigator Signature: _____

Principal Investigator

Print:

Date:

PROTOCOL SUMMARY

Title	A phase 2, randomized, 3-arm study of abiraterone acetate alone, abiraterone acetate plus degarelix, a GnRH antagonist, and degarelix alone for patients with prostate cancer with a rising PSA or a rising PSA and nodal disease following definitive radical prostatectomy
Lead site	Memorial Sloan-Kettering Cancer Center
Sponsor	Memorial Sloan-Kettering Cancer Center
Investigational agent	Abiraterone acetate (Janssen Scientific Affairs, LLC) 1000 mg (four 250 mg tablets) daily plus prednisone 5 mg once daily; abiraterone acetate plus prednisone with once monthly degarelix injection or; once monthly degarelix injection only.
Phase	Phase 2
Target population	Post-radical prostatectomy men with a serum testosterone of 150 ng/dL or greater who now have a rising PSA and a PSADT ≤ 9 months without metastatic disease. However, patients with pelvic and/or retroperitoneal nodes < 2 cm in short axis will be permitted on study, as they are considered not to have definitive metastases.
Start date/Duration	It is anticipated that the trial will remain open to accrual for 36 months with an additional 18 month follow-up after accrual closure.
Expected enrollment	120 patients
Rationale	Our central **hypothesis** is that the increased androgen suppression achieved with abiraterone acetate can eliminate disease that has recurred after radical prostatectomy with or without post-operative radiation therapy. The **objective** of this protocol is to study whether the abiraterone acetate, alone or in combination with a gonadotropin-releasing hormone antagonist can potentially cure a proportion of men with non-castrate testosterone levels after radical prostatectomy and now have a rising PSA and a PSADT ≤ 9 months without definitive metastatic disease. The initial screening endpoint to determine whether the approach is worthy of further study is an undetectable PSA with non-castrate levels of testosterone at 18 months from the time of treatment initiation (PSA0). Androgen depletion and/or blockade currently practiced with degarelix, a GnRH agonist/antagonist with or without an antiandrogen produces declines in PSA followed by tumor shrinkage, a period of quiescence during which the disease does not proliferate, followed by a rise in PSA and regrowth as a castration-resistant prostate cancer (CRPC) that for most men is invariably lethal. Androgen depletion as traditionally utilized does not completely inhibit androgen responsive gene expression (PSA, etc.),[1] it does not consistently produce levels of testosterone below 20 ng/dL,[2-4] and does not completely eradicate disease due to the presence of cells that can resist and/or survive in a low androgen environment when the disease is first manifest clinically.[5] Overall outcomes with ADT are inversely related to disease burden and the results of multiple series show that patients with

more advanced disease progress and die sooner in comparison to those with less advanced disease.[6,7] Even in the neoadjuvant setting where the disease is clinically confined to the gland, prostates removed after 3 months or up to 8 months of treatment are rarely tumor-free.[8]

We hypothesize that abiraterone-based treatments will be superior to androgen depletion with degarelix alone, and potentially cure (primary endpoint: progression-free survival at 18 months from the time of randomization) a proportion of men with a rising PSA and a rapid PSADT without definitive metastatic disease following radical prostatectomy. The potential clinical benefit of the approach under study includes the potential for cure, as well as the avoidance of repeated cycles of hormone therapy treatment, each of which is associated with short term and long term toxicities, some of which are cumulative.

The study is focused on men with a rising PSA and rapid PSADTs without definitive metastatic disease who are at risk for prostate cancer-specific morbidity and mortality.[9-11] This restriction limits therapy to those who require it, and builds on results in other tumor types where therapies that have shown activity in more advanced disease settings can cure a proportion of patients in the adjuvant setting with micrometastatic disease.[12-16]

The treatment regimen are easily administered and safe, build on established standards of care, and offer the highest probability of demonstrating clinical benefit in a short time frame. Three treatment groups will be studied: abiraterone acetate alone, abiraterone acetate plus degarelix, and degarelix alone. We have selected degarelix to avoid the initial serum testosterone elevations that occur with GnRH agonists/antagonists which are not completely blocked with the currently available anti-androgens.[3,17] Degarelix treatment reduces serum androgen levels to a castrate range within 48 hours.[18]

Study design

A randomized phase 2 screening design is used to compare the efficacy of abiraterone acetate and abiraterone acetate plus degarelix to degarelix alone for prostate cancer patients in the rising PSA clinical state.

After obtaining informed consent, patients who satisfy the eligibility requirements will be randomized prospectively:

Arm 1
- Abiraterone acetate 1000 mg daily x 8 months
- Prednisone 5 mg once daily x 8 months

Arm 2
- Abiraterone acetate 1000 mg daily x 8 months
- Prednisone 5 mg once daily x 8 months
- Degarelix subcutaneous depot injection(s) q 1 month x 8 months

Arm 3
- Degarelix subcutaneous depot injection(s) q 1 month x 8 months

Criteria for

Primary endpoint:
The primary endpoint for each cohort is progression-free survival (PFS) at 18

evaluation

months from the start of treatment initiation (PSA0). PFS is defined as an undetectable PSA (at the institution of participant registration) with a non-castrate level of testosterone (>150 ng/dL). Pathological lymph nodes (whether target or non-target) must also have reduction in short axis to <10 mm (Complete Response per RECIST) in order to meet the criteria for PFS.

Secondary endpoints:

- PSA response rate (Percentage of patients with an undetectable PSA at 8 months from PSA0).
- Effects of each arm on overall quality of life, with particular attention to libido, potency, anxiety, depression, hot flashes, and fatigue.
- Frequency and intensity of non-hematologic adverse events.
- Testosterone and leuteinizing hormone (LH) recovery rates.

Tertiary endpoint:

- Correlative tissue analysis with clinical outcomes while on study treatment.

Statistical method

One hundred and twenty patients will be randomized to the three treatment groups. Each abiraterone acetate group will be compared to the degarelix alone group. With 40 patients per group, it is assumed that the probability of a success in the degarelix alone group is ≤ 0.25 and the probability of a success is at least 0.20 greater than degarelix alone in the abiraterone acetate-based groups. Under these projections, there is greater than an 80% chance of finding for either abiraterone acetate-based treatment relative to degarelix alone using Fisher's exact test with a one-sided 0.20 significance level.

The choice of a 0.20 significance level is intended to reduce the sample size required for this comparative study. A significant outcome does not imply definitive evidence of superiority for either abiraterone acetate-based treatment relative to degarelix alone due to this high type 1 error, but instead provides sufficient evidence that testing of abiraterone acetate should proceed to a large-scale randomized phase 3 study in this patient population.

Safety analysis

Safety analysis will be summarized using the Safety Population defined as any patient receiving any part of study treatment.

Extent of exposure to study treatment will be summarized and details will be provided. Treatment emergent adverse events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be coded using the MedDRA coding system and all AEs will be graded according to the most current National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

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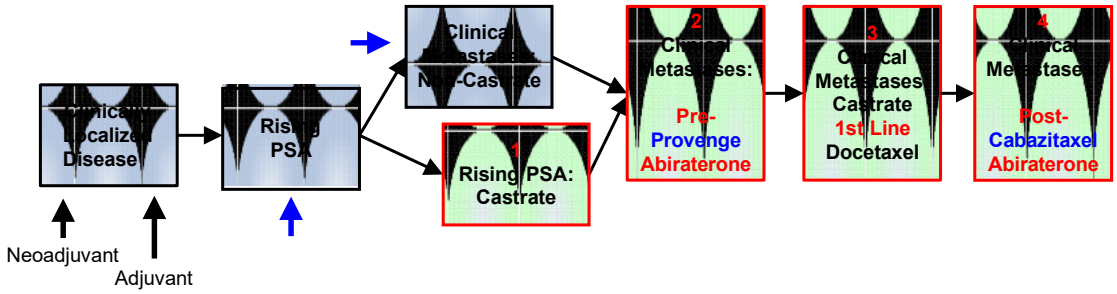
1. INTRODUCTION

1.1 Disease Background

The course of prostate cancer from diagnosis to death can be categorized as a series of clinical states (Figure 1) based on the status of the primary tumor, presence or absence of visible metastatic disease on an imaging study, and the measured level of testosterone in the blood.[19] The states are localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate state.

Figure 1. Clinical states of prostate cancer



1.2 Rising PSA Clinical State

Although surgery, radiation, or a combination of both can be curative for patients with localized disease, a significant proportion of these patients have recurrent disease as evidenced first by a rising level of PSA. For these individuals, the issue is to determine whether the disease is local or systemic, and if the later, the risk of developing metastatic disease – a transition to the lethal phenotype of the illness and in what time frame. A number of nomograms based on the characteristics of the primary tumor, time to a detectable PSA following surgery, and rate of rise in PSA or PSA doubling time (PSADT) have been developed to estimate prognosis, which for the group as a whole is heterogeneous.[20-24]

In one series of patients with rising PSA enrolled on clinical protocols (N = 148) PSADT was a statistically significant independent predictor for metastatic progression (P = 0.001).[25] Moreover, a shorter PSADT is significantly associated with prostate cancer-specific and all-cause mortality with virtually all men who ultimately die of the disease having a PSADT of 3 months or less.[26,27] In practice, most men with a PSADT of 12 months or less are treated, but we are restricting eligibility to men with a PSADT of 9 months or less based on the recently reported metastases free survival times in a contemporary series (Table 1).

Table 1. Metastasis-free survival (MFS) after PSA recurrence according to PSADT

	PSADT < 3 mos (N = 46)	PSADT 3-9 mos (N = 106)	PSADT 9-15 mos (N = 86)	PSADT ≥ 15 mos (N = 212)
Median MFS, years (95% CI)	1 (0,1)	4 (2,4)	13 (6, >15)	15 (15, >17)
Metastasis-free rate at 5 years, % (95% CI)	5 (1, 21)*	27 (16, 39)	77 (63, 86)	91 (85, 95)
Metastasis-free rate at 10 years, % (95% CI)	N/A	7 (1, 22)	51 (34, 66)	72 (59, 83)

*Last subject censored at 4 years. In each subgroup, the median MFS as well as the 5- and 10-year probabilities of MFS from the time of PSA recurrence are shown. N/A, not applicable.

In this series, 73% of men with a PSADT in the range of 3-9 months, and 95% of men with a PSADT of less than 3 months developed visible metastatic disease at 5 years.

We are also including men with visible pelvic and/or retroperitoneal nodes < 2 cm in short axis, as nodal disease at this site of spread is particularly sensitive to and will often completely regress on androgen depletion therapy, and will not recur at the time of relapse.

1.3 Androgen Depletion and/or Blockade for PSA Progression

Androgen depletion and/or blockade (ADT) as currently practiced with a gonadotropin-releasing hormone (GnRH) agonist/antagonist with or without an antiandrogen produces declines in PSA followed by tumor shrinkage, a period of quiescence during which the disease does not proliferate, followed by a rise in PSA and regrowth as a castration-resistant prostate cancer (CRPC) that for most men is invariably lethal. Overall outcomes are inversely related to disease burden and the results of multiple series show that patients with more advanced disease progress sooner in comparison to those with less advanced disease.[6,7]

We hypothesize that abiraterone-based treatments will be superior to androgen depletion with degarelix alone, and potentially cure (primary endpoint: progression-free survival at 18 months from the time of randomization) a proportion of men with a rising PSA and a PSADT ≤ 9 months without definitive metastatic disease following radical prostatectomy.

1.3.1 ADT does not completely suppress androgen signaling

Androgen depletion as traditionally utilized does not completely inhibit androgen responsive gene expression (PSA, etc.),[1] it does not consistently produce levels of testosterone below 20 ng/dl,[2-4] and does not completely eradicate disease due to the presence of cells that can resist and/or survive in a low androgen environment when the disease is first manifest clinically.[5] Overall outcomes with ADT are inversely related to disease burden and the results of multiple series show that patients with more advanced disease progress and die sooner in comparison to those with less advanced disease.[6,7] Even in the neoadjuvant setting where the disease is clinically confined to the gland, prostates removed after 3 months or up to 8 months of treatment are rarely tumor-free.[8]

To understand the mechanisms contributing to treatment resistance, we performed mRNA expression profiles of prostate cancers representing untreated and post-hormone treated primary tumors, and castration resistant metastatic disease. In pre-prostatectomy hormone treated patients, we found that androgen receptor (AR) gene expression in the residual tumor in the prostate after 3 months of ADT alone was reduced but persistent and many of the post-hormone treated samples continued to express AR target genes such as PSA, prostatic acid phosphatase, prostate specific transglutaminase (TGP), KLK1, and TMPRSS2.[1] An association was shown between the level of PSA mRNA and protein expression and biochemical relapse.[28] The finding that intratumoral androgen levels are only reduced by 75% following conventional ADT, at the time when androgen levels in the blood are in the castrate range,[29] may explain in part, the failure to eliminate disease completely in the primary site. In 1979, Geller and colleagues first demonstrated increased intratumoral androgens in the prostates of men who had undergone castration,[30] a finding confirmed by others. Adrenal androgen synthesis was the postulated source, although a failure to completely suppress androgen production could not be excluded.[29,31-33] Subsequently, Holzbeierlein et al[1] reported an up to 5-fold induction of several enzymes involved in steroid hormone production, also confirmed by others,[34,35] suggesting the possibility of intratumoral production of androgens as the primary source.

1.3.2 Intermittent hormone therapy as a therapeutic option

Most of the approvals for the hormonal therapies to treat prostate cancer have been on the basis of an equivalent effect on serum testosterone levels, or an improved safety profile relative to other available agents.[36-38] None have shown superiority in a cancer specific outcome such as an improvement in disease related symptoms, time to progression or overall survival. Recently, a Canadian study comparing intermittent vs. continuous therapy was reported which showed no difference in cancer specific outcomes, but a marked improvement in overall quality of life for men treated on the intermittent approach.[39] Other groups have explored the approach with "on cycles" of varied duration, but in most studies, the maximal response is observed by 8 months, which is duration of therapy we have selected for the current study.[40]

1.3.3 Time to testosterone recovery

The incidence of, and length of time to recovery tends to decline with subsequent off-treatment cycles and is a function of longer treatment schedules, lower pretreatment baseline PSA testosterone levels, and advancing age.[41] Overall, testosterone levels return to a non-castrate range with 6 months of stopping treatment in 75% of cases (Figure 2).

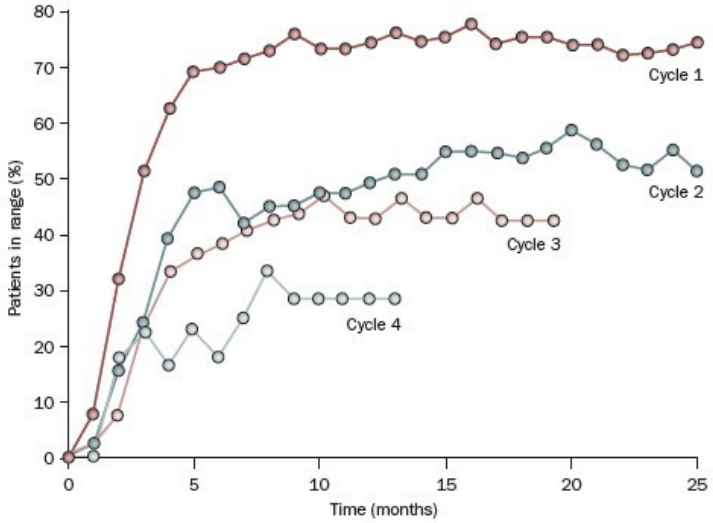


Figure 2. Recovery of testicular function after androgen suppression.
The proportion of patients with serum testosterone levels ≥7.5 nmol/l is plotted as a function of time after the interruption of androgen withdrawal therapy. These results show that testosterone recovery occurs in many patients, especially in the first off-treatment phase.[41]

1.4 Abiraterone Acetate

Abiraterone acetate is a steroidal inhibitor of CYP17 that blocks two important enzymatic activities in the synthesis of testosterone. It was developed originally for use in the non-castrate hormone naïve (non-castrate) setting, an indication that was largely abandoned after an initial proof of concept trial. Of particular interest was the demonstration that abiraterone acetate treatment resulted in testosterone levels to the 1-2 ng/dL range which is significantly lower than the20-30 ng/dL range achieved with conventional androgen-depletion with a surgical orchiectomy or GnRH agonist/antagonist with or without an antiandrogen.[42] The maximal dose administered in the trial was 750 mg daily, below the currently approved 1000 mg dose.

In April 2011, the FDA approved abiraterone acetate for use in combination with prednisone for the treatment of patients with metastatic CRPC who have received prior chemotherapy containing docetaxel. In December 2012, the FDA approved abiraterone acetate for use in

combination with prednisone for the treatment of patients with metastatic CRPC who have not yet received chemotherapy.

1.4.1 Description and mechanism of action

Pharmacology

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17, 20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone.

Pharmacokinetics and Metabolism

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

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

At the dose of 1000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 232 ± 177 ng/mL and of AUC were 1060 ± 681 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$ 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.

1.4.2 Warnings and precautions

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Use abiraterone acetate with caution in patients with a history of cardiovascular disease. Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Adverse Reactions (1.4.3) and Description of Mechanisms of Action (1.4.1)]*. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. The safety of

abiraterone acetate in patients with left ventricular ejection fraction <50% or NYHA Class III or IV heart failure has not been established because these patients were excluded from the randomized clinical trial. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with abiraterone acetate.

Adrenocortical Insufficiency

Adrenocortical insufficiency has been reported in clinical trials in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. 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 *[see Warnings and Precautions (1.4.2)]*.

Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred *[see Adverse Reactions (1.4.2)]*. 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. In patients with baseline moderate hepatic impairment receiving a reduced abiraterone acetate dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two 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. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt abiraterone acetate treatment and closely monitor liver function.

Re-treatment with abiraterone acetate at a reduced dose level may take place only after 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 *[see Study Treatments (5)]*.

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.

Food Effect

Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Study Treatments (5) and Mechanism of Action (1.4.1)]*.

1.4.3 Adverse reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, but had no prior chemotherapy (COU-AA-302), abiraterone acetate was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 546). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 542). The median duration of treatment with abiraterone acetate was 13.8 months and was 8.3 months in the placebo plus prednisone group.

The most common adverse drug reactions (≥10% of subjects in any treatment group) reported in two large, randomized, double-blind, placebo-controlled Phase 3 abiraterone acetate studies (COU-AA-301 and COU-AA-302) were fatigue (44%), back pain (33%), nausea (28%), arthralgia (30%), constipation (26%), bone pain (24%), peripheral edema (26%), hot flush (21%), and diarrhea (21%). Most events were of Grade 1 or 2 toxicity. Noteworthy exceptions include muscle spasms, upper respiratory tract infection, hypertension, and increased alanine aminotransferase (ALT), all of which were reported at higher rates in COU-AA-302 compared with COU-AA-301.

For the combined treatment groups, the most common adverse drug reactions that resulted in drug discontinuation were disease progression, spinal cord compression, back pain, aspartate aminotransferase increased, and alanine aminotransferase increased. In COU-AA-302, ALT increased was the most commonly reported AE leading to treatment discontinuation (1.7% of subjects in the abiraterone acetate group and 0.2% of subjects in the placebo group).

Adverse events of special interest with abiraterone acetate therapy include fluid retention/edema, hypokalemia, hypertension, cardiac disorders, and hepatotoxicity. AEs of special interest were reported more commonly in patients treated with abiraterone acetate (61% of combined subjects in phase 3 trials) than in patients treated with placebo (48%). Events of hypokalemia were reported in 18% of subjects in the abiraterone acetate group versus 9% of subjects in the placebo group for study COU-AA-301; for study COU-AA-302, these proportions were 17% and 13%, respectively (see Table 2).

In patients treated with abiraterone acetate, grades 3 to 4 hypokalemia occurred in 5% of patients in the COU-AA-301 study and 3% of patients in the COU-AA-302 study. Grades 3 to 4 hypertension was reported in 1% of patients in COU-AA-301 and 4% of patients in COU-AA-302 *[see Warnings and Precautions (1.4.2)]*.

Table 2 shows adverse reactions due to abiraterone acetate that occurred with either a ≥ 1% absolute increase in frequency compared to placebo, or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities).

Table 2. Adverse reactions due to abiraterone acetate in a placebo-controlled phase 3 trial

	Abiraterone acetate with Prednisone (N=791)		**Placebo with Prednisone (N=394)**	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0

Cardiac failure[8]	2.3	1.9	1.0	0.3

1 Adverse events graded according to CTCAE version 3.0

2 Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

3 Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness

4 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

5 Includes all fractures with the exception of pathological fracture

6 Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia

7 Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).

8 Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Cardiovascular Adverse Reactions

Cardiovascular adverse reactions in the phase 3 trial are shown in Table 2. The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the abiraterone acetate arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the abiraterone acetate arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity

Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been reported in patients treated with abiraterone acetate. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred *[see Warnings and Precautions (1.4.2)]*. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of abiraterone acetate, both patients had normalization of their liver function tests and one patient was re-treated with abiraterone acetate without recurrence of the elevations.

In clinical trials, the following patients were excluded: patients with active hepatitis, patients with baseline ALT and/or AST ≥ 2.5X ULN in the absence of liver metastases, and patients with ALT and/or AST > 5X ULN in the presence of liver metastases. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption, dose modification and/or discontinuation *[*see *Study*

Treatments (5) *and Warnings and Precautions (1.4.2)]*. Patients with elevations of ALT or AST > 20X ULN were not re-treated.

Other Adverse Reactions

Adrenal insufficiency occurred in two patients on the abiraterone acetate arm of the phase 3 clinical trial (< 1%).

Laboratory Abnormalities of Interest

Table 3 shows laboratory values of interest from the phase 3 placebo-controlled clinical trial. Grade 3-4 low serum phosphate (7.2%) and potassium (5.3%) occurred more frequently in the abiraterone acetate arm.

Table 3. Laboratory abnormalities of interest in a phase 3 placebo-controlled clinical trial

	Abiraterone (N=791)		Placebo (N=394)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Laboratory Abnormality	%	%	%	%
High Triglyceride	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Low Potassium	28.3	5.3	19.8	1.0
Low Phosphorus	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

1.4.4 Clinical development of abiraterone in castration resistant disease

The known effects of abiraterone on adrenal androgen biosynthesis led to a series of studies in pre-chemotherapy CRPC patients with significant and in many cases durable responses.[43] Trials in post-chemotherapy CRPC followed with similar results.[44] This lead to a phase 3 program in which abiraterone acetate plus prednisone was compared to placebo plus prednisone in the post-chemotherapy (Cougar-AA-301) setting, which showed a significant survival benefit,[45] and pre-chemotherapy (Cougar-AA-302), which showed an improvement in radiographic progression-free survival and a trend toward improved overall survival.[53]

1.4.5 Development of abiraterone in non-castrate disease

A proof of concept phase 1 trial conducted at the Royal Marsden showed that a dose of 800 mg daily produced testosterone levels of 0.77 nmol/l which, in one patient, was not sustained due an increase in luteinizing hormone (LH) levels.[46] The currently approved dose of 1000 mg daily was not evaluated. Subsequent profiling studies of human primary prostate carcinomas showed that a proportion of non-castrate primary tumors have increased expression of the enzymes in androgen biosynthetic pathway including CYP17,[1,33,34,47] while a second study showed that CYP17A1 gene expression was upregulated in high risk, high grade, primary prostate tumors.[48]

1.4.6 Abiraterone acetate in combination with lupron, a GnRH agonist/antagonist increases response in the primary tumor

Based on these findings, Investigators at the Dana-Farber Cancer Institute and the Fred Hutchinson Cancer Center are conducting a prospective trial in which patients receive either Lupron (leuprolide acetate) alone or Lupron plus abiraterone acetate plus

prednisone for 12 weeks followed by a repeat biopsy to assess intratumoral androgen levels and androgen regulated gene expression. Both groups then receive 12 weeks of Lupron plus abiraterone acetate plus prednisone followed by a radical prostatectomy. Specimens are then assessed for pathologic response, intratumoral androgen, and AR regulated gene expression. To date, the majority of patients enrolled have been high risk and dramatic antitumor responses seen, which suggests that the additional 1 log reduction in androgen levels by abiraterone acetate can increase response rates (personal communication, M. Taplin).

1.5 Clinical Benefits of Proposed Treatment

The potential clinical benefit of the approach under study includes the potential for cure, as well as the avoidance of repeated cycles of hormone therapy treatment, each of which is associated with short term and long term toxicities, some of which are cumulative. We are focused on men with a rising PSA and a PSADT ≤ 9 months without definitive metastatic disease, who are at risk for prostate cancer-specific mortality.[9-11] Patients with pelvic and/or retroperitoneal nodes < 2 cm in short axis will be permitted on study, as they are considered not to have definitive metastases. The focus on men who require treatment because of their risk of prostate cancer-specific morbidity and morbidity restricts therapy to those who require it. This approach builds on results in other tumor types where therapies that have shown activity in more advanced disease settings can cure a proportion of patients in the easily monitored adjuvant micrometastatic setting.[12-16].

1.6 Rationale for Therapeutic Intervention

Men with a rising PSA following radical prostatectomy are motivated and want treatment to avoid metastatic disease. The minimal disease setting in which the disease can be monitored easily, with a treatment regimen that builds on established standards of care with an easily administered regimen, offers the highest probability of demonstrating clinical benefit in a short time frame.

Our central hypothesis is that abiraterone-based treatments will be superior to conventional androgen depletion. To test our hypothesis we will evaluated three treatment groups: abiraterone acetate alone, abiraterone acetate plus degarelix, and degarelix alone. We have selected degarelix to avoid the initial serum testosterone elevations that occur with GnRH agonists/antagonists which are not completely blocked with the currently available anti-androgens.[3,17] Degarelix treatment reduces serum androgen levels to a castrate range within 48 hours.[18]

1.7 Choice of Undetectable PSA as the Primary Endpoint

Survival is recognized as a "gold standard" primary endpoint in clinical trials. As is the case for the treatment of the primary tumor, we postulate that disease eradication as evidenced by an undetectable PSA is a clinically meaningful therapeutic objective for men with a rising PSA and a PSADT ≤ 9 months without definitive metastatic disease. Patients with pelvic and/or retroperitoneal nodes < 2 cm in short axis will be permitted on study, as they are considered not to have definitive metastases.

For men who are successfully treated surgically, the serum PSA level should decline to below detectable levels within 21 to 30 days based on its half-life.[49,50] The reported level of detectable serum PSA by current commercial assays is 0.1 ng/mL (undetectable levels are expressed as <0.1 ng/mL).[49] Consequently, the most acceptable threshold for a detectable PSA after prostatectomy is 0.05 ng/mL, which is a measurable value above the level detectable by assay. In this trial all PSA assays will be performed at the location of participant registration using a routine PSA assay.

2. OBJECTIVES

2.1 Primary Objective

The objective of this protocol is to study abiraterone acetate, alone or in combination with degarelix, a GnRH antagonist, in men with non-castrate levels of testosterone and a rising PSA following radical prostatectomy without clinically metastatic disease to determine whether abiraterone acetate can potentially cure (primary endpoint: progression-free survival at 18 months from the time of treatment initiation) a proportion of men of this population. Men with pelvic and/or retroperitoneal nodes < 2 cm in short axis will be permitted on study, as they are considered not to have definitive metastases.

2.2 Secondary Objectives

- To determine the PSA response rate.
- To determine the effects of each arm on overall quality of life, with particular attention to libido, potency, anxiety, depression, hot flashes, and fatigue.
- To determine the frequency and intensity of non-hematologic adverse events.
- To determine testosterone and LH recovery rates.

3. PATIENT SELECTION

3.1 Target Population

Post-radical prostatectomy men with a serum testosterone of 150 ng/dL or greater who now have a rising PSA and a PSADT ≤ 9 months without metastatic disease. However, patients with pelvic and/or retroperitoneal nodes < 2 cm in short axis will be permitted on study, as they are considered not to have definitive metastases.

3.2 Inclusion Criteria

To be included in this study, patients must meet all of the following criteria:

- Willing and able to provide written informed consent and Authorization for Use and Release of Health and Research Study Information (HIPAA authorization)

  NOTE: HIPAA authorization may be either included in the informed consent or obtained separately.

- Male aged 18 years and above
- Patients must have undergone local treatment via radical prostatectomy
    - Patients who have received primary radiation therapy followed by a salvage radical prostatectomy are eligible.
    - Patients who have had post-operative radiation therapy for presumed locally recurrent disease are eligible
- Histologically confirmed prostate cancer (per standards at Institution of participant registration) currently with progressive disease, defined as:

- Rising PSA (50% or more increase to a level of 1 ng/mL or more, based on at least 3 PSA determinations obtained at least 1 week apart). The 50% rise in PSA is across the 3 determinations, and these determinations do not need to be sequential.

AND

- PSADT ⩽ 9 months as calculated according to the Memorial Sloan-Kettering Cancer Center nomogram (http://www.mskcc.org/mskcc/html/10088.cfm)

- Patients with pelvic and/or retroperitoneal nodes < 2 cm in short axis are eligible as they are not considered to have definitive metastases.
- Patients must have a serum testosterone of 150 ng/dL or greater
- ECOG performance status of ⩽ 2 (Appendix A)
- Adequate bone marrow, hepatic, and renal function, as evidenced within 14 days prior to treatment initiation by:
  - Absolute neutrophil count (ANC) ≥ 1500/mm^3
  - Platelet count ⩾ 100,000/mm^3
  - Hemoglobin ⩾ 9 g/dL without need for hematopoietic growth factor or transfusion support within 30 days prior to treatment initiation
  - Aspartate aminotransferase (AST) ≤ 1.5 times the upper limit of the normal range (x ULN)
  - Alanine aminotransferase (ALT) ≤ 1.5 x ULN
  - Total bilirubin ≤ 1.5 x ULN
  - Serum creatinine of ⩽ 1.5 mg/dl or Calculated creatinine clearance of ⩾ 60 mL/min
  - Serum albumin ⩾ 3.0 g/dL
  - Serum potassium ⩾ 3.5 mEq/L
- At least 4 weeks and recovery to Grade 0 - 1 from reversible effects of prior surgery (i.e., incisional pain, wound drainage)
- Able to swallow the study drug whole as a tablet
- Willing to take abiraterone acetate on an 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 who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator during the study and for 1 week after last dose of abiraterone acetate.

3.3 Exclusion Criteria

Patients that meet any of the criteria listed below will not be eligible for study entry:

- Prior cytotoxic chemotherapy or biologic therapy for prostate cancer
- More than 8 months of prior hormonal therapy (e.g., gonadotropin-releasing hormone analogs, megestrol acetate, or Casodex)

Note: Patients who have been on prior hormonal therapy must wait at least 1 year after the drug is fully metabolized to start treatment on protocol.

- Prior ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer.
- Known brain metastasis or evidence of metastatic disease by CT scan, physical exam, or bone scan within 4 weeks of registration
    - Patients with equivocal uptake on a bone scan that in the clinician's opinion do not definitively constitute metastatic disease are eligible
- Currently active second malignancy, except non-melanoma skin cancer
- Significant medical condition other than cancer, that would prevent consistent and compliant participation in the study that would, in the opinion of the investigator, make this protocol unreasonably hazardous including but not limited to:
    - Active infection or other medical condition that would make prednisone/prednisolone (corticosteroid) use contraindicated
    - Severe hepatic impairment (Child-Pugh Class C)
    - History of gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents
    - Uncontrolled hypertension (systolic BP $\geq$ 160 mmHg or diastolic BP $\geq$ 95 mmHg); patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment
    - Active or symptomatic viral hepatitis or chronic liver disease
    - History of pituitary or adrenal dysfunction
    - Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III or IV heart disease or cardiac ejection fraction measurement of < 50 % at baseline
    - Atrial fibrillation, or other cardiac arrhythmia requiring medical therapy
    - Uncontrolled diabetes mellitus
    - Active psychiatric condition
- Use of any prohibited concomitant medications (Section 5.5.2) within 30 days prior to Cycle 1, Day 1
- Pre-existing condition that warrants long-term corticosteroid use in excess of study dose
- Grade > 2 treatment-related toxicity from prior therapy
- Known allergies, hypersensitivity or intolerance to abiraterone acetate, prednisone or degarelix
- Administration of an investigational therapeutic within 30 days of Cycle 1, Day1
- Any condition which, in the opinion of the investigator, would preclude participation in this trial

4. PATIENT REGISTRATION

A centralized registration procedure will be used. After eligibility screening, patients who are selected to participate will be registered with the Lead Center (MSKCC). A record of patients who fail to meet entry criteria (i.e., screen failures) will be maintained. Patient registration must be complete before beginning any treatment or study activities.

4.1 Lead Center (MSKCC) Registration

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

4.1.2 For participating sites

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC) via Prostate Cancer Clinical Trials Consortium, LLC (PCCTC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at PCCTC to notify him/her of the participant registration. **The site staff then needs to email registration/eligibility documents to the PCCTC via email at PCCTC@mskcc.org**.

The following documents must be sent for each enrollment within 24 hours of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

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

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has been activated by MSKCC, and the site is in good standing with MSKCC, the PCCTC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as

stated in section 4.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

4.1.3 Randomization

Details regarding randomization are found in section 5.4. Staff at the registering site will receive the treatment plan for the randomized participants via email at the time they receive their participant ID.

4.2 Institutional Registration

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

4.2.1 Informed consent

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

Authorized study personnel should fully explain the scope of the study (Section 6) to each patient before obtaining informed consent. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy.

When obtaining informed consent, study personnel should:

First: Confirm that the patient has received the research authorization/HIPAA form. This must be reviewed before confirming eligibility and obtaining informed consent.

Next: Confirm eligibility as defined in Sections 3.2 and 3.3 (Inclusion and Exclusion Criteria).

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Study Drug (Abiraterone acetate)

Abiraterone acetate 250-mg tablets are oval, white to off-white and contain abiraterone acetate and compendial (USP/NF/EP) grade lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and purified water, in descending order of concentration (the water is removed in tableting). Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

5.1.2 Degarelix

Degarelix is supplied as a powder to be reconstituted with Sterile Water for Injection, USP. A starting dose of 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL will be administered. The starting dose is followed by maintenance doses of 80 mg administered per institutional guidelines at a concentration of 20 mg/mL every 28 days (± 3 days)

5.1.3 Prednisone

Prednisone (5 mg tablets) will be prescribed to patients assigned abiraterone acetate to be taken orally once daily with food. If a subject has been receiving glucocorticoids other than prednisone or prednisolone, it will be necessary to switch the glucocorticoid to prednisone or prednisolone 5 mg once daily prior to Day 1.

5.2 Treatments Administered

5.2.1 Group 1: Abiraterone acetate and prednisone

Patients randomized to abiraterone acetate and prednisone (Group 1) will be instructed to take 1000 mg (four 250 mg tablets) of abiraterone acetate orally (PO) at least 1 hour before a meal and 2 hours after a meal every day. These patients will also be treated with prednisone 5 mg once daily with food.

5.2.2 Group 2: Abiraterone acetate plus degarelix and prednisone

Patients randomized to abiraterone acetate plus degarelix and prednisone (Group 2) will be instructed to take 1000 mg (four 250 mg tablets) of abiraterone acetate orally (PO) at least 1 hour before a meal and 2 hours after a meal every day and prednisone 5 mg once daily with food. Patients will also be given two subcutaneous injections of degarelix 120 mg on Cycle 1, Day 1(starting dose) and 80 mg subcutaneous doses (maintenance doses) every 28 days (±3 days) thereafter.

5.2.3 Group 3: Degarelix alone

Patients randomized to degarelix alone (Group 3) will be given two subcutaneous injections of degarelix 120 mg on Cycle 1, Day 1 (starting dose) and 80 mg subcutaneous doses (maintenance doses) every 28 days (± 3 days) thereafter.

5.3 Selection and Timing of Dose for Each Patient

Each treatment cycle consists of 28 consecutive days (4 weeks). Patients will take study treatment for 8 cycles (32 weeks) or until disease progression or patient withdrawal. The treatments are not blinded. The dose of prednisone will remain unchanged in the event that the study drug dose is changed. The dose of prednisone will only be changed at the discretion of the treating physician. Treatment with abiraterone acetate will be continuous from Day 1. If a dose is missed, the next dose should be given as planned without making up the missed dose. Degarelix will be administered approximately every 28 days.

5.4 Randomization

Patients will be randomized after the investigator has verified that all eligibility criteria have been met and the patient is registered to the study. Patients will be randomized to receive abiraterone acetate and prednisone (Group 1), abiraterone acetate plus degarelix and prednisone (Group 2) or degarelix alone (Group 3) in a 1:1:1 ratio.

5.5 Concomitant Medications

Because of the potential for drug-drug interaction, the concurrent use of all other drugs, over-the-counter medications, and alternative therapies must be documented. The principal investigator should be alerted if the patient is taking any prohibited agents. Concurrent enrollment in another therapeutic clinical investigation is prohibited.

5.5.1 Supportive care medications

Supportive care medications are permitted with their use following institutional guidelines.

The following supportive care medications are considered permissible during the study:

- Conventional multivitamins, selenium and soy supplements
- Additional systemic glucocorticoid administration such as "stress dose" glucocorticoid is permitted if clinically indicated for a life threatening medical condition, and in such cases, the use of steroids will be documented as concomitant drug

5.5.2 Prohibited within 30 days prior to administration of study treatment

- Spironolactone
- 5 α–reductase inhibitors (e.g., finasteride, dutasteride)
- Saw Palmetto
- Use of other investigational drug therapy

5.5.3 Prohibited before enrollment and during administration of study treatment

- Androgen Receptor Partial Agonists
- Ketoconazole (Ketoconazole shampoo or topical cream/ointment for treatment of a past fungal infection does not exclude patients)
- Previous abiraterone acetate or other investigational CYP17 inhibitors (e.g., TAK-700)
- Chemotherapy (e.g., docetaxel, mitoxantrone, vinorelbine)
- Immunotherapy (e.g., cancer vaccines, GM-CSF)
- Estrogens
- PC-SPES or PC-HOPE herb mixtures Radiopharmaceuticals (e.g., ^{89}Sr, ^{153}Sm, Fludrocortisone acetate)

5.5.4 Prohibited during administration of study treatment

- Antiandrogens
    - Non-steroidal antiandrogens (e.g., bicalutamide, flutamide, nilutamide)
    - Steroidal antiandrogens (e.g., megestrol acetate, cyproterone)

5.5.5 The following medications are not excluded or prohibited, but are strongly discouraged:

- Digoxin; hypokalemia which is an expected adverse effect of abiraterone may enhance digoxin toxicity. Investigators are encouraged to consider whether patients needing digoxin could be managed with a different drug.
- Pomegranate juice/supplements; pomegranate juice has been associated with stabilization of PSA in a phase II study.
- Indole-3-carbinol; indole-3-carbinol has been suggested to have estrogenic effects, which theoretically could affect prostate cancer. However, no clinical trial results in men with prostate cancer are available.
- Flaxseed Oil; flaxseed oil has been associated with having estrogenic and antiestrogenic effects and can potentially lower potassium level. Flaxseed oil may theoretically lead to progression of some forms of cancer, including prostate cancer. However, no clinical trial results in men with prostate cancer are available.

5.5.6 Potential for drug-drug interactions

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6 and CYP2C8. 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 abiraterone acetate.

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during abiraterone acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the abiraterone acetate dosing frequency.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone acetate

5.6 Packaging and Labeling

Abiraterone acetate tablets will be provided to each site packaged for patient assignment at the time of randomization. Patients will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 3 day window. Information presented on the labels for investigational product will comply with applicable local regulations. Site pharmacist or medically qualified staff will dispense the study treatment to each patient in accordance with this protocol.

Degarelix will be prescribed from open pharmacy stock.

Prednisone will be prescribed by the treating physician.

5.7 Storage and Accountability

5.7.1 Storage requirements

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).

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.

5.7.2 Drug dispensing log and pill diary

Study site personnel will record all study drugs administered during this trial on the drug-dispensing log.

The drug dispensing log will contain the following information:

- patient initials and study identification number
- date(s) of study drug dispensed
- quantity of study drug dispensed
- drug lot number
- expiration date (if known)
- initials of dispensing pharmacist

Subjects will be provided with a diary in which to record their intake of study drug. However, the actual number of tablets taken by the subject must be calculated from the number of tablets dispensed and returned.

5.8 Criteria for Discontinuation of Study Treatment

In the absence of treatment delays because of adverse events, treatment will continue for 8 months until one of the following criteria applies:

- Patient decides to withdraw from the study
- PSA progression determined as follows:

  PSA is assessed every 28 days (± 3 days) using a routine PSA assay. If a measured PSA is higher than the preceding value, then the rising PSA will be confirmed in 4 weeks (± 3 days). If that third PSA value is higher still and the range of values is 50% above the baseline, then the patient is off study treatment. If not, the patient will remain on study, and the PSA will once again be checked when the patient presents for his monthly clinic visit.
- Radiographic progression (in the opinion of the investigator)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) that may or may not be directly related to treatment but that, in the judgment of the treating physician, makes it dangerous for the patient to be retreated

- General or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator
- Initiation of non-study therapy for metastatic prostate cancer

Because an excessive rate of withdrawals can render the study uninterruptable, unnecessary withdrawal of patients should be avoided. When a patient discontinues treatment early, the investigator should make every effort to contact the patient and to perform a final evaluation. The reason(s) for withdrawal should be recorded.

When protocol therapy is discontinued based on subject or investigator decision and the subject has not withdrawn consent, that subject will be followed for adverse events (AEs) for 30 days after the last dose of study medication. In the event that a serious adverse event (SAE) regardless of causality is ongoing or newly reported 30 days after the last dose of study medication, the subject will be followed until resolution of the event.

5.9 Criteria for Discontinuation of Post-Treatment Follow-Up

All patients who complete 8 months of protocol therapy will be followed for 10 additional months until one of the following criteria applies:

- Patient decides to withdraw from the study
- PSA progression determined as detectable PSA per the assay at the institution of registration and confirmed by consecutive observation at the next scheduled visit.
- Radiographic progression (in the opinion of the investigator)
- Initiation of non-study therapy for metastatic prostate cancer

6. STUDY PROCEDURES

The following assessments and procedures will occur during the study. A schedule of assessments is provided in Table 4.

Table 4 Study Calendar

	Screening		Treatment Period (8 cycles)			Post-treatment Follow-up (Every 28 days ±7 days for 10 months)
	Within 30 days prior to protocol therapy initiation	Within 14 days prior to protocol therapy initiation	Day 1 of each 28 day cycle (± 3 days)	Day 15 (± 2 days) of cycles 1,2,3 [Abiraterone treatment arms only]	End of Treatment[2]	
Informed consent and research authorization	X					
Demographics, medical history	X					
Interim medical history	X		X		X	X
Physical examination[3]	X		X		X	X
Histologic and radiographic confirmation of disease	X					
ECOG or Karnofsky performance status	X		X		X	X
CT of the chest, abdomen, and pelvis	X				X[8]	X[3,8]
Radionuclide bone scan	X				X[8]	X[3,8]
12-lead ECG	X					
ECHO or MUGA	X					
Laboratory tests[4,7]		X	X	X[7]	X	X
PSA		X	X		X	X
Serum testosterone and LH	X				X	X
PRO assessments	X		X		X	X
Correlative studies (optional)[8]	X					
Toxicity/AE assessment[9]	X----------					---------- X
Concomitant medications	X----------					---------- X
Abiraterone acetate + Prednisone (Arms 1 & 2)[6]			Daily x 8 months			
Degarelix injection (Arms 2 & 3)[6]			Monthly x 8 months			

Abbreviations: CT, computerized tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Group; LH, luteinizing hormone; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition; PRO, patient-reported outcome

1. Physical examination includes vital signs. Weight will be recorded at every visit. Height will be recorded at screening visit only. Vital signs include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
2. End of treatment visit will take place 28 ± 3 days after Cycle 8 day one, or within 7 days of last dose of study drug for those who discontinue treatment prematurely.
3. Post-treatment imaging conducted at post-treatment follow-up 10 (±14 days), or if patient discontinues follow-up for reasons described in Section 5.9
4. Laboratory tests are outlined in Section 6.5.1
5. Prostate tissue samples will be collected for those patients who give their consent (Section 6.10)
6. Daily abiraterone acetate administered with once daily prednisone. Details on all treatments administered are outlined in Section 5.2
7. Liver function tests (AST, ALT and total bilirubin) should be performed on Day 15 (±2 days) of the first three cycles.

8. If patients have had scans within 30 days of their visit, scans do not need to be repeated.
9. AEs will be assessed and recorded after informed consent is obtained through 30 days of last dose, or the event resolves, stabilizes, returns to baseline condition or is attributed to agents other than study product, or to factors unrelated to study conduct, whichever occurs first

6.1 Informed Consent

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

- The nature and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- Alternatives to the proposed study. This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.
- The name of the investigators responsible for the protocol.
- The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.
- Text regarding the PCCTC should be added to all institutional informed consent documents and sections in the research authorization/HIPAA forms (e.g., "Prostate Cancer Clinical Trial Consortium")

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

6.2 Medical History

Medical history, such as previous treatments, procedures, and conditions will be collected during the screening period.

6.3 Physical Examination

Evaluations should be performed by the same evaluator throughout the study whenever possible. Weight will be recorded at every visit. Height will be recorded at screening visit only.

Vital signs include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

6.4 Cardiac Function

To assess cardiac function at baseline, a 12-lead ECG and a Multiple Gated Acquisition (MUGA) scan should be obtained. Echocardiography can be used if MUGA is not available or when echocardiography is standard of care at the study site. Baseline measurement of left ventricular ejection fraction (LVEF) will be performed. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly during active treatment.

6.5 Clinical laboratory Tests

6.5.1 Laboratory parameters

Clinical laboratory tests will include the following (Table 5):

Table 5. List of laboratory tests

Hematology: - Hematocrit (Hct) - Hemoglobin (Hgb) - Platelet count - Red blood cell (RBC) count - White blood cell (WBC) count with differential	**Serum Chemistry**: - Alkaline phosphatase (ALK-P) - Alanine aminotransferase (ALT; SGPT) - Aspartate aminotransferase (AST; SGOT) - Blood urea nitrogen (BUN) - Carbon dioxide (CO2) - Chloride (Cl) - Creatinine (Cr) - Glucose (Glu) - Lactate Dehydrogenase (LDH) - Potassium (K) - Sodium (Na) - Total bilirubin - Calcium (Ca) - Albumin (Alb)

6.5.2 Sample collection, storage and shipping

Local laboratories will analyze all hematology, blood chemistry collected for the study. Samples will be analyzed at a facility meeting Clinical Laboratory Improvement Amendments (CLIA) requirements and/or using methods documented in a methods validation report.

6.6 Efficacy/Response Assessments

PSA will be assessed every 28 days (± 3 days) using a routine PSA assay.

6.6.1 Primary efficacy endpoint

Progression-free survival (PFS) defined as achieving and maintaining an undetectable PSA level (per institution of registration) with a non-castrate level of testosterone (>150 ng/dL) will be assessed at 18 months from the start of randomization (PSA0).

6.6.2 Secondary response endpoint

Treatment response defined as achieving and maintaining an undetectable PSA level (per institution of registration) with a non-castrate level of testosterone (>150 ng/dL) will be assessed at 8 months from PSA0.

6.7 Testosterone and Luteinizing Hormone Recovery Rates

Serum testosterone and LH recovery rates will be measured at 8 months from the start of treatment and at each month of the 10 month follow up period (**secondary endpoint measure**).

6.8 Patient-reported Outcomes

Effects of each arm on health-related quality of life will be assessed via PRO Survey (Appendix B) completed on paper by the patient at the following study visits: Screening, each Day 1 of Treatment Cycle, End of Treatment, and each Post-Treatment Follow-up. The following adverse symptom events will be assessed by 15 items from the NCI PRO-CTCAE: libido, potency, anxiety, depression, hot flashes, fatigue, joint swelling, muscle discomfort, diarrhea, and cough. Quality of life will also be assessed by the Linear Analog Scale Assessment (LASA) single item

measure of overall quality of life.[51] This item has been shown to be more responsive than multi-item measures and to cause less patient burden, and is used across NCI cooperative group trials, particularly in the NCCTG, ACOSOG, and CALGB. All items in the PRO Survey employ a 7-day recall period. The PRO Survey contains a total of 16 items and will take 5-8 minutes to complete.

6.9 Safety Evaluation

Frequency and intensity of non-hematologic adverse events will be recorded (**secondary endpoint measure**) per Section 9.2.

6.10 Correlative Studies

Baseline tumor tissue will be collected for those patients who give their consent for correlative analyses and pharmacogenomic studies. Tissue blocks (preferred) or unstained slides known to contain cancer should be obtained on primary tumors from patients. Tumor tissue from the radical prostatectomy is preferred; however, if it is unavailable, tumor from a diagnostic prostate biopsy is acceptable. All samples will be processed at MSKCC. Sample shipment to the central laboratory (MSKCC) may occur any time during the study.

Tissue samples will be utilized for morphologic assessment, percent tumor involvement (if applicable), and immunohistochemistry. The immunohistochemical markers assessed may be AR, PTEN, PSMA, fatty acid synthase (FASN), phospho-AMPK, phospho-ACC, phospho-S6 kinase, phospho-Akt for the assessment of the AMPK, lipid synthesis, mTOR pathways, and immunological markers.

Gene expression profiling may be performed from residual samples by utilizing various technologies (e.g. qRT-PCR, NanoString DASL assay). Tissue or purified DNA and RNA from these samples may also be examined to detect genomic abnormalities (somatic mutations, deletions, amplifications) in selected genes by various methods (e.g. FISH, sequencing, microarrays).

A Central Laboratory will analyze all tissue samples collected for the study. Samples will be analyzed at a facility meeting regulatory requirements and/or using methods documented in a methods validation report.

6.10.1 Additional research

MSKCC and PI shall not conduct any research on biological samples which is not required by the protocol for the conduct of the study at or by MSKCC and at each site during the study.

6.10.2 Storage, handling and disposal

PCCTC and PI shall ensure biological samples being analyzed in the study at each site are handled, stored and disposed of at the end of the study in accordance with the terms of the applicable consents and permissions for each donor and in accordance with all applicable laws.

7. STUDY ACTIVITIES

7.1 Within 30 Days Prior to Protocol Therapy Initiation

Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, any alternative treatment options, their right to withdraw from the study at any time for any reason, and their right to privacy. After this explanation, patients should be asked to sign and date a

research authorization/HIPAA form and an IRB-approved statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50)

The screening visit will determine patient eligibility according to the inclusion and exclusion criteria (Sections 3.2 and 3.3). The following assessments will be performed at this visit:

- Obtain informed consent and research authorization
- Record demographics (including age) and medical history (including prior treatment for prostate carcinoma and PSA kinetics)
- Interim medical history
- Conduct physical exam (vital signs, height/weight, etc.)
- Obtain histologic and radiographic confirmation of disease
- Blood samples for serum testosterone and LH levels
- Assess ECOG performance status (Appendix A)
- PRO Survey (Appendix B)
- CT of the chest, abdomen, and pelvis
- Radionuclide bone scan
- ECG
- MUGA or ECHO
- Discuss concurrent medications (see Section 5.5 for a listing of medications with the potential for drug interactions)
- Collection of prostate tissue for correlative studies (optional; see Section 6.10).

  Note: Tissue blocks (preferred) or unstained slides known to contain cancer should be obtained on primary tumors from patients. Tumor tissue from the radical prostatectomy is preferred; however, if it is unavailable, tumor from a diagnostic prostate biopsy is acceptable. Sample shipment to the central laboratory may occur any time during the study.

Relevant information should be documented. The institutional registration should be finalized, and appropriate documents (i.e., signed informed consent, research authorization/HIPAA form, and supporting source documentation for eligibility questions) faxed or emailed to the lead site.

7.2 Within 14 Days Prior to Protocol Therapy Initiation

A visit within 14 days prior to initiation of protocol therapy will further determine patient eligibility and collect baseline patient data. The visit must include the assessments listed below:

- Blood samples for laboratory tests (Section 6.5) and PSA

7.3 Treatment Period (Day 1 ±3 days to Week 32 ± 3 days)

Patients will receive study treatment for up to eight 28-day treatment cycles or less if one of the following occurs: disease progression, unacceptable toxicity, death, patient refusal or treatment delay beyond the time frame that is permitted for each treatment (See Section 5.8). All assessments must take place before scheduled degarelix injection (Group 2 and Group 3).

7.3.1 Day 1(± 3 days)

On Day 1 of every 28-day cycle the following study activities will occur while a patient is continuing on protocol therapy:

- Interim medical history
- Physical exam
- Assess ECOG performance status (Appendix A)
- PRO Survey (Appendix B)
- Toxicity/AE assessment
- Degarelix injection (Group 2 and Group 3)
- Blood samples for laboratory tests (Section 6.5) and PSA
- Discuss concurrent medications (see Section 5.5 for a listing of medications with the potential for drug interactions)

7.3.2 Day 15(± 2 days) – For patients in the Abiraterone acetate treatment arms only

On Day 15 of cycles 1, 2 and 3 the following study activities will occur while a patient is continuing on protocol therapy:

- Liver function laboratory tests (AST, ALT and total bilirubin)

7.3.3 End-of-treatment

28 ± 3 days after Cycle 8 Day 1 visit, or within 7 days of last dose for those who discontinue protocol treatment prematurely.

- Interim medical history
- Physical exam
- Assess ECOG performance status (Appendix A)
- PRO Survey (Appendix B)
- Toxicity/AE assessment
- Blood samples for laboratory tests (Section 6.5) and PSA
- Discuss concurrent medications (see Section 5.5 for a listing of medications with the potential for drug interactions)
- Blood samples for serum testosterone and LH levels
- CT of the chest, abdomen, and pelvis

Radionuclide bone scanPatients withdrawn from the study because of AEs do not need blood samples for serum testosterone and LH levels, CT of the chest, abdomen and pelvis, or a radionuclide bone scan at their End-of-treatment visits.

7.4 Post-treatment Follow-up

Patients completing 8 cycles of protocol therapy, in the absence of documented disease progression or initiation of non-study therapy for metastatic prostate cancer, will be seen every 28 days (± 7 days) for up to 10 months from the date of their End of Treatment visit. The following assessments will be completed at each post-treatment follow-up visit:

- Interim medical history
- Physical exam
- Assess ECOG performance status (Appendix A)
- PRO Survey (Appendix B)
- Toxicity/AE assessment
- Blood samples for laboratory tests (Section 6.5) and PSA
- Discuss concurrent medications
- Blood samples for serum testosterone and LH levels
- CT of the chest, abdomen, and pelvis (Follow-up 10 only, or for patients who discontinue follow-up due to reasons described in section 5.9)
- Radionuclide bone scan (Follow-up 10 only, or for patients who discontinue follow-up due to reasons described in section 5.9)

Patients who have discontinued protocol treatment due to AEs will be followed until the adverse event has either resolved or stabilized. Reasons for premature withdrawal should be determined and noted.

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 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.

8.1.2 Adverse Events of Special Interest

Please refer to Prescribing Information Packet for all relevant safety information.

8.1.3 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.

8.1.4 J&J Medicinal Product

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

8.1.5 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.

8.1.6 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered ‘‘serious’’ if it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
  - An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if 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,
- 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.

8.1.7 Special Reporting Situations

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

- Overdose of a 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
- 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
- Medication error involving a 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.

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

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:

An SAE or Special Reporting Situation 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.

8.3 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. Only abnormal laboratory values that are deemed clinically significant by the treating investigator are considered adverse events should be graded and attributed accordingly (per section 8.4).

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: Reasons described in the Protocol, (e.g., drug administration, protocol-required testing)

B. Surgery or procedure planned prior to entry into the Study.

If 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 which 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).

8.4 Grading Adverse Events

8.4.1 Grading severity

All adverse events will be graded for intensity on a scale of 0 to 5. Severity grades will be recorded and based on the CTCAE v4.0.

8.4.2 Attributing causality

After grading for severity, the investigator must evaluate all clinical AEs and clinically significant abnormal laboratory values for possible causal relationship to abiraterone acetate or degarelix. Causality attribution will be decided using the criteria outlined in Table 6.

Table 6. Relationship of adverse event to study drug

Relationship	Description
Unrelated	AE is clearly not related to study drug
Unlikely	AE is doubtfully related to study drug
Possible	AE may be related to study drug
Probable	AE is likely related to study drug
Definite	AE is clearly related to study drug

Abnormal laboratory values of clinical significance that were present at baseline and did not change in severity or frequency during experimental therapy or intervention and those that can obviously be attributed to underlying disease will be recorded as unrelated.

8.5 Reporting Adverse Events

8.5.1 Reporting serious adverse events

All SAEs, events determined to be medically significant by the treating Investigator, and unknown reactions or unexpected events should be reported to MSKCC Principal Investigator and PCCTC within 24 hours of knowledge of the event using the contact information below. The initial report should include the following information at a minimum:

- Protocol # and title
- Study identification number, sex, age at time of event
- Date the event occurred
- Description of the SAE
- Causal relationship to the study drug

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

medications, outcome, etc should be reported to the PCCTC as soon as possible. Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to PCCTC upon receipt.

The PCCTC will facilitate all SAE reporting to the MSK IRB/PB and Janssen Scientific Affairs, LLC within 24 hours of PCCTC awareness or identification of the event using the Janssen SAE Report Form (Appendix C). PCCTC is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE report from the MSK IRB/PB. PCCTC is responsible for informing all participating sites within 24 hours or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

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

SAE contact information for the MSKCC PI and PCCTC is listed below:

Lead Site Study PI
Howard Scher, MD
Memorial Sloan Kettering Cancer Center
Genitourinary Oncology Service
1275 York Avenue
New York, NY 10065
scherh@mskcc.org

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

8.5.2 Reporting serious adverse events to Janssen Scientific Affairs, LLC

Information regarding SAEs, AEs of Special Interest, Special Reporting Situations and PQCs will be transmitted to Janssen Scientific Affairs, LLC using their Serious Adverse Event Form (Appendix C), which must be completed and signed by a member of the investigational team within 24 hours of becoming aware of the event. PCCTC will facilitate all submissions to Janssen Scientific Affairs, LLC.

The following methods are acceptable for transmission of safety information to the COMPANY:

- Electronically vis Janssen SECURE email service at IIS-BIO-VIRO-GCO@its.jnj.com, or
- For business purposes if SECURE email is non-functional;
  - Facsimile (fax) at 1-866-451-0371, of receipt of which is evidenced in a successful fax transmission report

8.5.3 Safety Reports

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

8.5.4 Unanticipated Problems

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

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

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

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

8.6 Dose Modifications Procedure for Adverse Event Management

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Table 4. The NCI CTCAE v4.0 will be used to grade AEs.

At each study visit for the duration of their participation in the study, patients will be evaluated for AEs (all grades), SAEs, and AEs that require study drug interruption or discontinuation. Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 30 days after the last dose of the study drug.

The most common adverse reactions (≥ 5%) related to abiraterone acetate are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, factures and upper respiratory tract infection [*see Adverse reactions (1.4.3)*]

Following prolonged therapy with corticosteroids, subjects may develop Cushing's syndrome characterized by central adiposity, thin skin, easy bruising, and proximal myopathy. Withdrawal of the corticosteroid may result in symptoms that include fever, myalgia, fatigue, arthralgia, and malaise. This may occur even without other evidence of adrenal insufficiency.

8.6.1 Management of hypokalemia

Subjects who experience hypokalemia are to be managed as presented in Table 7.

Table 7. Hypokalemia management

Serum K+	Grade	Action	Further Action or Maintenance
Low K+ or history of hypokalemia		Weekly (or more frequent) laboratory electrolyte evaluations.	Titrate dose to maintain a serum K+ ≥3.5 mM ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<3.5 mM – 3.0 mM	1	Initiate oral or i.v. K+ supplementation. Consider monitoring magnesium and replacement if needed.	Titrate dose to maintain a serum K+ >3.5 mM ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<3.0 mM – 2.5 mM	3	Withhold abiraterone acetate (study) treatment and initiate oral or i.v. K+ and cardiac monitoring. Consider monitoring magnesium and replacement if needed	Titrate dose to maintain a serum K+ >3.5 mM ≤5.0 mM (maintenance of subjects at ≥4.0 mM is recommended)
<2.5 mM	4	Withhold abiraterone acetate (study) treatment and initiate oral or i.v. K+ and cardiac monitoring. Consider monitoring magnesium and replacement if needed.	Off study

8.6.2 Management of hypertension

- If Grade 1 or 2 adverse events occur, management per investigator. No study medication dose reduction.
- If Grade 3 or 4 adverse events occur, hold study medication. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone. When hypertension resolves to ≤Grade 1, resume study medication at full dose.
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue study medication.

8.6.3 Management of edema, fluid retention

- If pedal edema occurs, supportive management per investigator. No study medication dose reduction.
- If anasarca or pulmonary edema requiring supplemental oxygen occurs, hold study medication. Adjust or add medications to mitigate the toxicity and consider the specific mineralocorticoid receptor blocker, eplerenone. When toxicity resolves to ≤Grade 1, resume study medication at full dose.
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When resolved to ≤Grade 1, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).

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

8.6.4 Management of hepatic impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of abiraterone acetate to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone acetate and do not re-treat patients with abiraterone acetate.

8.6.5 Management of hepatotoxicity

For patients who develop hepatotoxicity during treatment with abiraterone acetate (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with abiraterone acetate *[see Warnings and Precautions (1.4.2)].* 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 abiraterone acetate. 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.

8.6.6 Management of other non-mineralocorticoid based side effects

- If Grade 1-2 toxicities occur, give supportive care per institutional guidelines. No study medication dose reduction.
- If Grade 3 or higher toxicities occur, including headache (interferes with activities of daily living), nausea (total parenteral nutrition/intravenous fluids), vomiting (6 or more episodes in 24 hours, total parenteral nutrition/intravenous fluids), diarrhea (intravenous fluids, hospitalization, hemodynamic collapse), or any other toxicity judged related to study treatment is observed where the subjects safety is jeopardized, hold study medication.
- When toxicity resolves to ≤ Grade 1, resume study medication at full dose.

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

8.6.7 Management of concomitant use with strong CYP3A4 inducers

Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during ZYTIGA treatment. Although there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers, because of the potential for an interaction, if a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued.

9. TREATMENT EVALUATION AND OUTCOMES

All baseline evaluations will be performed within 30 days of the beginning of treatment except for laboratory tests and PSA which will be performed within 14 days of the beginning of treatment. For subsequent evaluations, the method of assessment and techniques will be the same as those used at baseline.

Chest image and CT scan of abdomen and pelvis prior to, during and after study are to make sure patient does not have metastatic disease. The same method of assessment and the same technique will be used at baseline and for subsequent evaluations.

By consensus, post-treatment PSA changes are not described as "responses."[52] Moreover, there are no clinically validated criteria for PSA "response" for subjects with non-castrate disease. As such, outcome reporting based on PSA percentage declines, or on the proportion of subjects showing normalization of an abnormal level does not apply to this subset of subjects.

9.1 Primary Endpoint

The primary endpoint is progression-free survival (PFS) defined as an undetectable PSA (using a routine PSA assay) with non-castrate level of testosterone (>150 ng/dL) at 18 months from the time of treatment initiation.

9.1.1 Undetectable PSA

An undetectable PSA is defined per the institution of participant registration.

A confirmatory PSA must be drawn no less than 2 weeks following the first undetectable PSA. If that confirmatory PSA also exceeds the above parameter, then the subject is defined as a biochemical failure.

If the confirmatory PSA fails to confirm a biochemical failure, then the subject will remain on study.

9.1.2 Soft tissue complete response

In addition to an undetectable PSA, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (Complete Response per RECIST) in order to meet the criteria for PFS.

Outcome in subjects who develop radiographically evident metastatic disease while on study will be considered treatment failures independent of their respective PSA values.

9.2 Secondary Endpoints

9.2.1 PSA response rate

The percentage of patients with a non-castrate level of testosterone (>150 ng/dL) and an undetectable PSA at 8 months from PSA0 will be measured.

9.2.2 Testosterone and luteinizing hormone recovery rates

Testosterone and LH recovery rates will be measured at 8 months from the start of randomization and at each month of the 10 month follow up period.

9.2.3 Quality of life

Effects of each arm on quality of life, specifically: libido, potency, anxiety, depression, hot flashes, fatigue, joint swelling, muscle discomfort, diarrhea, and cough, and overall quality of life, will be assessed separately for each item as the change at 8 months from Day 1 Cycle 1, and as area under the curve (AUC) between Day 1 Cycle 1 and 8 months after Day 1 Cycle 1.

9.2.4 Safety profile

Safety will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations and clinical laboratory tests throughout the conduct of the study. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. The frequency and intensity of non-hematologic adverse events will be recorded until the subject has completed his participation in the study (See Section 11.5).

9.3 Tertiary Endpoint

9.3.1 Correlative tissue analysis

Correlative tissue analysis with clinical outcomes while on study.

10. DATA REPORTING AND REGULATORY REQUIREMENTS

10.1 Data Collection and Management

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

10.1.1 Electronic Case Report Forms (eCRFs)

The participating sites will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based MSK and PCCTC Caisis Electronic Data Capture (EDC) system. Completion Guidelines will be created by the PCCTC to provide instruction and guidance on how eCRFS should be completed. . Access and training for PCCTC Caisis EDC will be made available to participating sites upon local regulatory approval. The participating site PI is responsible for ensuring eCRFs are completed accurately and in a timely manner.

10.1.2 Source documents

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

10.1.3 Record retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. The investigator will ensure that all regulatory documents and participating site IRB correspondences are maintained in an on site regulatory binder. After study closure, the participating sites must maintain all source documents, study related documents and eCRFs for 3 years.

10.1.4 Source Documentation Submission for Registration at Participating Sites

Participating sites should email any source documentation that corresponds to data entered at registration to PCCTC at PCCTC@mskcc.org within 24 hours (see Section 4.1.2).

10.1.5 Data Submission Timelines

All baseline data should be transmitted to PCCTC within 24 hours of the visit.

All study data should be transmitted to PCCTC within 14 days of visit except for SAE submission (see Section 8.3.1) as described in the Data Management Plan.

10.1.6 Data Review and Queries

PCCTC will review data and source documentation as it is submitted. Data will be monitored and source data verified as necessary and discrepancies will be sent as queries to the participating sites. In addition, PCCTC will review data for logic, consistency, and obvious anomalies. Queries will be sent by PCCTC to participating sites as needed. Participating sites should respond to data queries within 14 days of receipt.

10.2 Study Monitoring and Quality Assurance

Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials

programs. There are several committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the MSKCC Research Council and Institutional Review Board. As a moderate risk trial, this study will be monitored by DSMC twice per year.

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

10.2.1 Data Auditing and Quality Assurance

In addition to review by DSMC, PCCTC will conduct regularly scheduled remote monitoring every 6 weeks and audits as specified below. Registration reports will be generated by the PCCTC to monitor subject accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the Principal Investigator for discussion and action.

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

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

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

Audit findings will be reviewed by PI, Dr. Howard Scher, and disseminated to the Site PIs and staff.

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

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

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

11. STATISTICAL METHODS

11.1 General Considerations

A randomized phase 2 screening design is used to compare the efficacy of abiraterone acetate and abiraterone acetate plus degarelix to degarelix alone for prostate cancer patients in the rising PSA clinical state. It is anticipated that the trial will remain open to accrual for 36 months with an additional 18 month follow-up after accrual closure.The primary endpoint for the study is achieving and maintaining a PSA level defined by the institution of participant registration for eighteen months from treatment initiation(PSA0). A patient that achieves and maintains a PSA0 will be denoted as a success in this design. Patients that are not followed through the 18 month follow-up mark will be counted as failures.

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

11.2 Sample Size Determination

One hundred and twenty patients will be randomized to the three treatment groups. Each abiraterone acetate group will be compared to the degarelix alone group. With 40 patients per group, it is assumed that the probability of a success in the degarelix alone group is ≤ 0.25 and the probability of a success is at least 0.20 greater than degarelix alone in the abiraterone-based groups. Under these projections, there is greater than an 80% chance of finding for either abiraterone-based treatment relative to degarelix alone using Fisher's exact test with a one-sided 0.20 significance level. The type 1 and type 2 errors are applied separately to each abiraterone acetate group comparison.

The choice of a 0.20 significance level is intended to reduce the sample size required for this comparative study. A significant outcome does not imply definitive evidence of superiority for either abiraterone-based treatment relative to degarelix alone due to this high type 1 error, but instead provides sufficient evidence that testing of abiraterone acetate should proceed.

11.3 Analysis Population

The analysis population will include all subjects who receive at least 1 dose of study drug.

11.4 Demographics and Baseline Characteristics

Demographic variables will include age, race, ethnicity, height, and weight. Baseline disease characteristics will include time from diagnosis, time from radical prostatectomy to PSA progression and time from radical prostatectomy to initiation of study drug.

11.5 Safety Analysis

11.5.1 Adverse events

Safety analysis will be summarized using the Safety Population defined as any patient receiving any part of study treatment.

Extent of exposure to study treatment will be summarized and details will be provided. Treatment emergent adverse events (AEs) are those events that occur or worsen on or after first dose of study drug up through 30 days post last dose. Adverse events will be coded using the MedDRA coding system and all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

11.5.2 Clinical laboratory tests

All Grade 3 and 4 abnormal laboratory test results will be reported according to the NCI-CTCAE Version 4.0 criteria.

12. REGULATORY AND PROTECTION OF HUMAN SUBJECTS

12.1 Roles and Responsibilities

12.1.1 Lead Site/Sponsor Principal Investigator

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

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

12.1.2 PCCTC

The PCCTC is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals and required regulatory documents from each site.
- Managing subject registration
- Developing and maintaining Clinical Data Management documents and procedures
- CRF development, setup of study database, and subsequent design changes
- Participating in review of content of the CRF against the protocol requirements
- EDC system administration (user/site accounts setup, maintenance and revocation)
- Data review, cleaning, query management and resolution
- Establishing procedures for documentation, reporting and submitting of AE's and SAEs to the PCCTC.
- Reviewing AEs and SAEs
- Submitting AEs and SAEs to Janssen

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- Training participating sites on EDC
- Collecting and compiling data from each participating site
- Data reviewing from all participating sites
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.
- Overseeing the management of study drug at pariticipating sites

12.1.3 Participating Sites

Participating sites are responsible for performing the following tasks:

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

12.2 Ethical Considerations

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

12.3 Regulatory Documentation

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

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

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical licenses for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and normals

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

12.4 Protocol Amendments

Each change to the protocol document must be organized and documented by the PCCTC, reviewed and approved by Janssen Scientific Affairs, LLC, and approved by the MSKCC IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating sites. All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating sites must obtain approval for all amendments from their IRB within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continue enrolling new participants until site IRB approval of the revised protocol document granted and submitted to the PCCTC, who will in turn submit the approval documenaton to MSKCC.

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

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

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

12.5 Additional IRB Correspondences

Continuing Review Approval

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

Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections 8.5.1 and 8.5.4.

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

Prospective Deviations

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

Retrospective Deviations

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

Participating Site IRB Reporting

Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to PCCTC who will in turn submit to MSK IRB/PB upon receipt.

Other correspondence

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

12.6 Written Informed Consent

Patients will be required to sign and date (in triplicate) a statement of informed consent that meets the requirements of the Code of Federal Regulations (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the IRB. The medical record will include a statement that written informed consent was obtained (and document the date that it was obtained) before the patient is enrolled in the study. The original signed document will become part of the patient's medical record, a copy will be forwarded to the lead site pursuant to registration and to the PCCTC, and a copy will be sent home with each patient. Details regarding Informed Consent can be found in Section 6.1.

Informed Consent Procedures for Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to Good Clinical Practice and protocol guidelines

12.7 Protection of Privacy

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

12.8 Terminating or Modifying the Study

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

12.9 Noncompliance

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

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APPENDIX A: ECOG PERFORMANCE STATUS SCALE

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

APPENDIX B: PRO SURVEY

Patient Study ID: _____
Study Visit: _____
Date Completed: _____

Symptom Questionnaire

Please answer the following questions about your symptoms in the last 7 days:

1. In the last 7 days, what was the SEVERITY of your **fatigue, tiredness, or lack of energy** at its WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe

2. In the last 7 days, how much did **fatigue, tiredness, or lack of energy** INTERFERE with your usual or daily activities:

- € Not at all
- € A little bit
- € Somewhat
- € Quite a bit
- € Very much

3. In the last 7 days, what was the SEVERITY of your **aching joints (such as elbows, knees, shoulders)** at their WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe

4. In the last 7 days, what was the SEVERITY of your **aching muscles** at their WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe

Please continue on the next page →

5. In the last 7 days, what was the SEVERITY of your **decreased sexual interest** at its WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe

6. In the last 7 days, what was the SEVERITY of your **difficulty getting or keeping an erection** at its WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe
- € Not sexually active
- € Prefer not to answer

7. In the last 7 days, how OFTEN did you have **ejaculation problems**:

- € Never
- € Rarely
- € Occasionally
- € Frequently
- € Almost Constantly
- € Prefer not to answer

8. In the last 7 days, how OFTEN did you have **hot flashes**:

- € Never
- € Rarely
- € Occasionally
- € Frequently
- € Almost Constantly

9. In the last 7 days, what was the SEVERITY of your **hot flashes** at their WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe

Please continue on the next page →

10. In the last 7 days, how OFTEN did you have **loose or watery stools (diarrhea)**:

€ Never
€ Rarely
€ Occasionally
€ Frequently
€ Almost Constantly

11. In the last 7 days, what was the SEVERITY of your **anxiety** at its WORST:

€ None
€ Mild
€ Moderate
€ Severe
€ Very Severe

12. In the last 7 days, how much did **anxiety** INTERFERE with your usual or daily activities:

€ Not at all
€ A little bit
€ Somewhat
€ Quite a bit
€ Very much

13. In the last 7 days, what was the SEVERITY of your feelings that **nothing could cheer you up** at their WORST:

€ None
€ Mild
€ Moderate
€ Severe
€ Very Severe

14. In the last 7 days, what was the SEVERITY of your **sad or unhappy feelings** at their WORST:

€ None
€ Mild
€ Moderate
€ Severe
€ Very Severe

Please continue on the next page →

15. In the last 7 days, what was the SEVERITY of your **cough** at its WORST:

- € None
- € Mild
- € Moderate
- € Severe
- € Very Severe

16. How would you describe your **overall quality of life**, during the past week, including today?

€0	€1	€2	€3	€4	€5	€6	€7	€8	€9	€10
As Bad As It Can Be										As Good As It Can Be

Thank you for completing this questionnaire.

APPENDIX C: JANSSEN SERIOUS ADVERSE EVENT REPORT FORM (FOR PCCTC)

CLINICAL SERIOUS ADVERSE EVENT REPORT
Janssen Services, LLC

FAX COVER PAGE

Protocol Number: _____ EUDRACT Number: (if applicable) N/A

To: _____ Fax No: _____

Pages: _____ ☐ Initial report ☐ Follow-up report Date of Report: d d M O N y y

SITE INFORMATION

Site ID Number _____ Dummy Initials*: [redacted] Subject ID Number: _____

Country where SAE occurred: _____

Date Investigator/Investigational Staff became aware of SAE: d d M O N y y

Principal Investigator's Name: _____ Reported By: _____

Site Address: _____

Telephone #: _____ (country code) Fax #: _____ (country code)

**(Dummy) initials to be removed by GTM/LTM for trials where study subjects will be identified by the Subject ID and Date of Birth (DOB).*

REPORTING

Investigator's Statement (Principal or Sub-Investigator)

I have verified the data on this SAE Report and have determined they are accurate and compatible with source documents.

Investigator Name (Please print): _____

Investigator Signature (required): _____ Date: d d M O N y y

FOR SPONSOR USE ONLY

Date SAE report received: d d M O N y y GMS Reference Number: _____

Sponsor Rep/Agent who received this report: (*please print name clearly*) _____

Clinical Contact's Telephone Number, please include country code: _____

Additional information requested? ☐ No ☐ Yes, specify: _____

Investigator: File original SAE report in TCF.
Sponsor: File a copy of the SAE report in the Investigator File with a copy of the attachments.

Janssen Services, LLC

CLINICAL SERIOUS ADVERSE EVENT REPORT
FAX COVER PAGE

SAE DESCRIPTION

ATTACH SAE CRF PAGES AND COPIES OF OTHER RELEVANT CRF PAGES/DOCUMENTS AND INDICATE IN CHECKBOXES BELOW:

☐SAE CRF ☐Concomitant Therapy ☐Medical History ☐Exposure/Study Drug Administration ☐Relevant Labs, X-rays

☐ Other:

Investigator Narrative : For **EACH SAE** describe the course of events, timing and suspected causes

Signs & Symptoms	
Risk Factors	
Investigations and Supporting Diagnostics (eg labs)	
Differential Diagnosis	
Course of Events	
Treatment for SAE/ Response to Treatment	
Suspected Causes	
Other Comments	
Dechallenge	If applicable, describe whether and which event(s) abated on withdrawal of the study agent(s).
Rechallenge	If applicable, describe whether and which event(s) re-occurred on re-initiation of the study agent(s).

Investigator: File original SAE report in TCF.
Sponsor: File a copy of the SAE report in the Investigator File with a copy of the attachments.

Janssen Services, LLC
Protocol Number 212082PCR2013 EUDRACT Number *N/A*

CLINICAL SERIOUS ADVERSE EVENT REPORT

☐ Initial Report ☐ Follow-up report | (Dummy) Initials* [redacted] | Subject ID Number:

SUBJECT

Sex:	Height:	Weight:	Date of Birth:	Age at Onset of SAE
☐ Male ☐ Female ☐ Undifferentiated	☐ cm ☐ in	☐ kg ☐ lb	d d M O N y y y y	☐ Days ☐ Months ☐ Years

SAE DIAGNOSIS

If this is a follow-up report, please indicate for each SAE, whether the SAE Diagnosis provided is ***replacing*** *the initial diagnosis, or if the SAE Diagnosis is a new term, reported* ***in addition to*** *the SAE Term(s) reported in the initial report.*
** (Dummy) initials to be removed by GTM/LTM for trials where study subjects will be identified by the Subject ID and Date of Birth (DOB).*

	SAE (if diagnosis unknown, list symptoms)	SAE (if diagnosis unknown, list symptoms)	SAE (if diagnosis unknown, list symptoms)
SAE DIAGNOSIS			
Onset	d d M O N y y 24 hour clock	d d M O N y y 24 hour clock	d d M O N y y 24 hour clock
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe

	Causality	Action taken with agent	Causality	Action taken with agent	Causality	Action taken with agent
Agent A	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
Agent B	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable

Related to Trial Procedure? Is SAE related to any trial procedure **not** including study agent therapy? If yes, please specify the specific trial procedure in narrative

Related to Trial Procedure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
SAE Outcome	☐ Recovered/resolved ☐ Recovered/resolved with sequelae Recovery date: d d M O N y y ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal[1] ☐ Unknown	☐ Recovered/resolved ☐ Recovered/resolved with sequelae Recovery date: d d M O N y y ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal[1] ☐ Unknown	☐ Recovered/resolved ☐ Recovered/resolved with sequelae Recovery date: d d M O N y y ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal[1] ☐ Unknown
SAE Seriousness Category	☐ Death[2] ☐ Hospitalization required[3] ☐ Prolonged hospitalization ☐ Life threatening ☐ Persistent or significant disability/incapacity ☐ Congenital anomaly/ birth defect ☐ Other medically important condition	☐ Death[2] ☐ Hospitalization required[3] ☐ Prolonged hospitalization ☐ Life threatening ☐ Persistent or significant disability/incapacity ☐ Congenital anomaly/ birth defect ☐ Other medically important condition	☐ Death[2] ☐ Hospitalization required[3] ☐ Prolonged hospitalization ☐ Life threatening ☐ Persistent or significant disability/incapacity ☐ Congenital anomaly/ birth defect ☐ Other medically important condition

[1] If the SAE outcome is "Fatal", please ensure that the "Death" checkbox in the "SAE Seriousness Category" section is marked.
[2] Record death information on the following page in the "SAE General" section. [3] Record hospital admission date on the following page in the "SAE General" section.

Continue on next page

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Enter Name of R&D Company here
Protocol Number 212082PCR2013 EUDRACT Number *N/A*

CLINICAL SERIOUS ADVERSE EVENT REPORT (continued)

☐ Initial Report ☐ Follow-up report	(Dummy) Initials*: [redacted]	Subject ID Number:

** (Dummy) initials to be removed by GTM/LTM for trials where study subjects will be identified by the Subject ID and Date of Birth (DOB).

Death

Date of death*: d d M O N y y

Was autopsy performed? ☐ No ☐ Yes (If yes, attach copy of report if available)

Hosp

Hospital admission date: d d O N y y

Hospital discharge date: d d M O N y y

Trial Design

☐ Open-label only
☐ Blinded only
☐ Multi-phased: ☐ Open-label phase ☐ Blinded phase

If blinded trial or blinded phase of trial:
Random. No:

Blind broken?
☐ No
☐ Yes**

STUDY AGENT(S) AND DOSING

☐ **Subject has NEVER received any study agent (skip remainder of this section)**

Start Date	Start Time	Stop Date	Stop Time	Indication
d d M O N y y	24 hour clock	d d M O N y y	24 hour clock	

Agent A	Batch/Lot No.	Med. Kit No.

Dose	Unit	Frequency	Route

Start Date	Start Time	Stop Date	Stop Time	Indication
d d M O N y y	24 hour clock	d d M O y y	24 hour clock	

Agent B	Batch/Lot No.	Med. Kit No.

Dose	Unit	Frequency	Route

* Ensure this Date of death is entered on the 'End of Trial' (Death information) or other disposition page in the subject's CRF.
** If blind broken, ensure that 'Date randomization code was broken' is entered on the appropriate CRF page.

Investigator: File original SAE report in TCF.
Sponsor: File a copy of the SAE report in the Investigator File with a copy of the attachments.

APPENDIX D: PCCTC SAE REPORT FORM FOR ALL SITES

Please see the PCCTC Serious Adverse Event Report Form

APPENDIX E: GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
ADT	androgen-deprivation therapy
AE	adverse event
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
ASAEL	Agent Specific Adverse Event List
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BP	blood pressure
BUN	blood urea nitrogen
C02	carbon dioxide
CAEPR	Comprehensive Adverse Event and Potential Risks
CBC	complete blood count
CFR	Code of Federal Regulations
Cl	chloride
CLIA	Clinical Laboratory Improvement Amendments
Cr	creatinine
Cmax	maximum plasma concentration
CRDB	Clinical Research Database
CRF	case report form
CRPC	castration resistant prostate cancer
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome p-450
dL	deciliter
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
DSM	data and safety monitoring
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FDG-PET	2-[18F]fluoro-2-deoxyglucose positron emitting tomography
FDHT	18-fluoro-dehydrotestosterone
GM-CSF	granulocyte-macrophage colony-stimulating factor

GnRH	gonadotropin-releasing hormone
Hct	hematocrit
Hgb	hemoglobin
HEENT	head, eyes, ears, nose and throat examination
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
K+	potassium
KLK1	kallikrein 1

LD	longest diameter
LDH	lactate dehydrogenase
LH	luteinizing hormone
LVEF	left ventricular ejection fraction
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximum tolerated dose
MUGA	multi gated acquisition scan
N	number of subjects or observations
Na	sodium
NCI	National Cancer Institute
NIH	National Institutes of Health
NYHA	New York Heart Association
NSAID	nonsteroidal anti-inflammatory drug
PCCTC	Prostate Cancer Clinical Trials Consortium
PCWG	Prostate Cancer Working Group
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PO	per os (by mouth)
PQC	product quality complaint
PR	partial response
PSA	prostate-specific antigen
PSA-DT	prostate-specific antigen doubling time
PSMA	prostate specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
QOL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP	radical prostatectomy
RPC	Research Program Coordinator
RSA	Research Study Assistant
SAE	serious adverse event
SC	subcutaneous
SUV	standardized uptake value

T	testosterone
TB	pulmonary tuberculosis
TDP	time to disease progression
TGP	prostate-specific transglutaminase
TMPRSS2	transmembrane protease, serine 2
ULN	upper limit of normal
WBC	white blood cell