A Phase II Trial of Abiraterone acetate, Radiotherapy and Short-Term Androgen Deprivation in Men with Unfavorable Risk Localized Prostate Cancer

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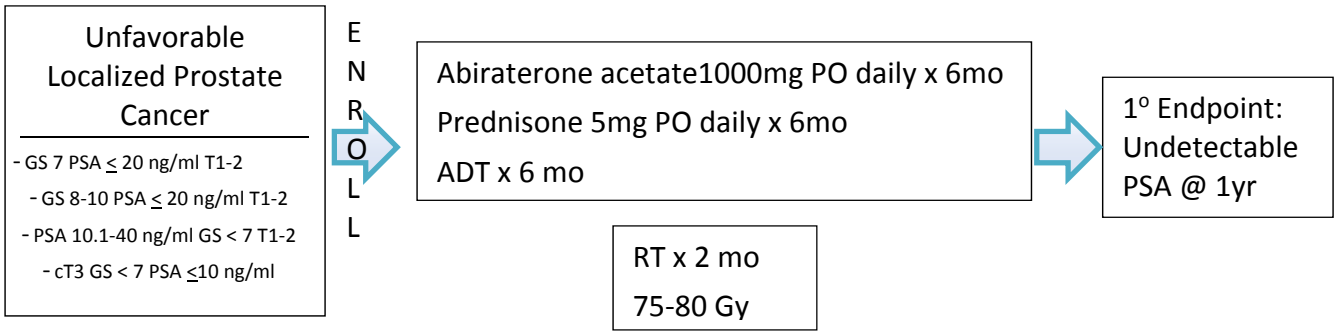
1 SCHEMA



2 LIST OF ABBREVIATIONS

ADR	adverse drug reaction
ADT	androgen deprivation therapy, ie LHRH Agonist or Antagonist
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANC	absolute neutrophil count
BP	blood pressure
CBC	complete blood count
CRF	case report form
CTQA	Clinical Trials Quality Assurance
DW/DCE-MRI	diffusion weighted/dynamic contrast enhanced magnetic resonance imaging
ECOG	Eastern Cooperative Oncology Group
EPIC	Expanded Prostate Cancer Index Composite (EPIC)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
LHRH	luteinizing hormone-releasing hormone
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PI	Principal Investigator
PSA	prostate-specific antigen
RDSPs	Research Data Security Plans
RT	radiotherapy
SAE	serious adverse event
SOC	Safety Oversight Committee
SOP	Standard Operating Procedure
STADT	short-term androgen deprivation therapy
ULN	upper limit normal

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 Purpose

This research protocol seeks to determine the tolerability and efficacy of abiraterone acetate given concurrently with short-term androgen deprivation therapy (STADT) and radiotherapy (RT) as definitive management of unfavorable newly diagnosed prostate cancer.

Study Hypothesis

We hypothesize that the addition of abiraterone acetate to definitive RT and STADT will increase the frequency of undetectable PSA at one year from 10 to 30%.

Primary Objective

To determine the proportion of men with intermediate/high risk localized prostate cancer treated with RT, STADT, and abiraterone acetate who achieve an undetectable (<0.1 ng/dl) PSA at 1 year following initiation of abiraterone acetate.

Secondary Objectives

1... To evaluate the effect of abiraterone acetate in combination with RT/STADT:
   a. Time to PSA nadir, and PSA nadir values at 1 and 2 years,
   b. time to biochemical progression-free survival (Phoenix definition),
   c. time to metastasis or systemic therapy,
   d. time to testosterone recovery, and
   e. proportion of men with 1, 2, 3, 4 and 5 year PSA < 1.5ng/ml in setting of non-castrate testosterone.

2... To evaluate the short and long term safety and tolerability of 6 months of abiraterone acetate with prednisone and ADT combined with standard RT in men with intermediate/lower high risk localized prostate cancer.

Exploratory Objectives

1... To evaluate the effect of abiraterone acetate in combination with RT/STADT on change in tumor volume and vascularity by diffusion-weighted and dynamic contrast-enhanced magnetic resonance imaging (DW/DCE-MRI; only at Duke).

2... To collect 1, 2, 3, 4 and 5 year quality of life outcomes on men treated with abiraterone acetate, STADT and RT using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.

3... To determine change in muscle cross sectional area of the dominant thigh by MRI in a subset of up to 5 patients (only at Duke).

3.2 Background and Significance

Definitive RT for prostate cancer offers curative therapy without major surgery, and is the choice of treatment for approximately one-third of the 240,000 men diagnosed with prostate cancer each year.[1] However, outcomes for patients with elevated risk features have sub-optimal outcomes with radiotherapy alone. Addition of androgen deprivation therapy[2-4] has improved biochemical control, disease-specific mortality, and overall survival. However, significant concern exists over the toxicities associated with long-term androgen deprivation,

including erectile dysfunction, metabolic syndrome, and osteoporosis.[5] Strategies are needed to further complement radiation therapy in order improve treatment efficacy and reduce the burden of long-term androgen deprivation.

Abiraterone acetate inhibits cytochrome P450 c17 (hydroxylase and lyase) and therefore acts early in testosterone synthesis and has been approved by the FDA for use in castration-refractory prostate cancer.[6] The ability of abiraterone acetate to inhibit intracrine/autocrine as well as adrenal androgen production is the likely mechanism of action leading to clinical benefit. Abiraterone acetate with low dose prednisone in this post-docetaxel metastatic CRPC setting has demonstrated improvements in PSA response, radiographic response, overall survival, and time-to-progression, with a favorable side effect profile. Adverse events have included symptoms/signs of mineralocorticoid excess (hypertension, hypokalemia, peripheral edema), congestive heart failure (3%), fatigue, and diarrhea.[6] Abiraterone acetate with prednisone has also shown similar favorable efficacy and safety in the pre-docetaxel metastatic CRPC treatment setting.[7] Given its activity in castration-resistant cancer, abiraterone acetate may be able to provide complementary action in combination with ADT and radiotherapy to more effectively eradicate aggressive localized prostate cancer. Localized tumors have also shown persistently high androgen and androgen precursor levels in the tumor microenvironment and may respond favorably to combinations of traditional ADT with abiraterone acetate. As STADT with radiation is considered standard of care in the intermediate to high risk localized PC setting, this research protocol seeks to determine the tolerability and efficacy of abiraterone acetate given concurrently with STADT and RT as definitive management of unfavorable newly diagnosed prostate cancer.

3.3 Design and Procedure

This is a single arm two-site study of 37 men with unfavorable prostate cancer (defined as having a single high risk factor). The study will be conducted within the Department of Defense Prostate Cancer Clinical Trials Consortium (DOD PCCTC), a cooperative group dedicated to evaluating novel approaches to the treatment of prostate cancer. Duke is the lead site and sponsor of the trial and will provide oversight and monitoring of this study and central statistical and data management. Patients will concurrently initiate 6 months of standard-of-care ADT and once daily abiraterone acetate/prednisone. For this study, ADT includes administration of any approved LHRH agonist or antagonist. After 2 months of lead-in hormonal treatment, definitive standard-of-care prostate/seminal vesicle radiotherapy will be delivered, to a total dose of 75-80 Gy. The primary endpoint, undetectable PSA, will be measured 6 months after completion of ADT/abiraterone acetate/prednisone therapy. Follow up will continue for two years after initiation of abiraterone acetate.

During therapy, laboratory and clinical monitoring will be performed regularly. To investigate changes in the tumor microenvironment, three research MRIs will be performed in a subset of patients at the primary institution: 1) baseline, before lead-in ADT/abiraterone acetate; 2) before starting RT, and 3) post-RT. An MRI of the dominant thigh will be performed at these same time points as well.

3.4 Selection of Subjects

Inclusion Criteria

1. Adenocarcinoma of the prostate proven by biopsy within 180 days of study registration with one of the following high risk criteria:
   - Gleason Score 7 with PSA ≤ 20 ng/ml and clinical T1-2, or
   - Gleason Score 8-10, PSA ≤ 20 ng/ml and clinical T1-2, or
   - PSA 10.1-40 ng/ml with GS < 7 and clinical T1-2, or
   - Clinical T3 with Gleason Score < 7 and PSA ≤ 10 ng/ml.
2. ECOG Performance Status ≤ 1
3. Digital rectal exam within 90 days of registration on study
4. CBC/differential obtained within 30 days prior to registration on study, with adequate bone marrow function defined as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
   - Platelets > 100,000/μL
   - Hemoglobin ≥ 9g/dL
5. Chemistry panel obtained within 30 days prior to registration on study, with adequate organ function defined as follows:
   - Serum potassium ≥ 3.5 mEq/L

     Hypokalemia can be managed and corrected at the physician's discretion. Patients who have hypokalemia must have a repeat serum potassium level drawn within 7 days before starting study drug. Patients with a supported potassium level at >/= 3.5 can be considered eligible at the physician's discretion.
   - Serum albumin ≥ 3.0 g/dl
   - Total bilirubin < 1.5 X of institutional upper limit of normal (ULN)
   - AST(SGOT)/ALT(SGPT) < 1.5 X ULN
6. Calculated creatinine clearance > 60 mL/min
7. Age > 18 years
8. Able to swallow a whole tablet and take abiraterone acetate on an empty stomach (defined as no food for two hours before and one hour after abiraterone acetate ingestion)
9. Ability to understand and sign a written informed consent document
10. Written authorization for use and release of health and research study information has been obtained
11. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol
12. Subjects who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protections as determined acceptable by the Principal Investigator during the study and for 1 week after the last dose of abiraterone acetate.

Exclusion Criteria

1. Evidence of bone, brain, visceral, or soft tissue metastasis, including lymph nodes on pelvic CT (≥2 cm in longest diameter)
2. Prior therapy for prostate cancer [Exceptions: LHRH agonist or antagonist may have been initiated within 30 days prior to enrollment. Bicalutamide may have been given within 60 days of enrollment as long as it has been stopped at least 7 days before enrollment and total duration was no longer than 30 days. This is to allow enrollment of those who have been given bicalutamide as a bridge for LHRH agonist/antagonist. It is highly unlikely a short non-overlapping course of bicalutamide will interact with abiraterone acetate in a measurable way. Previous alpha-reductase inhibitor use allowed IF patient has not been taking for at least 30 days prior to abiraterone acetate initiation, OR if alpha reductase inhibitor was not used as a primary treatment of prostate cancer and the PSA on alpha-reductase inhibitor remains within eligibility when doubled.]
3. Known serum testosterone ≤ 150 ng/dl or symptoms of hypogonadism (fatigue, hot flashes, hair loss, loss of muscle mass, osteoporosis, low libido, depression) prior to ADT initiation not explained by other medical co-morbidity OR history of testosterone supplement. If questionable, serum testosterone level greater than 150 ng/dl can be used to exclude hypogonadism.
4. Previous malignancy within 3 years other than non-melanomatous skin cancer and non-muscle invasive bladder cancer
5. Previous pelvic radiotherapy that would prevent prostate/SV irradiation
6. Receiving any investigational agents currently or within 30 days prior to study screening
7. Prior demonstrated hypersensitivity, intolerance or allergy to abiraterone acetate, prednisone or their excipients
8. Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy
9. History of gastrointestinal disorders that may interfere with the absorption of study drug (including gastric bypass surgery)
10. Active co-morbidity, defined as follows:
    - Chronic liver disease with cirrhosis (Child-Pugh B or C) or active hepatitis B or C
    - History of pituitary or adrenal dysfunction
    - Poorly controlled diabetes mellitus (A1c >9% or history of complications including peripheral neuropathy, end organ damage, hospitalization, amputation)
    - Poorly controlled glaucoma
    - Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III-IV heart disease or known cardiac ejection fraction measurement of < 50% at baseline
    - Clinical evidence of active infection of any type, including active or symptomatic viral hepatitis

- Known immune deficiency and/or HIV-positive patients
- Any medical condition that warrants long-term corticosteroid use in excess of study dose

11. Concurrent spironolactone use
12. Patients taking strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital).
13. Significant concurrent medical condition that would make prednisone/prednisolone use contraindicated or would interfere with the patient's ability to participate in the trial
14. Any condition that, in the opinion of the Principal Investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing the study requirements.

3.5 Subject Recruitment and Compensation

Patients will be identified by their physicians or research nurses within the radiation oncology, medical oncology, or urology clinic at each site. The study will be introduced to the patient by their treating physician. No compensation will be offered for participation in this study.

3.6 Consent Process

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

When obtaining informed consent, study personnel should:
First: Confirm that the patient is a potential candidate for study participation.
Next: Obtain dated and signed informed consent.
Finally: Confirm that the patient is eligible as defined in sections 7.1and 7.2(Inclusion/Exclusion Criteria).

3.7 Subject's Capacity to Give Legally Effective Consent

Subjects who do not have capacity to give legally effective consent will not be enrolled.

3.8 Study Interventions

After consent and enrollment, patients will receive a LHRH analog injection. [Because this is a standard of care treatment, LHRH analog initiation is permitted within 30 days prior to enrollment.] They will receive education about how to take abiraterone acetate and prednisone, avoidance of contraindicated concurrent medications, safe handling, and side effects of these medications. They will then receive abiraterone acetate 1000 mg PO daily from the investigational pharmacy and a prescription for prednisone 5mg daily. Patients will take abiraterone acetate and prednisone once daily for 6 months (26 weeks). During that time, laboratory monitoring will occur every 2 weeks for 2 months, and then monthly for 4 months. Symptom monitoring will occur at least monthly during that time.

Radiation therapy will be delivered to the prostate and seminal vesicles during weeks 9-17, using IMRT or proton therapy. Radiotherapy will be permitted locally. For patients enrolled at

the primary institution (Duke Cancer Institute), up to 16 patients will be asked to undergo three research MRIs with IV contrast and with or without endorectal coil: a baseline, before lead-in abiraterone acetate(within 30 days prior to day 0); 2) before starting RT (week 7 +/- 14 days), and 3) at completion of RT (week 17 +/- 14 days). These MRIs will be used to evaluate for tumor changes from abiraterone acetate and radiotherapy. If patient performs Research MRI portion of study, fiducial markers must NOT be placed until after second research MRI.

On completion of all therapy, patients will return to clinic every three months for symptom, laboratory, and prostate cancer monitoring, including PSA and testosterone. Study termination is five years after initiation of abiraterone acetate.

3.9 Risk/Benefit Assessment

Potential risks of this study include the potential for abiraterone acetate and prednisone toxicity, including hypokalemia, hypertension, liver toxicity, cardiac adverse events, and effects of mineralocorticoid excess. There is the potential risk of under-treatment as only 6 months of ADT will be used. However, there is also the potential benefit that the addition of abiraterone acetate to STADT may improve cancer outcomes and minimize the side effects associated with long-term ADT use. Additional risks of study inclusion include potential loss of confidentiality, although all steps will be taken to protect the patient's privacy and confidentiality.

3.10 Costs to the Subject

Patients and their insurers will be expected to pay costs of routine care, including radiation therapy, ADT, and prednisone. Research visits/procedures and cost of abiraterone acetate will be covered by research funds.

3.11 Data Analysis and Statistical Considerations

This study is a single stage design to test a hypothesis about the proportion of patients with undetectable PSA (defined as PSA <0.1 ng/ml) at 1 year. The null hypothesis to be tested in patients treated with abiraterone acetate in combination with radiotherapy/STADT is that the proportion of patients with undetectable PSA response at 1-year is 10% vs. the alternative hypothesis that proportion of patients with undetectable PSA response is 30%. Assuming a type I error rate of 5% and 90% power, 33 patients are needed. If seven or more patients experience undetectable PSA response at 1-year the null hypothesis will be rejected and the treatment will be considered worthy for study in a phase III setting. Allowing for 10% ineligibility/withdrawal rate, the target sample size is 37. Accrual is expected to be completed within 19 months after study activation assuming a monthly accrual rate of 2 patients. All patients will be followed for disease progression for a maximum period of 5 years from the date the patient received abiraterone acetate.

All eligible patients will be included in the analyses, but patients who are ineligible or who cancel registration will not. The proportion of patients with undetectable PSA at 1-year, PSA response rates, toxicity rates and 95% confidence intervals for the response and toxicity rates will be computed using the binomial distribution. Toxicity will be reported by type, frequency, severity and attribution. In addition, the Kaplan-Meier method will be used to estimate time to

undetectable PSA, progression-free survival, time to PSA failure and overall survival distributions.

3.12 Data and Safety Monitoring

A study safety committee consisting of the sponsor-investigator and clinical representation from each site will review enrollment and adverse events monthly. All SAEs will be reviewed in real-time by the site PI and Sponsor-Investigator. While there are no dose-limiting toxicities defined in this phase II study, stopping rules designed to indicate significant risk to enrolled patients will trigger suspension of enrollment until the study safety committee can review and recommend continuation or termination of the study.

3.13 Privacy, Data Storage, and Confidentiality

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Duke Research Data Security Plans (RDSPs) will be approved by the appropriate Duke institutional clinical research unit. An external data/safety monitoring plan is provided under separate cover.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in a room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated web-access secure database which is housed in an encrypted and password-protected server behind the Duke firewall. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine. Upon completion of the study, research records will be archived and handled per institutional HRPP policy. Janssen Scientific Affairs, LLC will have unrestricted access to de-identified data at their request and at the completion of the study (defined as two years after last therapy delivered).

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

4 BACKGROUND

4.1 Radiation Therapy for Prostate Cancer

Definitive radiotherapy (RT) for prostate cancer offers curative therapy without major surgery, and is the choice of treatment for approximately one-third of the 240,000 men diagnosed with prostate cancer each year.[1] While the majority of men are cured, prostate cancer is still the second leading cause of cancer death in men in the US.[8] Low-risk prostate cancer can be effectively treated with either external beam RT or brachytherapy.[9, 10] However, outcomes for patients with elevated risk features have sub-optimal outcomes with radiotherapy alone. Dose escalation[11, 12] and addition of long-term (2-3 year duration) androgen deprivation therapy[2-4] have improved biochemical control, disease-specific mortality, and for the latter, overall survival. However, significant concern exists over the toxicities associated with long-term androgen deprivation, including erectile dysfunction, metabolic syndrome, and osteoporosis.[5] Strategies are needed to further complement radiation therapy in order improve treatment efficacy and reduce the burden of long-term androgen deprivation.

4.2 *Radiation Alone (Dose Escalation)*

Dose escalation has improved biochemical outcomes but has not yet been associated with an overall survival benefit. Table 4.2.1 summarizes prospective trial experience with dose escalation. In 2009, Viani et al performed a meta-analysis showing that dose escalation benefitted all risk categories.[13] Dose escalation has also been performed using a brachytherapy boost with good biochemical control shown in single arm studies.[14-16]

4.2.1 Response Rates for Dose Escalation Studies

Study	Eligibility	Treatment Arms	Outcome
MDACC[11]	T1-3 No ADT.	70 Gy	**8y FFBCF 41%**
		78 Gy	**22%**
MRC RT01[17]	T1b-3a, PSA <50. 3-6mo ADT.	64 Gy	**5y BPFS 60%**
		74 Gy	**71%**
Dutch[18]	T1-4, PSA <60. 22% ADT.	68 Gy	**7y FFBF 45%**
		78 Gy	**6%**
Zietman 2005[19]	T1-2, PSA <15. No ADT.	70.2 GyE	**5y FFBF 61%**
		79.2 GyE	**80%**
MSKCC[12]	T1-3. No ADT.	64.8-70.2 Gy	**5y BRFS† 28%**
		75.6 Gy	**44%**
		81 Gy	**67%**

ADT androgen deprivation therapy; FFBF freedom from biochemical failure; BPFS biochemical progression free survival; Bold indicative of $p < 0.05$. †indicates only unfavorable risk data shown.

4.3 Androgen Deprivation Therapy

The addition of androgen deprivation does increase overall survival (Table 4.3.1). In intermediate risk patients, RTOG 9408 showed a benefit of 6 months ADT for intermediate risk patients.[4] The EORTC has shown that three years of ADT improves survival for men with high risk prostate cancer.[2, 3]

4.3.1 Studies of Radiotherapy with Androgen Deprivation

Study	Eligibility	Length of ADT	Outcome
EORTC[3]	T3-4 or hg T1-2. 70 Gy	0 mo	**10y OS 40%**
		36 mo	**58%**
RTOG 85-31[20]	c/pT3. 65-70 Gy	0 mo	**10y OS 39%**
		24 mo	**49%**
RTOG 86-10[21]	T2-4. 65-70 Gy	0 mo	**10y DSM 36%**
		4 mo	**23%**
DFCI[22]	T1-2b. PSA 10-40 or GS7-10. 70 Gy	0 mo	**8y OS 61%**
		6 mo	**74%**
RTOG 94-08[4]	T1-2. PSA <20. 66.6 Gy	0 mo	**10y OS 57%**
		4 mo	**62%**
RTOG 92-02[23]	T2c-4. PSA <150. 65-70 Gy	4 mo	**10y DSM 16%**
		28 mo	**11%**
EORTC 22961[2]	T2-4. PSA <160. 70 Gy	6 mo	**5y OS 81%**
		36 mo	**85%**

ADT androgen deprivation therapy; hg high grade; OS overall survival; c/p clinical or pathologic; DSM disease-specific mortality. Bold indicates $p < 0.05$.

While it does improve survival for men treated with radiotherapy, androgen deprivation comes with several toxicities. Erectile dysfunction is perhaps the most feared, but other complications include hot flushes, fatigue, changes in muscle and fat content, osteoporosis, and metabolic syndrome, which carry increased risks of diabetes and cardiovascular disease.[24] ADT use has been associated with worse physical and emotional quality of life for men with non-metastatic prostate cancer compared to healthy controls.[5, 25]

The current strategy of combining radiotherapy with androgen deprivation utilizes LHRH agonists and androgen receptor blockers to reduce circulating androgens and prevent activation of androgen receptors on prostate tumor cells. The benefit of long-term ADT over short-term ADT for high risk prostate cancer suggests prostate tumor heterogeneity in androgen dependence even in castrate-responsive tumors. One hypothesis for which androgen suppression by the LHRH pathway may not be effective is that prostate cancer cells synthesize intracellular testosterone,[26] thereby self-stimulating growth and bypassing the hypothalamic-pituitary-testis pathway. Mechanisms to attack an intracellular testosterone pathway may prevent this “back-door” resistance to traditional androgen deprivation therapy and provide

more effective treatment and/or synergy with radiotherapy. Likewise, development of a more effective androgen-based therapy may eliminate the need for long-term androgen deprivation in high risk patients, thereby reducing the significant quality of life burden caused by this treatment.

4.4 Abiraterone acetate and Prostate Cancer

Abiraterone acetate inhibits cytochrome P450 c17 and therefore acts early in testosterone synthesis. Abiraterone acetate was originally approved by the FDA for second-line use in castration-refractory prostate cancer. This approval was based on a phase III trial of 1195 men with castrate-resistant prostate cancer with progression on docetaxel. Median overall survival was improved in the group receiving abiraterone acetate and prednisone compared to placebo-prednisone (14.8 versus 10.9 months, p<0.001).[6] In this study abiraterone acetate was also found to delay time to PSA progression and reduce pain from metastases. Given its activity in castration-resistant cancer, abiraterone acetate may be able to provide complementary action in combination with ADT and radiotherapy to more effectively eradicate aggressive localized prostate cancer.

The drug was well-tolerated, with most adverse effects occurring at similar rates as placebo, except for urinary tract infections and mineralocorticoid effects including fluid retention and hypokalemia. Liver function elevation was not significantly increased but a grade 4 toxicity was noted, with future recommendation for careful LFT follow-up with abiraterone acetate. [6] Prednisone is also given concurrently to suppress endogenous mineralocorticoid synthesis.[27]

4.5 Abiraterone acetate Side Effects

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a LHRH agonist or were previously treated with orchiectomy, abiraterone acetate was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with abiraterone acetate was 8 months. The most common adverse reactions (≥ 5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, fractures, and upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased liver function enzymes, urosepsis, and cardiac failure (each in <1% of patients taking abiraterone acetate).

Table 4.5.1 shows adverse reactions due to abiraterone acetate that occurred with either a ≥ 2% absolute increase in frequency compared to placebo or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities) in a randomized phase III clinical trial.

4.5.1 Abiraterone Acetate Adverse Reactions

	Abiraterone acetate with Prednisone	
System Organ Class Adverse reaction	**All Grades %**	**Grade 3-4 %**
Musculoskeletal and connective tissue disorders		
Joint swelling/ discomfort	29.5	4.2
Muscle discomfort	26.2	3
General disorders		
Edema	26.7	1.9
Vascular disorders		
Hot flush	19.0	0.3
Hypertension	8.5	1.3
Gastrointestinal disorders		
Diarrhea	17.6	0.6
Dyspepsia	6.1	0
Infections and infestations		
Urinary Tract Infection	11.5	2.1
Upper Respiratory Tract Infection	5.4	0
Respiratory, thoracic and mediastinal disorders		
Cough	10.6	0
Renal and urinary disorders		
Urinary frequency	7.2	0.3
Nocturia	6.2	0
Cardiac disorders		
Arrhythmia	7.2	1.1
Chest pain or chest discomfort	3.8	0.5
Cardiac failure	2.3	1.9
Fractures	5.9	1.4
Laboratory Abnormality		
High triglyceride	62.5	0.4
High AST	30.6	2.1
Low potassium	28.3	5.3
Low phosphorus	23.8	7.2
High ALT	11.1	1.4
High total bilirubin	6.6	0.1

4.6 PSA Nadir as Early Endpoint

Prostate cancer endpoints are slow to achieve, and thus early surrogate endpoints have been investigated. PSA nadir <0.5 has been shown to be independently associated with improved overall survival in men treated with RT alone or RT plus ADT.[28, 29] PSA recovery after short-term ADT has not been well documented, but in a historical series of Duke University

intermediate risk patients treated with short-term ADT, the vast majority (~90%) had a detectable PSA six months after ADT completion (unpublished). A recent report that PSA 12 months after brachytherapy was a significant independent predictor of long-term PSA relapse-free survival provides additional support for early PSA surrogate.[30]

4.7 DW/DCE-MRI

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive functional imaging technique that monitors the passage of a contrast agent bolus through a patient's vasculature. Analysis of the magnitude and rate of this signal enhancement yields valuable information about tumor perfusion, vascular density, and vascular permeability (collectively termed "pharmacokinetic parameters (PK)") that can be used to evaluate disease progression, define tumor boundaries, and assess response to therapy Three kinetic parameters, the vascular transfer constant (Ktrans), the rate constant (kep) and the extracellular extravascular volume fraction (ve = Ktrans/kep) are used to quantify treatment-induced changes. The parameter of greatest interest is Ktrans, which reflects both tissue perfusion (contrast delivery) and permeability of vessels (contrast transport across the vascular endothelium).

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a specialized technique that measures the degree of diffusion of water molecules within extracellular space and between intracellular and extracellular space. Apparent diffusion coefficient (ADC) maps and images can be generated using water diffusion as the contrast. The greater the cellularity of a given tissue, the lower is its ADC. Together these two techniques will allow us to follow for tumoral changes during the period of abiraterone actate+ADT alone and after prostate RT.

An exploratory objective of determining change in muscle cross sectional area by MRI will be done in up to five patients (only at Duke) at the same time points of the DCE-MRI of the prostate. It is well-established that ADT causes significant muscle wasting and muscle loss based on pervious studies. For instance, an indirect measure of intramuscular lipid content, as well as the muscle cross-sectional area (CSA) in 39 men with prostate cancer showed that muscle attenuation of the rectus femoris muscle was significantly reduced following the initiation of ADT by 18.9%. In addition, there was a significant decrease in the CSA for the sartorius, quadriceps and rectus femoris muscles [31]. These results indicate that not only muscle size but also muscle quality may be adversely affected by the undertaking of ADT in men with prostate cancer. Accordingly, measurement of skeletal muscle function in the present using gold-standard, quantitative assessments is of obvious importance, especially with the use of next generation androgen biosynthesis inhibitors such as abiraterone. Only one study has looked at changes in body composition after treatment with abiraterone. This study was a post hoc analysis of patients enrolled in early phase I and II clinical trials of treatment with abiraterone [32]. In this study, axial CT cross sectional area measurement showed a 2.9-4.3% loss of muscle area and a 9.9-16.6% loss in adipose area after six months of treatment. Prospectively characterizing the changes in muscle area will be an important step to then design strategies such as exercise to mitigate toxicities of abiraterone, especially if it is to be used in earlier disease settings in the prostate cancer continuum.

5 STUDY HYPOTHESIS AND OBJECTIVES

5.1 Study Hypothesis

We hypothesize that the addition of abiraterone acetate to definitive radiotherapy and short-term androgen deprivation will increase the frequency of undetectable PSA at one year from 10 to 30%.

5.2 Study Objectives

5.2.1 Primary Endpoint:

To determine the proportion of men with intermediate/high risk localized prostate cancer treated with external beam radiotherapy, short term androgen deprivation, and abiraterone acetate who achieve an undetectable (<0.1 ng/dl) PSA at 1 year following initiation of abiraterone acetate.

5.2.2 Secondary Endpoints:

1) To evaluate the effect of abiraterone acetate in combination with RT/STADT:
    a. Time to PSA nadir, and PSA nadir values at 1 and 2 years,
    b. time to biochemical progression-free survival (Phoenix definition),
    c. time to metastasis or systemic therapy,
    d. time to testosterone recovery, and
    e. proportion of men with 1, 2, 3, 4 and 5 year PSA < 1.5ng/ml in setting of non-castrate testosterone.
2) To evaluate the short and long term safety and tolerability of 6 months of abiraterone acetate with prednisone and ADT combined with standard RT in men with intermediate/lower high risk localized prostate cancer.

5.2.3 Exploratory Endpoints:

1) To evaluate the effect of abiraterone acetate in combination with ADT and RT on change in tumor volume and vascularity by diffusion-weighted and dynamic contrast-enhanced MR imaging (DW/DCE-MRI).
2) To collect 1, 2, 3, 4 and 5 year quality of life outcomes on men treated with abiraterone acetate, STADT and RT using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.
3) To determine change in muscle cross sectional area of the dominant thigh by MRI in a subset of up to 5 patients (only at Duke).

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a two-site phase II single arm open-label study initiated by the Principal Investigator with a target enrollment of 37 patients. It is eligible for patients newly diagnosed with intermediate and high risk prostate cancer who have a single unfavorable risk factor and clinically low volume disease. Patients will receive six months of ADT and abiraterone acetate/prednisone concurrent with definitive RT to the prostate and seminal vesicles. This protocol will be open at Duke University Medical Center and MD Anderson Cancer Center.

6.2 Treatment Schema

The investigational plan will be to give concurrent abiraterone acetate, prednisone, and STADT and prednisone for six months in conjunction with 2 months RT to the prostate and seminal vesicles. Abiraterone acetate will be dosed at 1000 mg daily (4 250 mg tablets) on an empty stomach according to the product label. Prednisone will be administered by prescription at 5 mg once daily by mouth. ADT will be administered as per standard of care treatment guidelines with a LHRH analog for a total duration of 6 months. Radiation therapy will be delivered by IMRT or proton therapy with image guidance using daily fiducial markers or GPS beacon (unless declined by patient). 75-80 Gy to the prostate and seminal vesicles will be delivered once daily with a maximum five treatments per week.

Dosing guidelines for pharmacologic and radiation intervention

Therapy	Dose	Frequency	Route
Approved LHRH Analog	Per approved dosing and administration guidelines	Total therapy 6 months Per approved dosing and administration guidelines	Per approved dosing and administration guidelines
Abiraterone acetate	1000 mg	Daily	Oral
Prednisone	5 mg	Daily	Oral
Prostate/SV Radiation	75-80 Gy	Daily 5 fractions per week	

6.3 Rationale for Dose, Regimen, and Treatment Duration

6.3.1 Drug Therapy

Abiraterone acetate dosing of 1000 mg once daily was found to be safe and effective in a phase III trial of men with metastatic prostate cancer. [6] In that study, prednisone was dosed as 5mg twice daily. However, data presented in abstract form at ASCO 2012 showed that once daily

dosing of prednisone was also extremely well tolerated with no grade 4+ events.[33] LHRH analog dosing is standard of care for men with intermediate risk prostate cancer. The addition of abiraterone acetate is hypothesized to accommodate for the shorter use of ADT than typical for high risk prostate cancer.

6.3.2 Radiation Therapy

Radiation dose is based on benefit seen with dose escalation and the dose range provided allows treating physician leeway based on clinical preference. Dose constraints are provided in Section 10 to ensure protection of nearby normal tissues.

6.4 Rationale for Correlative Studies

DW/DCE-MRI has been useful in preclinical studies as a predictor of RT success. Therefore MRI comparison pre and post-RT will be analyzed with biochemical outcome to determine whether changes in tumor volume or vascularity can be used to predict patients with good (or poor) radiation response. This information may be used in the future to further tailor treatment plans to the nature of the cancer.

Regarding dominant thigh MRIs, prospectively characterizing the changes in muscle area in patients on this study will be an important step to then design strategies such as exercise to mitigate toxicities of abiraterone, especially if it is to be used in earlier disease settings in the prostate cancer continuum.

These MRIs will be done on Duke Patients only.

6.5 Study Termination

The study will be terminated five years after the last patient at any site initiated abiraterone acetate. However, this study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 9.4, which describes procedures and process for prematurely withdrawn patients.

7 PATIENT SELECTION

Target Population: Men with previously untreated prostate cancer with a single unfavorable risk factor: Gleason Score 7-10, PSA 21-40 ng/ml, or clinical T3 disease. The target accrual is 37 men.

7.1 Inclusion Criteria

1. Adenocarcinoma of the prostate proven by biopsy within 180 days of study registration with one of the following high risk criteria:
   - Gleason Score 7 with PSA $\leq$ 20 ng/ml and clinical T1-2, or
   - Gleason Score 8-10, PSA $\leq$ 20 ng/ml and clinical T1-2, or
   - PSA 10.1-40 ng/ml with GS < 7 and clinical T1-2, or
   - Clinical T3 with Gleason Score < 7 and PSA $\leq$ 10 ng/ml.
2. Performance Status (ECOG) ≤ 1(see Appendix A)
3. Digital rectal exam within 90 days of registration on study
4. CBC/differential obtained within 30 days prior to registration on study, with adequate bone marrow function defined as follows:
   - Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
   - Platelets > 100,000/µL
   - Hemoglobin $\geq$ 9g/dL
5. Chemistry panel obtained within30 days prior to registration on study, with adequate organ function defined as follows:
   - Serum potassium $\geq$ 3.5 mEq/L
     Hypokalemia can be managed and corrected at the physician's discretion. Patients who have hypokalemia must have a repeat serum potassium level drawn within 7 days before starting study drug. Patients with a supported potassium level at >/= 3.5 can be considered eligible at the physician's discretion.
   - Serum albumin $\geq$ 3.0 g/dl
   - Total bilirubin < 1.5 X of institutional upper limit of normal (ULN)
   - AST(SGOT)/ALT(SGPT) < 1.5 X ULN
6. Calculated creatinine clearance > 60 mL/min
7. Age > 18 years
8. Able to swallow a whole tablet and take abiraterone acetate on an empty stomach (defined as no food for two hours before and one hour after abiraterone acetate ingestion)
9. Ability to understand and sign a written informed consent document
10. Written authorization for use and release of health and research study information has been obtained
11. Be willing/able to adhere to the prohibitions and restrictions specified in this protocol
12. Subjects who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protections as determined acceptable by the Principal Investigator during the study and for 1 week after the last dose of abiraterone acetate.

7.2 Exclusion Criteria

1. Evidence of bone, brain, visceral or soft tissue metastasis, including lymph nodes on pelvic CT (≥2 cm in longest diameter)
2. Prior therapy for prostate cancer [Exceptions: LHRH agonist or antagonist may have been initiated within 30 days. Bicalutamide may have been given within 60 days of enrollment as long as it has been stopped at least 7 days before enrollment and total duration was no longer than 30 days. This is to allow enrollment of those who have been given bicalutamide as a bridge for LHRH agonist/antagonist. It is highly unlikely a short non-overlapping course of bicalutamide will interact with abiraterone acetate in a measurable way. Previous alpha-reductase inhibitor use allowed IF patient has not been taking for at least 30 days prior to abiraterone acetate initiation, OR if alpha reductase inhibitor was not used as a primary treatment of prostate cancer and the PSA on alpha-reductase inhibitor remains within eligibility when doubled.].
3. Known serum testosterone ≤ 150 ng/dl or symptoms of hypogonadism (fatigue, hot flashes, hair loss, loss of muscle mass, osteoporosis, low libido, depression) prior to ADT initiation not explained by other medical co-morbidity OR history of testosterone supplement. If questionable, serum testosterone level greater than 150 ng/dl can be used to exclude hypogonadism.
4. Previous malignancy within 3 years other than non-melanomatous skin cancer and non-muscle invasive bladder cancer.
5. Previous pelvic radiotherapy that would prevent prostate/SV irradiation
6. Receiving any investigational agents currently or within 30 days prior to study screening
7. Prior demonstrated hypersensitivity, intolerance or allergy to abiraterone acetate, prednisone or their excipients
8. Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg). Patients with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy.
9. History of gastrointestinal disorders that may interfere with the absorption of study drug (including gastric bypass surgery)
10. Active co-morbidity, defined as follows:
    - Chronic liver disease with cirrhosis (Child-Pugh B or C) or active hepatitis B or C
    - History of pituitary or adrenal dysfunction
    - Poorly controlled diabetes mellitus (A1c >9% or history of complications including peripheral neuropathy, end organ damage, hospitalization, amputation)
    - Poorly controlled glaucoma
    - Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III-IV heart disease or known cardiac ejection fraction measurement of < 50% at baseline.
    - Clinical evidence of active infection of any type, including active or symptomatic viral hepatitis.
    - Known immune deficiency and/or HIV-positive patients
    - Any medical condition that warrants long-term corticosteroid use in excess of study dose

11. Concurrent spironolactone use
12. Patients taking strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital)
13. Significant concurrent medical condition that would make prednisone/prednisolone use contraindicated or would interfere with the patient's ability to participate in the trial.
14. Any condition that in the opinion of the Principal Investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing the study requirements

8 REGISTRATION ON STUDY

8.1 Duke Cancer Institute (DCI)

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

When obtaining informed consent, study personnel should:

First: Confirm that the patient is a potential candidate for study participation.
Next: Obtain dated and signed informed consent.
Finally: Confirm that the patient is eligible as defined in sections 7.1 and 7.2 (Inclusion/Exclusion Criteria).

8.1.1

DCI patients who sign consent (regardless of eligibility) are entered into the Duke clinical trial subject registry.

8.2 MD Anderson Cancer Center (MDACC)

8.2.1

Following consent and completion of the Eligibility Checklist documents will be submitted for review and registration of subject.

8.2.2

Enrolled subjects will be assigned a unique study ID. Refer to Subject Registration Instructions for details.

8.3

Patients may be enrolled on study only after eligibility criteria are met and verified. Patients may decline or be medically unable to undergo MRI and still be enrolled on the primary intervention.

9 PATIENT ASSESSMENTS

Schedule of Events

Assessment	Pre Treatment (within 30 days)	Day 0	Weeks 2, 4, 6 and 8*	Weeks 9-17*	Weeks 20 and 24*	End of Study Visit (Week 26)*	Follow-up (q3mo from Week 26) *	Follow-up year 4 and 5*
History and physical	X		X[1] Week 4 only			X[1]	X[1]	
Radiation Therapy and weekly Treatment Checks[9]				X				
LHRH Analog[7]	X[7]			X[7]				
PSA	X						X[10]	X[10]
Testosterone	X						X[10]	X[10]
Pelvic Imaging (CT and/or MRI)	X[6]							
Bone Scan	X[6]							
Concurrent Medications	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		
Comprehensive Metabolic Panel	X		X	X[3]	X		X[4]	
CBC w Differential	X							
Study Drug Diary			X[2]	X[2]	X[2]	X[2]		
Adverse Event Assessment			X	X[3]	X	X		
EPIC Questionnaire	X		X[8]			X	X[8]	X[8]
Pelvic Research DCE-MRI and dominant thigh MRI with creatinine*	X		X[5]	X[5]				

1. Disease focused H&P. At each visit, a disease-focused history must be performed. Exam may be performed at the physician's discretion. Blood pressure and pulse measurement should be performed at each visit.
2. Document at weeks 0, 2, 4, 8, 12, 16, 20, 24, 26.
3. Weeks 12, 16, 20 and 24 until last dose of abiraterone acetate
4. At first follow-up visit then as clinically indicated to monitor an abiraterone acetate toxicity
5. Research DW/DCE-MRI immediately prior to RT initiation (week 7 +/-14d) and at RT completion (week 17 +/-14d)
6. Pelvic Imaging and Bone Scan allowed within 90 days prior to enrollment on study
7. LHRH Analog may be given up to 30 days prior to abiraterone acetate start. Timing of subsequent injections will depend on administered dose. Total treatment time with LHRH analog will be 6 months, but may be extended to 7 months to cover the full administration time of abiraterone acetate.
8. EPIC questionnaire will be completed pre-treatment, week 8, week 26, 6 months and 18 months after completion of abiraterone acetate, and if possible, 30, 42 and 54 months after completion of abiraterone acetate.
9. Treatment checks must include blood pressure and pulse.
10. If possible, PSA and Testosterone will be collected q3mo (+/- 28 days) for years 2-3, and at year 4 and 5 (+/- 3 mo) after initiation of abiraterone acetate

*** indicates window of allowance for visit of +/- 7 days. RT may begin +/- 14 days.**
Research MRI date may occur +/- 14 days. Follow-up visits +/- 14 days up to year 2, then +/- 28 days for PSA/Testosterone collection for years 2-3, then +/- 3 months for PSA/Testosterone and EPIC questionnaire collected at year 4 and 5 (if possible).

9.1 Pre-Treatment Evaluation

9.1.1 History and Physical Examination within 4 weeks of study enrollment including performance status assessment

9.1.2 Pelvic and thigh imaging (CT and/or MRI) and Bone Scan within 90 days of study enrollment.

9.2 On Treatment Assessments

9.2.1 Clinical Assessment

Patients will be seen and evaluated before the start of RT (week 4), weekly during RT by their treating radiation oncologist, and at completion of abiraterone acetate (week 26). Patients will be seen every 3 months thereafter for up to 2 years from initiation of abiraterone acetate. Clinical assessment follow-up beyond 2 years will be at the discretion of the treating physician for clinical care purposes. Clinical assessment will include monitoring for hypertension and fluid retention at least once a month. Blood pressure and pulse should be checked at every clinical visit. Home BP monitoring should be encouraged.

9.2.2 Patient Reported Outcome-Quality of Life:

The Expanded Prostate Cancer Index Composite (EPIC) questionnaire is a comprehensive instrument designed to evaluate urinary, bowel, and sexual function and bother after prostate cancer treatment. EPIC will be completed by the patient either on paper or through web-based database entry within 14 days of enrollment, week 8, week 26, and 6 months and 18 months after completion of abiraterone acetate therapy (for those who discontinue drug prematurely, the survey will be completed within the same time points, as though the individual had completed 26 weeks of drug). If possible, EPIC questionnaire will also be completed by the patient at 30, 42 and 54 months after completion of abiraterone acetate (3, 4 and 5 years after initiation of abiraterone acetate). If the patient will not return to clinic, the questionnaire may be completed and returned by mail at year 3, 4 and 5.

9.2.3 Laboratory Assessments

Comprehensive metabolic panel (CMP: glucose, calcium, albumin, total protein, sodium, potassium, carbon dioxide (CO2), chloride, blood urea nitrogen (BUN), creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase, also called SGPT), AST (aspartate amino transferase, also called SGOT) and bilirubin) will be checked prior to initiation of abiraterone acetate, every two weeks for the first two months, and then once per month throughout treatment with abiraterone acetate.

Outside laboratory reports will be accepted. If values rise above baseline, lab work will be continued after abiraterone every 3-4 months thereafter until values normalize. Complete blood count will be checked prior to study treatment and then as clinically indicated. (see Schedule of Events).

9.2.4 Radiology Assessments

Research MRI: 16 patients enrolled at Duke Cancer Institute will be asked to participate in three research MRI scans. If patient agrees to the optional research MRIs, these will be performed at baseline (pre-abiraterone acetate), pre-RT (week 7), and at RT completion. A study creatinine (expressly for purposes of study MRI) will be obtained up to 7 days prior to MRI. The patient will then undergo MRI imaging with DW/DCE-MRI techniques with or without endorectal coil as deemed appropriate for image quality. Gadolinium contrast will be used if GFR ≥ 60 (for the tumor site only and not the thigh). The MRI will be stored electronically indefinitely in a password-protected server behind the Duke University firewall, so that analysis of changes between baseline, pre-RT, and post-RT scan can be performed. This is an exploratory endpoint (2.2.3). Access to the scans will be limited to study personnel.

Muscle Cross Sectional Area (CSA) of the dominant thigh will be assessed in up to 5 patients using magnetic resonance imaging (MRI) without contrast at the same time points as above and also stored in an identical manner as above (only at Duke).

Imaging for Metastatic Workup is recommended to be performed for clinical suspicion of recurrence at the treating provider's discretion.

9.3 Post Treatment Assessments

9.3.1 H&P: After completion of abiraterone acetate, patients will be followed q3 months for 18 months, at which point follow-up will be at the discretion of the treating physician. At each visit, a disease-focused history must be performed. Exam may be performed at the physician's discretion. Blood pressure measurement should be performed at each visit. If a subject is unable to travel to the research site during follow-up q3 months, the Disease focused H&P and blood pressure measurement may be performed by subjects' local physician.

9.3.2 Labwork: PSA and testosterone will be checked every three months for 24 months after initiation of abiraterone acetate. Then if possible, PSA and Testosterone will be checked q3 months up to 36 months and once at year 4 and 5 after initiation of abiraterone acetate. If CMP values rise above baseline, those tests will also be continued after completion of abiraterone acetate every 3-4 months thereafter until values return to baseline. If a subject is unable to travel to the research site during follow-up, this labwork may be done locally.

9.4 Criteria for Removal From Protocol

- Progression of disease defined as PSA rise 2ng/ml above nadir, initiation of systemic therapy, or imaging consistent with new metastatic disease;
- Unacceptable toxicity (at the discretion of the treating physician) — Reason(s) for removal must be clearly documented in the physician progress note
- Noncompliance with oral medication
- A delay in radiotherapy > 2 weeks;
- The patient may withdraw from study treatment at any time for any reason and still be followed per protocol with patient consent, including PSA and testosterone levels and completion of EPIC questionnaire.

At withdrawal all on-going study-related toxicities and SAEs should be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease. Subjects should be followed up for new AEs for 30 calendar days after the last dose of abiraterone acetate. All new AEs possibly related to study treatment occurring during that period should be collected.

10 RADIATION THERAPY

10.1 Fiducial Markers (unless declined by patient)

Each patient will have fiducial markers placed transrectally into the prostate for image-guided radiation therapy unless patient declines marker placement. If patient does decline, use of daily cone-beam CT or ultrasound-targeting is encouraged.

10.1.1 Fiducial markers should not be placed until AFTER research MRI. GPS beacon (ie Calypso™) may not be used in patients undergoing research MRIs.

10.2 Radiotherapy Planning

10.2.1 Patients will undergo daily image-guided radiotherapy.

10.2.2 Patients will undergo both CT, and if medically appropriate, MRI imaging for treatment planning.

- MRI: The patient will undergo MRI imaging including DCE -MRI technique. Gadolinium contrast will be used if medically appropriate. If endorectal coil is used, prostate displacement must be considered during planning.

10.2.3 The prostate, seminal vesicles, rectum, bladder, and bowel must be contoured. Optional contours include "LNs" (common iliac, internal iliac, external iliac vessels to top of femoral head) and penile bulb.

10.2.4 Pelvic nodal irradiation will be at the discretion of the radiation oncologist. CTV and PTV volumes should be sufficient to include all area at risk of microscopic disease and organ motion. Suggested expansions include

- prostate 4-6mm in all dimensions
- seminal vesicles 4-10mm in all dimensions

10.2.5 Dose will be prescribed in 1.8-2 Gy fractions to a final dose of 75-80 Gy. If multiple PTVs are used, sequential plans with a cone-down must be used instead of an integrated boost technique. IMRT or proton therapy is required. Constraints are described below.

IMRT Structure Dose Constraints

Structure	Dose	Volume
PTV	Rx	>95%
Bladder	80 Gy	≤ 5%
	70 Gy	≤ 20%
	40 Gy	≤ 50%
Rectum	80 Gy	≤ 5%
	60 Gy	≤ 40%
	40 Gy	≤ 60%
Left Femoral Head	50 Gy	≤ 1%
Right Femoral Head	50 Gy	≤ 1%
Bowel	50 Gy	≤ 1%

10.3 Radiotherapy for Duke Subjects

Duke subjects are permitted to undergo radiation therapy at Duke University Medical Center or Durham Regional Hospital, provided it conforms to protocol-specified treatment and dosing specifications. Non-Duke facilities are permitted with approval by the PI and study coordinator as long as local facility follows the protocol and submits the radiation data form, weekly on-treatment visit notes, and laboratory data per protocol to the Duke research personnel as designated by the PI.

10.4 Radiation Therapy Adverse Events

10.4.1 All patients will be seen weekly by their treating radiation oncologist while undergoing EBRT. Any observations with respect to the following symptoms/side effects will be recorded using CTCAE v4.0 grading:

- Bowel/rectal irritation manifesting as cramping, diarrhea, urgency, proctitis, or hematochezia
- Urinary frequency, urgency, dysuria, hematuria, urinary tract infection, or incontinence

- Radiation dermatitis

10.4.2 Clinical discretion should be used in managing radiotherapy-related side effects. Suggested medical management may be but is not limited to:

- diarrhea/rectal frequency/urgency - diphenoxylate or loperamide
- Bladder irritation - phenazopyridine
- Urinary frequency/urgency - anticholinergic agents or alpha-blockers
- Erectile dysfunction - phosphodiesterase (PDE) inhibitors

Questions regarding RT planning details should be directed to:

Bridget Koontz, M.D.
Duke University
[redacted]
Email : bridget.koontz@duke.edu

11 DRUG THERAPY

11.1 Abiraterone Acetate

Abiraterone acetate will be supplied by Janssen Scientific Affairs, LLC free of charge.

11.1.1 Description

Abiraterone acetate inhibits cytochrome P450 c17 and therefore acts early to block testosterone synthesis from both testicular and adrenal sources.

11.1.2 Dosage and Administration

Abiraterone acetate will be administered once daily orally at 1000 mg per day (four 250 mg tablets). This dosage will be prescribed for 6 months total (180 days). Abiraterone acetate will initiate within 30 days of starting ADT. No food should be consumed at least two (2) hours before and for at least one hour after the dose of abiraterone acetate is taken. Exposure of abiraterone acetate increases up to 10 fold when abiraterone acetate is taken with meals.

11.1.3 Supply, Storage and Handling

Abiraterone acetate 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. It is stored at room temperature (or (20°C to 25°C or 68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)). This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

11.1.4 Packaging and Shipment to Secondary Site

Abiraterone acetate 250 mg tablets will be supplied by Janssen Scientific Affairs, LLC to DCI Investigational Pharmacy Services in high-density polyethylene bottles of 120 tablets (one month supply) labeled with name, dosage, storage and handling instructions. Upon acknowledgement of first patient registration at MDACC, DCI Investigational Pharmacy Services will ship a partial supply to MDACC Investigational Pharmacy Services by FedEx.

11.1.5 Labeling and Dispensing

After receipt of prescription by the site Investigational Pharmacy Services, a secondary label will be applied with patient's name, date, prescription, expiration, contact information, and indication to take on an empty stomach. Abiraterone acetate will not

be repackaged from original container. Abiraterone acetate 250mg will be dispensed monthly (120 tablets) by the site investigational pharmacy services.

11.1.6 Compliance and Accountability

Drug accounting on receipt, shipment, and dispensing will be carried out per site Investigational Pharmacy Services SOP. Patient compliance with prescription will be monitored by a study drug diary which will be reviewed with the research nurse staff monthly.

11.1.7 Disposal and Destruction

Any abiraterone acetate tablets returned unused by patients will be documented by the site Investigational Pharmacy Services and then incinerated according to SOP.

11.1.8 Abiraterone acetate Monitoring

Labwork will be obtained at weeks 2, 4, 6, 8, 12, 16, 20, and 24. Patients will be seen by their treating radiation oncologist 4 weeks after initiation of abiraterone acetate, weekly during the patient's radiation therapy, and at completion of abiraterone acetate. All toxicity will be reported using CTCAE v4.0. Concomitant medication will be evaluated at RN or MD visit weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, and 26 during abiraterone acetate therapy.
Study activities required at the week 12 and 16 RN or MD visits may be collected remotely and reported by phone, email, and/or fax at the discretion of the site PI. Blood pressure assessments may be reported to site via phone throughout the course of the study.

11.1.9 Dose Modification

Patients should be carefully monitored for toxicity related to treatment. Toxicity due to abiraterone acetate administration may be managed by symptomatic treatment, dose interruptions and adjustment of the abiraterone acetate dose. Dosage modifications are not recommended for grade 1 events. Therapy with abiraterone acetate should be interrupted upon the occurrence of a grade 2 or 3 related adverse experience. Once the adverse event has resolved or decreased in intensity to grade 1, then abiraterone acetate therapy may be restarted at full dose or as adjusted according to Table 11.1.9.1. Once the dose has been reduced it should not be increased at a later time. If a grade 4 experience occurs, therapy should be discontinued. Doses of abiraterone acetate omitted for toxicity should not be added to the end of treatment.

General Toxicity Abiraterone acetate Dose Modification Guidelines

Any toxicity possibly related to abiraterone acetate will require dose modification as below:

11.1.9.1 General Dose Modification Guidelines

CTCAE 4.0 Grade	Action	Dose Adjustment on Restart (% of starting dose)
Grade 1	Maintain Dose Level	n/a
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	100
2nd appearance	Interrupt until resolved to grade 0-1	50
3rd appearance	Discontinue permanently	
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75
2nd appearance	Interrupt until resolved to grade 0-1	50
3rd appearance	Discontinue permanently	
Grade 4		
1st appearance	Discontinue permanently	

- HYPOKALEMIA Specific Guideline

  Potassium level must be monitored at least once per month during abiraterone acetate therapy. Hypokalemia must be corrected before and during treatment with abiraterone acetate. Dose modification of abiraterone acetate for hypokalemia should follow Table 11.1.9.1 guidelines. If hypokalemia does develop during abiraterone acetate therapy, monitoring should continue every 3-4 months after abiraterone acetate is complete until values normalize.

- HYPERTENSION and FLUID RETENTION Specific Guideline

  Blood pressure and evaluation for symptoms of fluid retention must be monitored at least once per month during abiraterone acetate therapy. Hypertension requires correction with anti-hypertensive in addition to modification of abiraterone acetate dose as described below:

- If Grade 1 or 2 adverse events occur, management per investigator. No study medication dose reduction.
- If Grade 3 or 4 adverse events occur, hold study medication. Adjust or add medications to mitigate the toxicity or consider the specific mineralocorticoid receptor blocker, eplerenone. When hypertension improves to ≤150/90, resume study medication at full dose.
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When blood pressure improves to ≤150/90, resume study medication with the first dose level reduction (3 tablets, 750 mg of study medication).
- If toxicity recurs, hold study medication, and adjust or add medications to mitigate the toxicity. When hypertension improves to ≤ 150/90, resume study medication with the second dose level reduction (2 tablets, 500 mg of study medication). If blood pressure remains ≤ 150/90 for at least one month, the site investigator has the option of increasing the patient's dose by (1 tablet) 250mg to 750mg (3 tablets).
- If toxicity recurs despite optimal medical management and 2 dose level reductions, discontinue study medication.

Monitoring should continue every 3-4 months after abiraterone acetate is complete until blood pressure normalizes to pre-enrollment levels.

- HEPATOTOXICITY Specific Guideline

  Liver function testing (ALT, AST, bilirubin) must be performed prior to starting abiraterone acetate, every two weeks for the first three months of treatment, and once a month thereafter until abiraterone acetate therapy is complete. If clinical symptoms or signs arrive that are suggestive of hepatotoxicity, liver function testing should be completed even if unscheduled. Elevations of ALT, AST, or bilirubin should prompt more frequent monitoring.

  For patients with baseline hepatic impairment or those that develop hepatotoxicity, please refer to Table 11.1.9.1mandatory dose modification guidelines. For patients who develop hepatotoxicity during treatment, defined as ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN, hold abiraterone acetate until recovery. Retreatment may be initiated at a reduced dose of 750 mg once daily once LFTs have returned to patient's baseline or AST/ALT less than or equal to 2.5X ULN and total bilirubin ≤ 1.5X ULN. For patients who resume treatment, LFTs must be monitored every two weeks while they remain on abiraterone acetate.

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

Abiraterone acetate should be discontinued if patients develop severe hepatotoxicity (AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN), as the safety of abiraterone acetate re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

- ADRENOCORTICAL INSUFFICIENCY Specific Guideline

  Adrenocortical insufficiency has been reported in clinical trials in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

11.2 **Prednisone**

11.2.1 Description

Prednisone is a naturally-occurring corticosteroid, glucocorticoid-type; short-acting; t1/2: 80-118 min.

11.2.2 Dosage and Administration

Prednisone will be administered once daily at 5mg per dose. This dosage will be prescribed for 6 months total (180 days) beginning with the first day of abiraterone acetate and continuing until the discontinuation of abiraterone acetate.

11.2.3 Supply, Storage and Handling

A prescription for prednisone will be provided by the treating physician to be filled at the patient's commercial pharmacy. Consult the package insert for storage handling.

11.2.4 Prednisone Side Effects

Consult the package insert for comprehensive toxicity information but described below are potential toxicities associated with prednisone.

- Heart: Sodium retention, fluid retention, CHF in susceptible patients, hypertension, myocardial rupture following recent myocardial infarction

- Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture
- GI: Fluid and electrolyte disturbance, potassium loss, hypokalemic alkalosis, negative nitrogen balance due to protein catabolism, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large bowel (particularly in patients with inflammatory bowel disease), pancreatitis, abdominal distention, ulcerative esophagitis
- Dermatologic: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, increased sweating, may suppress reactions to skin tests, other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic edema
- Neurologic: Convulsions, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, vertigo, headache, psychic disturbances
- Hormonal: Development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics; hirsutism
- Ophthalmic: Posterior sub capsular cataracts, increased intraocular pressure, glaucoma, exophthalmos
- Hypersensitivity: Thromboembolism, weight gain, increased appetite, nausea, malaise.

11.2.5 Prednisone Dose Modifications

Prednisone may be tapered in an individualized manner in accordance with the instructions of the Principal Investigator. Adrenal insufficiency (<1%) has been reported following interruption of daily corticosteroids and/or with concurrent infection or stress in clinical trials of patients receiving abiraterone acetate at the recommended dose in combination with prednisone.

11.3 **Androgen Deprivation Therapy (ADT)**

11.3.1 Description

ADT will be delivered by administration of LHRH agonists or antagonists, which are long-acting analogs of the native luteinizing hormone releasing hormone peptide and are effective at reducing serum testosterone.

11.3.2 Dosage and Administration

ADT will consist of LHRH analog monotherapy. LHRH analogs may be interchanged. However, anti-androgen therapy is not allowed. Either leuprolide acetate (22.5mg IM) or goserelin acetate (10.8mg SC) will be administered every 3 months for 2 doses following manufacturer's instructions. An alternate, approved LHRH analog drug and/or alternate dosing may be used as long as total time of active drug from time of enrollment is no more or less than 6 months. ADT may initiate up to 30 days prior to the start of abiraterone acetate administration, in which case the total length of ADT may extend up to 7 months.

11.3.3 Supply, Storage and Handling

A medication order for administration of leuprolide acetate or goserelin acetate (or other approved LHRH analog, at discretion of treating physician) will be provided by the treating physician to be administered by the clinic nursing staff.

11.3.4 ADT Side Effects

Consult the package insert for comprehensive toxicity information. Class-related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances have occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely allergic generalized rash and difficulty breathing.

11.4 **Missed Doses**

The patient will be instructed that if a dose of abiraterone acetate or prednisone is missed, to take the dose as scheduled the following day. However, if more than one dose is missed, the patient should contact their study physician immediately. Missed doses should not be added to the end of treatment.

11.5 Concomitant Medications

Concomitant medication will be evaluated at RN or MD visit weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, and 26 during abiraterone acetate therapy. For week 12 and 16 RN or MD visits, this information may be reported by email, and/or fax at the discretion of the site PI.

11.5.1 CYP2D6 inhibitor Drug Interactions

Abiraterone acetate should not be taken concomitantly with CYP2D6 inhibitors (listed in Appendix B). Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of abiraterone acetate with CYP2D6 substrates with a narrow therapeutic index (e.g. thioridazine). If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. Results from a CYP2C8 drug-drug interaction trial in healthy subjects indicate that no clinically meaningful increases in exposure are expected when ZYTIGA is combined with drugs that are predominantly eliminated by CYP2C8, however, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA.

11.5.2 Drugs that Inhibit or Induce CYP3A4 Enzymes

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during treatment with abiraterone acetate are to be avoided, or used with careful evaluation of clinical efficacy. For purposes of this study, use of strong CYP3A4 inducers is an exclusion criterion. However, inhibitors of CYP3A4 are allowed.

12 RESEARCH MRI IMAGING (Duke site only)

MRI data will be acquired on either the 1.5 Tesla whole body MR scanner in the Radiation Oncology Department using an endorectal coil, or the 3 Tesla research MR scanner at Duke north without endorectal coil. Each patient will complete all three scans on the same scanner. The MRI contrast agent Gadolinium-DTPA will be used to assess tumor perfusion/diffusion, vascular density, and oxygen tension. Per scan, 0.1 mmol/kg of gadolinium will be administered. Due to the recently identified association between contrast administration and nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD), we will obtain serum creatinine levels prior to each MRI scan. GFR must be >/= 60 ml/min in order to proceed with gadolinium injection.

Voxel-based pharmacokinetic analysis will be performed using post-processing software from iCAD, Inc. (Nashua, NH). The tissue concentration time curves will be numerically fitted to the modified Tofts model using the Levenberg-Marquardt algorithm to estimate K^{trans}, v_e and v_p.

Images in the same slice locations as the DCE acquisition (above) will be acquired using diffusion b-values of 0 and 500 sec/mm^2 in the three directions. After these diffusion weighted images are acquired, the ADC values will be calculated using a linear least square fitting according to $\ln(I_b) = \ln(I_0) - b \bullet ADC$ using the MRI system vendor's (GE Medical Systems) workstation to calculate an ADC image that is the average of the ADC images in each of the three directions (related to the trace of the diffusion tensor).

The PK parameters and ADC will be compared for the three scans to determine a coefficient of variability (C_v). Mean value sample estimates (x) and standard deviations (s) will be calculated. The coefficient could then be obtained by the equation $C_v = s/x$.

Regarding the dominant thigh MRI in up to 5 Duke patients, imaging will be performed using sequence gradient echo recall scans at the mid-femur level. Seven serial slices will be obtained with one at the juncture of the middle third of the femur (this point will be landmarked to ensure within subject reproducibility). The CSA of the quadriceps, hamstrings, and total mid-thigh muscle will be assessed using semiautomatic generation of the region of interest using console software.

13 SAFETY MONITORING AND REPORTING

13.1 Study Safety Committee

A Study Safety Committee consisting of the Sponsor-Investigator and clinical representation from each site will review enrollment and adverse events monthly. All SAEs will be reviewed in real-time by the site PI and Sponsor-Investigator. While there are no dose-limiting toxicities defined in this phase II study, stopping rules designed to indicate significant risk to enrolled patients will trigger suspension of enrollment until the study safety committee can review and recommend continuation or termination of the study.

13.2 Identification of Adverse Events

The site PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred. The site PI will review all SAEs before reporting them to the IRB, the Sponsor-Investigator, and Janssen Scientific Affairs, LLC.

13.3 Event Monitoring

From the time the subject signs the informed consent form through 30 days after receiving the last dose of abiraterone acetate/prednisone, all AEs must be recorded in the subject medical record and adverse events case report form. Any serious adverse event or Special Reporting Situation that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

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

AEs will be assessed according to the CTCAE version 4.0. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

13.3.1 Adverse Events (AEs)

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to use of the study drug. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs, but laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

13.3.2 Serious Adverse Events (SAEs)

An AE is considered "serious" when it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience;
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- Any pregnancy occurring on study must be reported per institutional requirements as a medically significant event.

13.3.3 Adverse Events of Special Interest (AESI), Special Reporting Situations, and Product Quality Complaints

AESI are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious).

Special Reporting Situations include overdose of abiraterone acetate, inadvertent or accidental exposure to abiraterone acetate including pregnancy exposure (maternal or paternal) or exposure by breastfeeding, suspected abuse/misuse of abiraterone acetate, any failure of expected pharmacological action (i.e., lack of effect) of abiraterone acetate, unexpected therapeutic or clinical benefit from abiraterone acetate, medication error involving abiraterone acetate, or suspected transmission of any infectious agent via abiraterone acetate. Special Reporting Situations also include all of the above in relation to any Johnson and Johnson medicinal product (that the study team is aware of).

Product Quality Complaint (PQC) are any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of any Johnson and Johnson medicinal product of which the study team is aware. 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.

13.3.4 Adverse Drug Reaction (ADR)

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

13.4 Stopping Rules

13.4.1 In addition to AEs/SAEs, certain stopping rules have been designed to maximize patient safety. If such an event occurs that the treating investigator attributes as at least possibly related to study treatment, enrollment will be placed on hold until the event can be reviewed by the Study Safety Committee and recommendation made for continuation of study or early termination. These events include:

- Inability of patient to complete full radiation course
- Medical event preventing second LHRH analog injection

13.5 Management of AEs, SAEs and Special Reporting Situations

13.5.1 Maintenance of Safety Information

Safety information will be maintained in a clinical database in a retrievable format. At a minimum, at the end of the treatment phase (last patient off treatment) as well as the end of the follow-up phase (last patient off study), the PI shall provide all adverse events, both serious and non-serious, in report format to Janssen Scientific Affairs, LLC. However, in certain circumstances more frequent review of the safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at request by Janssen Scientific Affairs, LLC .

13.5.2 Reporting Timelines (to Lead Study Coordinator and Sponsor-Investigator)

All AEs must be reported to the DCI Sponsor-Investigator and lead study coordinator through the study database. All SAEs and Special Reporting Situations must be communicated to the Sponsor-Investigator, site IRB (per institutional IRB policy), DCI

IRB (per institutional IRB policy), and Janssen Scientific Affairs, LLC within 24 hours, whether or not it is considered drug related. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Janssen Scientific Affairs, LLC. The PI must record non-serious adverse events and report them to Janssen Scientific Affairs, LLC according to the timetable for reporting as specified either in the Request for Agreement or to fulfill regulatory reporting requirements.

13.5.3 Reporting Timelines (to Duke and Janssen Scientific Affairs, LLC)

All non-serious AEs should be reported according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data. All safety information (SAEs, AESIs, SRSs, and PQCs) should be reported within 24 hours of becoming aware of the event(s) along with their determination of whether the event was caused by abiraterone acetate. The PI will transmit these SAE and Special Reports in a form to be provided (or a form substantially similar to the form provided and approved for use by Janssen Scientific Affairs, LLC) in accordance with the above transmission methods within 24 hours of becoming aware of the event(s).

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

The PI is responsible for ensuring that these cases from clinical studies are complete and if not that they are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the PI and that follow-up information is summarized e.g. hospital records, coroner's reports, autopsy results and recorded on the appropriate forms. A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.

All safety information (SAEs, AESIs, SRSs, and PQCs) should be reported to the Principal Investigator and the lead site/sponsor within 24 hours using the provided Janssen SAE Report Form and the DCI SAE Review Form (Site Assessment), and sent to:

The DCI Safety Desk fax: [redacted]

If the safety desk cannot be reached within 24 hours, the Principal Investigator or Co-Principal Investigator should be contacted: Dr. Bridget Koontz ([redacted] email: bridget.koontz@duke.edu); Dr. Andrew Armstrong ([redacted] email: andrew.armstrong@duke.edu).

The initial report for each SAE or death should include <u>at minimum</u> the following information:

- protocol # and title
- patient initials, study identification number, sex, age
- date the event occurred
- description of the SAE
- dose level and cycle number at the time the SAE occurred
- description of the patient's condition
- indication whether the patient remains on study
- causality

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible.

Upon receipt of the Serious Adverse Event Reporting form by DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI Safety SAE Report Review Form. The DCI safety desk will, in turn, send the Janssen SAE Report Form to Janssen Scientific Affairs, LLC. Safety information will be sent to Janssen Scientific Affairs, LLC by encrypted email using Cisco Registered Envelope Service to [redacted]Delivery and read receipt of the secure email will serve as evidence of successful communication.

Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with abiraterone acetate in the course of the Study, must be sent by encrypted email to Janssen Scientific Affairs, LLC within 24 hours of such report or correspondence being sent to applicable health authorities.

13.5.4 Dissemination of Safety Information from Janssen Scientific Affairs, LLC to Sponsor-Investigator

Janssen Scientific Affairs, LLC will provide to DCI and the Sponsor-Investigator IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports

generated by the Janssen Scientific Affairs, LLC for abiraterone acetate as they become available until all subjects in the protocol have completed their last study visit (i.e. 2 years after completion of abiraterone acetate).

These reports will be sent to the DCI Safety Desk at the following address:

DCI Safety Surveillance
[redacted]

The DCI Safety Desk will be responsible for distributing these reports to the sub-site.

13.5.5 Reporting SAEs at Participating Institutions

Staff at participating sites are responsible for reporting all SAEs to the lead site/sponsor within 24 hours of becoming aware of the event. **The DCI Safety Desk at** [redacted] should be contacted when reporting an SAE or death. If this person cannot be reached within 24 hours, the Principal Investigator should be contacted:
Dr. Bridget Koontz (phone: [redacted]; email: bridget.koontz@duke.edu)

13.6 DCI Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 14.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring

The DCI Monitoring Team will conduct monitoring visits of both sites to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring of each site after the site's third subject is enrolled, followed by annual monitoring of 1 – 3 subjects at each site until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, Duke Clinical Trials Quality Assurance (CTQA), the Safety Oversight Committee (SOC), the Sponsor-Investigator, the site Principal Investigator(s), or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

14.2 Data Management and Processing

14.2.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

14.2.2 Case Reports Forms (CRFs)

The CRF will be the primary data collection document for the study. It will be entered electronically into a password-protected web-access secured database housed within Duke's firewall. The CRFs will be updated in a timely manner following acquisition of new source data. Only the research staff listed on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF. An audit trail will be maintained automatically by the database system. All users of this system will complete user training, as required or appropriate per regulations.

14.2.3 Data Management Procedures and Data Verification

Completeness of entered data will be checked automatically by the database system, and users will be alerted to the presence of data inconsistencies. Queries may also be issued by the study data manager or project leader. Missing or implausible data will be queried for completion or correction (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc). The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

14.2.4 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness

15 STATISTICAL CONSIDERATIONS

All statistical analysis will be performed under the direction of the statistician designated in key personnel.

15.1 Definitions of Study Endpoints

15.1.1 Primary Endpoint

Undetectable PSA at 1 year from initiation of abiraterone acetate (<0.1 ng/ml)

15.1.2 Secondary Endpoints

- time to PSA nadir
- biochemical progression-free survival
  - From the first dose of abiraterone acetate to the date of progressive disease or death from any cause.
  - Disease progression defined as Phoenix definition of nadir + 2ng/ml, initiation of systemic therapy, or imaging consistent with new metastatic disease
- time to testosterone recovery
  - Defined from date of last dose of abiraterone acetate to date of free and serum testosterone recovery within reference normal range
- One, two, three, four and five year PSA rates of < 1.5 ng/ml in setting of non-castrate testosterone (serum testosterone >50 ng/dL)
- distant metastasis-free survival
  - From the date of first dose of abiraterone acetate to the date of distant metastasis or death from any cause
- safety and tolerability of 6 months of abiraterone acetate with prednisone and ADT combined with standard RT in men with intermediate/lower high risk localized prostate cancer.

15.1.3 Exploratory Endpoints

- change in tumor volume by DCE-MR imaging (only at Duke)
- one, two, three, four and five year quality of life outcomes
- Change in muscle cross sectional area of dominant thigh, 5 patients (only at Duke)

15.2 Sample Size and Enrollment

This study is a single stage design to test a hypothesis about the proportion of patients with undetectable PSA (defined as PSA <0.1 ng/ml) at 1 year. The null hypothesis to be tested in patients treated with abiraterone acetate in combination with radiotherapy/STADT is that the proportion of patients with undetectable PSA response at 1-year is 10% vs. the alternative hypothesis that proportion of patients with undetectable PSA response is 30%. Assuming a type I error rate of 5% and 90% power, 33 patients are needed. If seven or more patients experience undetectable PSA response at 1-year the null hypothesis will be rejected and the treatment will be considered worthy for study in a phase III setting. Allowing for 10% ineligibility/withdrawal rate, the target sample size is 37. Accrual is expected to be completed within 19 months after study activation assuming a monthly accrual rate of 2 patients. All patients will be followed for disease progression for a minimum of 2 years and no more than period of 5 years from the date that the patient received abiraterone acetate.

15.3 Accrual and Follow-up

The target sample size is 37. To complete enrollment within 19 months, 2 patients must be enrolled per month. A second institution through the Department of Defense Prostate Cancer Clinical Trials Consortium (MD Anderson Cancer Center) will be added to the protocol to ensure completion on schedule. Each patient will be followed for disease progression for a minimum period of 2 years and no more than period of 5 years from the date that the patient received abiraterone acetate.

15.4 Analysis Plan

Ineligible patients and patients who cancel registration will not be included in the analyses.

15.4.1 Primary Endpoint

The proportion and 95% confidence interval of patients with undetectable PSA at 1-year will be computed using the binomial distribution. In addition, the Kaplan-Meier product-limit method will be used to estimate time to undetectable PSA distribution.

15.4.2 Secondary Endpoints

The proportion of patients with PSA response rates, toxicity rates and 95% confidence intervals for PSA response, and toxicity rates will be computed using the binomial distribution. Toxicity will be reported by type, frequency severity and attribution. In addition, the Kaplan-Meier product-limit method will be used to estimate time to biochemical progression-free survival, time to testosterone recovery, distant metastasis free survival, and overall survival distributions. The correlative science analyses will be exploratory as the limited sample size will not permit definitive analyses for these objectives.

16 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

16.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

16.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

16.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal Investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or designee must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

16.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Duke Research Data Security Plans (RDSPs) will be approved by the appropriate Duke institutional clinical research unit.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated web-access secure database which is housed in an encrypted and password-protected DCI file server. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per institutional HRPP policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

16.5 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

16.6 Records Retention

The Principal Investigator at each site will maintain study-related records at least six years after study completion.

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18 APPENDIX A ECOG

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

18 APPENDIX B CYP2D6 Medications to Avoid

All tricyclic antidepressants, e.g.
- imipramine
- amitriptyline
- etc.

Most SSRIs (antidepressant), e.g.
- fluoxetine
- paroxetine
- fluvoxamine

venlafaxine (SNRI antidepressant)
mianserin (tetracyclic antidepressant)
opioids
- codeine
- tramadol
- oxycodone

antipsychotics, e.g.
- haloperidol
- risperidone
- perphenazine
- thioridazine
- zuclopenthixol
- aripiprazole
- chlorpromazine
- levomepromazine
- remoxipride

minaprine (RIMA antidepressant)
beta-blockers
- metoprolol
- timolol
- alprenolol
- carvedilol
- bufuralol
- nebivolol
- propranolol

debrisoquine (antihypertensive)
Class I antiarrhythmics
- flecainide
- propafenone
- encainide
- mexiletine
- lidocaine
- sparteine

ondansetron (antiemetic)
donepezil (acetylcholinesterase inhibitor)
phenformin (antidiabetic)
tropisetron (5-HT3 receptor antagonist)

amphetamine (in ADHD, narcolepsy)
atomoxetine (in ADHD)
chlorphenamine (antihistamine)
dexfenfluramine (serotoninergic anorectic)
dextromethorphan (antitussive)
duloxetine (SNRI)
metoclopramide (dopamine antagonist)
Methoxyamphetamine
perhexiline (antianginal agent)
phenacetin (analgesic)
promethazine (antihistamine antiemetic)