TITLE: Phase II clinical trial of abiraterone acetate without exogenous glucocorticoids in men with castration-resistant prostate cancer with correlative assessment of hormone intermediates.

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Sponsor-Investigator:
[redacted]

Principal Investigators:
[redacted]

Coordinating Center:
Dana-Farber Cancer Institute
[redacted]

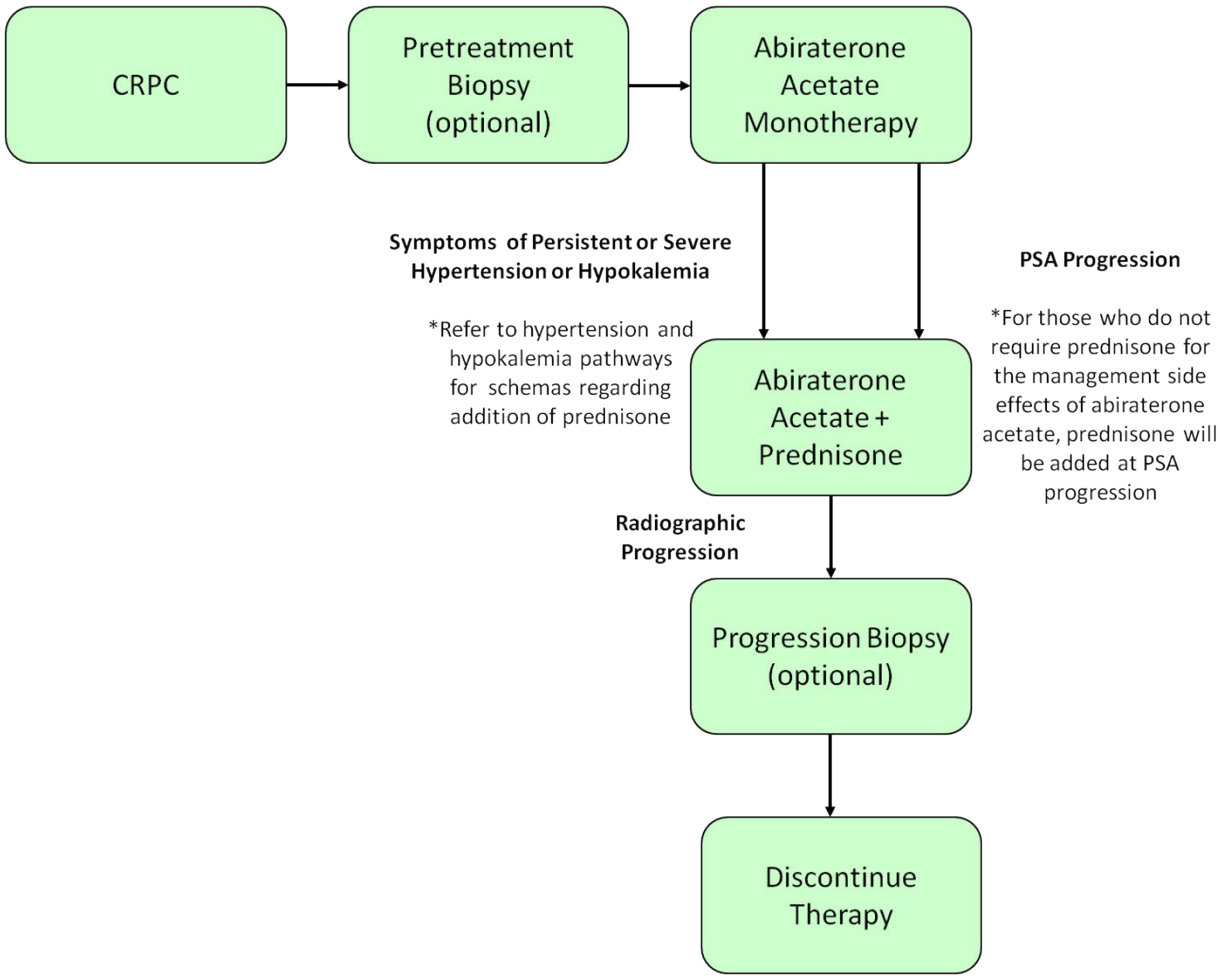
Agent(s):
Abiraterone acetate
Prednisone
Janssen Scientific Affairs, LLC is providing funding and drug support.

ABBREVIATIONS

Abiraterone acetate – AA
Adrenocorticotropic hormone – ACTH
Adverse event – AE
Alanine transaminase – ALT
American Society of Anesthesiologists – ASA
ANC – Absolute neutrophil count
Androgen deprivation therapy – ADT
Androgen Receptor – AR
Area under the concentration-time curve – AUC
Aspartate transaminase – AST
Body-mass-index – BMI
Cancer and Leukemia Group B – CALGB
Cancer Therapy Evaluation Program – CTEP
Case Report Form – CRF
Castration resistant prostate cancer – CRPC
Circulating Tumor Cells – CTCs
Clinical Trials Research Informatics Office – CTRIO
Code of Federal Regulations – CFR
Complete response – CR
Partial response – PR
Computed tomography – CT
Dana Farber Cancer Institute – DFCI
Dana-Farber/Harvard Cancer Center – DF/HCC
Dana-Farber/Partners Cancer Care – DF/PCC
Data Safety and Monitoring Committee – DSMC
Dehydroepiandrosterone – DHEA
Dehydroepiandrosterone-sulfate – DHEA-S
Deoxyribonucleic acid – DNA
Dihydrotestosterone – DHT
Eastern Cooperative Oncology Group – ECOG
Echocardiogram – ECHO
Electrocardiogram – ECG
Food and Drug Administration – FDA
Good Clinical Practice – GCP
Health Insurance Portability and Accountability Act – HIPAA
Hematoxylin and eosin – H&E
Human immunodeficiency virus – HIV
Immunohistochemistry – IHC
Institutional Review Board – IRB
International Normalized Ratio – INR
Investigational New Drug – IND
Laser capture microdissection – LCM
Liver function test – LFT
Lower limit of normal – LLN

Luteinizing hormone-releasing hormone – LHRH
Magnetic Resonance Imaging – MRI
Maximum concentration – C_{max}
Mineralocorticoid excess – ME
Multi Gated Acquisition Scan – MUGA
National Cancer Institute Common Terminology Criteria for Adverse Events – NCI CTCAE
New York Heart Association – NYHA
Not Reached – NR
Office of Data Quality – ODQ
Office for Human Research Studies – OHRS
Overall survival – OS
Partial thromboplastin time – PTT
Positron emission tomography – PET
Principal Investigator – PI
Product Quality Complaint - PQC
Progression free survival – PFS
Progressive disease – PD
Prostate specific antigen – PSA
Prostate Cancer Clinical Trials Working Group – PCWG
Prothrombin time – PT
Response Evaluation Criteria In Solid Tumors – RECIST
Reverse transcription polymerase chain reaction – RT-PCR
Ribonucleic acid – RNA
Serious adverse event – SAE
Single-nucleotide polymorphism – SNP
Stable disease – SD
Time to PSA Progression – TTPP
Unknown – UN
Upper limit of normal – ULN
WBC – White blood cell count

STUDY SCHEMA



SCHEMA OF INITIATING PREDNISONE FOR SYMPTOMS OF HYPERTENSION

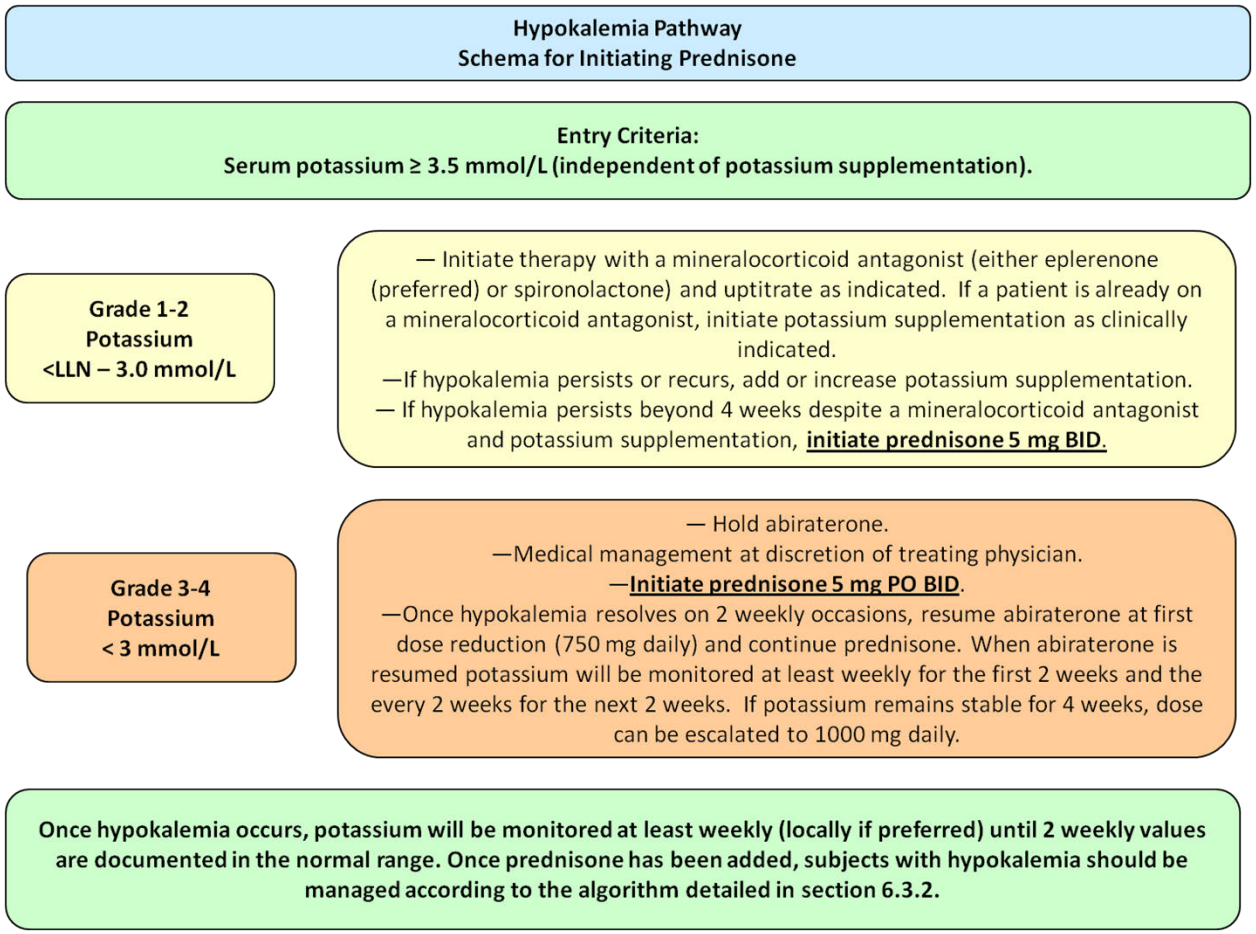
Hypertension Pathway

Entry Criteria:
Blood Pressure < 140/90 on no more than three anti-hypertensive agents.
Drug formulations containing two or more anti-hypertensive agents will be counted based on the number of active agents in each formulation.

Grade 1 Blood	Management per investigator. No abiraterone dose reduction.
Grade 2 Blood	– Initiate therapy with a mineralocorticoid antagonist (either eplerenone (preferred) or spironolactone) and uptitrate as indicated. If a patient is already on a mineralocorticoid antagonist, another anti-HTN agent (choice of agent at physician discretion) may be used or existing medications may be uptitrated. – If HTN persists or recurs, can add a second anti-HTN agent (choice of agent at physician discretion) and uptitrate as indicated. – If HTN persists for 4 weeks or recurs despite addition of 2 anti-HTN agents, **initiate prednisone 5 mg PO BID**.
Grade 3 Blood	– Hold abiraterone. – Initiate therapy with a mineralocorticoid antagonist (either eplerenone (preferred) or spironolactone) and uptitrate as indicated. If a patient is already on a mineralocorticoid antagonist, another anti-HTN agent (choice of agent at physician discretion) may be used or existing medications may be uptitrated. – Once HTN improves to <140/<90 on 2 weekly occasions, resume full dose abiraterone. – If HTN persists or recurs, hold abiraterone if not already held, add a second anti-HTN agent (choice of agent at physician discretion) and uptitrate as indicated. – Once HTN improves to <140/<90 on 2 weekly occasions, resume full dose abiraterone. – If HTN persists for 2 weeks or recurs despite addition of 2 anti-HTN agents, hold abiraterone if not already held, and **initiate prednisone 5 mg PO BID**. – Once HTN improves to <140/<90 on 2 weekly occasions, resume full dose abiraterone.
Grade 4 Hypertensive	– Hold abiraterone. – Medical management at discretion of treating physician. – **Initiate prednisone 5 mg PO BID**. – Once HTN improves to <140/<90 on 2 weekly occasions, resume abiraterone at first dose reduction (750 mg daily) and continue prednisone. If blood pressure remains stable for 4 weeks, dose can be escalated to 1000 mg daily.

If a patient is found to have a blood pressure reading ≥140/≥90, the blood pressure should be repeated up to 3 times and the lowest reading recorded. For patients with an elevated blood pressure, readings should be checked at least 3 times over a week before determining the grade of hypertension (i.e. one elevated blood pressure reading on the clinic day does not confirm the grade of hypertension). Once HTN occurs, blood pressure will be monitored at least weekly until improvement to <140/<90 on 2 weekly occasions. The above algorithm assumes compliance with medications and no other significant change in a patient's clinical status (concomitant illness or injury). Once prednisone has been added, subjects with HTN should be managed according to the algorithm detailed in Section 6.3.1.

SCHEMA OF INITIATING PREDNISONE FOR SYMPTOMS OF HYPOKALEMIA*



*For patients with grade 1-2 hypokalemia, initiation of therapy with a mineralocorticoid antagonist should be administered only if the Principal Investigator, [redacted], deems the toxicity to be related to abiraterone acetate. If the grade 1-2 hypokalemia is not thought to be related to abiraterone acetate, potassium levels should be monitored weekly until potassium levels return to the entry criteria. Entry criteria for serum or plasma potassium is greater than or equal to 3.5 mmol/L or Institutional LLN (independent of potassium supplementation).

STUDY SYNOPSIS

1. Population: Men with CRPC.

2. Treatment: Participants will be treated with AA in 28-day cycles. Participants will be monitored (weekly for the first two cycles, then on Day 1 of each subsequent cycle) for symptoms of persistent or severe mineralocorticoid excess (including hypertension, hypokalemia). Day 8, 15, 22 monitoring of cycles 1-2 can occur locally if preferred. For participants who experience symptoms of persistent or severe hypertension or hypokalemia as detailed in the above schema, prednisone 5 mg by mouth twice daily will be added. Specific management of symptoms of hypertension and hypokalemia after addition of prednisone is detailed in Section 6.3. We will monitor for other symptoms of AA toxicity to include fluid retention and fatigue. Management of these symptoms is detailed in Section 6.3. For participations who tolerate AA monotherapy without the addition of prednisone to manage symptoms of persistent or severe mineralocorticoid excess, prednisone 5 mg by mouth twice daily will be added at PSA progression. Participants will be continued on study until radiographic progression or taken off study for another reason as detailed in Section 5.4. Toxicity will be defined by NCI CTCAE (version 4).

   Participants will undergo optional pre-treatment and progression tumor biopsies. After the progression biopsy is performed, protocol therapy will be discontinued. Participants who stop protocol therapy before receiving four cycles of AA will not be asked to undergo the optional second biopsy.

3. Correlative Studies: Participants will undergo assessment of serum corticosteroid intermediates and ACTH at baseline and subsequent treatment visits for correlation with symptoms of mineralocorticoid excess. Participants will also undergo (optional) pre-treatment and progression tumor biopsies for assessment of possible mechanisms of AA resistance.

4. Planned Enrollment: 60 participants.

5. Milestone Plan:

Milestone	Timeline
Planned Interim Analysis (see below)	6 months from enrollment of first subject
Enrollment of 100% of Target Enrollment	12 months from enrollment of first subject
Last Subject/Last Visit on Study	24 months from enrollment of first subject
Collection and Analysis of Primary and Secondary Endpoint Data	3 months following last subject/last visit
Completion of Final Study Report	6 months following last subject/last visit

   Six months following enrollment of the first participant, we will conduct a planned analysis to assess the number of participants requiring therapy with prednisone for management of symptoms of mineralocorticoid excess.

6. DSMC/Safety Review: Quarterly.

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1. OBJECTIVES

The primary objectives of this trial are to determine the incidence of mineralocorticoid toxicity, characterize symptoms of mineralcorticoid toxicity, and evaluate the need for exogenous glucocorticoids in participants treated with AA monotherapy for CRPC. A correlative aim is to assess clinical signs of mineralocorticoid toxicity with changes in serum ACTH and corticosteroid intermediates. Additionally, we will seek to assess the efficacy, in terms of PSA response, of the addition of prednisone to AA at PSA progression. Lastly, we will evaluate possible mechanisms of AA resistance via optional serial metastasis biopsies.

1.1 Study Design

1. This is a phase II, prospective, multicenter, single-arm study accessing safety of AA without exogenous glucocorticoids in participants with CRPC. Participants will be treated with AA in 28-day cycles. Participants will be monitored (weekly for the first two cycles, then on Day 1 of each subsequent cycle) for symptoms of persistent or severe mineralocorticoid excess (including hypertension, hypokalemia). Cycle 1 Day 8 and 22 monitoring of cycle 1 can occur locally if preferred. For participants who experience symptoms of persistent or severe hypertension or hypokalemia as detailed in the above schema, prednisone 5 mg by mouth twice daily will be added. Specific management of symptoms of hypertension and hypokalemia after addition of prednisone is detailed in Section 6.3. Cycle 1 Day 15 mnoitoring must occur at the study institution and the participant must be seen by a study MD or NP. We will monitor for other symptoms of AA toxicity to include fluid retention and fatigue. Management of these symptoms is detailed in Section 6.3. For participations who tolerate AA monotherapy without the addition of prednisone to manage symptoms of persistent or severe mineralocorticoid excess, prednisone 5 mg by mouth twice daily will be added at PSA progression. Participants will be continued on study until radiographic progression or taken off study for another reason as detailed in Section 5.4. Toxicity will be defined by NCI CTCAE (version 4).

   Participants will undergo optional pre-treatment and progression tumor biopsies. After the progression biopsy is performed, protocol therapy will be discontinued. Participants who stop protocol therapy before receiving four cycles of AA will not be asked to undergo the optional second biopsy.

1.2 Primary Objectives

- To determine the proportion of participants requiring the addition of prednisone to manage symptoms of persistent or severe mineralocorticoid excess.

1.3 Secondary Objectives

- To assess safety and tolerability associated with AA monotherpy and the addition of prednisone to AA.

- To determine the proportion of participants requiring the addition of prednisone to manage symptoms of severe fatigue.

- To assess changes in serum concentrations of corticosteroid intermediates between baseline and subsequent assessment visits.

- To assess changes in serum concentrations of ACTH between baseline and subsequent assessment visits.

- To assess changes in serum concentrations of androgen (including testosterone, DHT and androgen precursors) between baseline and subsequent assessment visits.

- To assess changes in BMI and hemoglobin-A1c between baseline and subsequent assessment visits.

- To assess PSA response and duration of PSA response to AA monotherapy.

- To assess PSA response and duration of PSA response to addition of prednisone to AA at time of PSA progression on AA monotherapy.

- To assess response of measurable disease and time to progression of measurable disease to AA monotherapy.

- To assess response of measurable disease and time to progression of measurable disease to addition of prednisone to AA at time of PSA progression on AA monotherapy.

- To investigate subsequent lines of therapy, including line of agent, name of agent, and PSA kinetics following study drug discontinuation and to correlate with response to study drug.

1.4 Exploratory Objectives

- To analyze possible mechanisms of AA resistance in serial CRPC metastasis biopsies (including AR expression by IHC, AR regulated gene expression by IHC, tissue androgen levels by mass spectrometry, and whole-exome and transcriptome sequencing).

- To measure CTCs as a marker of response/resistance to abiraterone.

- To analyze CTCs for mechanisms of AR resistance including AR nuclear localization, AR splice variant expression and AR sequence.

- To analyze circulating tumor DNA for mechanisms of AR resistance and correlate to response to abiraterone.

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Abiraterone acetate (JNJ212082)

Abiraterone (17-(3-pyridyl)androsta-5,16-dien-3β-ol) is a rationally designed, inhibitor of CYP17. Key design features of this compound include the 3-pyridyl substitute, resulting in more potent inhibition of CYP17, and 16,17-double bond, which is essential for irreversible inhibition of CYP17.[1, 2] CYP17 is a key enzyme in cortisol synthesis via its 17α-hydroxylase activity and plays a central role in androgen biosynthesis via its 17,20-lyase activity (Figure 1).[3] Abiraterone is a potent inhibitor with an apparent inhibition constant of 0.5 nM.[2]

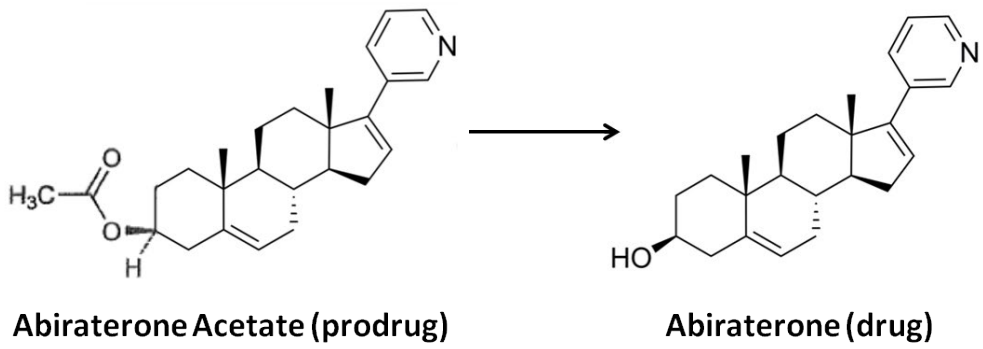


Figure 1. The pro-drug AA is converted to abiraterone after absorption.

Abiraterone has poor bioavailability. AA is the 3-acetylated analog and pro-drug of abiraterone suitable for oral administration (Figure 2). The chemical nomenclature of AA is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene. Its empirical formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Once absorbed after oral administration, AA is rapidly deacetylated and converted to the active form abiraterone. Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6.[4]

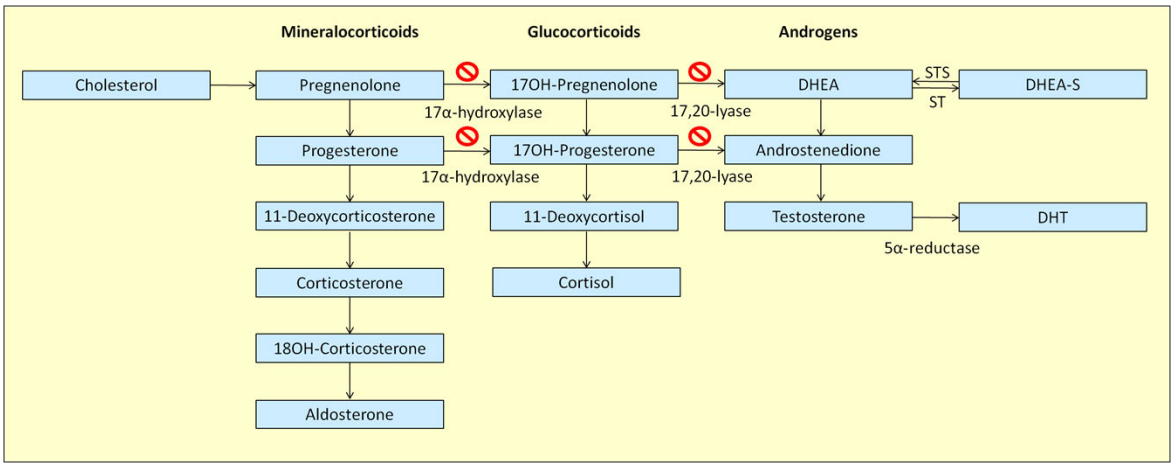


Figure 2. The steroid biosynthesis pathway. Abiraterone inhibits 17α-hydroxylase (crossed in red) which results in reduction of serum cortisol and consequent increase in ACTH that drives the steroid biosynthesis pathway. Abiraterone also inhibits 17,20-lyase (crossed in red) resulting in significant suppression of DHEA, androstenedione, and testosterone. Dehydroepiandrosterone sulfate, DHEA-S; Dehydroepiandrosterone, DHEA; Dihydrotestosterone, DHT; ST, sulfotransferase; STS, steroid sulfatase.

Physiologic Rational for Safety of Inhibition of CYP17

Congenital CYP17 deficiencies result in a rare form of congenital adrenal hyperplasia, which cause impaired adrenal and gonadal steroidogenesis.[3] Although the production of cortisol, androgens, and estrogens is impaired, corticosterone synthesis is unaffected. Given that corticosterone is a weak glucocorticoid, patients do not develop adrenal insufficiency, though they have higher levels of ACTH. Raised levels of ACTH result in increased steroid precusors upstream of CYP17 which results in a syndrome of mineralocorticoid excess, characterized by fluid overload, hypertension, and hypokalemia. This syndrome may be effectively managed with mineralocorticoid antagonists with or without low doses of glucocorticoids to suppress ACTH production.[5]

Rational for Using Abiraterone Acetate in Prostate Cancer

Ketoconazole, a weak and nonspecific CYP17 inhibitor, is commonly used in clinical practice. Ketoconazole, an imidazole antifungal agent, inhibits several enzymes in the steroid biosynthesis pathway including desmolase and 11β-hydroxylase, in addition to CYP17.[6] When administered at a dose of 400 mg three times daily, ketoconazole reduced testosterone, androstenedione and DHEA.[7]

Numerous phase II studies have demonstrated that treatment with ketoconazole resulted in PSA response rates (defined as a ≥50% decrease in PSA levels from baseline) ranging from 40-62% with median duration of response lasting between 3.3-7 months.[5] In the CALGB 9583 phase III trial comparing androgen withdrawal to androgen withdrawal plus ketoconazole, response rates were 11 and

27%, respectively (p=0.02), however there was no difference in overall survival between the two groups, which may reflect 82% crossover rate.[8]

Treatment with ketoconazole has been limited by toxicity. In the phase III CALGB trial, grade 3 and 4 toxicity was reported in 21% of patients and comprised primarily fatigue, and hepatic, neurologic or respiratory issues. Other limitations include multiple drug interactions that limit its use in patients with comorbidities. Additionally, it requires frequent daily dosing and hydrocortisone daily for glucocorticoid replacement.

The development of a therapy with once daily administration, limited drug-drug interactions, that lacks a requirement for concomitant corticosteroids would represent a significant advancement in the management of CRPC and desirable alterative to therapy with ketoconazole.

Clinical Data with Abiraterone Acetate
AA has been tested in patients in phase I, II and III trials. Below we will summarize the results of these trials with a focus on safety and efficacy (Table 1).

Table 1. Summary of clinical trials of Abiraterone Acetate.

Study	Patient	Drug	Efficacy	Toxicity
Phase 1 Attard et al (2008)[9]	21 Chemo-naive Keto-naive (non-metastatic and metastatic)	AA 250-2000 mg daily, fasting, 5 dose escalations	Increased ACTH, upstream steroids; decreased testosterone, downstream androgenic steroids; PSA decline to ≥30%, 50%, and 90% were 66%, 57%, and 29%, respectively; Median TTPP 69 to ≥ 578 days; 62% partial RECIST response	Hypertension (29%), hypokalemia (48%), lower-limb edema (5%); No grade 3 or 4 toxicities; Precipitation of migraine and asthma, 1 patient each, both of whom required dexamethasone
Phase I Ryan et al (2010)[10]	33 Chemo-naive Keto-naive (14) (non-metastatic and metastatic)	AA 250-1000 mg daily, fed and fasting cohorts, 4 dose escalations	Decreased testosterone, downstream, androgenic steroids; PSA decline ≥50% at week 12 in 55% (47% vs. 64% prior keto vs. no keto); Median TTPP 234 days (283 vs. 230 days prior keto vs. no keto)	Hypertension (36%), hypokalemia (24%), peripheral edema (24%), fatigue (67%), headache (33%), nausea (33%), diarrhea (30%); Grade 3 hypertension

				(12%), grade 3/4 hypokalemia (9%)
Phase II Attard et al (2009)[11]	42 Chemo-naive (non-metastatic and metastatic)	AA 1000 mg daily, fasting	PSA decline ≥50% observed in 67% (≥90% observed in 19%); Median TTPP 225 days; 38% partial RECIST response; CTC declined to <5/7.5 mL in 59%; 33% from phase I/II had reversal of resistance with dexamethasone	Hypertension (40%), hypokalemia (8%), fluid overload (31%); Managed with eplerenone except in 3 patients who required dexamethasone
Phase II Danila et al (2010)[12]	58 Chemo-treated Keto-naive (27) (metastatic only)	AA 1000 mg daily (fasting) + prednisone 5 mg twice daily	PSA decline to ≥30%, 50%, and 90% were 47%, 36%, and 16%, respectively (PSA decline ≥50% 26% vs. 45% prior keto vs. no keto); Median TTPP 169 days (99 vs. 198 prior keto vs. no keto); 18% partial RECIST response; CTC declined <5/7.5 mL in 34%	Hypertension (4%), hypokalemia (5%), peripheral edema (9%), abnormal LFTs (15%); No grade 3/4 hypertension, hypokalemia, peripheral edema; No use of eplerenone
Phase II Reid et al (2010)[13]	47 Chemo-treated (metastatic)	AA 1000 mg daily, fasting	PSA decline to ≥30%, 50%, and 90% were 68%, 51%, and 15%, respectively; Median TTPP 169 days; 27% partial RECIST response; CTC declined <5/7.5 mL in 45%	Hypokalemia (55%), hypertension (17%), fluid retention (25%); Grade 3 hypokalemia (2%)
Phase III de Bono et al (2011)[14]	1195 Chemo-treated (metastatic only)	AA 1000 mg daily versus placebo (fasting) + prednisone 5 mg twice daily	AA-prednisone vs. placebo-prednisone median OS 14.8 vs. 10.9 months (p<0.001), TTPP 10.2 vs. 6.6 months (p<0.001), PFS 5.6 vs. 3.6 months	AA-prednisone vs. placebo-prednisone hypertension 10% vs. 8%, hypokalemia 17% vs. 8%, fluid

			(p<0.001), PSA response rate 29% vs. 6% (p<0.001)	retention 31% vs. 22%
Phase III Ryan et al (2012)[15]	1088 Chemo-naive (metastatic only)	AA 1000 mg daily versus placebo (fasting) + prednisone 5 mg twice daily (2:1)	AA-prednisone vs. placebo-prednisone median OS NR vs. 27.2 months (p=0.01), PFS 16.5 vs. 8.3 months (p<0.001), median time-to-opiate use NR vs. 23.7 months (p<0.001), median time to initiation of cytotoxic chemotherapy 25.2 vs. 16.8 months (p<0.001), median time to decline in performance status 12.3 vs. 10.9 months (p=0.005), median TTPP 11.1 vs. 5.6 months (p<0.001)	AA-prednisone vs. placebo-prednisone hypertension 22% vs. 13%, hypokalemia 17% vs. 13%, fluid retention 28% vs. 24%, increased ALT 12% vs. 5%, increased AST 11% vs. 5%, cardiac disorder 19% vs. 16%

AA = abiraterone acetate; keto = ketoconazole; chemo = chemotherapy; ACTH = adrenocorticotropic hormone; PSA = prostate specific antigen, TTPP = time-to-PSA progression; CTC = circulating tumor cells; LTs = liver function tests; OS = overall survival; PFS = progression-free survival; ALT = alanine transaminase; AST = aspartate transaminase.

Early phase I studies showed good bioavailability at doses of greater than 200 mg, a half-life of approximately 28 hours, and significant increased absorption with food.[16] The initial studies included men who were not on LHRH agonist. In this population, a compensatory surge in luteinizing hormone led to an increase in testosterone by day 4 of treatment with AA in some men, suggesting the need for AA to be given concomitantly with suppressed testicular function.

A Phase I/II study evaluated AA in chemotherapy-naive men with CRPC resistant to multiple prior hormone therapies.[9, 11] The phase I study (n=21) evaluated once, daily, continuous AA, which escalated through five doses (250-2,000 mg) in three-patient cohorts. In this study, AA was well tolerated. There were no treatment related grade 3 and grade 4 toxicities. Hypertension, hypokalemia, and lower-limb edema was observed in 29%, 48%, and 5% patients, respectively. These side effects were controlled with eplerenone, a selective mineralocorticoid receptor antagonist. AA was associated with increased levels of ACTH (5-fold) and steroids upstream of CYP17 (10-40-fold) with suppression of serum testosterone (<1 ng/dl), downstream androgenic steroids, and estradiol in all patients. Declines in PSA ≥30%, 50%, and 90% were observed in 14 (66%), 12

(57%), and 6 (29%) patients, respectively and lasted between 69 to ≥ 578 days. Five (62%) of eight patients with measurable disease at baseline had confirmed partial response by RECIST. The addition of dexamethasone 0.5 mg/d resulted in salvage of 4/15 patients who had PSA progression.

The phase II expansion of this study included 42 patients.[11] A decline in PSA of ≥50% was observed in 67% of patients and declines of ≥90% were observed in 19% of patients. The median TTPP was 225 days. Of the 24 patients with measurable disease, 38% experienced partial response by RECIST. Decreases in CTC counts were documented (decline to <5/7.5 mL in 59% of patients). In an exploratory analysis of all 54 patients in the phase I/II trial, addition of dexamethasone at PSA progression reversed resistance in 33% of patients. In long term follow up, after all patients were discontinued from therapy with AA, 38/42 (90%) patients experienced signs of mineralocorticoid excess including hypertension, hypokalemia, and peripheral edema. This was effectively treated with eplerenone without exogenous glucocorticoids in 35/38 (92%) patients. Only 3/38 (5%) patients required administration of exogenous glucocorticoids (dexamethasone 0.5 mg daily). The median time to initiation of eplerenone was 28 days.

Two phase II studies in post-docetaxel CRPC patients have also been conducted.[12, 13] PSA declines of ≥50% occurred in 22/58 (36%) and 24/47 (51%) patients, respectively, with the median TTPP of 169 days for both studies. Partial responses were seen in 4/22 (18%) and 8/30 (27%) patients with RECIST-evaluable target lesions, respectively.

The efficacy of AA was demonstrated in a phase III trial in which 1,195 men previously treated with docetaxel were randomly assigned to AA plus prednisone or placebo plus prednisone.[14] After a median follow-up of 13 months, AA significantly increased OS (median 14.8 versus 10.9 months, p<0.0001), time to PSA progression (10.2 versus 6.6 months, p<0.0001), radiographic PFS (5.6 versus 3.6 months, p<0.001), and PSA response rate (29% versus 6%, p<0.001) compared with placebo plus prednisone. Based on this trial, AA plus prednisone was approved by the FDA in April 2011 for the treatment of patients with metastatic CRPC following docetaxel.[14]

A randomized, phase III study evaluated AA in chemotherapy-naive patients with metastatic CRPC. The trial showed that treatment with AA plus prednisone produced a statistically significant improvement in radiographic PFS (16.5 vs. 8.3 months, p<0.001) and a strong trend for increased OS (NR vs. 27.2 months, HR 0.75, 95% CI 0.61-0.93, p=0.01) over placebo plus prednisone. Based on the results of this trial, In December 2012, the FDA expanded the indication for AA plus prednisone for the treatment of patients with chemotherapy-naive metastatic CRPC. On February 7, 2018, abiraterone acetate received FDA approval for use, incombination with prednisone, for the treatment of patients with metastatic, high-risk castration-sensitive prostate cancer (CSPC).

Clinical Safety Data

The most common AEs related to AA monotherapy, as detailed by the aforementioned clinical trials, include fatigue as a result of reduced serum cortisol secondary to CYP17 inhibition and hypertension, fluid retention, and hypokalemia secondary to mineralocorticoid excess caused by compensatory high levels of ACTH. Two phase I and two phase II trials evaluated the safety of AA without exogenous glucocorticoids. The rates of hypertension, fluid retention, and hypokalemia are detailed in Table 1. In general, symptoms of mineralocorticoid excess were managed with eplerenone, a selective mineralocorticoid receptor antagonist, or other agents including beta-blockers or diuretics. Exogenous glucocorticoids were occasionally used to manage symptoms of mineralocortcoid excess.

Treatment with AA is also associated with LFT abnormalities. In the post-docetaxel phase III trial, rates of LFT abnormalities were 10% vs. 8% and in the AA-prednisone vs. placebo-prednisone, respectively. In the chemotherapy-naive phase III trial, increased ALT and AST (12% vs. 5% and 11% vs. 5% for all grades) was noted in the AA-prednisone vs. placebo-prednisone arm, respectively.

Pharmacokinetics of Abiraterone Acetate

Pharmacokinetics were evaluated in two phase I trials and are detailed in table 2.[9, 10] In the Attard et al study, a plateau of endocrine effects was reported at doses >750 mg, and 1000 mg was selected as the dose for phase II evaluation. There were significant variations in the AUC and C_{max} among patients. When administered with food high in fat content, drug exposure increased 4.4 fold compared to fasting. There was no significant increase in C_{max}, but absorption was significantly extended after food. In the Ryan et al study, C_{max} was achieved within 1.5-5 hours.[10] Less than proportional increases in both C_{max} and AUC were observed across dose levels in fed and fasted patients.

Table 2. Abiraterone Acetate Pharmacokinetics Parameters.

Parameter	Abiraterone acetate
Absorption	Systemic absorption (C_{max} and AUC) increases with increasing fat content of meals. The AUC was approximately 5-fold higher when administered with a low-fat meal, and approximately 10-fold higher when administered with a high-fat meal. Due to normal variation and composition of meals, no food should be consumed for at least 2 hours before the dose of AA and for at least one hour after the dose.
Metabolism	Following oral administration, AA is hydrolyzed to abiraterone (active metabolite) through esterases and not CYP. The 2 main circulating metabolites are abiraterone sulphate (inactive; formed via SULT2A1) and N-oxide abiraterone sulphate (inactive; formed via CYP3A4 and SULT2A1).
Elimination	88% recovered in feces and 5% in urine (55% as unchanged AA, 22% as abiraterone).
Half-life	Mean terminal half-life= 12 ±5 hours.
Protein Binding	Highly protein bound (>99%); it is not a substrate for but is an inhibitor of P-glycoprotein.

2.2 Study Disease

Prostate cancer is the most common cancer in men in the United States, with a life time risk of 16%, and the second leading cause of death in this population.[17] In 2012, it is estimated that 241,740 men will be diagnosed with prostate cancer and 28,170 will die of the disease.[17]

ADT is the mainstay of systemic therapy for patients with prostate cancer. In patients with advanced disease, despite initial response rates of 80-90%, nearly all men develop progressive disease within 18-24 months of therapy.[18] Men with CRPC have a poor prognosis with median survival of 16-18 months and fewer than 20% of patients surviving beyond three years.[19]

2.3 Rationale

In the castrate state, ligands to the AR have been thought to be derived from the adrenal glands and intra-tumoral androgen production, which is thought to play a critical role in disease progression.[18] ADT removes 90% of circulating androgens,

mainly produced in the gonads, however as much as 10% of circulating testosterone remains in part due to the peripheral conversion of adrenal steroids to testosterone. Furthermore, in patients with castrate levels of testosterone, tissue levels of androgens remain sufficient to activate the AR. Additional mechanisms of resistance to castration include: 1) increased AR expression leading to activation in the presence of low levels of ligand, 2) AR gene mutations leading to promiscuous activation of AR signaling by various ligands, 3) AR splice variants leading to constitutive activation of AR signaling, and 4) increased intra-tumor expression of enzymes involve in steroidogenesis.[6, 8, 20]

Inhibition of extratesticular sources of androgens is a desirable therapeutic strategy in the management of men with prostate cancer. CYP17, via its 17,20-lyase activity, plays a crucial role in androgen biosynthesis and is considered a key therapeutic target. AA is a selective and irreversible inhibitor of CYP17 which has demonstrated clinical efficacy in patients with CRPC.

Currently AA is administered with concomitant prednisone. Point mutations of the AR, which appear to cluster in the ligand-binding domain, are rare in therapy naive patients but occur in 15-45% of castration-resistant disease and can increase AR affinity for a wide range of steroids.[21] Richards et al recently demonstrated that treatment with exogenous glucocorticoids *in vitro* can activate mutant AR at clinically relevant doses observed in CRPC patients treated with AA and therefore could serve as a mechanism of resistance to AA.[22]

In addition, numerous toxicities have been attributed to glucocorticoids, including dermatologic toxicity, ocular toxicity, gastritis and peptic ulcer disease, osteoporosis, hypokalemia and fluid shifts, neuropsychiatric issues, hyperglycemia, lipid abnormalities, and increased infections. Estimates of the frequency and severity of AEs, as well as the respective dose and duration of therapy that may result in such AEs, are limited by the modest number of prospective trials that address this question. Several large retrospective reviews (conducted in patients with rheumatoid arthritis on chronic low-dose steroids) have shown that long-term glucocorticoid use, even in low doses, is a significant independent predictor of numerous SAEs and that risk is both dose and time dependent.[23, 24] Given that prostate cancer disproportionately affects the elderly (with the highest incidence rates seen in those aged 70 to 80 years of age), who frequently suffer from multiple co-morbid medical conditions (with rates of multi-morbidity at 35% in Americans aged 65-79 and 70% in those ≥80 years), therapy with chronic glucocorticoids may be associated with increased toxicity in this population.

Given the potential toxicity associated with chronic glucocorticoids and the potential for glucocorticoids to activate promiscuous AR, we propose to evaluate the safety profile of AA monotherapy without the administration of exogenous glucocorticoids.

2.4 Correlative Studies Background

Treatment with AA results in elevated levels of upstream intermediates to CYP17. Based on phase I data, treatment with AA monotherapy results 5-fold increases in ACTH, which provides a positive drive for mineralocorticoid biosynthesis.[9] This results in a 10-fold increase in deoxycorticosterone and 40-fold increase in corticosterone.[9] Given symptoms of mineralocorticoid excess including hypertension, hypokalemia, and volume overload, renin is suppressed, providing a negative feedback to decrease aldosterone production. In a phase II study, treatment with AA resulted in a marked rise in urinary metabolites of steroids upstream of CYP17.[25] In this study, there was no evidence of a difference in mean urinary excretion of mineralocorticoid precursor metabolites and the dose of eplerenone required to control toxicity. In this study, we hypothesize that baseline and on treatment serum ACTH and mineralocorticoid intermediates may predict risk for developing mineralocorticoid toxicity.

Given that AR signaling continues to play a critical role in prostate cancer progression, we plan to analyze possible mechanisms of AA resistance in serial CRPC metastasis biopsies. AA treatment has been associated with upregulated intratumoral CYP17 and increased expression of AR splice variants.[26] Our laboratory has established techniques for measuring AR signaling using gene expression profiling.[27] Additionally we are able to measure intracellular testosterone and DHT levels using mass spectrometry.[28, 29]

3. PARTICIPANT SELECTION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria, the investigator should consult [redacted] and the DFCI study team before enrolling the subject in the study.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Be a male ≥ 18 years of age.

3.1.2 Participants must have histologically or cytologically confirmed adenocarcinoma of the prostate without >50% neuroendocrine differentiation or small cell histology.

3.1.3 Participants must have progressive disease as defined by one or more of the following:

- Castrate resistant disease as defined by PCWG2.[30] Participants must have a rise in PSA on two successive determinations at least one week apart and PSA levels ≥ 2 ng/ml (only the screening PSA needs to be ≥ 2 ng/ml) and testosterone levels < 50 ng/dL.
- Soft tissue progression defined by RECIST 1.1.
- Bone disease progression defined by PCWG2 with two or more new lesions on bone scan.[30]

3.1.4 Participants without orchiectomy must be maintained on LHRH agonist/antagonist therapy.

3.1.5 Participants must have a testosterone level < 50 ng/dL.

3.1.6 Participants may have had any number of previous hormonal therapies (antiandrogens including enzalutamide, estrogens, finasteride, dutasteride, ketoconazole) provided these were discontinued ≥ 4 weeks before starting the trial. Prior therapy with steroids is allowed though these must be discontinued ≥ 2 weeks before starting the trial. Inhaled, topical, and intra-articular steroids are allowed.

3.1.7 Participants may have had up to two previous cytotoxic therapeutic regimens provided these were discontinued ≥ 4 weeks before starting the trial.

3.1.8 At least a 4 week interval from previous prostate cancer treatment other than LHRH agonist/antagonist therapy, bisphosphonates, denosumab to the start of protocol therapy.

3.1.9 Participants receiving bisphosphonates therapy or denosumab can be maintained on this therapy. If participants have not started bisphosphonates, it is recommended that they start treatment after the first (optional) biopsy.

3.1.10 ECOG performance status < 2 (Karnofsky >60%, see Appendix A).

3.1.11 Participants must have normal organ and marrow function as defined below:

- Platelets > 50,000/mcL
- Serum or plasma potassium ≥ 3.5 mmol/L or Institutional LLN (independent of potassium supplementation)
- Serum albumin ≥ 3.0 g/dL
- AST, ALT, and total bilirubin ≤ 1.5 x Institutional ULN
- PTT ≤ 60, INR ≤ 1.5 Institutional ULN unless on warfarin therapy (investigator would need to determine if safe for participant to stop warfarin prior to (optional) biopsy)

3.1.12 Controlled blood pressure (systolic blood pressure <140 and diastolic blood pressure <90) on no more than three anti-hypertensive agents. Drug formulations containing two or more anti-hypertensive agents will be counted based on the number of active agents in each formulation.

3.1.13 Left ventricular ejection fraction ≥ 50%.

3.1.14 Have signed an informed consent document indicating that the subjects understands the purpose of and procedures required for the study and are willing to participate in the study.

3.1.15 Be willing/able to adhere to the prohibitions and restrictions specified in this protocol.

3.1.16 Written Authorization for Use and Release of Health and Research Study Information (US sites only) has been obtained.

3.1.17 Able to swallow the study drug whole as a tablet.

3.1.18 Willing to take AA on an empty stomach; no food should be consumed at least two hours before and for at least one hour after the dose AA is taken.

3.1.19 Participants 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 PI during the treatment period and for 1 week after last dose of AA.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Uncontrolled illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or would make prednisone/prednisolone (corticosteroid) use contraindicated.

3.2.2 Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart disease or cardiac ejection fraction measurement of < 50 % at baseline.

3.2.3 Thromboembolism within 6 months of Cycle 1, Day 1.

3.2.4 Severe hepatic impairment (Child-Pugh Class C).

3.2.5 History of pituitary or adrenal dysfunction.

3.2.6 Poorly controlled diabetes.

3.2.7 History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.

3.2.8 Have a pre-existing condition that warrants long-term corticosteroid use. Inhaled steroids are allowed.

3.2.9 Individuals with a history of a different malignancy are ineligible except for the following circumstances: 1) individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy, or 2) individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: superficial bladder cancer, basal cell or squamous cell carcinoma of the skin.

3.2.10 Known brain metastasis.

3.2.11 Prior therapy with AA.

3.2.12 Have known allergies, hypersensitivity, or intolerance to AA or prednisone or their excipients.

3.2.13 Surgery or local prostatic intervention within 4 weeks of the first dose. In addition, any clinically relevant issues from the surgery must have resolved prior to Cycle 1, Day 1.

3.2.14 Major surgery or radiation therapy within 4 weeks of Cycle 1, Day 1.

3.2.15 Strontium-89, samarium-153, or radium-223 therapy within 4 weeks of Cycle 1, Day 1.

3.2.16 Radiotherapy, chemotherapy or immunotherapy within 4 weeks, or palliative radiation to bone metastases within 14 days of administration of Cycle 1, Day 1.

3.2.17 Current enrollment in an investigational drug or device study or participation in such a study within 4 weeks of Cycle 1, Day 1.

3.2.18 Any acute toxicities due to prior chemotherapy and/or radiotherapy that have not resolved to a NCI CTCAE (version 4) grade of ≤ 1. Chemotherapy induced alopecia and grade 2 peripheral neuropathy are allowed.

3.2.19 Condition or situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with participant's participation in the study.

3.2.20 Individuals not willing to comply with the procedural requirements of this protocol.

3.2.21 HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with AA.

3.3 Inclusion of Minorities and Other Underrepresented Populations

Every effort will be made to include men from minority populations. The enrollment of minority men will reflect the proportion of minority participants at the sites participating in the trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the DFCI by the Study Coordinator. All sites should call the DFCI Study Coordinator to verify treatment availability.

Following registration, participants should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Participating Institutions

To register a participant, the following documents should be completed by the research nurse or data manager and faxed to [redacted] or e-mailed to the Study Coordinator:

- Copy of forms specified in Appendix B
- Signed participant consent form
- HIPAA authorization form

The research nurse or data manager at the participating site will then call or e-mail e-mail the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

5. TREATMENT PLAN

All protocol required therapy will be prescribed by prescription and taken by the participant on an outpatient basis. Participants will be treated with four 250 mg tablets (1,000 mg) of AA taken orally. No food should be consumed for at least two hours before the dose and for at least one hour after the dose. The tablets should be swallowed whole with water. Tablets should not be crushed or chewed. All participants without orchiectomy will be maintained on LHRH agonist/antagonist therapy.

Participants will be treated with AA in 28-day cycles. Participants will be monitored (weekly for the first cycle, then on Day 1 of each subsequent cycle) for symptoms of persistent or severe mineralocorticoid excess (including hypertension, hypokalemia). Cycle 1 Day 8, and 22 monitoring of cycle 1can occur locally if preferred. Cycle 1 Day 15 monitoring must occur at the study institution and the participant must be seen by a study MD or NP. For participants who experience symptoms of persistent or severe hypertension or hypokalemia as detailed in the above schema, prednisone 5 mg by mouth twice daily will be added. Specific management of symptoms of hypertension and hypokalemia after addition of prednisone is detailed in Section 6.3. We will monitor for other symptoms of AA toxicity to include fluid retention and fatigue. Management of these symptoms is detailed in Section 6.3. For participations who tolerate AA monotherapy without the addition of prednisone to manage symptoms of persistent or severe mineralocorticoid excess, prednisone 5 mg by mouth twice daily will be added at PSA progression. Participants will be continued on study until radiographic progression or taken off study for another reason as detailed in Section 5.4. Toxicity will be defined by NCI CTCAE (version 4).

Participants may undergo an optional pre-treatment and/or progression tumor biopsy. The optional pre-treatment biopsy will be after registration to the trial and prior to starting protocol therapy. If a progression biopsy is done, it should be performed before protocol therapy is discontinued.

Expected toxicities and potential risks as well as dose modifications for AA monotherapy are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant’s malignancy.

Treatment Description					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Abiratereone acetate	No food should be consumed for at least two hours before the dose and for at least one hour after the dose. The tablets should be swallowed whole with water. Do not crush or chew tablets.	1000 mg	Oral	Once daily	28 days
Prednisone* *Prednisone will only be added to manage symptoms of mineralocorticoid excess or at PSA progression.	Take with food	5 mg	Oral	Twice daily	

5.1 Pre-treatment Criteria

5.1.1 For Cycle 1, Day 1, the following parameters must be met:

- Serum or plasma potassium ≥ 3.5 mmol/L or Institutional LLN (independent of potassium supplementation)
- AST/ALT ≤ 1.5 x Institutional ULN
- Total bilirubin ≤ 1.5 x Institutional ULN
- Systolic blood pressure < 140 mmHg or diastolic blood pressure < 90 mmHg

If these parameters are not met, the participant can be evaluated on a weekly basis. Hypertension should be treated as appropriate.

For subsequent cycles, refer to dose modifications as outlined in Section 6.

5.2 Agent Administration

5.2.1 Abiraterone acetate

- Administration: 1,000 mg orally once daily. Treatment can continue until evidence of radiographic progression or the participant is taken off the study for another reason as detailed in Section 5.4.

- Dosing: 1,000 mg orally taken once daily as four 250 mg tablets. Possible dose modifications are outlined in Section 6.

- Vital Signs: Vital signs including blood pressure, pulse, weight and temperature should be taken on day 1 of each cycle, and at the time of any symptom evaluation. For the first two cycles, blood pressure will be checked weekly and then on day 1 of each subsequent cycle.

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

  If a dose is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing. Participants will be asked to record actual dosing in a drug diary (Appendix C). There is no specified order of administration of the study drugs prescribed in this protocol.

5.2.2 Prednisone

- Administration when required per protocol: 5 mg orally twice daily. Treatment can continue until evidence of radiographic progression or the participant is taken off the study for another reason.

- Dosing when required per protocol: 5 mg orally twice daily. Dose modification is not allowed.

- Vital Signs: Vital signs including blood pressure, pulse, weight and temperature should be taken on day 1 of each cycle, and at the time of any symptom evaluation. For the first two cycles, blood pressure will be checked weekly and then on day 1 of each subsequent cycle.

- Oral Doses: Prednisone should be taken with a meal. If a dose is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing. Participants will be asked to record actual dosing in a drug diary.

There is no specified order of administration of the study drugs prescribed in this protocol.

5.3 General Concomitant Medications and Supportive Care Guidelines

Supportive Care Radiation
Palliative radiation to a metastasis or local recurrence is allowed if the patient otherwise meets criteria to remain on study and the treating MD believes the patient is still benefitting from study drug.

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

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

In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 600 mg daily for 6 days) followed by a single dose of AA 1000 mg, the mean plasma AUC∞ of AA was decreased by 55%. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment with AA are to be avoided. In a separate clinical pharmacokinetic interaction study of healthy subjects, coadministration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of AA. If the treating investigator determines a strong inducer of CYP3A4 is warranted, please contact the PI. A list of strong CYP3A4 inducers and inhibitors can be found in Appendix F.

If at any time an investigator suspects a drug-drug interaction due to AA therapy, the PI, [redacted] should be contacted at [redacted] or paged at [redacted] Additional information is provided in the AA Investigator's Brochure and USPI for AA (www.zytiga).

5.4 Duration of Therapy

Duration of therapy will depend on response, evidence of disease progression, and tolerance. In the absence of treatment delays due to AEs, treatment may continue until one of the following criteria:

- Radiographic disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Participant decided to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treated investigator.

Protocol therapy may be held for up to six weeks in the event of an AE and the participant may be restarted on therapy when the toxicity has resolved to ≤ grade 1, In the event of therapy being held for more than six weeks, it is recommended that the participant come off protocol however the treating physician may obtain permission to continue on the protocol with permission of the PI, [redacted] if the treating physician feels it is in the participant's best interest.

5.5 Duration of Follow-Up

Participants will be followed for up to 5 years post-study discontinuation or until death, whichever comes first. Participants will be followed for subsequent lines of therapy, including line of agent, name of agent, and PSA kinetics following study drug discontinuation and correlate with response to study drug. This information will be updated every 6 months. The research team will collect this information during patient clinic visits, by phone, or via medical record review.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific CRF. Alternative care options will be discussed with the participant.

Participants will be removed from treatment at the time of unacceptable AEs but will remain on study (i.e. enrolled on the protocol) until resolution or stabilization of any AEs.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the PI, [redacted] at [redacted] or page [redacted]

6. EXPECTED TOXICITIES, TOXICITY MONITORING, TOXICITY MANAGEMENT AND DOSING DELAYS/MODIFICATIONS

6.1 Expected Toxicities

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.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic CRPC who were using a LHRH agonist or were previously treated with orchiectomy. In both studies, AA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the AA arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the AA arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

In the combined data for the two phase III studies of AA, cardiac failure occurred more commonly in patients treated with AA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking AA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In both studies, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the AA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the AA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the AA arms.

6.1.1 Adverse Reactions for AA

Hypertension, Hypokalemia and Fluid Retention

AA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with AA.

Co-administration of a corticosteroid suppresses ACTH drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating participants 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. Use AA with caution in participants with a history of cardiovascular disease. The safety of AA in participants with left ventricular ejection fraction < 50% or NYHA Class III or IV heart failure (in study of metastatic CRPC following chemotherapy) or NYHA Class II to IV heart failure (in study of metastatic CRPC prior to chemotherapy) was not established because these participants were excluded from these randomized clinical trials. Monitoring participants for hypertension, hypokalemia, and fluid retention is detailed in section 6.2.1. Management of hypertension, hypokalemia and fluid retention is detailed in section 6.3. Control hypertension and correct hypokalemia before and during treatment with AA.

Adrenocorticol Insufficiency
Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking AA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving AA 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 participants 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 AA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity
In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received AA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking AA. No deaths clearly related to AA were reported due to hepatotoxicity events. Monitoring participants for hepatotoxicity is detailed in section 6.2.3. Management of hepatotoxicity is detailed in section 6.3.

For guidance on management of side effects related AA please contact the PI, [redacted] or page [redacted]

See current package insert for AA (Zytiga) for additional information on AA (http://www.zytiga.com/).

6.1.2 AEs for Prednisone

A daily dose of 10 mg of prednisone is near the physiologic steroid dose and thus it is not expected that prednisone will cause significant side effects. Potential side effects of prednisone are listed below:

Cardiovascular: Congestive heart failure (in susceptible patients), hypertension
Central nervous system: Emotional instability, headache, intracranial pressure increased, psychic derangements (including euphoria, insomnia, mood swings, personality changes, severe depression), seizure, vertigo
Dermatologic: Bruising, facial erythema, petechiae, thin fragile skin, urticaria, wound healing impaired
Endocrine and metabolic: Adrenocortical and pituitary unresponsiveness (in times of stress), carbohydrate intolerance, Cushing's syndrome, diabetes mellitus, fluid retention, hypokalemic alkalosis, hypothyroidism enhanced, menstrual irregularities, negative nitrogen balance due to protein catabolism, potassium loss, sodium retention
Gastrointestinal: Abdominal distension, pancreatitis, peptic ulcer (with possible perforation and hemorrhage), ulcerative esophagitis
Hepatic: ALT increased, AST increased, alkaline phosphatase increased
Neuromuscular and skeletal: Aseptic necrosis of femoral and humeral heads, muscle mass loss, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures
Ocular: Exophthalmos, glaucoma, intraocular pressure increased, posterior subcapsular cataracts
Other: Allergic reactions, anaphylactic reactions, diaphoresis, hypersensitivity reactions, infections

Close monitoring of blood sugars is recommended in diabetic participants. Close monitoring for infections is also recommended. It is recommended the prednisone never be stopped suddenly. Gradual tapering of the dose and/or schedule of prednisone is recommended when discontinuing therapy. Monitoring for signs and symptoms of adrenal insufficiency during prednisone administration and tapering is recommended.

6.2 Toxicity Monitoring

6.2.1 Monitoring for Hypertension, Hypokalemia and Fluid Retention

Participants will be monitored closely for symptoms and signs of hypertension, hypokalemia and fluid retention. On Day 1 of each 28-day cycle, participants will undergo blood pressure assessment, physical examination to assess for fluid retention, and laboratory evaluation to assess for hypokalemia. Additionally, on Day 8and 22 of the first 28-day cycle, participants will undergo assessment of blood pressure and serum or plasma potassium levels.

6.2.2 Monitoring for Adrenal Insufficiency
Participants will be monitored closely for symptoms and signs of adrenal insufficiency. On Day 1 of each 28-day cycle, participants will be evaluated via history, physical, vital signs and laboratory assessment (including but not limited to serum chemistry) for signs of adrenal insufficiency. If clinically indicated, appropriate tests to confirm the diagnosis of adrenocortical insufficiency will be performed.

6.2.3 Monitoring for Hepatotoxicity
Participants will be monitored closely for symptoms and signs of hepatotoxicity. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with AA, weekly for the first cycle, then on Day 1 of each subsequent cycle 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 participant's baseline should prompt more frequent monitoring. For subjects who developed hepatotoxicity, please refer to section 6.3 monitoring parameters and toxicity management.

6.3 Toxicity Management and Dosing Delays/Modifications

The starting dose of AA will be 1,000 mg daily. In the presence of any AA related toxicities > grade 2 (NCI CTCAE version 4) during treatment with AA at the starting dose level, excluding the management of hypertension, hypokalemia, limb edema, fatigue, and hepatotoxicity, which is detailed below, AA will initially be held. Once toxicity improves to grade 1 or better, AA can be resumed at 750 mg daily in the subsequent dose level. Two levels of dose de-escalation are planned for the study. If > grade 2 toxicity occurs at dose level -2, participants will be removed from the protocol.

Dose Level	Abiraterone acetate
Starting dose level	1000 mg orally once daily
-1	750 mg orally once daily
-2	500 mg orally once daily

Dose delays and modifications will not necessitate changes in study assessment days.

Dose delays and modifications will be made using the following recommendations: Toxicity assessments will be done using the CTEP Active Version of the NCI CTCAE (version 4) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

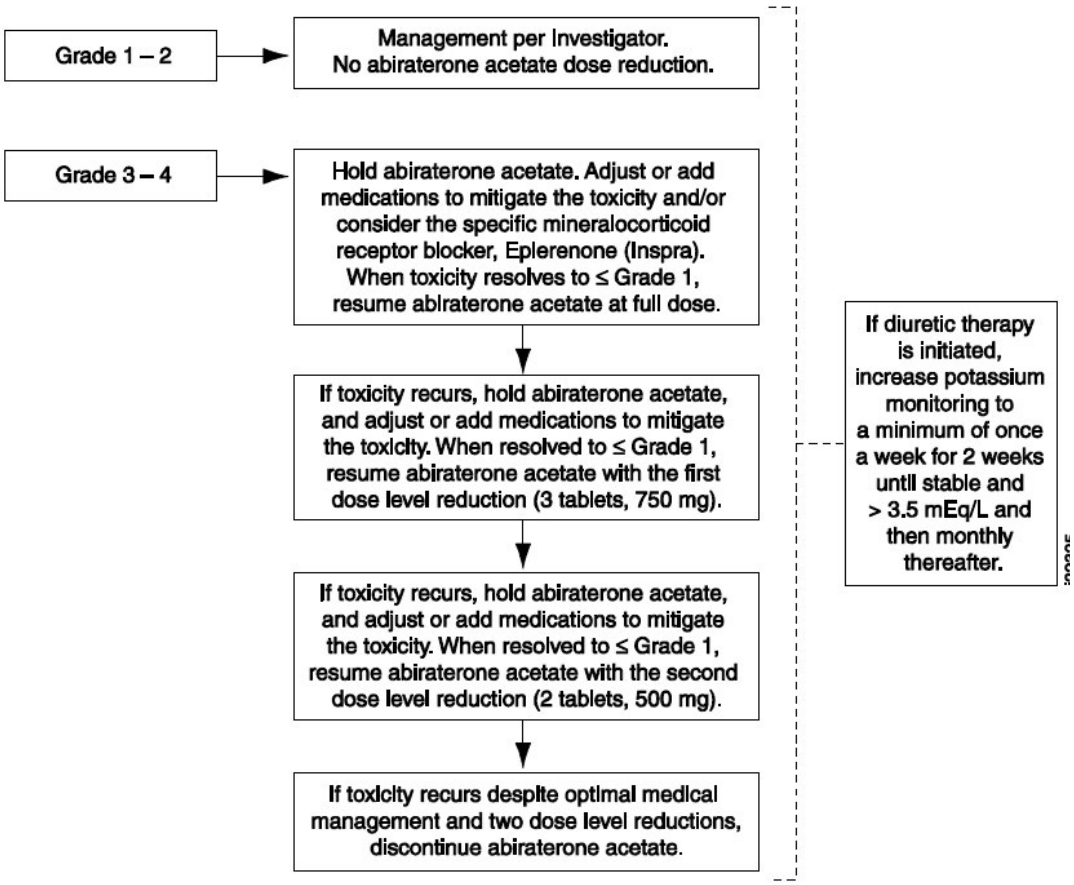
All AEs experienced by participants will be collected from the time of signed consent, through the study and until 30 days following the last dose of study drug. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.3.1 Management of Hypertension

- For management of hypertension prior to the initiation of prednisone, refer to the Hypertension Pathway (Begining of protocol).

- Please note, addition of prednisone should not be made based on one blood pressure reading. For patients with an elevated blood pressure, readings should be checked at least three times over a week before determining the grade of hypertension.

- After prednisone has been initiation, use the below algorithm for management of hypertension.



6.3.2 Management of Hypokalemia

- For management of hypokalemia prior to the initiation of prednisone, please refer to Hypokalemia Pathway.

- After prednisone has been initiation, use the below algorithm for management of hypokalemia.

- Grade 1-2 Hypokalemia (<LLN – 3.0 mmol/L):
    - For recurrent grade 1-2 hypokalemia despite the addition and uptitration of a mineralocorticoid antagonist, addition of prednisone 5 mg twice daily, and potassium supplementation, adjust potassium supplementation as clinically indicated. Once hypokalemia occurs, potassium levels will be monitored weekly until 2 weekly values are documented in the normal range.

- Grade 3-4 Hypokalemia (< 3 mmol/L):
    - For recurrent grade 3-4 hypokalemia despite the addition and uptitration of a mineralocorticoid antagonist, addition of prednisone 5 mg twice daily, and potassium supplementation, hold AA. Adjust potassium supplementation as clinically indicated. Once hypokalemia occurs, potassium levels will be monitored

weekly until 2 weekly values are documented in the normal range, at which point AA will be resumed (at first dose reduction level, 750 mg daily, or if already at first dose reduction then resume at second dose reduction, 500 mg daily). When AA is resumed potassium will be monitored at least weekly for the first 2 weeks and the every 2 weeks for the next 2 weeks.
- If grade 3-4 hypokalemia recurs at a separate point in time despite two dose level reductions of AA, prednisone 5 mg twice daily, potassium supplementation, and optimal medical management, discontinue AA.

6.3.3 Management of Limb Edema

The syndrome of mineralocorticoid excess is classically associated with hypertension, hypokalemia, and limb edema. It is atypical for limb edema to be the only symptom of mineralocorticoid excess associated with AA treatment. In a study by Attard *et al* of 42 patients treated with AA monotherapy, zero patients developed limb edema as the only symptom of mineralocorticoid excess.[25] Given such, prednisone should not be used in the management of isolated limb edema without other symptoms of mineralocorticoid excess to include hypertension and/or hypokalemia. If hypertension and/or hypokalemia occur, refer to section 6.3.1 and 6.3.2 respectively for appropriate management. If grade 3 limb edema occurs, please refer to section 6.3 for instruction regarding dose delays/reductions.

6.3.4 Management of Fatigue

- Grade 1-2 Fatigue:
  - Management per investigator. No investigational product dose reduction.

- Grade 3 Fatigue:
  - Hold AA. Once the toxicity has resolved to ≤ grade 1 or baseline, resume AA at the first dose level reduction (750 mg daily).
  - If grade 3 fatigue recurs at a separate point in time, hold AA and initiate prednisone 5 mg twice daily. Once the toxicity has resolved to ≤ grade 1 or baseline, resume AA at the second dose level reduction (500 mg) and continue prednisone 5 mg twice daily.
  - If grade 3 fatigue recurs at a separate point in time despite two dose level reductions of AA, prednisone 5 mg twice daily, and optimal medical management, discontinue AA.

6.3.5 Management of LFT abnormalities

Hepatic Impairment

In participants with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of AA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an 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 participants 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 ULN or total bilirubin greater than 3X ULN occur in participants with baseline moderate hepatic impairment, discontinue AA and do not re-treat participants with AA.

Avoid AA in participants with baseline severe hepatic impairment (Child-Pugh Class C), as AA has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

- Grade 1 LFT Abnormalities (increase in AST or ALT from ULN to 3.0 x ULN; increase in total bilirubin from ULN to 1.5 x ULN):
    - The frequency of LFT monitoring should be increased, if the investigator judges that the laboratory abnormalities are potentially related to abiraterone. No abiraterone dose reduction is required.
- Grade 2 LFT Abnormalities (increase in AST or ALT > 3.0 – 5 x ULN; increase in total bilirubin from > 1.5 – 3 x ULN):
    - The frequency of LFT monitoring should be increased to ≥ once a week, if the investigator judges that the laboratory abnormalities are potentially related to abiraterone. No abiraterone dose reduction is required.
- Grade 3 LFT Abnormalities (increase in AST or ALT to > 5 x ULN – 20.0 x ULN; increase in total bilirubin to > 3 x ULN – 10.0 x ULN):
    - Hold abiraterone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the LFTs return to baseline value or grade 1. Hold until return to baseline of AST or ALT ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN. If abiraterone resumption is considered for subjects who have experienced grade 3 increases in AST, ALT, or bilirubin, and the PI agrees, resume abiraterone with the first dose level reduction (750 mg) when grade 3 toxicities resolve to grade 1 or baseline. For participants who resume treatment, monitor LFTs at a minimum of every 2 weeks for 3 months and monthly thereafter.
    - If grade 3 increases in AST, ALT, or bilirubin recur after the first dose reduction hold abiraterone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the LFTs return to baseline value or grade 1. If abiraterone resumption is considered for participants who have experienced grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, and the PI agrees, resume abiraterone with the second dose level reduction (500 mg) when AST, ALT, or bilirubin returns to

baseline value or grade 1. For participants who resume abiraterone, monitor LFTs at a minimum of every 2 weeks for 3 months and monthly thereafter.

- Grade 4 LFT Abnormalities (increase in AST or ALT to > 20 x ULN; increase in total bilirubin to > 10 x ULN):
    - Participants must discontinue abiraterone immediately and will not be re-challenged. They should be followed until resolution of LFT abnormalities to ≤ grade 1 or baseline.
- Concurrent elevation of AST/ALT > 3x ULN with bilirubin >2x ULN (unless the concurrent elevation is related to biliary obstruction or other causes unrelated to study treatment)
    - Discontinue abiraterone acetate. No change or consider tapering prednisone if abiraterone acetate discontinued.

6.3.6 Management of other toxicities

See beginning of section 6.3. For all other toxicities, once toxicity improves to grade 1 or better, AA can be resumed at appropriate dose modification. Clinical need for steroids per treating MD's discretion and after discussion with the PI, [redacted] is allowed but discouraged unless the situations outlined in Section 6.3 apply.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Abiraterone acetate

Additional information is provided in the AA Investigator's Brochure and USPI for AA (www.zytiga).

7.1.1 Description

The chemical nomenclature of AA is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene. Its empirical formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Once absorbed after oral administration, AA is rapidly deacetylated and converted to the active form abiraterone. Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6.[4] For pharmacokinetics, refer to section 2.1.1 and Table 2.

7.1.2 Form

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

7.1.3 Storage and Stability

Pharmacy Storage Requirements

The investigational product must be stored in a secure area and administered only to participants entered into the clinical study in accordance with the conditions specified in this protocol. Bottles of investigational product should be stored at a room temperature between 20º-25º C with the cap kept on tightly and should not be refrigerated. Additional information is provided in the AA Investigator's Brochure.

Storage Requirements for the Participant

Bottles of investigational product should be stored at room temperature with the cap kept on tightly and should not be refrigerated. Participants should be advised to keep all medications out of the reach and out of sight of children.

7.1.4 Compatibility

Treatment with AA monotherapy will be administered via oral tablets and should be administered without food. Participants may receive prednisone on this study. AA has been tested in combination with prednisone and AA is currently approved by the FDA for use with concomitant prednisone. We do not anticipate incompatibility from the combination of AA with prednisone.

7.1.5 Handling

Investigational product must only be dispensed by a Pharmacist or medically qualified staff. Investigational product is to be dispensed only to participants enrolled in this study. Once the investigational product is prepared for a participant, it can only be administered to that participant.

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

7.1.6 Availability

AA tablets will be provided to each site. Participants will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 3 day window. Patients will be dispensed a 30, 60, or 90-day supply depending on the frequency of their protocol visits determined by the treating physician. Information presented on the labels for investigative product will comply with applicable local regulations. Site pharmacist will dispense the investigational product to each participant in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure. Abiraterone Acetate is supplied and will be provided by Janssen Scientific Affairs, LLC.

7.1.7 Ordering

Except in very unusual circumstances, each participating institution will order AA directly from the supplier. Janssen Scientific Affairs, LLC will not directly provide AA to each participating site. This will be coordinated through a third party drug distribution supplier. A participating site may order AA only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the supplier.

7.1.8 Accountability

Accountability for investigational product is the responsibility of the investigator.

The study site must maintain accurate records demonstrating dates and amount of investigational product (AA) received, to whom dispensed (participant by participant accounting), and accounts of any investigational product accidentally or deliberately destroyed. At the end of the study, reconciliation must be made between the amount of investigational product supplied, dispensed, and subsequently destroyed.

At the time of delivery of investigational product to the site, the investigator, designee, or Pharmacist (where appropriate) will confirm that the supplies for the study have been received. This following information will be confirmed: lot numbers, quantities shipped/delivered, and date of receipt.

7.1.9 Destruction and Return

Drug should be destroyed at the site, after the sponsor–investigator approves the drug destruction policy at the site. Drug will not be returned to Janssen Scientific Affairs, LLC. Destruction will be documented in the Drug Accountability Record Form. Evidence of drug destruction will need to be provided to Janssen Scientific Affairs, LLC to verify destruction.

7.2 Prednisone

7.2.1 Description

Prednisone is a corticosteroid.

7.2.2 Form

Prednisone 5-mg tablets are small, white tablets.

7.2.3 Storage and Stability

Prednisone should be stored at 25°C, excursions permitted to 15° to 30°C.

7.2.4 Compatibility

We do not anticipate any excess toxicity combining AA with prednisone. There are no overlapping toxicities and no apparent drug-drug interactions (either pharmacokinetic or combined inhibition of enzymes in the any of the adrenal steroid synthesis pathways). Prednisone has been used in phase I-III trials combined with AA as described above.

7.2.5 Handling

There are no specific instructions for handling prednisone.

7.2.6 Availability

Prednisone will not be provided by the study and will be prescribed by standard prescriptions.

Prednisone is commercially available and will NOT be provided free of charge for this study.

Prednisone is a commercially available agent that is available from various manufacturers.

8. CORRELATIVE/SPECIAL STUDIES

A correlative aim is to assess clinical signs of mineralocorticoid toxicity with changes in serum ACTH and corticosteroid intermediates. The corticosteroids intermediates which will be measured will include the following: pregnenolone, progesterone, deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxypregnenolone, 17α-hydroxypregesterone, 11-deoxycortisol, cortisol. These hormones will be assayed by novel mass spectrometry techniques.

Additional exploratory correlative studies will include analysis of tumor obtained from optional serial CPRC metastasis biopsies for possible mechanisms of AA resistance (AR expression by IHC, AR regulated gene expression by IHC, tissue androgen levels by mass spectrometry, and whole-exome and transcriptome sequencing). In addition, serum androgens will be assayed by novel mass spectrometry techniques. Blood will be collected for CTC analysis including enumeration, AR nuclear localization, AR splice variant expression and AR sequence and circulating tumor DNA analysis to assess mechanisms of AR resistance to AA. The correlative studies (with the exception of the optional biopsies) are required. Lastly, blood will be collected for circulating tumor DNA analysis.

Subject samples (including blood and tissue samples) at time of collection will be handled and procured by a dedicated technician or physician at each study site. Samples processing will take place by dedicated technicians and physicians. Samples will be processed for correlative studies and remaining samples will be stored for future use to include assessment of biological and molecular predictive and prognostic biomarkers. CTC samples and cfDNA samples for circulating tumor DNA analysis will be sent to and analyzed at Memorial Sloan-Kettering Cancer Center (MSKCC) and the Lang Lab at the University of Wisconsin. Any further future analyses not specified in this protocol or above will be agreed upon by prior approval from Janssen Scientific Affairs, LLC. Instructions on sample collection and processing are contained in the Laboratory Manual with instructions on sample collection and processing.

8.1 Data Analysis

Determination of all molecular endpoints will occur as listed above so as to ensure each sample processed will be annotated with respect to: AR activity (continuous variable from microarray data); TMPRSS2:ERG translocation status (yes/no from RT PCR); AR splice variation (native vs. alternative from RT PCR); quantitative AR and AKR1C3 IHC (continuous variable); gene expression of androgen metabolisms genes (continuous, from microarray data); testosterone and DHT levels (continuous variable from mass spectroscopy data); and the signaling activity of different pathways (determined by IHC and/or gene expression analysis). These values will be provided to the study statistician (DFCI). Descriptive statistics of levels and changes in measures will be provided. Whether AR signaling is augmented with AA will be evaluated along with analysis of the association of AR splice variants, TMPRSS2 fusion genes, AR

signaling, tumor androgens, serum androgens with PSA and radiographic response to AA.

Sequencing results from tumor samples will be compared to matched normal DNA samples and analyzed for base mutations, small insertions/deletions, copy number alterations, and structural rearrangements present in DNA from CRPC.

9. STUDY CALENDAR

	Pre-Study[a]	Cycle 1 (+/-2 days)[b]				Cycle 2 (+/- 2 days)		Cycle 3 (+/- 2 days)		Cycle ≥ 4 (+/- 2 days)	Every 12 weeks (+/- 1 week)	End of Treatment Visit[u]
		1	8[c]	15[c]	22[c]	1	15	1	15	1		
Informed Consent	X											
History and Physical[d]	X	X		X		X		X		X		X
Document Anti-Hypertensive Medications	X	X	X	X	X	X		X		X		X
ECOG Performance Status	X	X		X		X		X		X		X
Vital Signs[e]	X	X	X (BP Only)	X	X (BP Only)	X		X		X		X
BMI[f]	X	X		X		X		X		X		X
Hematology[g]	X	X		X		X		X		X		X
Serum Chemistry[h]	X	X	X (K Only)	X	X (K Only)	X		X		X		X
Liver Function Tests[i]	X	X	X	X	X	X		X		X		X
Coagulation Factors[j]	X										X	
HgA1c	X	X									X	X
Fasting Serum Lipids	X										X	X
MUGA scan or ECHO	X											
Testosterone	X											
Research Lab[k]		X				X		X			X	X
Research Lab[l]		X									X	X
Research Lab[m]	X											
Serum ACTH[n]		X				X		X			X	X
PSA[o]	X	X				X		X		X		X
CT/MRI[p]	X										X	
Bone Scan[q]	X										X	
AA Distribution[r]		X				X		X		X		
AA Compliance Assessment		X		X		X		X		X		
Prior and Concomitant Medications	X	X		X		X		X		X		
Adverse Events[s]	X	X	X	X	X	X		X		X		X

Tumor Biopsy[t]	X											X[t]

a: Baseline evaluations are to be conducted within 30 days prior to registration. Scans must be done within 30 days prior to registration. All baseline screening should be done prior to registration.
b: A cycle will be defined as 28 days. After prednisone is added, if the treating physician feels the patient would benefit from having clinic visits and assessments done every 8-12 weeks, that is acceptable. Clinical labs can be collected locally in the interim if clinically indicated.
c: Cycle 1 Day 8 and 22 checks can occur locally if preferred. Cycle 1 Day 15 checks must occur at the study institution and the participant must be seen by a study MD or NP.
d: Physical examination should include general description of participant, head, eyes, ears, nose, and throat, chest, abdominal, extremities, neurologic, skin, and lymph node examination. Any other evaluation is up to the discretion of the practitioner. It will not be considered a violation if the exam is not described as outlined here.
e: Vital signs included upright blood pressure, heart rate, respiratory rate, body temperature and weight. Blood pressure will be checked weekly for the first cycle to monitor for hypertension and then day 1 of every subsequent cycle. The repeated BPs described in the Hypertension Pathway may be measured over 7 days.
f: Calculate BMI = weight/(height)^2.
g: Hematology testing to include WBC, ANC, hemoglobin, and platelet count.
h: Serum or plasma chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose , calcium, albumin, magnesium. Potassium levels will be checked weekly for the first cycle to monitor for hypokalemia and then day 1 of every subsequent cycle. Cycle 1 Day 8 and Cycle 1 Day 22 potassium checks may be done locally.
i: LFTs to include AST, ALT, alkaline phosphatase, total bilirubin and direct bilirubin. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with AA, every two weeks for the first three months of treatment and monthly thereafter. LFTs may be done locally on Cycle 2 Day 15 and Cycle 3 Day 15 only.
j: Coagulation factors to include PT, PTT, and INR.
k: Blood will be collected for serum corticosteroid analysis (pregnenolone, progesterone, deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxypregnenolone, 17α-hydroxypregesterone, 11-deoxycortisol, cortisol). Labs should be drawn prior to the administration of the first dose of treatment. As of June 23, 2020, these research samples no longer need to be collected while patients are on active treatment. Study teams should only collect these samples at EOT.
l: Blood will be collected for serum androgen analysis (DHEA, androstenedione, testosterone, DHT). Labs should be drawn prior to the administration of the first dose of treatment. Additionally, CTCs will be collected. Cycle 1/day 1 and off study CTC samples (whole blood) will be shipped overnight. CTCs collected every 12 weeks will be processed (buffy coat) and stored for delivery. Lastly, blood for circulating tumor DNA will be collected at the specified time points. As of June 23, 2020, these research samples no longer need to be collected while patients are on active treatment. Study teams should only collect these samples at EOT.
m: Blood will be collected for germline DNA and RNA analysis.
n: This will be measured by standard testing. Should be checked prior to the administration of the first dose of treatment.
o: If a digital rectal examination is performed, PSA must be sampled prior to the examination.
p: If the treating physician feels the patient would benefit from having CT/MRI scans done every 4-6 months, that is acceptable. If baseline CT chest does not demonstrate prostate cancer, they do not need to be repeated on study unless the investigator suspects new findings based on clinical signs/symptoms.
q. If the treating physician feels the patient would benefit from having bone scans done every 4-6 months, that is acceptable.
r: Study agent is AA. Subjects with be continued on LHRH agonist/antagonist as prescribed. Subjects will begin taking study agent on Day 1/Cycle 1.
s: Adverse events should be collected from the date informed consent is signed until 30 days after discontinuation from the study.
t: Tumor biopsy is optional . Participants will need to be screened and registered before having a biopsy. If a pre-treatment biopsy is being performed, it must be performed prior to starting study medication. Friday should be avoided due to difficulty of processing bone biopsies on the weekend. For DFCI participants,when a pelvic bone biopsy is being performed a bone marrow aspirate will also be obtained from the same needle stick.
u: The optional tumor biopsy at the end of the study can be done +/- 28 days of the determination of progression.
v: The End of Treatment Visit will be the visit at which it is determined that the patient will no longer be taking treatment given disease progression, toxicity, or other reason. Participants will be followed for up to 5 years post-study discontinuation or until death, whichever comes first. Participants will be followed for subsequent lines of therapy, including line of agent, name of agent, and PSA kinetics following study drug discontinuation and correlate with response to study drug. This information will be updated every 6 months. The research team will collect this information during patient clinic visits, by phone, or via medical record review.

10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants will be assessed by RECIST (1.1), bone scan and PSA criteria. For the purposes of this study, participants will be reevaluated every four weeks by PSA and every 12 weeks by CT and bone scan. However, if the treating physician feels the patient would benefit from having scans done every 4-6 months, as opposed to every 12 weeks, that is acceptable. At time of PSA progression (as defined below by PCGW2 criteria), those participants remaining on AA monotherapy, will be treated with prednisone 5 mg orally twice daily. Participants should not be taken off treatment with AA plus prednisone until documented progression by imaging.

The following will be used to determine progression in this study:

- PSA Progression (based on PCWG2 criteria): For those who experience a decline on PSA from baseline, PSA progression will be defined as an increase in PSA that is ≥ 25% and ≥ 2 ng/mL above nadir which is confirmed by a second value three or more weeks later. The first value will be the documented date of progression. For participants who do not experience a decline from baseline, PSA progression will be defined as PSA ≥ 25% and ≥ 2 ng/mL after 12 weeks.

- Radiographic Disease Progression (based on PCWG2 criteria): For bone disease, radiographic progression will be defined by PCWG2 criteria for progression of bone disease (≥2 new lesion on bone scan and for the first 12 week assessment, defining disease progression requires a confirmatory scan performed 6 or more weeks later which shows a minimum of 2 additional new lesions).[30] See Appendix D for imaging procedural information and measurement of tumor flare. For soft tissue/lymph node disease, radiographic progression will be defined using RECIST 1.1 criteria.

10.1 Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by RECIST 1.1.

10.1.1 Definitions

Evaluable for Target Disease Response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.

Evaluable for Non-Target Disease Response: Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease response. These participants will have their response classified according to the definitions stated below. Participants ho exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.

10.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques (CT, MRI, x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Ultrasound cannot be used to measure lesions. A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm) or pathological lymph nodes with ≥ 10 to < 15mm short axis, are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by chest x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as

CT or MRI can be considered target lesions if the soft tissue component meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions. All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

10.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and > 10 mm in diameter as assessed by using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Tumor markers. Tumor markers alone cannot be used to assess response. The following parameters will be recorded on a monthly basis:

- PSA decline will be measuring according to revised PCWG-2 (2008) criteria.[30]
- PSA changes will be recorded on all participants.
- TTPP will be based on revised PCWG-2 (2008) criteria.
- The maximal decline in PSA for each participant will be recorded.
- The date of the maximal PSA decline (nadir date) will be recorded for each participant, as will the duration from the start of therapy to the nadir PSA.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex:

new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* and/or unequivocal progression of existing non-target lesions.

When the participant also has measurable disease, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare. When the participant has only non- measurable disease, worsening in non-target disease cannot be easily quantified. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in measurable

lesions), an increase in pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from 'localized' to 'widespread.'

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Note: Bone scan flares have been reported in 33-48% of metastatic, CRPC patients treated with AA.[32] In this situation bone scan reports frequently describe tumor progression. If a participant has PSA, CT scan and clinical stability/response and bone scan progression during the first three months of AA therapy (at the 12 week restaging scans), the treating physician should consider the possibility of bone scan flare and continue the participant on treatment until the next scheduled radiographic assessment. The treating physician is encouraged to discuss the diagnosis of bone scan flare with the site PI. See Appendix D for imaging procedural information and measurement of tumor flare.

10.1.4.3 Evaluation of Best Overall Response

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

For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response for when Confirmation is Required:
CR	CR	No	CR	≥4 wks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks confirmation
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

10.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent or progressive disease is objectively documented or death due to any

cause. Participants without events reported are censored at the last disease evaluation.

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

10.1.6 Time to Progression

Time to Progression: Time to progression is defined as the time from registration to progression, or censored at the date of last disease evaluation for those without progression reported.

10.1.7 Response Review

Central review of the radiology assessments is planned using tumor metrics core at the DFCI.

10.2 Other Response Parameters

Serum androgen levels will be evaluated every 3 cycles. Serum corticosteroid intermediates and ACTH will be evaluated every cycle.

10.2.4 Descriptive statistics (including mean, standard deviation, minim, minimum, median, interquartile range) will be provided on levels of serum hormone and changes from baseline (serum androgen including DHEA, DHEA-S, androstenedione, testosterone, DHT; serum corticosteroid/ mineralocorticoid intermediates to include pregnenolone, progesterone, deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxypregnenolone, 17α-hydroxypregesterone, 11-deoxycortisol, cortisol; serum ACTH).

11. ADVERSE EVENT REPORTING REQUIREMENT

11.1 Definitions

11.1.1 Johnson & Johnson Medicinal Product

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

11.1.2 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.

11.1.3 Special Reporting Situations

When a report contains a Johnson & Johnson 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.

11.1.4 AE

Any untoward medical occurrence in a participant 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.

11.1.5 AE of Special Interest

Events that JANSSEN SCIENTIFIC AFFAIRS, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). There are no AEs of special interest identified for abiraterone acetate.

11.1.6 Adverse Drug Reaction

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. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

11.1.7 SAE

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

- Death
- A life-threatening AE
    - Life-threatening AE or life-threatening suspected adverse reaction: An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the PI, its occurrence places the participant or subject at immediate risk of death. It does not include an AE 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 participant 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.

Events **not** considered to be SAEs are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen

- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.8 Expectedness

AEs can be 'Expected' or 'Unexpected.'

- Expected AE

  Expected AEs are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an AE is considered expected when it appears in the current AE list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

  Refer to Section 6.1 for a listing of expected AEs associated with the study agent(s).

- Unexpected AE

  For the purposes of this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current AE list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.9 Attribution

Attribution is the relationship between an AE or SAE and the investigational product. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the investigational product.
- Probable – The AE is likely related to the investigational product.
- Possible – The AE may be related to the investigational product.
- Unlikely - The AE is doubtfully related to the investigational product.
- Unrelated - The AE is clearly NOT related to the investigational product.

11.2 Procedures for AE and SAE Recording

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

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

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE. 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:

- Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- Surgery or procedure planned prior to entry into the Study.

If, in the PIs judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. EKG, angiogram), physical exam finding, or vital sign, a corresponding clinical AE should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE, 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 AE, using appropriate medical terminology (e.g thrombocytopenia, peripheral edema, QT prolongation).

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

The DF/HCC will serve as the Sponsor Investigator [redacted] of this multi-site trial. Each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the PI. Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating

investigator to report SAEs to the Sponsor Investigator [redacted] and/or others as described below.

11.4 Reporting to the Sponsor Investigator

11.4.1 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.

11.4.2 SAE Reporting

All SAEs that occur after informed consent is signed, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Sponsor-Investigator on the local institutional SAE form and JANSSEN SCIENTIFIC AFFAIRS, LLC (by the Sponsor-Investigator or designee) on a J&J SAE Form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each SAE to the DF/HCC Sponsor Investigator within 24 hours but no later than 1 business day of learning of the occurrence. In the event that the participating investigator does not become aware of the SAE within 24 hours (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the AE. Report SAEs by telephone, email or facsimile to:

[redacted]

Within the following 24-48 hours, the participating investigator must provide follow-up information on the SAE. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

If the significant other of a study participant becomes pregnant while the study subject is in the trial, the pregnancy must be reported to JANSSEN SCIENTIFIC AFFAIRS,LLC (by the Sponsor-Investigator or designee) within the SAE reporting timelines (1 business day).

All SAEs, regardless of relationship to AA PQC, and special reporting situations must be reported to JANSSEN SCIENTIFIC AFFAIRS, LLC (by the Sponsor-Investigator or designee) on a J&J SAE Form within 24 hours but no later than one business day of study personnel becoming aware of the event. If only limited information is initially available, follow-up reports are required. JANSSEN SERVICES SAE [redacted]

11.4.3 Non-SAE Reporting

Non-SAEs will be reported to the DF/HCC Overall PI on the toxicity CRFs.

All non-SAEs must be reported to JANSSEN SCIENTIFIC AFFAIRS, LLC on a yearly basis and at study end. The summary of non-serious AEs should include a listing of: Participant ID, AE term (uncoded), severity, relationship to AA, and action taken with AA.

11.5 Reporting to the IRB

Investigative sites within DF/HCC will report all SAEs directly to the DFCI OHRS.

Other investigative sites should report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting AEs. A copy of the submitted institutional SAE form should be forwarded to:

The DF/HCC PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting AEs.

11.6 Reporting to the FDA

If this study is not IND Exempt the following reporting requirements to the FDA will be followed.

The DF/HCC Overall Principal Investigator will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the investigational product.

Unexpected fatal or life-threatening experiences associated with the use of the investigational product will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the investigational product will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA using Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.8 Monitoring of AEs and Period of Observation

All AEs, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the

event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the Sponsor Investigator [redacted] or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall PI and their respective IRB of any unanticipated death or AE occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The Clinical Trials Research Informatics Office (CTRIO) will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the CTRIO is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with CTRIO.
On Study Form	Within 14 days of registration.
Baseline Assessment Form	Within 14 days of registration.
Treatment Form	Within 10 days of the last day of the cycle.
AE Report Form	Within 10 days of the last day of the cycle. If AEs are ongoing at the end of the last cycle, continue to submit AE reports until resolution or 30 days post-treatment.
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation.
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason.
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call.

12.2 Safety Meetings

The DF/HCC DSMC will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the PI and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; dose-limiting toxicity information; all grade 2 or higher unexpected AEs that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall PI (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

See Appendix E (Data Safety Monitoring Plan) section 5: Monitoring :Quality Control) for additional details on study monitoring.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB and Janssen Scientific Affairs, LLC prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall PI (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Research Practices

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US CFR governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects [redacted]
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators [redacted]
    - Title 21 Part 56 – Institutional Review Boards [redacted]

- Title 21 Part 312 – Investigational New Drug Application [redacted]

- State laws

- DF/HCC research policies and procedures [redacted]

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC. The specific responsibilities of the DF/HCC Overall PI (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the DF/HCC Multi-Center Data and Safety Monitoring Plan (see Appendix E).

- The DF/HCC Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and AE reporting at each site.

- Except in very unusual circumstances, each participating institution will order AA directly from the supplier. Janssen Scientific Affairs, LLC will not directly

provide AA to each participating site. This will be coordinated through a third party drug distribution supplier. A participating site may order AA only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the supplier.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

Mineralocorticoid excess (ME) failure will be defined as the use of exogenous steroids (prednisone) to control symptoms of ME related to hypokalemia and hypertenstion. Based on the results of the randomized, phase III study that evaluated AA in chemotherapy-naive patients with metastatic CRPC (n=1,088 patients).[15], the incidence of hypertension was 9.4% grade 2 and 3.9% grade 3. The incidence of hypokalemia was 0.9% grade 2, 2.2% grade 3, and 0.2% grade 4. Therefore, the acceptable rate of ME failure in this study will be 10%. The ME failure rate is expected to be similar between metastatic and non-metastatic populations. The sample size is 60 participants.

Although the management of hypertension and hypokalemia is expected to be adequate according to the prescribed guidelines, the study cohort will be continuously monitored for excessive ME failure. Through sequential testing, at a given analysis, there will be a rule for suspending or continuing the experiment by making additional observations. Specifically, criteria for identifying an excessive number of participants with ME failure will be based on the sequential probability test with α=0.10, β=0.10, po=0.10 and pa=0.25.[33] Every time a participant is classified as having ME failure, the cumulative number of participants (X) with ME failure is compared with the number of participants evaluable for toxicity (N) and an associated cutoff of evaluable participants (Nx). If the number of participants, N, is greater Nx, accrual will continue. If the number of participants, N, is less than Nx, accrual will be suspended. Table 1 below gives the criteria for suspending accrual to evaluate more fully the data on ME toxicity. For example, when the 3rd event of ME failure is observed, the trial will suspend for further review of ME toxicity data if the number of evaluable participants is less than or equal to 6 participants.

Table 1. Criteria for Excessive ME Failure

po=10% and pa=25%; alpha=0.10 and beta=0.10	
# pts who experienced ME failure	**Suspend trial if # evaluable pts N is </= N_x**
X	**N_x**
3	</= 6
4	</= 12
5	</= 18
6	</= 24
7	</= 30
8	</= 36
9	</= 42
10	</= 48
11	</= 54
12	</= 60

With the above rules, there is low probability that the trial would be flagged for excessive ME failure if the true chance of ME failure were 10% and a high probability the trial would be flagged for excessive ME failure if the true chance of ME failure were about 25%. The table below summarizes these probabilities based on 10,000 simulations. These values are deemed accurate to +/- 0.01 based on a 95% confidence interval. If the true underlying proportion of ME failure is 10% then the probability of identifying excessive ME failure is 0.082 whereas if the true underlying proportion is 25% the probability is 0.907.

Table 2. Probability of Identifying Excessive ME Failure Under Various True ME Failure Rates

True ME Failure Rate	5%	10%	15%	20%	25%	30%
Probability of Identifying Excessive ME Failure	0.006	0.082	0.345	0.688	0.907	0.984

The target accrual rate is 4-5 patients per month for an accrual duration of approximately 12 - 15 months for enrollment of 60 participants. The accrual mix is expected to be divided equally between metastatic and non-metastatic participants.

14.2 Analysis of Secondary Endpoints

Safety and tolerability associated with AA monotherapy and AA + prednisone for those with PSA progression on AA monotherapy will be evaluated separately. All

participants who receive at least 1 dose of study drug will be included in these analyses. A summary of all Grade 1-4 treatment-related toxicities will be provided by toxicity type and maximum grade. The maximum grade consolidates the reports of a given type of toxicity for a participant over time by taking the maximum grade across time (i.e. a participant appears only once for a given type of toxicity). Participants with reports of multiple toxicities of different types are reported multiple times under the relevant toxicity categories. 'Treatment-related' toxicities are defined by an attribution as possible, probable or definite. With 60 participants, the maximum width of a 90% CI for a given toxicity rate is 22%. Within a given metastatic status subgroup (n=30), the maximum width is 32%. The probability of observing at least one rare severe toxicity (true rate=5%) is 95% for the overall cohort and 78.5% within a metastatic status subgroup. The number of cycles completed with and without dose modifications and treatment delays as well as prednisone use will be tabulated overall and by metastatic status subgroup.

Serum levels and changes over time of ACTH, corticosteroid intermediates, serum androgen concentrations, BMI and Hgb A1-C will be summarized using descriptive statistics (mean, median, standard deviation, interquartile range). Correlation between measures will be assessed graphically with scatter plots and using Pearson correlation coefficients. The paired t-test will be used to determine if treatment with AA monotherapy is associated with a change in levels pre- to post- treatment. Assuming the standard deviation (SD) of percentage change is 50%, given n=54 treated participants with samples at both timepoints (90% sample yield), the paired t-test will have 80% power to detect a change pre- to post-treatment of 19.4% (0.39 SD). Within a metastatic status subgroup, the effect size is 28% (0.56 SD) If the data display significant non-normality of distribution, non-parametric tests or data transformations will be employed.

PSA response to AA monotherapy (and AA + prednisone for those with PSA progression on AA monotherapy) will be summarized as frequency and percent. Participants who are unevaluable for response will be included in the denominator as nonresponders when calculating the response rate. Duration of PSA response for the regimen of AA monotherapy (and AA + prednisone for those with PSA progression on AA monotherapy) will be defined relative to the first achievement of PSA response and will be estimated using the method of Kaplan and Meier. The above analysis will also be performed within metastatic status subgroup.

Participants with measurable disease will be evaluated for response using RECIST 1.1 criteria. Time to progression of bone lesions or measurable disease will be estimated using Kaplan-Meier estimates.

We estimate that the overall yield of evaluable tissue samples for paired testing will be 43% of metastatic participants (n=13). This assumes approximately one-half (53%; n=16) of metastatic participants will have paired tissues samples submitted optionally. Based on our prior experience, we anticipate that 75% of men will undergo bone biopsy and 25% soft tissue biopsy. We anticipate that 75% (n=9/12) of bone biopsy specimens

and 100% (n=4/4) of soft tissue specimens will have sufficient tumor for nucleic acid analysis. Whole exome and transcriptome sequencing results will be analyzed for somatic mutations, insertions and deletions, copy number alterations, overexpressed genes, chimeric transcripts, and alternatively spliced variants and a complete set of potential driver alterations will be compiled at both time points. For each driver alteration, the proportion of patients with the alteration present will be calculated along with 90% confidence intervals. With the stated evaluable sample sizes, the maximum width on a given alteration rate at baseline or progression is approximately 49%. Further, there is greater than a 33% probability of observing one or more rare (true probability 3%) alteration.

Tissue androgen concentrations will also be quantified and summarized using descriptive statistics (mean, median, standard deviation (SD), minimum, maximum, interquartile range). In evaluating the effect of treatment, the paired T-test (or Wilcoxon signed-rank test, if appropriate) will be used to evaluate whether the change in level between collection time points is significant. With 13 evaluable paired samples, a 42% percent change in level can be detected with 80% power assuming a two-sided 0.05 alpha and standard deviation of percentage change of 50%. The effect size narrows to 37% assuming two-sided 0.10 alpha.

CTCs will be isolated and enumerated per standard unit of blood with assessment time points at baseline, during treatment (every 28-day cycle), and at progression. Mixed models will be used to evaluate longitudinal CTC counts treated as continuous and as ordinal according to 4 classes: 0 (undetectable), <5, 5-100, >100.[28] Time will be defined as months since start of treatment (day 1/cycle 1). Effects at each time point will be reported and evidence of significant change based on 0.05 alpha evaluated. CTCs will also be characterized by the percentage of the AR that is localized to the nucleus. Descriptive statistics including the median, minimum and maximum percentage of AR nuclear localization will be detailed. The relationship between CTC counts and nuclear AR localization will be evaluated graphically with scatter plots and using Pearson correlation coefficient. AR gene sequencing will also be performed on CTC samples with number and type of mutations as well as AR splice variants occurring over time tabulated. Agreement between AR mutation status per CTCs versus per tissue sequencing will be quantified for common mutations using Cohen's Kappa. Kappa is expected to be of substantial agreement (0.61-0.80). As exploratory, analyses will be performed within metastatic status subgroup.

Specific AR mutations will be evaluated in ctDNA pre-treatment, during treatment (every 3 cycles), and at progression. Frequency of AR mutations will be tabulated. Agreement between AR mutation status per ctDNA versus per tissue sequencing will be quantified for common mutations using Cohen's Kappa. Kappa is expected to be of substantial agreement (0.61-0.80). As exploratory, analyses will be performed within metastatic status subgroup.

The two-group t-test will be used to examine the difference in level and/or change pre- to post-treatment in biomarker levels by PSA and RECIST (measurable disease participants) response outcome overall and within metastatic status subgroup. Assuming a 90% sample yield, if PSA response rate is 25% (14 responders and 40 non-responders), there is 82% power to detect an effect of 0.89 SD at a two-sided significance level of 0.05. Continuous levels may be dichotomized at the median for further evaluation. Association between response and categorical biomarkers will be evaluated using Fisher's exact test. Analyses of these correlative endpoints will be exploratory and adjustments will not be made for multiple comparisons.

15. PUBLICATION PLAN

The data will be collected by [redacted] and analyzed by [redacted] and the statistical team at DFCI. The results will be shared with JANSSEN SCIENTIFIC AFFAIRS, LLC. The milestone plan is detailed below.

Milestone	Timeline
Planned Interim Analysis (see below)	6 months from enrollment of first subject
Enrollment of 100% of Target Enrollment	12 months from enrollment of first subject
Last Subject/Last Visit on Study	24 months from enrollment of first subject
Collection and Analysis of Primary and Secondary Endpoint Data	3 months following last subject/last visit
Completion of Final Study Report	6 months following last subject/last visit

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17. APPENDICES

APPENDIX A: Performance Status Criteria

APPENDIX B: Required Forms at Registration

APPENDIX C: Participant's Pill Diary

APPENDIX D: Imaging Procedural Information and Measurement of Tumor Flare

APPENDIX E: Data and Safety Monitoring Plan

17.1 APPENDIX A: Performance Status Criteria

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

17.2 APPENDIX B: Required Forms at Registration

The DFCI coordinator will Fax to DFCI ODQ:

- Current IRB approved consent form signed by participant and Investigator (MD only)
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated DFCI eligibility checklist (signed by MD or RN)
- The following source documentation is typically required:
- Please note: Additional documentation may be required by the lead institution.
    - Labs for PSA values used to determine eligibility (Lab values used to determine eligibility, including screening PSA)
    - Documentation of prior treatments/procedures performed to treat prostate cancer (e.g. Chemotherapy, Cryotherapy, Hormone Therapy,
    - Radiation therapy with start and stop dates and dosing information if applicable)
    - Reports documenting disease status
        - Chest CT
        - CT or MRI Abdomen and Pelvis
        - Bone Scan
    - Pathology Report
    - Concomitant medication list
    - Progress note or equivalent documentation of consenting visit
    - Progress note documenting medical history and oncologic history
    - All screening labs
    - Screening visit note, with BP, vital signs, ECOG Performance status
    - MUGA Scan or ECHO

17.3 APPENDIX C: PARTICIPANT'S PILL DIARY

Today's Date: _____
Participant Name: _____
Participant Study ID: _____
Cycle Number: _____

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle (28 days).
2. You will take ____ tablets each day by mouth. No food should be consumed for at least two hours before the dose is taken and for at least one hour after the dose is taken.
3. Record the date, the number of tablets you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the comments column.
5. Please bring your pill bottle and this form to your physician when you go to your next appointment.

Date	Day	Number of Tablets	Time	Comments	Date	Day	Number of Tablets	Time	Comments
	1					15			
	2					16			
	3					17			
	4					18			
	5					19			
	6					20			
	7					21			
	8					22			
	9					23			
	10					24			
	11					25			
	12					26			
	13					27			
	14					28			

Participant's Signature: _____ Date: _____

Physician's office will complete this section:
Date participant started protocol treatment:
_____
Date participant was removed from study:
_____
Participant's planned daily dose:
_____
Total number of pills taken this month: _____
Physician/Nurse/Data Manager's Signature: _____ Date: _____

17.4 APPENDIX D: Imaging Procedural Information and Measurement of Tumor Flare

All participants enrolled in the study will be evaluated with 99mTc-MDP skeletal scintigraphy at baseline and every 3 months after commencing therapy, according to the schedule shown in the study calendar. It is anticipated that bone scans and diagnostic CT studies will be obtained within a few days of each other, preferably over a 2-3 day period.

Image Acquisition Parameters
Imaging acquisition parameters should follow the local standard of care when possible, within the constraints detailed below.

Whole body bone scans should be acquired in the anterior and posterior projections approximately 3 hours following the IV administration of approximately 25 mCi99mTcmethylene diphosphonate (MDP). The imaging parameters should be consistent between baseline and follow-up time points. In specific cases of symptoms suggesting cord compression or impending fracture, additional imaging may be warranted such as radiographs or MRI.

For the purposes of clinical management, each bone scan will be assessed by an experienced nuclear medicine physician. For the purposes of the research study, all 99mTc-MDP bone scan images will be assessed by three experienced nuclear medicine physicians with final results based on consensus. For each participant, each bone scan series will be analyzed side by side on the same workstation with special care taken to display images at similar intensity settings. The baseline scans will be assessed qualitatively for the presence or absence of bone metastases. Bone scans will be called equivocal if scintigraphic abnormalities cannot be confidently categorized as benign or malignant. Bone scans obtained 3 months after the initiation of therapy will be assessed qualitatively for a change in intensity of lesions present on the baseline scan or for the presence of new lesions. Bone scans obtained 6 months after initiation of therapy will be compared to the baseline and 3-month scans for the intensity and number of skeletal lesions.

Tumor Flare Measurement
A flare will be recorded if there is stable or decreasing PSA and there is an increase in intensity or number of lesions between the baseline and 3-month scan and a subsequent reduction in intensity or number of lesions on the 6-month scan. Results will be correlated with RECIST (1.1) based on diagnostic CT obtained at baseline, 3-months and 6-months following therapy initiation. Results will also be correlated with participant outcome and with tissue analysis.

17.5 APPENDIX E: Multi-Center Data and Safety Monitoring Plan

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1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Children's Hospital Boston (CHB), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA)). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution,) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines . In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A unit within DF/HCC developed to computerize and manage data, and to provide a Quality Control and Quality Assurance function for DF/HCC trials.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, [redacted] will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials) as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

2.2 Coordinating Center

The Coordinating Center will assume the following general responsibilities:

- Assist in protocol development
- Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain FDA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
- Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc).
- Maintain documentation of all communications.
- Ensure that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP).

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable Federal Regulations and DF/HCC requirements, the protocol and HIPAA requirements. All Participating Institutions will provide a list of personnel assigned to the role for oversight of data management at their site to the Coordinating Center.

The general responsibilities for each Participating Institution are as follows:

- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder in accordance with DF/HCC requirements.
- Provide the Coordinating Center with regulatory documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements

and to the Coordinating Center, in accordance with DF/HCC requirements. Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Secure and store investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent

form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution's IRB
- Participating IRB's approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the Coordinating Center their IRB approval for amendments to a protocol.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB.
The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number (as described below) and DF/HCC protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification

3.7 DF/HCC Multi-Center Registration

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution research nurse or data manager and emailed to the DFCI Study Coordinator and Research Manager:

- Current IRB approved informed consent document signed by participant and investigator (participant information must be de-identified and participant initials should be written at the bottom of each page of the signed informed consent document).
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated DFCI eligibility checklist
- The following source documentation is typically required. Please note additional documentation may be required by the lead institution:
  - Labs for PSA values used to determine eligibility (lab values used to determine eligibility, including screening PSA)
  - Documentation of prior treatments/procedures performed to treat prostate cancer (e.g. Chemotherapy, Cryotherapy, Hormone Therapy, Radiation therapy with start and stop dates and dosing information if applicable)
  - Reports documenting disease status: Chest CT, CT or MRI Abdomen and Pelvis. Bone Scan
  - Pathology Report
  - Concomitant medication list
  - Progress note or equivalent documentation of consenting visit

- Progress note documenting medical history and oncologic history
- All screening labs
- Screening visit note, with BP, vital signs, ECOG Performance status
- MUGA Scan or ECHO

Participant identifiers must be redacted with the exception of participant initials and date of birth.

The Participating Site must review the source documents against the eligibility checklist to ensure eligibility prior to sending to the Coordinating Center. Source documents should not be sent to the Coordinating Center until all necessary documents are available. The Coordinating Center will begin its review of the source documents once the full registration packet is received. The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC ODQ
- Upon receiving confirmation of registration by the ODQ, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and if applicable the dose treatment level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during ODQ's normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's registration confirmation memo from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any exceptions to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.7.4 Verification of Registration, Dose Levels, and Arm Designation

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one business day

of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

3.8 DF/HCC Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for ODQ CRF/eCRF completion and correspondence, and correspondence with the Coordinating Center.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe derivations from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB.

Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 11.

Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Investigators will review any distributed AE reports, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.10.2 Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. The Participating Investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.11 Data Management

The DF/HCC QACT develops a set of either paper or electronic case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT provides a web based training for eCRF users. See section 12 of protocol.

3.11.1 Data Forms Review

When data forms arrive at the DF/HCC ODQ, they are reviewed for completeness, protocol treatment compliance, adverse events (toxicities) and response. Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst or study monitor. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed a minimum of four times a year.

4.0 REQUISITIONING INVESTIGATIONAL DRUG

Participating Institutions should order their own agent regardless of the supplier (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

See section 7.0 of study protocol for additional details on ordering study drug.

5.0 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

Source documents confirming eligibility are to be sent to DFCI by the participating institutions and reviewed by DFCI study staff including a clinician prior to external site participant registration.

The DF/HCC Lead Institution will implement monitoring activities ongoing to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management.

Site visits will generally occur twice a year for sites that are actively enrolling participants and have participants in treatment. Virtual monitoring (source documents are sent to DFCI for review) may be performed in lieu of a site visit if the study staff and PI determine that virtual monitoring is appropriate for the site. The decision to perform virtual monitoring in lieu of a site visit will be based upon the site's enrollment, study compliance history, history collaborating with DFCI on other multi-center studies, and number of participants in active treatment.

We hope to monitor approximately 50% of participants enrolled from external sites. The target number of participants monitored may change depending upon monitor findings.

Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

Teleconferences between DFCI and the participating sites will be conducted on approximately a monthly basis. Meeting minutes for teleconferences will be issued to all participating sites. Site initiation visits will be conducted via teleconference. Ongoing training will also be conducted via teleconference as needed. The Coordinating Center, Dana Farber Cancer Institute will be available to all participating sites for resolving questions, concerns and facilitating compliance.

5.2 Evaluation of Participating Institution Performance

All data submitted to the DF/HCC ODQ will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Lead Institution or designee and if applicable ODQ Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the Participating Institution's Coordinators, the Principal Investigators, and the Protocol Chair.

5.2.1 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participating in the study. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Sponsored Trials

The DF/HCC Sponsor may request that an audit be performed by the ODQ if instances of serious non-compliance are found during routine monitoring.

6.2 Participating Institution

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 DF/HCC Sponsor and Coordinating Center

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Sub-Standard Performance

The DF/HCC Sponsor, DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal regulations, will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation.

18. APPENDIX F: STRONG CYP3A4 INDUCERS AND INHIBITORS

Strong 3A4 Inducers

Carbamazepine (Tegretol)
Enzalutamide
Mitotane
Fosphenytoin (Cerebyx) (IV only)
Pentobarbital (Nembutal) (IV only)
Phenobarbital
Phenytoin (Dilantin)
Primidone
Rifampin
St. John's Wort

Strong 3A4 Inhibitors

Atazanavir
Boceprevir
Ceritinib
Clarithromycin (Biaxin)
Conivaptan
Darunavir
Idelalisib
Grapefruit juice
Indinavir
Itraconazole
Ketoconazole
Lopinavir/ritonavir
Mibefradil
Nefazodone
Nelfinavir
Ombitasvir-paritaprevir-ritonavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Voriconazole

A more comprehensive list and additional information can be found at the following address:
http://medicine.iupui.edu/flockhart/