Title: A phase II randomized study of enzalutamide + leuprolide versus enzalutamide + leuprolide + abiraterone acetate + prednisone as neoadjuvant therapy for intermediate-high risk prostate cancer undergoing prostatectomy.

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Sponsor - Investigator:
Mary-Ellen Taplin, MD
Associate Professor of Medicine
Dana-Farber Cancer Institute
Lank Center for Genitourinary Oncology
450 Brookline Avenue
Boston, MA 02215
Telephone: 617-582-7221
Fax: 617-632-2165
mtaplin@partners.org

Co-Investigators:
Rana McKay, MD, University of California, San Diego
Bruce Montgomery, MD, University of Washington and Fred Hutchinson Cancer Research Center
Kenneth J. Pienta, MD, John Hopkins University
Glenn Bubley, MD, Beth Israel Deaconess Medical Center

Coordinating Center:
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215

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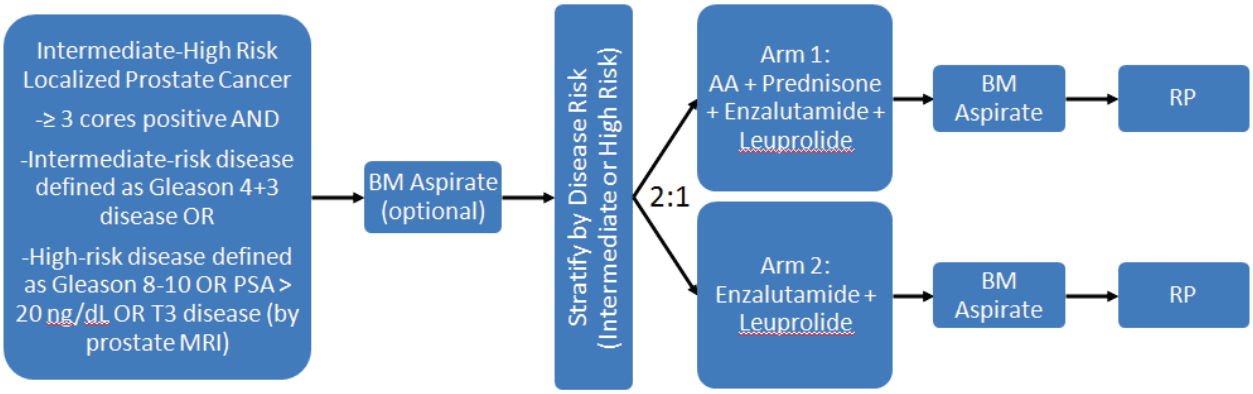
ABBREVIATIONS

AA – Abiraterone Acetate
Adrenocorticotropic hormone – ACTH
Adverse event – AE
Alanine transaminase – ALT
American Society of Clinical Oncology – ASCO
ANC – Absolute neutrophil count
Androgen deprivation therapy – ADT
Androgen Receptor – AR
Area under the concentration-time curve – AUC
Aspartate transaminase – AST
Canadian Urologic Oncology Group – CUOG
Cancer and Leukemia Group B – CALGB
Cancer Therapy Evaluation Program – CTEP
Case Report Form – CRF
Castration resistant prostate cancer – CRPC
Cerebrovascular Accident – CVA
Circulating Tumor Cells – CTCs
Code of Federal Regulations – CFR
Coefficient of Variation – CV
Computed tomography – CT
Coronary Artery Disease – CAD
Coronary Artery Bypass Graft – CABG
Dana Farber Cancer Institute – DFCI
Dana-Farber/Harvard Cancer Center – DF/HCC
Dana-Farber/Partners Cancer Care – DF/PCC
Data Safety and Monitoring Committee – DSMC
Dehydroepiandrosterone – DHEA
Deoxyribonucleic acid – DNA
Digital Rectal Examination – DRE
Dihydrotestosterone – DHT
Disease-free survival – DFS
Eastern Cooperative Oncology Group – ECOG
Echocardiogram – ECHO
Electrocardiogram – EKG
ETS-related gene – ERG
Fluoro-dihydrotestosterone-positron emission tomography – FHDT-PET
Food and Drug Administration – FDA
Good Clinical Practice – GCP
Half-life – $t_{1/2}$
Hazard ratio – HR
Health Insurance Portability and Accountability Act – HIPAA
Immunohistochemistry – IHC
IND – Investigation new drug
Institutional Review Board – IRB

International Normalized Ratio – INR
Liver function test – LFT
Luteinizing hormone-releasing hormone – LHRH
Magnetic Resonance Imaging – MRI
Maximum plasma concentration – C_{max}
Minimum plasma concentration – C_{min}
Minimum residual disease – MRD
Common Terminology Criteria for Adverse Events – CTCAE
National Surgical Adjuvant Breast and Bowel Project – NSABP
New York Heart Association – NYHA
Non-ST segment elevation myocardial infarction – NSTEMI
Office for Human Research Studies – OHRS
Overall survival – OS
Partial thromboplastin time – PTT
Pathologic complete response – pCR
Phosphatase and tensin homolog – PTEN
Principal Investigator – PI
Progression free survival – PFS
Prostate specific antigen – PSA
Quality Assurance Office for Clinical Trials – QACT
Residual cancer burden – RCB
Response Evaluation Criteria In Solid Tumors – RECIST
Radical Prostatectomy – RP
Serious adverse event – SAE
Skeletal related event – SRE
Small Bowel Obstruction – SBO
ST segment elevation myocardial infarction – STEMI
Time to PSA Progression – TTPP
Transient ischemic attack – TIA
Upper limit of normal – ULN
WBC – White blood cell count

Schema:


Intermediate-High Risk Localized Prostate Cancer
-≥ 3 cores positive AND
-Intermediate-risk disease defined as Gleason 4+3 disease OR
-High-risk disease defined as Gleason 8-10 OR PSA > 20 ng/dL OR T3 disease (by prostate MRI)
BM Aspirate (optional)
Stratify by Disease Risk (Intermediate or High Risk)
2:1
Arm 1: AA + Prednisone + Enzalutamide + Leuprolide
BM Aspirate
RP
Arm 2: Enzalutamide + Leuprolide
BM Aspirate
RP

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1. OBJECTIVES

1.1 Study Design

This is a multicenter, phase II, prospective, randomized trial designed to assess the pCR and MRD rate between neoadjuvant therapy with Abiraterone Acetate (AA)+ prednisone + enzalutamide + leuprolide (ARM 1) to therapy with enzalutamide + leuprolide (ARM 2) in men with intermediate-high risk prostate cancer who are candidates for RP. Participants will be stratified by disease risk (intermediate or high risk) and randomized from within each stratum to prevent imbalance between treatment groups. Participants will be randomized in a 2:1 ratio to neoadjuvant treatment with AA + prednisone + enzalutamide + leuprolide (ARM 1) with enzalutamide + leuprolide (ARM 2). Participants may enter the study with no more than one month of luteinizing-hormone-releasing hormone (LHRH) agonist treatment prior to cycle 1/day 1. Participants will receive the assigned study treatment for 24 weeks. Therapy will continue until one day prior to RP or until the participant meets criteria for withdrawal from the study.

1.2 Primary Objectives

- To evaluate the frequency of achieving a pCR or MRD (defined as residual tumor in RP specimen measuring ≤ 5 mm) at RP following therapy with ARM 1 compared to ARM 2.

1.3 Secondary Objectives

- To evaluate the frequency of achieving a pCR at RP following therapy with ARM 1 compared to ARM 2.

- To evaluate the frequency of achieving favorable RCB (defined as the 33rd percentile of the RCB index which is calculated as the tumor volume x cellularity) at RP following therapy with ARM 1 compared to ARM 2.

- To evaluate the frequency of the presence of cribriform or intraductal carcinoma at RP following therapy with ARM 1 compared to ARM 2.

- To evaluate the frequency of positive surgical margins, extracapsular extension, positive seminal vesicles, and positive lymph nodes at time of RP following treatment with ARM 1 compared to ARM 2.

- To determine changes in PSA (median nadir value, percentage of participants with PSA < 0.2 ng/mL, proportion of participants with achieving 50% and 90% decrease in PSA, time to PSA nadir) from baseline to prior to RP with ARM 1 compared to ARM .

- To determine the effect of treatment and pathologic response on freedom from biochemical failure post RP.

- To determine the effect of treatment and pathologic response on freedom from further therapy (to include radiation therapy, ADT, or other therapies) post RP.

- To assess the safety and tolerability of each treatment arm.

- To assess intra-operative and post-operative complications following RP between treatment arms.

- To assess quality of life parameters over time between treatment arms.

1.4 Correlative Objectives

- To assess time to testosterone recovery, body-mass index, lipids, and cardiovascular events for each treatment arm following RP.

- To assess changes in serum androgen levels (dehydroepiandrosterone (DHEA), androstenedione, testosterone, dihydrotestosterone (DHT), DHEA-S, DHEA-G, androsterone-S, androsterone-G) by mass spectroscopy from pretreatment to during treatment (day 1 +/- 3 days of cycle 4) and to prior to RP between the treatment arms.

- To correlate serum androgen levels (pretreatment, during treatment at day 1 +/- 3 days of cycle 4, and prior to RP) with pathologic response at RP.

- To assess changes in serum corticosteroid levels (pregnenolone, progesterone, deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxypregnenolone, 17α-hydroxyprogesterone, 11-deoxycortisol, cortisol) from baseline to start of cycle 4, and from baseline to prior to RP for ARM 1 and ARM 2.

- To assess changes in serum ACTH from pretreatment to during treatment (day 1 +/- 3 days of cycle 4) and to prior to RP between the treatment arms.

- To compare prostate androgen levels (DHEA, androstenedione, testosterone, DHT, DHEA-S, DHEA-G, androsterone-S, androsterone-G) by mass spectroscopy in the RP specimens between the treatment arms.

- To compare the expression of the AR and proteins involved in the androgen synthesis, apoptosis, WNT signaling, and PTEN-PI3K-AKT pathways by IHC and expression analysis in the RP specimens between the treatment arms.

- To assess changes in circulating tumor DNA from pretreatment to during treatment (day 1 +/- 3 days of cycle 4) and to prior to RP between the treatment arms.

- To assess changes in the whole exome and whole transcriptome by high throughput parallel sequencing technologies from pretreatment biopsy to RP between the treatment arms.

- To assess changes in AR/AR regulated genes and proliferation in disseminated tumor cells collected from bone marrow aspirates following high intensity AR suppression between treatment arms.

2. BACKGROUND

2.1 Study Disease

Prostate cancer is the most common cancer in men in the United States, with a life time risk of 16%, and the second leading cause of cancer death in this population.[1] Despite ongoing efforts, outcomes in high-risk patients undergoing RP have not significantly improved with time, likely related to systemic micrometastatic disease not adequately addressed at the time of local treatment.[2-4] Following RP upwards of 50% of patients with high-risk disease will experience a biochemical recurrence at 5 years.[4] In a retrospective analysis of 379 men who developed a biochemical recurrence after RP, approximately 80-90% of patients with high-risk prostate cancer died of their disease.[5] Consequently, new treatment strategies, including multimodality therapy, are needed to improve outcomes in high-risk patients.

2.2 Rationale

Treatment of patients with high-risk disease presents two therapeutic challenges: the need for local control of the primary disease site and need for systemic control of microscopic metastatic disease. Neoadjuvant systemic therapy prior to RP is an approach which can potentially maximize survival outcomes in patients with localized disease. This approach is under investigation and provides an opportunity to assess pathologic and biologic activity of novel treatments.

The paradigm of neoadjuvant systemic therapy is widely accepted in the treatment of patients with localized high-risk breast cancer and other solid tumor malignancies. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 was designed to determine whether four cycles of doxorubicin + cyclophosphamide administered preoperatively improved breast cancer disease-free survival (DFS) and overall survival (OS) compared with treatment administered postoperatively. At a median follow-up of 16 years, there were no statistically significant differences in DFS and OS between the two groups, however, there were trends in favor of preoperative chemotherapy for DFS and OS in women less than 50 years old.[6] A meta-analysis of nine randomized studies, including a total of 3,946 women, demonstrated that neoadjuvant therapy was equivalent to adjuvant therapy in terms of survival and overall disease progression.[7]Additionally, neoadjuvant therapy is routinely utilized in the treatment of bladder[8, 9], esophageal[5, 10, 11], and rectal cancer[12].

A central tenant of neoadjuvant therapy is that local tumor response correlates with long-term outcomes such as DFS and OS. For breast cancer, pCR is a significant predictor of improved clinical outcomes and has been adopted as the primary endpoint for neoadjuvant trials. In a review of 6,377 breast cancer patients from seven randomized trials receiving neoadjuvant anthracycline-taxane-based chemotherapy, pCR was associated with significantly superior DFS and a trend towards improved OS.[13] Residual disease after neoadjuvant treatment includes a broad range of actual responses from near pCR to frank resistance. Symmans and colleagues developed a method to measure residual disease in breast cancer by combining histopathologic components of residual disease (cellularity, overall diameter, number and extent of nodal involvement) into a numerical index of RCB.[14] In a pathologic review of 382 patients treated in two different cohorts, RCB was calculated as a continuous index for prediction of distant relapse-free survival in multivariate Cox regression analysis.[14] They determined that RBC was independently prognostic in a multivartiate model.

Table 1 provides a review of clinical trials of neoadjuvant ADT prior to RP.[15-26]

Table 1. Trials of neoadjuvant ADT.

Trial	Patients	Clinical Stage	Regimen	Outcomes (Neoadjvuant ADT + RP vs. RP alone)				Median Follow Up (Years)
				Positive Surgical Margin Rate	pCR Rate	PFS	OS	
Dalkin *et al* (1996) [15]	56	T1c-T2b	G x 3 mo	18% vs. 14%	NR	NR	NR	
Labrie *et al* (1997) [16]	161	T2-T3	L + F x 3 mo	7.8% vs. 33.8%[a]	6.7% vs. 0%	NR	NR	
Fair *et al* (1999) [17]	140	T1-T3	L + F x 3 mo	19% vs. 37%[a]	NR	No difference	NR	2.9
Van Der Kwast *et al* (1999) [18]	47	T1-T3	L + F x 3 mo vs. L + F x 6 mo	27.8% (3 mo) vs. 9.1% (6 mo)[a]	0 (3 mo) vs. 9% (6 mo)	NR	NR	
Schulman *et al* (2000) [19]	402	T2-T3	G + F x 3 mo	13% vs. 37% T2[a] 42% vs. 61% T3	NR	74% vs. 67%	No difference	4
Gleave *et al* (2001) [20]	547	T1b-T2	L + F x 3 mo vs. L + F x 8 mo	23% (3 mo) vs. 12% (8 mo)[a]	5.1% (3 mo) vs. 9.3% (8 mo)	NR	NR	
Soloway *et al* (2002) [23]	303	T2b	L + F x 3 mo	18% vs. 48%[a]	NR	64.8% vs. 67.6%	NR	5
Selli *et al* (2002) [22]	431	T2-T3	G + B x 3 mo vs. G + B x 6 mo	27.9% vs. 53.1% (3 mo)[a] 29.7% vs. 53.1% (6 mo)[a]	NR	NR	NR	
Aus *et al* (2002) [21]	126	T1b-T3a	T x 3 mo	23.6% vs. 45.5%[a]	NR	49.8% vs. 51.5%	No difference	6.85
Klotz *et al* (2003) [24]	213	T1b-T2	T x 3 mo	28% vs. 65%[a]	0% vs. 0%	60.2% vs. 68.2% 30.5% vs.18.8%[a] for PSA > 20 ng/ml	88.4% vs. 93.9%	6
Prezioso *et al* (2004) [25]	167	T1a-T2b	L + C x 3 mo	39% vs. 60%[a]	NR	NR	NR	
Yee *et al* (2009) [26]	148	T1b-T3	G + F x 3 mo	19% vs. 38%[a]	NR	80% vs. 78%	NR	8

[a] Denotes statistical significance.
ADT = androgen deprivation therapy; pCR = pathologic complete response = PFS = progression free survival; OS = overall survival; RP = radical prostatectomy; G = gosereline; mo = months; NR = not recorded; L = leuprolide; F = flutamide; B = bicalutamide; T = triptorelin; C = cyproterone.

The concept of utilizing neoadjuvant ADT prior to RP emerged in an attempt to improve the rate of organ-confined disease. Labrie and colleagues[16] were among the first to show improvement in pathologic outcomes with a randomized, prospective trial using leuprolide and flutamide for three months prior to RP compared to RP alone. The study showed that neoadjuvant combination ADT decreased positive surgical margins from 33.8% to 7.8% and resulted in down staging in 54% in the

neoadjuvant arm. In addition, pCRs were found in six RP specimens (6.7%). The authors postulated that longer duration of neoadjuvant ADT would potentially increase the degree of benefit.

Subsequently treatment durations ranging from three to eight months were evaluated.[18, 20, 22] The Canadian Urologic Oncology Group (CUOG) conducted the largest randomized trial evaluating neoadjuvant ADT prior to RP.[20] In this study, 547 men with cT1b-T2 were randomly assigned to treatment with leuprolide and flutamide for three or eight months before RP. Compared to the three month group, the eight month group had lower preoperative PSA (0.052 versus 0.133 ug/L, p=0.0141), lower positive surgical margin rate (12% versus 23%, p=0.0106), and higher rate of organ-confined disease (80% versus 68%, p=0.0019). The pCR rate was higher in the eight month group compared to the three month group, though this was not statistically significant (9.3% versus 5.1%, p=0.0711). There have been no reports of improvement in biochemical relapse rates or other clinical outcomes with longer ADT from this trial.

A meta-analysis of 10 studies of neoadjuvant ADT prior to RP showed that neoadjuvant therapy had a beneficial and statistically significant impact in lowering the pathologic T stage, increasing the organ-confined rate, lowering the positive surgical margin rate, and decreasing the number of pathologic N1 cases.[27] The effect on positive surgical margins and organ-confined rates was significantly better with eight months of neoadjuvant treatment as compared to only three months of treatment. Four trials included information about the pCR rate.[16, 18, 20, 24] The beneficial effects in pathologic outcomes, including pCR rate, did not translate to improved DFS or OS. The DFS at five years, defined either as biochemical or clinical progression, remained unchanged between the treatment and control groups. Only one trial found local recurrence rates to be decreased, but this was only in a subset of patients with T2 disease.[19] In the three studies which evaluated OS with mean follow-up periods of 4, 6, and 7 years, the meta-analysis found no significant difference in OS and no assessments with longer follow-up are available.[19, 21, 24]

The discordance between the improvement in immediate pathologic endpoints and the lack of benefit in DFS or OS is likely multi-factorial in nature. These trials were underpowered to detect realistic differences between treatment arms.[28] In addition, they included patients who did not have high-risk disease, as defined today, possibly attenuating the impact of neoadjuvant therapy on outcomes.[28] Longer durations of follow-up may be required to appreciate significant differences in outcomes.[28]

Recently approved novel hormone therapies, including AA, an inhibitor of CYP17 which is an enzyme required in testosterone biosynthesis, and enzalutamide, a potent androgen antagonist which also inhibits AR nuclear translocation and AR association with DNA, in patients with metastatic prostate cancer provide therapeutic options in the neoadjuvant setting and opportunities to improve outcomes for high-risk patients.[29-32]

We evaluated AA in a phase II neoadjuvant trial in participants with high-risk prostate cancer.[33] Fifty-eight participants with high-risk disease, defined as cT3-4, Gleason ≥ 8, PSA >20 ng/mL, or high PSA velocity, were randomized to treatment with AA in combination with leuprolide and prednisone (5 mg orally daily) or leuprolide alone for 12 weeks. At 12 weeks, prostate biopsy was performed to obtain tissue of measurement of intraprostatic hormones, as the primary endpoint of the trial was to analyze the differential effects of AA versus leuprolide in tissue hormones. After 12 weeks, all participants received another 12 weeks of combination AA, leuprolide and prednisone (5 mg orally daily). After 24

weeks of neoadjuvant therapy, participants underwent RP. Preliminary results were presented at the 2012 ASCO meeting and demonstrated that the pathologic pCR and near pCR rate (defined as tumor measuring < 5 mm) was 34% in participants treated with AA for 24 weeks and 15% in those treated with leuprolide alone followed by 12 weeks of combination therapy (p=0.089). PSA measurements did not reflect pathologic outcomes in participants in both arms of the trial. Though 86% of all participants had a nadir PSA ≤ 0.2 ng/mL at 24 weeks, 54% had pathologic T3 disease. Longer follow-up is needed to evaluate the effect of this therapy on long term cancer control. Grade 3 AEs included elevated AST/ALT 5/58 (9%) and hypokalemia 3/58 (5%). No grade 4 mineralocorticoid-related AEs were observed.

We are currently conducting a randomized phase II trial evaluating neoadjuvant enzalutamide alone versus enzalutamide, dutasteride, and leuprolide in men with localized intermediate and high-risk prostate cancer.[34] The primary endpoint of this trial is pCR and near pCR rate. Prostate cancer tissue from baseline biopsies and from RP specimens will be available for correlative assessment of mechanisms of castration resistance including selective changes in the AR and AR associated genes.

Though this data is promising, there is an opportunity for further improvement of pathologic outcomes. In preclinical models of human castration resistant prostate cancer (CRPC) xenografts, treatment with abiraterone resulted in increased expression of full-length AR, which can lead to AR sensitization to lower levels of androgens. Additionally, treatment was associated with increased expression of CYP17 and other key enzymes mediating conversion of adrenal androgen intermediates to testosterone, suggesting *de novo* steroidogenesis within the tumor microenvironment. This data highlights the rationale for combination abiraterone with a potent antiandrogen.

To build on our prior experience with neoadjuvant AA, the primary objective of this study is to evaluate pCR and MRD at RP following 24 weeks of neoadjuvant maximal suppression of the androgen axis with AA + prednisone + enzalutamide + leuprolide (ARM 1) compared to therapy with enzalutamide + leuprolide (ARM 2) in participants with intermediate-high risk prostate cancer. MRD will be defined as residual tumor in the RP specimen measuring < 5 mm. If the tumor is multifocal, the size of the largest focus will be used to determine the size of the residual tumor. We hypothesize that ARM 2 will have a pCR and MRD rate of 20% based on our prior experience. We hypothesize that treatment with ARM 2 will have a rate of 40%.

2.3 Study Agent(s)

2.3.1 Enzalutamide

Enzalutamide, formerly known as MDV3100, is a rationally-designed second generation AR inhibitor which functions by blocking several steps in the AR signaling cascade. Enzalutamide competitively binds the AR with great potency. Additionally, enzalutamide inhibits nuclear translocation of activated AR and inhibits the association of activated AR with DNA.[32]

Rationale for Using Enzalutamide in Prostate Cancer
First generation antiandrogens, including bicalutamide, nilutamide, and flutamide, are reversible inhibitors of the AR and have a several-fold lower affinity to the AR compared with androgens.

These agents have been used in the management of advanced prostate cancer for decades. Addition of an antiandrogen at the time of CRPC has been shown to lower PSA by 50% or more in approximately one-quarter of patients.[35-37] There is no data supporting the superiority of one antiandrogen over another, however nilutamide has been shown to induce PSA declines in men who have developed resistance to AR inhibition with flutamide or bicalutamide.[38]

It was first noted in the early 1990s that disease progression, despite the combination of an LHRH agonist and an antiandrogen, could be stopped and reversed simply through discontinuation of the antiandrogen. Stopping the antiandrogen in men with a rising PSA, termed antiandrogen withdrawal, can result in PSA declines in between 10-20% of men.[39] Further work demonstrated that in the setting of AR overexpression or mutation, conventional antiandrogens have the potential to exhibit paradoxical partial agonist activity, promoting prostate cancer progression.[40] Thus, more potent antagonists lacking agonist activity are necessary.

Preclinical Data with Enzalutamide

Using the nonsteroidal agonist RU59603 as the parent scaffold compound, Sawyers and colleagues identified two oral diarylthiohydantoins, RD162 and enzalutamide, from a screen of nonsteroidal antiandrogens that retain antiandrogen activity in the setting of increased AR expression.[32] Both compounds have enhanced affinity for the AR (5-8 fold) compared to the antiandrogen bicalutamide. Enzalutamide competitively binds the AR with an IC_{50} of 36 nM compared to 160 nM for bicalutamide. Additionally, enzalutamide inhibits nuclear translocation of activated AR, inhibits DNA binding to androgen response elements, and inhibits recruitment of coactivators, even in the setting of AR overexpression and in prostate cancer cells resistant to antiandrogens. By contrast with bicalutamide, enzalutamide is a pure antagonist with no detectable agonist effects in LNCaP/AR prostate cells, which overexpress AR. The drug also induces regression of established LNCaP/AR xenograft tumors growing in castrated male mice, a model in which bicalutamide treatment only slows tumor growth.

Clinical Data with Enzalutamide

A phase I/II first in man study was initiated in July 2007 at three sites to assess safety, pharmacokinetics, tolerability, and antitumor activity.[41] Patients with progressive, metastatic CRPC were eligible. The initial dose of enzalutamide was 30 mg daily, with subsequent dose-escalations in cohorts of 3-6 patients to a maximum dose of 600 mg daily. When significant >50% declines in PSA levels were observed in the first six patients, enrollment was expanded by an additional 24 patients (12 pre-chemotherapy, 12 post-chemotherapy) at every dose level starting at 60 mg daily. By 12/2008, 140 patients had been enrolled.

After administration of one dose, the drug was rapidly absorbed, and median time to maximum concentration (C_{max}) was one hour (range 0.42 minutes – 4 hours). The half-life was about 1 week (range 3 – 10 days) and was not affected by dose. Full pharmacokinetic profiles were linear and consistent over the dose range study. Plasma concentrations reached steady state after one month of treatment. Once achievement of steady state, the mean minimum concentration (C_{min}) in individual patients remained constant for several months, suggesting time-linear pharmacokinetics. Due to slow clearance from plasma, the daily fluctuation in steady-state enzalutamide concentrations were low. The mean C_{max}/C_{min} ratio was 1.2 (range 1.14-1.3) indicating that the average difference between the peak and trough concentrations was ≤ 30%.

AR binding was assessed in 22 patients at doses from 60-480 mg daily with FDHT positron emission tomography (PET). All patients showed clear reduction of FDHT uptake (range 20-100%).

Fatigue was the most frequently reported adverse events (AEs), with dose-dependent increases of grade 3 fatigue (0% at 150 mg/day, 9% at 240 mg/day, 15% at 360 mg/day, and 20% at 480 mg/day). The dose of 240 mg/day was defined as the maximum tolerated dose. At doses of 240 mg and above, an increasing proportion of patients needed dose reductions for fatigue. Dose reductions were needed in 1 of 29 patients (3%) that received 240 mg/day, 3 of 28 patients (11%) that received 360 mg/day, and 5 of 22 patients (23%) that received 480 mg/day, and 0 of 58 patients that received 30, 60, or 150 mg/day. After dose reductions, the symptoms resolved. Only 1 patient discontinued treatment due to fatigue with an onset coinciding with PSA rise. Overall, the most common mild (grade 2) AEs were fatigue (n = 38, 27.1%), nausea (n = 12, 8.6%), dyspnea (n = 11, 7.9%), anorexia (n = 8, 5.7%), and back pain (n = 8, 5.7%). Fatigue, nausea, and anorexia were the only mild AEs with an increasing incidence as the dose of enzalutamide was increased. None of the grade 2 events required dose modification or the discontinuation of treatment, apart from 1 patient treated at 480 mg/day who had nausea at baseline and stopped therapy after 7 weeks.

Two witnessed seizures occurred in patients receiving doses of 600 and 360 mg/day, and 1 possible seizure occurred at 480 mg/day. Whether enzalutamide was responsible for these seizures is unclear, since both patients who had witnessed seizures were concurrently taking drugs that could contribute to a lowered seizure threshold (olanzapine and prochlorperazine for the patient receiving 600 mg/day; methylphenidate for the patient receiving 360 mg/day). Both patients also had complicated medical problems that could have contributed to their seizures, including hypocalcaemia requiring intravenous calcium, anemia requiring red-cell transfusions, and skull metastases requiring skull radiation. Other causes of treatment discontinuation included rash in 1 patient that received 480 mg/day after 10 days and in 1 patient that received 600 mg/day after 3 days, and a myocardial infarction after 15 weeks of therapy in a patient with a history of diabetes, hypertension, and hypercholesterolemia that received 360 mg/day. All patients recovered without sequelae. No deaths and no other drug-related serious adverse events (SAEs) were reported.

In regards to efficacy, antitumor effects were noted at all doses including >50% declines in PSA in 78 (56%) patients, response in soft tissue in 13 (22%) of 59 patients, stabilized bone disease in 61 (56%) of 109 patients, and conversion from unfavorable to favorable circulating tumor cells (CTC) counts in 25 (49%) of 51 patients. Disease regression was dose dependent between daily doses of 30 mg and 150 mg, however no additional benefit was noted above this threshold.

Based on these results, two placebo-controlled, randomized phase 3 studies (AFFIRM and PREVAIL) were initiated to evaluate the efficacy and safety of enzalutamide in participants with advanced prostate cancer. The AFFIRM study evaluated the safety and efficacy of enzalutamide in 1,199 participants with CRPC after chemotherapy with docetaxel.[31] Participants were randomized in a 2:1 ratio to receive oral enzalutamide at a dose of 160 mg per day or placebo. The primary endpoint was OS. The study was stopped after a planned interim analysis at the time of 520 deaths. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in

the placebo group (hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.53-0.75, p<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary endpoints: ≥50% PSA reduction (54% vs. 2%, p<0.001), soft-tissue response rate (29% vs. 4%, p<0.001), the quality-of-life response rate (43% vs. 18%, p<0.001), time to PSA progression (8.3 vs. 3.0 months, p<0.001), time to first skeletal-related events (SREs) (16.7 vs. 13.3 months, p<0.001).

The rates of AEs between the enzalutamide and placebo group were similar. The enzalutamide group had a lower incidence of AEs of grade 3 or above (45.3% vs. 53.1%). The median time to first adverse event was 12.6 months in the enzalutamide group compared to 4.2 months in the placebo group. There was a higher incidence of all grades of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache in the enzalutamide group compared to placebo. Cardiac disorders were noted in 6% of participants receiving enzalutamide and in 8% of participants receiving placebo. Hypertension was observed in 6.6% of participants in the enzalutamide group compared to 3.3% in the placebo group. Liver-function test (LFT) abnormalities were reported as AEs in 1% and 2% of the enzalutamide and placebo group, respectively. Five of the 800 participants in the enzalutamide group (0.6%) were reported to have seizures and no seizures were reported in the placebo group. One case of status epilepticus required medical intervention while the other four seizures were self-limited. There were potentially predisposing factors in several participants, including two participants who had brain metastases, one participant who had inadvertently been administered lidocaine intravenously, and one participant with brain atrophy in the context of heavy alcohol use and initiation of haloperidol. Based on the results of this trial, the Food and Drug Administration (FDA) approved enzalutamide on 8/31/2012 for the treatment of participants with metastatic CRPC who have previously received docetaxel. For a detailed described for toxicity associated enzalutamide see section 6.1.1.

The PREVAIL trial is a double-blinded, randomized, placebo-controlled trial is investigating the effectiveness of enzalutamide in participants with metastatic CRPC who have not yet received chemotherapy. The primary endpoints are OS and progression-free survival (PFS). The trial has reached its target accrual of 1,680 participants.

Pharmacokinetics of Enzalutamide

The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic CRPC and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

Absorption

Following oral administration (enzalutamide 160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma enzalutamide concentrations is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 μg/mL (23% coefficient of variation (CV)) and 12.7 μg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 μg/mL (26% CV) and 13.0 μg/mL (30% CV), respectively.

With the daily dosing regimen, enzalutamide steady state is achieved by day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide

showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

A single 160 mg oral dose of enzalutamide was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the area under the curve (AUC) to enzalutamide or N-desmethyl enzalutamide.

Distribution and Protein Binding
The mean apparent volume of distribution of enzalutamide in patients after a single oral dose is 110 L (29% CV). Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins.

Metabolism
Following single oral administration of ^{14}C-enzalutamide 160 mg, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C-$AUC_{0-\infty}$.

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide).

For detailed information regarding potential drug interactions, refer to section 5.3.

Elimination
Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of ^{14}C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of enzalutamide and N-desmethyl enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide).

The mean apparent clearance of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h).

The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

2.3.2 AA

AA (17-(3-pyridyl)androsta-5,16-dien-3β-ol) is a rationally designed, inhibitor of CYP17. Key design features of this compound include the 3-pyridyl substitute, resulting in more potent inhibition of CYP17, and 16,17-double bond, which is essential for irreversible inhibition of CYP17.[42, 43] CYP17 is a key enzyme in cortisol synthesis via its 17α-hydroxylase activity and plays a central role in androgen biosynthesis via its 17,20-lyase activity (Figure 1).[44] Abiraterone is a potent inhibitor with an apparent inhibition constant of 0.5 nM.[43]

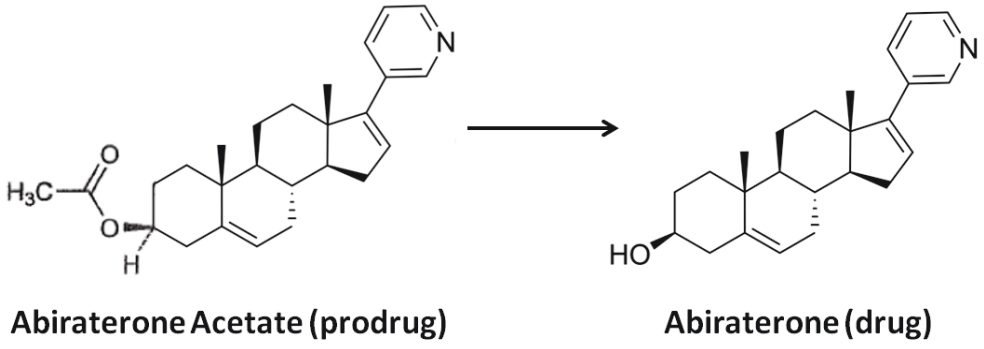

Figure 1. The pro-drug AA is converted to abiraterone after absorption.

AA is the 3-acetylated analog and pro-drug of abiraterone (given poor bioavailability) suitable for oral administration (Figure 2). AA is rapidly deacetylated and converted to the active form abiraterone. Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6.[45]

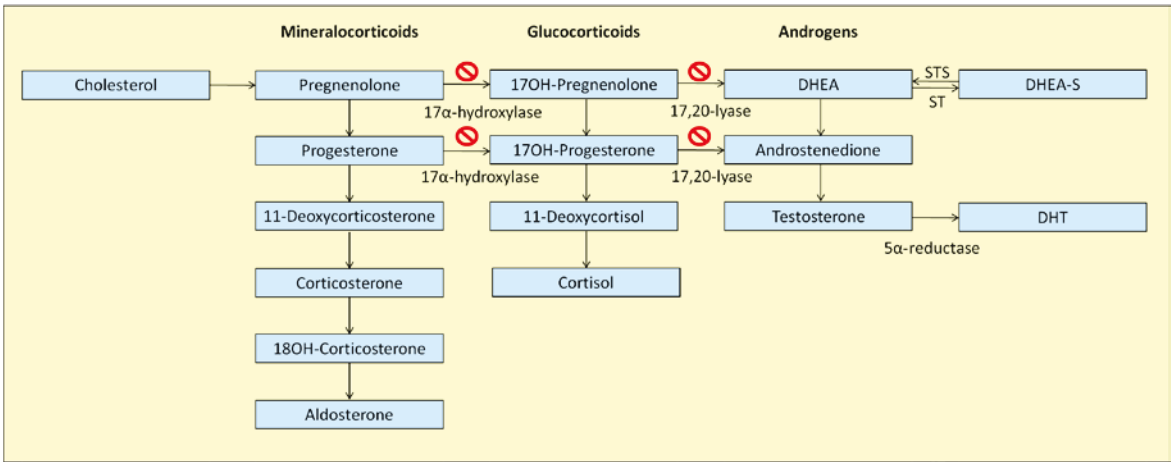

Figure 2. The steroid biosynthesis pathway. AA inhibits 17α-hydroxylase (crossed in red) which results in reduction of serum cortisol and consequent increase in adrenocorticotropic hormone (ACTH) that drives the steroid biosynthesis pathway. AA also inhibits 17,20-lyase (crossed in red) resulting in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

Rationale for Using AA in Prostate Cancer

Ketoconazole, a weak and nonspecific CYP17 inhibitor, is commonly used in clinical practice. Ketoconazole, an imidazole antifungal agent, inhibits several enzymes in the steroid biosynthesis pathway including desmolase and 11β-hydroxylase, in addition to CYP17.[46] When administered at a dose of 400 mg three times daily, ketoconazole reduced testosterone, androstenedione and DHEA.[47]

Numerous phase II studies have demonstrated that treatment with ketoconazole resulted in PSA response rates (defined as a ≥50% decrease in PSA levels from baseline) ranging from 40-62% with median duration of response lasting between 3.3-7 months.[48] In the Cancer and Leukemia Group B (CALGB) 9583 phase III trial comparing androgen withdrawal to androgen withdrawal plus ketoconazole, response rates were 11 and 27%, respectively (p=0.02), however there was no difference in OS between the two groups, which may reflect 82% crossover rate.[49]

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

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

Clinical Data with AA

Abiraterone acetate has been tested in patients in phase I, II and III trials. Below we will summarize the results of these trials with a focus on safety and efficacy (Table 2).

Table 2. Summary of clinical trials of AA.

Study	Patient	Drug	Efficacy	Toxicity
Phase 1 Attard et al (2008)[50]	21 Chemo-naive Keto-naive (non-metastatic and metastatic)	AA 250-2000 mg daily, fasting, 5 dose escalations	Increased ACTH, upstream steroids; decreased testosterone, downstream androgenic steroids; PSA decline to ≥30%, 50%, and 90% were 66%, 57%, and 29%, respectively; Median TTPP 69 to ≥ 578 days; 62% partial RECIST response	Hypertension (29%), hypokalemia (48%), lower-limb edema (5%); No grade 3 or 4 toxicities; Precipitation of migraine and asthma, 1 patient each, both of whom required dexamethasone
Phase I Ryan et al (2010)[51]	33 Chemo-naive Keto-naive (14) (non-metastatic and metastatic)	AA 250-1000 mg daily, fed and fasting cohorts, 4 dose escalations	Decreased testosterone, downstream, androgenic steroids; PSA decline ≥50% at week 12 in 55% (47% vs. 64% prior keto vs. no keto); Median TTPP 234	Hypertension (36%), hypokalemia (24%), peripheral edema (24%), fatigue (67%), headache (33%), nausea (33%), diarrhea (30%);

			days (283 vs. 230 days prior keto vs. no keto)	Grade 3 hypertension (12%), grade 3/4 hypokalemia (9%)
Phase II Attard et al (2009)[52]	42 Chemo-naive (non-metastatic and metastatic)	AA 1000 mg daily, fasting	PSA decline ≥50% observed in 67% (≥90% observed in 19%); Median TTPP 225 days; 38% partial RECIST response; CTC declined to <5/7.5 mL in 59%; 33% from phase I/II had reversal of resistance with dexamethasone	Hypertension (40%), hypokalemia (8%), fluid overload (31%); Managed with eplerenone except in 3 patients who required dexamethasone
Phase II Danila et al (2010)[53]	58 Chemo-treated Keto-naive (27) (metastatic only)	AA 1000 mg daily (fasting) + prednisone 5 mg twice daily	PSA decline to ≥30%, 50%, and 90% were 47%, 36%, and 16%, respectively (PSA decline ≥50% 26% vs. 45% prior keto vs. no keto); Median TTPP 169 days (99 vs. 198 prior keto vs. no keto); 18% partial RECIST response; CTC declined <5/7.5 mL in 34%	Hypertension (4%), hypokalemia (5%), peripheral edema (9%), abnormal LFTs (15%); No grade 3/4 hypertension, hypokalemia, peripheral edema; No use of eplerenone
Phase II Reid et al (2010)[54]	47 Chemo-treated (metastatic)	AA 1000 mg daily, fasting	PSA decline to ≥30%, 50%, and 90% were 68%, 51%, and 15%, respectively; Median TTPP 169 days; 27% partial RECIST response; CTC declined <5/7.5 mL in 45%	Hypokalemia (55%), hypertension (17%), fluid retention (25%); Grade 3 hypokalemia (2%)
Phase III de Bono et al (2011)[29]	1195 Chemo-treated (metastatic only)	AA 1000 mg daily versus placebo (fasting) + prednisone 5	AA-prednisone vs. placebo-prednisone median OS 14.8 vs. 10.9 months (p<0.001), TTPP 10.2 vs. 6.6 months	AA-prednisone vs. placebo-prednisone hypertension 10% vs. 8%, hypokalemia 17%

		mg twice daily	(p<0.001), PFS 5.6 vs. 3.6 months (p<0.001), PSA response rate 29% vs. 6% (p<0.001)	vs. 8%, fluid retention 31% vs. 22%
Phase III Ryan et al (2012)[30]	1088 Chemo-naive (metastatic only)	AA 1000 mg daily versus placebo (fasting) + prednisone 5 mg twice daily (2:1)	AA-prednisone vs. placebo-prednisone median OS NR vs. 27.2 months (p=0.01), PFS 16.5 vs. 8.3 months (p<0.001), median time-to-opiate use NR vs. 23.7 months (p<0.001), median time to initiation of cytotoxic chemotherapy 25.2 vs. 16.8 months (p<0.001), median time to decline in performance status 12.3 vs. 10.9 months (p=0.005), median TTPP 11.1 vs. 5.6 months (p<0.001)	AA-prednisone vs. placebo-prednisone hypertension 22% vs. 13%, hypokalemia 17% vs. 13%, fluid retention 28% vs. 24%, increased ALT 12% vs. 5%, increased AST 11% vs. 5%, cardiac disorder 19% vs. 16%

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

Early phase I studies showed good bioavailability at doses of greater than 200 mg, a half-life of approximately 28 hours, and significant increased absorption with food.[55] The initial studies included men who were not on LHRH agonist. In this population, a compensatory surge in luteinizing hormone led to an increase in testosterone by day 4 of treatment with abiraterone acetate in some men, suggesting the need for abiraterone acetate to be given concomitantly with suppressed testicular function.

A Phase I/II study evaluated abiraterone acetate in chemotherapy-naive men with CRPC resistant to multiple prior hormone therapies.[50, 52] The phase I study (n=21) evaluated once, daily, continuous AA, which escalated through five doses (250-2,000 mg) in three-patient cohorts. In this study, AA was well tolerated. There were no treatment related grade 3 and grade 4 toxicities. Hypertension, hypokalemia, and lower-limb edema was observed in 29%, 48%, and 5% patients, respectively. These side effects were controlled with eplerenone, a selective mineralocorticoid receptor antagonist. AA was associated with increased levels of ACTH (5-fold) and steroids upstream of CYP17 (10-40-fold) with suppression of serum testosterone (<1 ng/dL), downstream

androgenic steroids, and estradiol in all patients. Declines in PSA ≥30%, 50%, and 90% were observed in 14 (66%), 12 (57%), and 6 (29%) patients, respectively and lasted between 69 to ≥ 578 days. Five (62%) of eight patients with measurable disease at baseline had confirmed partial response by Response Evaluation Criteria In Solid Tumors (RECIST). The addition of dexamethasone 0.5 mg/d resulted in salvage of 4/15 patients who had PSA progression.

The phase II expansion of this study included 42 patients.[52] A decline in PSA of ≥50% was observed in 67% of patients and declines of ≥90% were observed in 19% of patients. The median time to PSA progression (TTPP) was 225 days. Of the 24 patients with measurable disease, 38% experienced partial response by RECIST. Decreased in CTC counts were documented (decline to <5/7.5 mL in 59% of patients). In an exploratory analysis of all 54 patients in the phase I/II trial, addition of dexamethasone at PSA progression reversed resistance in 33% of patients. In long term follow up, after all patients were discontinued from therapy with AA, 38/42 (90%) patients experienced signs of mineralocorticoid excess including hypertension, hypokalemia, and peripheral edema. This was effectively treated with eplerenone without exogenous glucocorticoids in 35/38 (92%) patients. Only 3/38 (5%) patients required administration of exogenous glucocorticoids (dexamethasone 0.5 mg daily). The median time to initiation of eplerenone was 28 days.

Two phase II studies in post-docetaxel CRPC patients have also been conducted.[53, 54] PSA declines of ≥50% occurred in 22/58 (36%) and 24/47 (51%) patients, respectively, with the median TTPP of 169 days for both studies. Partial responses were seen in 4/22 (18%) and 8/30 (27%) patients with RECIST-evaluable target lesions, respectively.

The efficacy of AA was demonstrated in a phase III trial in which 1,195 men previously treated with docetaxel were randomly assigned to AA plus prednisone or placebo plus prednisone.[29] The primary end point was OS. After a median follow-up of 12.8 months, AA significantly increased OS (median 14.8 versus 10.9 months, $p<0.0001$), TTPP (10.2 versus 6.6 months, $p<0.0001$), radiographic PFS (5.6 versus 3.6 months, $p<0.001$), and PSA response rate (29% versus 6%, $p<0.001$) compared with placebo plus prednisone. The effect of AA and prednisone on OS was consistent across all subgroups.

The most common AE was fatigue which occurred at a similar frequency in the two treatment groups. Other common AEs including back pain (30T in the AA group and 33% in the placebo group). Nausea (30% and 32%, respectively), constipation (26% and 31%), bone pain (25% and 28%), and arthralgia (27% and 23%). Most of these events were grade 1 or 2. Urinary tract infection was more frequent in the AA group (12% vs. 7% in the placebo group, $p=0.02$) and were primarily grade 1 or 2 events. AEs resulting in treatment discontinuation occurred with similar frequency in the abiraterone acetate and placebo groups (19% and 23%, respectively, $p=0.09$). AEs associated with elevated mineralocorticoid levels, cardiac disorders, and LFT abnormalities were more common in the AA group than in the placebo group (55% vs. 43%, $p<0.001$). The incidence of fluid retention and edema was higher in the AA group (31% vs. 22% in the placebo group). Hypokalemia occurred in a higher proportion of patients in the AA group (17% vs. 8%, in the placebo group, $p<0.001$). Cardiac events (primarily grade 1 or 2) occurred at a higher rate in the AA group than in the placebo group (13% vs. 11%, $p=-.14$), but this difference was not significant. The most frequently reported cardiac events tachycardia and atrial

fibrillation. A grade 4 elevation in LFTs early on the study led to a protocol amendment to specifying more frequent monitoring of LFTs. Overall however, abnormalities in LFTs occurred at a similar frequency in the AA and placebo groups. A lower proportion of patients in the AA group than in the placebo group had an AE that resulted in death (12% vs. 15%). Based on this trial, AA was approved by the FDA in April 2011 for the treatment of patients with metastatic CRPC following docetaxel.[29]

A randomized, phase III study evaluated AA in chemotherapy-naive patients with metastatic CRPC. In this double-blind study, 1,088 patients were randomly assigned to treatment with AA plus prednisone or placebo plus prednisone. The co-primary end points were radiographic PFS and OS. The study was unblinded after a planned interim analysis that was preformed after 43% of the expected deaths had occurred. The trial showed that treatment with AA plus prednisone produced a statistically significant improvement in radiographic PFS (16.5 vs. 8.3 months, $p<0.001$) and a strong trend for increased OS (not reached vs. 27.2 months, HR 0.75, 95% CI 0.61-0.93, $p=0.01$) over placebo plus prednisone. AA decreased the risk of decline in ECOG performance status score (time to decline 12.3 vs. 10.9 months, $p=0.005$), increased the median time to initiation of cytotoxic chemotherapy (25.2 vs. 16.8 months, $p<0.001$), delay in time to opiate use for cancer-related pain (not reached vs. 23.7 months, $p<0.001$), and median TTPP (11.1 vs. 5.6 months, $p<0.001$).

Grade 3 or 4 AEs were reported in 48% of patients in the AA group and 42% of the placebo group, serious AEs were reported in 33% and 26% of patients, AEs resulting in death were reported in 4% and 2% of patients, respectively. Common AEs included fatigue (39% vs. 34%), back pain (32% vs. 32%), arthralgia (28% vs. 24%), nausea (22% vs. 22%), constipation (23% vs. 19%), hot flush (22% vs. 18%), diarrhea (22% vs. 18%), bone pain (20% vs. 19%), muscle spasm (14% vs. 20%), pain in extremity (17% vs. 16%), and cough (17% vs. 14%). Grade 3 or 4 hepatotoxicity (elevated LFTs) occurred in 8% of patient in the AA group and 3% in the placebo group. AEs classified as cardiac disorders were reported in 19% of patient in the AA group and 16% in the placebo group. Hypertension (22% vs. 13%), hypokalemia (17% vs. 13%), and fluid retention or edema (28% vs. 24%), were mostly grade 1 or 2 events. Based on the results of this trial, in December 2012, the FDA expanded the indication for abiraterone acetate for the treatment of patients with chemotherapy-naive metastatic CRPC.

Pharmacokinetics of Abiraterone Acetate

Pharmacokinetics were evaluated in two phase I trials and are detailed in table 2.[50, 51] In the Attard et al study, a plateau of endocrine effects was reported at doses >750 mg, and 1000 mg was selected as the dose for phase II evaluation. There were significant variations in the AUC and C_{max} among patients. When administered with food high in fat content, drug exposure increased 4.4 fold compared to fasting. There was no significant increase in C_{max}, but absorption was significantly extended after food. In the Ryan et al study, C_{max} was achieved within 1.5-5 hours.[51] Less than proportional increased in both C_{max} and AUC were observed across dose levels in fed and fasted patients.

Table 2. AA Pharmacokinetics Parameters.

Parameter	**AA**

Absorption	Systemic absorption (C_{max} and AUC) increases with increasing fat content of meals. The AUC was approximately 5-fold higher when administered with a low-fat meal, and approximately 10-fold higher when administered with a high-fat meal. Due to normal variation and composition of meals, no food should be consumed for at least 2 hours before the dose of abiraterone acetate and for at least one hour after the dose.
Metabolism	Following oral administration, AA is hydrolyzed to abiraterone (active metabolite) through esterases and not CYP. The 2 main circulating metabolites are abiraterone sulphate (inactive; formed via SULT2A1) and N-oxide abiraterone sulphate (inactive; formed via CYP3A4 and SULT2A1).
Elimination	88% recovered in feces and 5% in urine (55% as unchanged AA, 22% as abiraterone).
Half-life	Mean terminal $t_{1/2}$= 12 ±5 hours.
Protein Binding	Highly protein bound (>99%); it is not a substrate for but is an inhibitor of P-glycoprotein.

For detailed information regarding potential drug interactions, refer to section 5.3.

3. PARTICIPANT SELECTION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. If there is a question about the inclusion or exclusion criteria, the investigator should consult with the appropriate sponsor representative before enrolling the subject in the study.

3.1 Eligibility Criteria

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

- Male ≥ 18 years of age.

- Histologically confirmed adenocarcinoma of the prostate without histological variants (including overt neuroendocrine differentiation, small cell neuroendocrine carcinoma features, sarcomatoid features, pure ductal adenocarcinoma, squamous or transitional cell carcinoma).

- Must have tissue available from the pre-treatment diagnostic biopsy (tissue blocks if possible; if not possible, 10 unstained slides from each positive core sample for a total of 30 slides whenever possible).

- Must have 3 core biopsies involved with cancer (a minimum of 6 core biopsies must be obtained). Prostate biopsy must be within seven months from screening. This includes prostate biopsy from men previously followed by active surveillance. Less than 3 core biopsies is allowed if the patient has >1cm or T3 disease on MRI.

- Participants must have the following features:
  - Intermediate-risk disease defined as Gleason 4+3=7 disease OR
  - High-risk disease defined as Gleason 8-10 OR PSA > 20 ng/mL OR T3 disease (by prostate MRI)

- No evidence of metastatic or nodal disease as determined by radionuclide bone scans CT/MRI. Non-pathological lymph nodes must be less than 20 mm in the short (transverse) axis.

- Participants must be candidates for RP and considered surgically resectable by urologic evaluation.

- ECOG performance status 0 to 1 (Appendix A).

- Diabetics on insulin or antihyperglycemics must be on a stable dose (i.e., no titrations within the last 2 weeks) at the time of study entry.

- Participants must have normal organ and marrow function as defined below:
  - WBC ≥ 3,000/mcL
  - ANC ≥ 1,500/mcL
  - Platelets ≥ 100,000/mcL
  - Serum potassium ≥ 3.5 mmol/L

- AST, ALT, and total bilirubin ≤ 1.5 x Institutional ULN
- Calculated creatinine clearance ≥ 60 mL/min
- PTT ≤ 60, INR ≤ 1.5 x Institutional ULN unless on warfarin therapy (investigator would need to determine if safe for participant to stop warfarin prior to biopsy and warfarin therapy)
- Controlled blood pressure defined as a systolic blood pressure ≤ 140 mmHg and diastolic blood pressure ≤ 90 mmHg on no more than three anti-hypertensive agents. Drug formulations containing two or more anti-hypertensive agents will be counted based on the number of active agents in each formulation.

3.2 Exclusion Criteria

- Prior hormone therapy for prostate cancer including orchiectomy, antiandrogens (including first-generation antiandrogens, enzalutamide, ARN-509 and others), CYP17 inhibitors (including abiraterone, TAK-700, galeterone, ketoconazole, and others), estrogens, LHRH agonist/antagonists. Topical ketoconazole and other topical antifungal agents are allowed. Prior therapy with 5α-reductase inhibitors is allowed. LHRH therapy allowed if begun within 4 weeks of day 1*.
  *Prior androgens are allowed if the patient had a testosterone within the normal range prior to starting androgens and the androgens have been stopped for at least 7 days.

- Prior chemotherapy, radiation therapy, or immunotherapy for prostate cancer.

- Prior systemic treatment with an azole drug within four weeks of screening visit.

- Hypogonadism or severe androgen deficiency as defined by screening serum testosterone < 200 ng/dL.

- Clinically significant cardiovascular disease including:

- Acute coronary syndrome within 6 months of screening visit;
  - Hypotension defined as a systolic blood pressure < 86 mmHg;
  - Bradycardia defined as a heart rate of < 50 beats per minute, unless pharmaceutically induced and thus reversible (i.e. beta blockers);
  - Uncontrolled angina (requiring escalating doses of nitrates) within 3 months of screening visit;
  - Congestive heart failure NYHA Class III or IV or subjects with a history of congestive heart failure NYHA Class III or IV, unless screening ECHO results in left ventricular ejection fraction that ≥ 45%;
  - History of clinically significant ventricular arrhythmias (e.g. ventricular tachycardia, ventricular fibrillation, torsades de pointes);
  - Prolonged corrected QT interval by the Fridericia correction formula (QTcF) on screening EKG > 470 msec;
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place;

- History of seizure or any condition or concurrent medication that may predispose to seizure.

- Diabetics on a stable dose of insulin or antihyperglycemic regimen are allowed if they have had no prior seizures and no history of loss of consciousness due to hypoglycemia.

- Thromboembolism within 6 months of screening visit.

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

- Active or symptomatic viral hepatitis or chronic liver disease.

- History of pituitary or adrenal dysfunction.

- Gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug.

- Pre-existing condition that warrants long-term corticosteroid use. Physiologic replacement is not permitted.

- Concomitant use of medications that may alter pharmacokinetics of abiraterone or enzalutamide.

- Individuals with a history of a different malignancy are ineligible except for the following circumstances: 1) individuals with a history of other malignancies are eligible as long as there is no evidence of metastases and life expectancy deemed > 2 years.

- Major surgery or radiation therapy within 30 days of screening visit.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

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

4. REGISTRATION PROCEDURES

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

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

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

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

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

    - Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration. A fax confirming randomization will be sent to the pharmacy, if applicable.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the DFCI by the Study Coordinator. All sites should contact the DFCI Study Team (coordinator, RN) to verify treatment availability. The required forms will be provided to all participating institutions by the DFCI study coordination.

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

4.4 Registration Process for Other Participating Institutions

To register a participant, the documents listed in Section 3.7.1 of the Data Safety Monitoring Plan (DSMP) should be completed by the research nurse or data manager and faxed to 617-632-6220 or emailed to the DFCI Clinical Research Coordinator and Research Nurse team.

The research nurse or data manager at the participating site will then call or email the DFCI Study Coordinator to verify eligibility. To complete the registration process, the DFCI Study Coordinator will:

- Register the participant on the study with QACT
- Fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

Note: Registration and randomization with the QACT can only be conducted during the business hours of 8am – 5pm Eastern Standard Time Monday - Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

Following registration participants will be randomized in a 2:1 ratio to neoadjuvant therapy with either: 1) AA (1000 mg oral daily) + prednisone (5 mg oral daily) + enzalutamide (160 mg oral daily) + leuprolide (either 7.5 mg monthly or 22.5 mg three-month intramuscular injection) (ARM 1), or 2) enzalutamide (160 mg oral daily) + leuprolide (either 7.5 mg monthly or 22.5 mg three-month intramuscular injection) (ARM 2). Participants may enter the study with no more than one month of an LHRH agonist treatment prior to cycle 1/day 1. Participants will receive the assigned study treatment for 24 weeks (+/-14 days to account for scheduling of RP). Therapy will continue until one day prior to RP or until the participant meets criteria for withdrawal from the study.

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

<table>
<tr><th colspan="6">Treatment Description</th></tr>
<tr><th>Agent</th><th>Pre-medications; Precautions</th><th>Dose</th><th>Route</th><th>Schedule</th><th>Cycle Length</th></tr>
<tr><td>AA</td><td>No food should be consumed for at least two hours before the dose and for at least one hour after the dose</td><td>1000 mg (four 250 mg tablets)</td><td>Oral</td><td>Once daily</td><td rowspan="4">28 days (4 weeks)

6 cycles maximum</td></tr>
<tr><td>Enzalutamide</td><td>Can be taken with or without food</td><td>160 mg (Four 40 mg capsules)</td><td>Oral</td><td>Once daily</td></tr>
<tr><td>Prednisone</td><td>Take with food, preferred to be taken in the morning</td><td>5 mg</td><td>Oral</td><td>Once daily</td></tr>
<tr><td>Leuprolide</td><td>None</td><td>Either 7.5 mg monthly or 22.5 mg every three months</td><td>Intramuscular</td><td>Monthly or every three months</td></tr>
<tr><td colspan="6">Enzalutamide and prednisone can be taken at the same time of day if desired. AA, enzalutamide and prednisone will be prescribed by prescription in an unblinded fashion and taken by the participant on an outpatient basis. AA should be taken without food or other medications. Leuprolide will be intramuscularly by a health care professional.</td></tr>
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5.1 Pre-treatment Criteria

5.1.1 For Cycle 1, Day 1, the following parameters must be met:
- WBC ≥ 3,000/mcL
- ANC ≥ 1,500/mcL

- Serum potassium ≥ 3.5 mmol/L (participants on exogenous potassium supplementation will require weekly monitoring of potassium levels for one month)
- AST/ALT ≤ 1.5 x Institutional ULN
- Total bilirubin ≤ 1.5 x Institutional ULN
- Systolic blood pressure < 160 mmHg or diastolic blood pressure < 95 mmHg

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

For subsequent cycles, refer to dose modifications as outlined in Section 6.
Day one labs must be reviewed prior to dispensing study drug for all cycles.

5.2 Agent Administration

5.2.1 Abiraterone Acetate

- Administration: 1,000 mg (oral) once daily. Treatment can continue for 24 (+/- 14 days) weeks. The last dose will be administered the day before RP.

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

  Oral Doses: AA must be taken on an empty stomach. No food or other medications should be consumed for at least two hours before the dose of AA is taken and for at least one hour after the dose of AA is taken. If a dose is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing. Participants will be asked to record actual dosing in a drug diary (Appendix C). AA should not be crushed, chewed, or dissolved in water. AA and Enzalutamide should not be taken together at the same time. There is no specified order of administration of the study drugs prescribed in this protocol.

5.2.2 Enzalutamide

- Administration: 160 mg (oral) once daily. Treatment can continue for 24 (+/- 14 days) weeks. The last dose will be administered the day before RP.

- Dosing: 160 mg (oral) taken once daily as four 40 mg capsules. Possible dose modifications are outlined in Section 6.

- Oral Doses: Enzalutamide can be taken with or without food. If a dose is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing. Participants will be asked to record actual dosing in a drug diary (Appendix C). Enzalutamide should not be crushed, chewed, or dissolved in water. Enzalutamide and AA should not be taken together at the same time,

but Enzalutamide may be taken at the same time as prednisone. There is no specified order of administration of the study drugs prescribed in this protocol.

5.2.3 Prednisone

- Administration: 5 mg (oral) once daily. Treatment can continue for 24 (+/- 14 days) weeks. The last dose will be administered the day before RP. This dose, as opposed to 5 mg orally twice daily, will be used given that we demonstrated that abiraterone + prednisone 5 mg orally daily was well tolerated in our phase II trial evaluating the benefit of abiraterone in the neoadjuvant setting. Grade 3 AEs included elevated AST/ALT 5/58 (9%) and hypokalemia 3/58 (5%). No grade 4 mineralocorticoid-related AEs were observed.

- Dosing: 5 mg oral) once daily taken as one 5 mg tablet. It is recommended that prednisone be taken in the morning. Dose modification is not allowed.

- Oral Doses: Prednisone should be taken with a meal. If a dose is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing. Participants will be asked to record actual dosing in a drug diary (Appendix C). Prednisone should not be crushed, chewed, or dissolved in water. Prednisone should not be taken at the same time as AA, but it may be taken at the same time as the Enzalutamide. There is no specified order of administration of the study drugs prescribed in this protocol.

5.2.4 Leuprolide

- Administration: Participants may enter the study with no more than one month of LHRH agonist treatment prior to cycle 1/day 1. Given such, participants will receive either 6 months of LHRH agonist treatment or at maximum 7 months of treatment (if they had received treatment with LHRH agonist at maximum of one month prior to cycle 1/day 1). Treatment will be administered intramuscularly by a health care professional.

- Dosing: Either 7.5 mg intramuscularly monthly or 22.5 mg intramuscularly every three months.

5.3 General Concomitant Medications and Supportive Care Guidelines

General Concomitant Medications

Medications taken within 14 days prior to the first dose of study treatment will be documented. Medications taken after the first dose of study medication and until 30 days following the last dose of study treatment will be documented as well. Prior and concomitant medications include all vitamins, herbal remedies, over-the-counter, and prescription medications.

The following medications are prohibited within 4 weeks (unless otherwise indicated below) of first study treatment administration and throughout the time on study:

- Androgens (testosterone, DHT), estrogens, or progestational agents for 6 months prior to randomization.
- 5α-reductase inhibitors.
- Ketoconazole, diethylstilbestrol, saw palmetto or other preparations thought to have endocrine effects on the prostate. Topical ketoconazole is allowed.
- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm).
- Spironolactone.
- Vaccine therapy.
- Other anti-tumor treatments not detailed in the study.

Study participants should not consume grapefruit and grapefruit juice while taking these study drugs.

Potential Drug Interactions with AA
AA is an inhibitor of the hepatic drug metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8 and 2.9 fold, respectively, when dextromethorphan 30 mg was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily.[68] The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold. Avoid co-administration of AA with substrates of CYP2D6 with a narrow therapeutic index (i.e. thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

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

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

In vitro, studies with human hepatic microsomes showed that AA is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19, and CYP3A4/5.

In a clinical study to determine the effects of AA 1000 mg daily plus prednisone 5 mg twice daily on a single 1000 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Potential Drug Interactions with Enzalutamide
Drugs that Inhibit or Induce CYP2C8
In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimum effect on C_{max}. Therefore, co-administration of enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of enzalutamide with a strong

CYP2C8 inhibitor cannot be avoided, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Enzalutamide 80mg will be the lowest dose and patients will not be eligible for further dose reductions. If the subject stops a strong CYP2C8 inhibitor, there will be a one week wash out prior to increasing the dose of enzalutamide.

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (i.e. rifampin) may alter the plasma exposure of enzalutamide and should be avoided.

Drugs that Inhibit or Induce CYP3A4
In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the $AUC_{0-\infty}$ of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on $C_{max.}$

The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of enzalutamide with strong CYP2C8 inducers (i.e. carbamazepine, phenobarbital, phenytoin, rifabutin, rifamin, rifapentine) may decrease the plasma exposure of enzalutamide and should be avoided. Moderate CYP3A4 inducers (i.e. bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of enzalutamide and should be avoided.

Effects of Enzalutamide on Drug Metabolizing Enzymes
In an *in vivo* phenotypic cocktail drug-drug interaction trial in patients with CRPC, a single oral dose of the CYP probe cocktail (for CYP2C8, CYP2C9, CYP2C19, CYP3A4) was administered before and concomitantly with enzalutamide (following at least 55 days of dosing at 160 mg daily). Results showed that *in vivo*, at steady state, enzalutamide reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Thus, enzalutamide is a strong CYP3A4 inducers and a moderate CYP2C9 and CYP2C19 inducer. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (i.e. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (i.e. phenytoin, warfarin) and CYP2C19 (i.e. S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, additional INR monitoring is warranted. In this study, enzalutamide did not cause clinically meaningful changes in exposure to the CYP2C8 substrate (pioglitazone).

In vitro, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; however, subsequent clinical data showed that enzalutamide is an inducer of CYP2C9, CYP2C19, and CYP3A4 and had no clinically meaningful effect on CYP2C8. *In vitro*, enzalutamide caused time-dependent inhibition of CYP1A2.

In vitro studies showed that enzalutamide caused induction of CYP3A4 and that enzalutamide is not expected to induce CYP1A2 at therapeutically relevant concentrations. *In vitro*, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for human P-glycoprotein. *In vitro*, enzalutamide and N-desmethyl enzalutamide are inhibitors of human P-glycoprotein, while the major inactive carboxylic acid metabolite is not.

Class	**Example Drugs**	**Recommendation**
Strong CYP2C8 Inhibitors	Gemfibrozil	If co-administration with gemfibrozil cannot be avoided, reduce enzalutamide dose
Strong CYP2C8 Inducers	Rifampin	Avoid concomitant use
Strong CYP3A4 Inhibitors	Itraconazole	No initial dose adjustment
Strong/Moderate CYP3A4 Inducers	Carbamazepine, phenobarbital, phenytoin, rifabutin, rifamin, rifapentine, osentan, efavirenz, etravirine, modafinil, nafcillin, and St. John's Wort	Avoid concomitant use
CYP3A4 Substrate	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus	Avoid concomitant use of substrates with a narrow therapeutic index
CYP2C9 Substrate	Phenytoin, warfarin	Avoid concomitant use of substrates with a narrow therapeutic index
CYP2C19 Substrate	S-mephenytoin	Avoid concomitant use of substrates with a narrow therapeutic index
CYP2C8 Substrate	Pioglitazone	No dose adjustment

If at any time an investigator suspects a drug-drug interaction, the PI, Dr. Mary-Ellen Taplin should be contacted at 617-582-7221 or paged at 617-632-3353 (beeper 41225). Backup: co-PI Dr. Bruce Montgomery, 206-559-5058 (24-hour pager). Additional information is provided in the AA and enzalutamide Investigator's Brochure.

5.4 Duration of Therapy

Treatment on study will be for 24 weeks (+/- 14 days). In the absence of treatment delays due to AEs, treatment may continue for the duration of the study until one of the following criteria:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable AEs

- Treatment emergent seizure
- Participant decided to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treated investigator.
- Participant completed required RP

Protocol therapy may be held for up to six weeks in the event of an AE and the participant may be restarted on therapy when the toxicity has resolved to ≤ grade 1, In the event of therapy being held for more than six weeks, it is recommended that the participant come off protocol however the treating physician may obtain permission to continue on the protocol with permission of the PI, Dr. Mary-Ellen Taplin (mtaplin@partners.org) or Co-PI Dr. Bruce Montgomery, (rbmontgo@uw.edu), if the treating physician feels it is in the participant's best interest.

5.5 Duration of Follow-Up

Participants will be followed for 5 years from the time of RP to assess for biochemical progression, subsequent lines of therapy, development of metastases, and death. Participant follow up will begin 30 days after removal from study and will take place at the research clinic every 3 months (+/- 1 month) following RP for the first 2 years. After the first 2 years, participant follow up will continue every 6 months (+/- 1 month) for up to 5 years or until death, whichever occurs first. After the first 2 years of follow up, follow up assessments may be performed locally and information may be collected via medical record review. Participants removed from study for unacceptable AEs will be followed until resolution or stabilization of the AEs.

5.6 Criteria for Removal from Study

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

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

In the event of unusual or life-threatening complications, participating investigators must immediately notify the PI, Dr. Mary-Ellen Taplin, at 617-582-7221 or page 617-632-3352 (beeper 41225). Backup: co-PI Dr. Bruce Montgomery, 206-559-5058 (24-hour pager).

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

It should be noted that we do not anticipate any excess toxicity as there are no overlapping toxicities and no apparent drug-drug interactions (either pharmacokinetics or combined inhibition of enzymes in the androgen signaling cascade). Given that there is limited clinical data of combination AA and enzalutamide, we will closely monitor for treatment-related toxicities.

Anticipated toxicities re detailed below. Toxicity assessments will be done using the CTCAE (version 4) which is identified and located on the Cancer Therapy Evaluation Program (CTEP) website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

All AEs experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the post-RP 30-day and 90-day follow up visits. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Recommendations regarding dose delays and modifications are detailed below in section 6.2.

6.1 Anticipated Toxicities

Anticipated toxicities are detailed below. Toxicity assessments will be done using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (version 4).

6.1.1 AEs for Enzalutamide

In the randomized clinical trial in patients with metastatic CRPC who had previously received docetaxel, patients received enzalutamide 160 mg orally once daily (N = 800) or placebo (N = 399). The median duration of treatment was 8.3 months with enzalutamide and 3.0 months with placebo. All patients continued ADT. Patients were allowed, but not required, to take glucocorticoids. During the trial, 48% of patients on the enzalutamide arm and 46% of patients on the placebo arm received glucocorticoids. All AEs and laboratory abnormalities were graded using CTCAE version 4.
The most common AEs (≥ 5%) reported in patients receiving enzalutamide in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3 and higher AEs were reported among 47% of enzalutamide -treated patients and 53% of placebo-treated patients. Discontinuations due to AEs were reported for 16% of enzalutamide-treated patients and 18% of placebo-treated patients. The most common AEs leading to treatment discontinuation was seizure, which occurred in 0.9% of the enzalutamide-treated patients compared to none (0%) of the placebo-treated patients.

Seizures
In the randomized clinical trial, 7 of 800 (0.9%) patients treated with enzalutamide 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of enzalutamide. Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved. There is no clinical trial experience regarding re-administering enzalutamide to patients who experienced seizures. See Appendix D for representative medications that may predispose to seizure.

Laboratory Abnormalities
In the randomized clinical trial, Grade 1-4 neutropenia occurred in 15% of patients on enzalutamide (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on enzalutamide and 1% on placebo experienced Grade 3-4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on enzalutamide (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on enzalutamide and 2% of patients on placebo.

Infections
In the randomized clinical trial, 1.0% of patients treated with enzalutamide compared to 0.3% of patients on placebo died from infections or sepsis. Infection-related SAEs were reported in approximately 6% of the patients on both treatment arms.

Falls and Fall-related Injuries
In the randomized clinical trial, falls or injuries related to falls occurred in 4.6% of patients treated with enzalutamide compared to 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with enzalutamide and included non-pathologic fractures, joint injuries, and hematomas.

Hallucinations
In the randomized clinical trial, 1.6% of patients treated with enzalutamide were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

See current package insert for enzalutamide (Xtandi) for additional information.

6.1.2 AEs for AA

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

Co-administration of a corticosteroid suppresses ACTH drive, resulting in a reduction in the incidence and severity of these adverse reactions. The safety of abiraterone acetate in patients with left ventricular ejection fraction < 50% or NYHA Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials.

Adrenocortical Insufficiency
Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking abiraterone acetate and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving AA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with AA.

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

For guidance on management of side symptoms of mineralocorticoid excess, symptoms related to castration (androgen deprivation), severe and refractory headaches, fatigue, or other toxicities please contact the PI, Dr. Mary-Ellen Taplin at 617-582-7221 or page 617-632-3352 (beeper 41225).

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

6.1.3 AEs for Prednisone

A daily dose of 5 mg of prednisone is below the daily physiologic steroid dose and thus it is not expected that prednisone will cause significant side effects. Potential side effects of prednisone are listed below:

Cardiovascular: Congestive heart failure, hypertension.
Central nervous system: Emotional instability, headache, intracranial pressure increased, psychic derangements (including euphoria, insomnia, mood swings, personality changes, severe depression), seizure, vertigo.
Dermatologic: Bruising, facial erythema, petechiae, thin fragile skin, urticaria, wound healing impaired.
Endocrine and metabolic: Adrenocortical and pituitary unresponsiveness (in times of stress), carbohydrate intolerance, Cushing's syndrome, diabetes mellitus, fluid retention, hypokalemic alkalosis, hypothyroidism enhanced, menstrual irregularities, negative nitrogen balance due to protein catabolism, potassium loss, sodium retention.

Gastrointestinal: Abdominal distension, pancreatitis, peptic ulcer (with possible perforation and hemorrhage), ulcerative esophagitis.
Hepatic: ALT increased, AST increased, alkaline phosphatase increased.
Neuromuscular and skeletal: Aseptic necrosis of femoral and humeral heads, muscle mass loss, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.
Ocular: Exophthalmos, glaucoma, intraocular pressure increased, posterior subcapsular cataracts.
Other: Allergic reactions, anaphylactic reactions, diaphoresis, hypersensitivity reactions, infections.

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

6.1.4 AEs for Leuprolide

Side effects of leuprolide are mainly secondary to intended therapeutic effects of castrate levels of testosterone. Common AEs include edema, headache, depressed mood, fatigue, insomnia, skin reaction at injection site, hot flashes, testicular atrophy, hyperlipidemia, decreased libido, nausea/vomiting, bowel function alteration, joint pain, weakness, bone loss, and flu-like symptoms.

6.2 Toxicity Management

6.2.1 Management of Enzalutamide Related Toxicity

Enzalutamide is generally well-tolerated based on phase III data. The starting dose of enzalutamide will be 160 mg daily. In the presence of any enzalutamide related toxicities > grade 2 (CTCAE version 4) during treatment with enzalutamide at the starting dose level, the dose of enzalutamide will initially be held until toxicity improves to grade 1 or better. Then treatment will be resumed at 120 mg daily in the subsequent dose level when toxicity improves to ≤ grade 1. Two levels of dose de-escalation are planned for the study. If > grade 2 toxicity occurs at dose level -2, participants will be removed from the protocol.

Dose Level	Enzalutamide
Starting dose level	160 mg orally once daily
-1	120 mg orally once daily
-2	80 mg orally once daily

Evidence of seizure will result in cessation of treatment with enzalutamide. Management of other toxicities is detailed below.

- Grade 1-2 Toxicities: Management per investigator. No study treatment dose reduction indicated.

- Grade 3 of Higher Toxicities: Hold enzalutamide. When toxicity resolves to ≤ grade 1, resume at first dose modification level (120 mg daily). Prophylactic medications should be considered. If toxicity recurs, hold study medication and adjust or add medications to mitigate the toxicity. When recurrent toxicity has resolved to ≤ grade 1, resume enzalutamide at 80 mg daily. If grade 3 toxicity recurs, the patient will be discontinued from the study.

6.2.2 Management of AA Related Toxicity

The starting dose of AA will be 1000 mg daily. In the presence of any AA related toxicities > grade 2 (CTCAE version 4) during treatment with AA at the starting dose level, the dose of abiraterone acetate will be held until toxicity improves to grade 1 or better. Then treatment will be resumed to 750 mg daily in the subsequent dose level when toxicity improves to ≤ grade 1. Two levels of dose de-escalation are planned for the study. If > grade 2 toxicity occurs at dose level -2, participants will be removed from the protocol. Management of other toxicities is detailed below.

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

Management of Hypertension

- Grade 1-2 Hypertension:
  - Management per investigator. No study treatment dose reduction.

- Grade 3-4 Hypertension:
  - Hold AA. Adjust or add anti-hypertensive medications to mitigate the toxicity. When toxicity resolves to ≤ grade 1, resume AA at full dose.
  - If grade 3 toxicity recurs, hold AA, and adjust or add anti-hypertensive medications to mitigate the toxicity. When toxicity resolves to ≤ grade 1, resume AA at first dose level reduction (750 mg).
  - If grade 3 toxicity recurs, hold AA, and adjust or add anti-hypertensive medications to mitigate the toxicity. When toxicity resolves to ≤ grade 1, resume AA at second dose level reduction (500 mg daily).
  - If grade 3 toxicity recurs despite optimal medical management and two dose level reductions, discontinue AA.

Management of Hypokalemia

- Subjects entering study on exogenous potassium supplementation:
  - Monitor potassium levels weekly for one month to ensure appropriate maintenance of levels.
- Grade 1-2 Hypokalemia:
  - Initiate potassium supplementation. Once toxicity presents potassium will be monitored weekly until 2 consecutive values are documented in the normal range.
  - If grade 1-2 hypokalemia recurs at a separate point in time, management should include adjustment or addition of medications, including potassium supplementation, to mitigate toxicity. Once toxicity presents, potassium will be monitored weekly until 2 consecutive values are documented in the normal range.
- Grade 3-4 Hypokalemia:
  - Hold AA. Adjust or add medications, including potassium supplementation, to mitigate the toxicity. Monitor potassium levels at least weekly until two consecutive values are documented in the normal range. Once toxicity resolves (i.e. normalized potassium), resume AA at the next lower dose level. When AA is reinitiated, potassium should be monitored at least weekly for the first two weeks and then every 2 weeks for 4 weeks, and then monthly.
  - If grade 3 hypokalemia recurs at a separate point in time, hold AA, and management should include adjustment or addition of medications, including potassium supplementation, to mitigate toxicity. Once toxicity presents, potassium will be monitored at least weekly until 2 consecutive values are documented in the normal range. Once toxicity resolves (i.e. normalized potassium), resume AA at the next lower dose level. When AA is reinitiated, potassium should be monitored at least weekly for the first two weeks and then every 2 weeks for 4 weeks, and then monthly.
  - If grade 3 hypokalemia recurs again despite supplementation and 2 dose reductions, the participant must discontinue AA immediately. The participant must be followed until resolution of hypokalemia to ≤ grade 1 or baseline.

Management of LFT abnormalities

- Grade 1 LFT Abnormalities (i.e. increase in AST or ALT from Institutional ULN to 3.0 x Institutional ULN; increase in total bilirubin from Institutional ULN to 1.5 x Institutional ULN):
  - The frequency of LFT monitoring should be increased, if the investigator judges that the laboratory abnormalities are potentially related to abiraterone acetate. No AA dose reduction is required.
- Grade 2 LFT Abnormalities (i.e. increase in AST or ALT > 3.0 – 5 x Institutional ULN; increase in total bilirubin from > 1.5 – 3 x Institutional ULN):
  - The frequency of LFT monitoring should be increased to ≥ once a week, if the investigator judges that the laboratory abnormalities are potentially related to AA. No AA dose reduction is required.
- Grade 3 LFT Abnormalities (i.e. increase in AST or ALT to > 5 x Institutional ULN – 20.0 x Institutional ULN; increase in total bilirubin to > 3 x Institutional ULN – 10.0x Institutional ULN):

- Hold AA and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once weekly) should be conducted until the LFTs return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.
- If AA resumption is considered for subjects who have experienced Grade 3 increases in AST, ALT, or bilirubin, and the PI agrees, resume AA with the first dose level reduction (750 mg) when Grade 3 toxicities resolve to Grade 1 or baseline. For participants who resume treatment, monitor LFTs at a minimum of every 2 weeks for 3 months and monthly thereafter.
- If Grade 3 increases in AST, ALT, or bilirubin recur after the first dose reduction hold AA and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the LFTs return to baseline value or Grade 1. Liver enzyme measurements should be made immediately, regardless of when the next study visit or monitoring interval is scheduled.
- If AA resumption is considered for participants who have experienced Grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, and the PI agrees, resume AA with the second dose level reduction (2 tablets, 500 mg of study treatment) when AST, ALT, or bilirubin returns to baseline value or Grade 1. For participants who resume AA, monitor LFTs at a minimum of every 2 weeks for 3 months and monthly thereafter.

- Grade 4 LFT Abnormalities (i.e. increase in AST or ALT to > 20 x Institutional ULN; increase in total bilirubin to > 10 x Institutional ULN):
  - Participants must discontinue AA immediately and will not be re-challenged. They should be followed until resolution of LFT abnormalities to ≤ grade 1 or baseline.

6.2.3 Management of Prednisone and Leuprolide Related Toxicity

For subjectively tolerable grade 1 and grade 2 toxicities deemed acceptable by investigator treatment may continue, for grade 3 toxicity or grade 2 intolerable toxicity, contact PI for discussion.

6.3 Dose Modifications/Delays

Instructions on management (including dose modifications and delays) of treatment related toxicities > grade 2 (CTCAE version 4) are detailed in section 6.2. Instructions on management of enzalutamide treatment related toxicities and hypertension, hypokalemia, and LFT abnormalities associated with AA are detailed in section 6.2.

Dose delays do not affect the study assessment schedule.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Enzalutamide

Refer to the package insert for enzalutamide information.

7.1.1 Description

Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide.
The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$.

7.1.2 Mechanism of Action

Enzalutamide is an AR inhibitor that acts on different steps in the AR signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit AR nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model.

7.1.3 Form

Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water. Enzalutamide is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

7.1.4 Storage and Stability

Pharmacy Storage Requirements
The study treatment will be stored in a secure area and administered only to participants entered into the clinical study in accordance with the conditions specified in this protocol. Bottles of study treatment should be stored at a room temperature between 20º-25º C in a dry place and kept with container tightly closed.

Storage Requirements for the Participant
Bottles of study treatment should be stored at room temperature with the cap kept on tightly and should not be refrigerated. Participants should be advised to keep all medications out of the reach and out of sight of children.

Enzalutamide should not be handled by pregnant women.

7.1.5 Compatibility

We do not anticipate any excess toxicity combining enzalutamide, AA, prednisone and leuprolide. There are no overlapping toxicities and no apparent drug-drug interactions

(either pharmacokinetic or combined inhibition of enzymes in the any of the adrenal steroid synthesis pathways).

7.1.6 Handling

There are no specific instructions for handling enzalutamide. Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once the study treatment is prepared for a participant, it can only be administered to that participant.

7.1.7 Availability

Enzalutamide capsules will be provided to each site. Participants will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 3 day window. Information presented on the labels for investigative product will comply with applicable local regulations. Site pharmacist will dispense the study treatment to each participant in accordance with this protocol under the guidelines of the site's dispensation standard operating procedure.

7.1.8 Ordering

Medivation Inc./Astellas will provide participating study sites with the required paperwork to order their supply of enzalutamide.

7.1.9 Accountability

Accountability for study treatment is the responsibility of the investigator.

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

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

7.1.10 Destruction and Return

Drug should be destroyed at the site, after the sponsor– investigator approves the drug destruction policy at the site. Destruction will be documented in the Drug Accountability Record Form.

7.2 AA

Refer to the package insert for AA information.

7.2.1 Description

The chemical nomenclature of AA is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene. Its empirical formula is C26H33NO2 and it has a molecular weight of 391.55. Once absorbed after oral administration, AA is rapidly deacetylated and converted to the active form abiraterone. Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6.[45] For pharmacokinetics, refer to section 2.1.1 and Table 2.

7.2.2 Form

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

7.2.3 Storage and Stability

Pharmacy Storage Requirements

The study treatment must be stored in a secure area and administered only to participants entered into the clinical study in accordance with the conditions specified in this protocol. Bottles of study treatment should be stored at a room temperature between 15º-30º C with the cap kept on tightly and should not be refrigerated. Additional information is provided in the AA Investigator's Brochure.

Storage Requirements for the Participant

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

7.2.4 Compatibility

We do not anticipate any excess toxicity combining enzalutamide, AA, prednisone and leuprolide. There are no overlapping toxicities and no apparent drug-drug interactions (either pharmacokinetic or combined inhibition of enzymes in the any of the adrenal steroid synthesis pathways).

7.2.5 Handling

There are no specific instructions for handling AA. Study treatment must only be dispensed by a Pharmacist or medically qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once the study treatment is prepared for a participant, it can only be administered to that participant.

Women who are pregnant or who may be pregnant should wear gloves if they need to touch AA tablets. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

7.2.6 Availability

Participants will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 3 day window. Information presented on the labels for investigative product will comply with applicable local regulations. Site pharmacist will dispense the study treatment to each participant in accordance with this protocol under the guidelines of the

site's dispensation standard operating procedure. The agent will be provided free-of-charge to study participants.

7.2.7 Ordering
Medivation Inc./Astellas will provide participating study sites with the required paperwork to order their supply of abiraterone acetate.

7.2.8 Accountability
Accountability for study treatment is the responsibility of the investigator.

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

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

7.2.9 Destruction and Return
Drug should be destroyed at the site, after the sponsor– investigator approves the drug destruction policy at the site. Destruction will be documented in the Drug Accountability Record Form.

7.3 Prednisone

7.3.1 Description
Prednisone is a corticosteroid.

7.3.2 Form
Prednisone 5-mg tablets are small, white tablets.

7.3.3 Storage and Stability
Prednisone will be prescribed by prescription and prescriptions may be filled at a pharmacy chosen by the participant.

7.3.4 Compatibility
We do not anticipate any excess toxicity combining enzalutamide, AA, prednisone and leuprolide. There are no overlapping toxicities and no apparent drug-drug interactions (either pharmacokinetic or combined inhibition of enzymes in the any of the adrenal steroid synthesis pathways).

7.3.5 Handling
There are no specific instructions for handling prednisone.

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

7.4 Leuprolide

7.4.1 Description
Leuprolide is a LHRH agonist.

7.4.2 Form
Leuprolide is a sterile solution administered as an intramuscular injection.

7.4.3 Storage and Stability
Leuprolide will be stored at the DFCI infusion pharmacy.

7.4.4 Compatibility
We do not anticipate any excess toxicity combining enzalutamide, AA, prednisone and leuprolide. There are no overlapping toxicities and no apparent drug-drug interactions (either pharmacokinetic or combined inhibition of enzymes in the any of the adrenal steroid synthesis pathways).

7.4.5 Handling
There are no specific instructions for handling leuprolide.

7.4.6 Availability
Leuprolide will not be provided by the study and will be prescribed by standard prescriptions.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Correlative Studies Background

AR Signaling Axis

Although effective CYP17 inhibition by abiraterone represents a significant advance in the treatment of metastatic CRPC, studies of resistance mechanisms to abiraterone provide the rational for adding antiandrogen therapy. *In vitro,* abiraterone treatment increases CYP17 expression, AR expression, and expression of AR splice variant. Based on preclinical models of enzalutamide resistant cell lines, researchers have identified a novel missense mutation in the AR ligand-binding domain (F876L) that confers agonistic activity to enzalutamide. This mutation is hypothesized to drive phenotypic resistance. Additionally, in preclinical models splice variant AR expression driven by AR gene rearrangements demonstrated resistance to enzalutamide given activity as independent effectors of the AR transcriptional program. Other postulated mechanisms of castration resistance include aberrant AR co-regulators leading to altered AR transcriptional activity and cross-talk with alternative signaling pathways, including the PI3K/Akt/mTOR and RAS/MAPK pathways.

We hypothesize that following treatment with either treatment arm, we will observe changes in the AR signaling axis in RP specimens. We will assess the AR axis by assaying serum androgens prior to treatment, during treatment, and prior to RP. Additionally, we will assay tissue androgens and perform IHC/expression analysis for AR proteins involved in androgen synthesis and proteins involved in other critical pathways in RP specimens. Nuclear localization of AR will be performed by IHC.

PTEN and the PI3K Pathway

The PTEN gene is a tumor suppressor that encodes a protein phosphatase recurrently mutated in cancer. PTEN activity removes a phosphate from phosphoinositides at the plasma membrane and negatively regulates the PI3K–AKT–mTOR. Thus, either loss or inactivation of PTEN genes leads to PI3K pathway activation. Genomic evidence of PTEN loss in prostate cancer through point mutation, deletion, or rearrangement has been observed in at least 50% of metastatic CRPCs. Interestingly, recent studies have demonstrated a relationship for ERG fusions and androgen signaling with PTEN loss, suggesting that PTEN loss and ETS fusions are not mutually exclusive events. Additionally, preclinical models have demonstrated cross-talk between the PI3K pathway and AR signaling axis and regulation via reciprocal feedback.[47]

During this study, we will use IHC/expression analysis to assess apoptosis, WNT signaling, and the PTEN-PI3K-AKT pathways in RP specimens.

Circulating Tumor DNA

There is an unmet clinical need for reliable biomarkers that can be used for early detection of cancer recurrence and to guide therapy. Detecting ctDNA in plasma or serum could serve as a ‘liquid biopsy’, which would be useful for numerous diagnostic applications. Use of such a liquid biopsy delivers the possibility of taking repeated blood samples, consequently allowing the changes in ctDNA to be traced during the natural course of the disease or during cancer treatment. The

physiological events that lead to the increase of ctDNA during cancer development and progression are still not well understood. However, analyses of ctDNA will allow for the detection of tumor-related genetic and epigenetic alterations that are relevant to cancer development and progression. We and others have previously shown that detection of ctDNA is feasible. In a study of 640 patients with various types of cancer, ctDNA was identified in >75% of cases. We have thus far been able to detect ctDNA in post RP patients treated on our previously mentioned abiraterone neoadjuvant study.

Whole Exome and Transcriptome Sequencing

Considerable evidence now exits that prostate cancer, like all malignancies, is a genomic disease. Understanding the genetic basis of prostate cancer is therefore crucial for the creation of more powerful preventative interventions, diagnostics, and targeted therapies. The prevalence of genomic aberrations in clinically meaningful prostate cancer raises the hypothesis that such changes may influence the castration-resistant phenotype.

The initial pilot study representing the first whole genome sequencing analysis of primary human prostate cancer consisted of radical prostatectomy specimens from seven patients with high-risk primary tumors.[53] This analysis showed that several tumors contained complex chains of balanced rearrangements that occurred within or adjacent to known cancer genes. Rearrangement breakpoints were enriched near open chromatin, AR, and ERG DNA binding sites in the setting of the ETS gene fusion TMPRSS2-ERG, but inversely correlated with these regions in tumors lacking ETS fusions. Three tumors contained rearrangements that disrupted CADM2 and four harbored events disrupting either PTEN, a prostate tumor suppressor, or MAG12, a PTEN interacting protein.

To gain insights into the genomic alterations that may underpin lethal prostate cancer, we plan to perform whole exome and transcriptome characterization of prostate tumor samples (obtained from pretreatment biopsy and fresh-frozen tissue from RP specimen) and their matched normal counterparts (from whole blood obtained from the same patient). This will be accomplished by paired-end, massively parallel sequencing of tumor and normal DNA using the Illumina platform.

Determine features of tissue microenvironments that promote disseminated tumor cell survival and resistance to AR pathway therapeutics

Though tumor cell intrinsic mechanisms can clearly promote treatment resistance (e.g. AR LBD mutations), there is ample evidence that tissue microenvironments also dictate resistance phenotypes. Microenvironmental influences include: (i) physical contacts and spatial ‘niches’ that alter tumor cell proliferation and dormancy states; (ii) concentrations of cytokines and growth factors, (iii) interactions with immune cell components, and (iv) altered metabolism or penetrance of therapeutic drugs. We detailed the profound influence of genotoxic damage in generating pro-resistance secretory programs derived from benign cells of the prostate stroma, and we have recently shown that cyclophosphamide can promote prostate cancer bone metastasis via a transient increase in bone marrow myeloid cells and myelogenic cytokines. In the context of AR-directed therapeutics, while provocative preclinical studies suggest an important role for AR in modulating prostate cancer progression via monocyte/macrophage AR, studies demonstrating AR-mediated alterations in cell types comprising tumor microenvironemnt in humans are lacking. We will exploit the clinical samples obtained in the context of intense ADT to evaluate resistance mechanism operating through cell extrinsic microenvironmental mechanisms.

Please see the study lab manual for additional information on the processing, storage and shipping of study samples. The lab manual will be maintained as a separate document.

9. STUDY CALENDAR

	Pre-Study[a]	Day 1 of Cycle 1 and Cycle 4 (+/- 3 days)[b]	Day 1 of Each Cycle (+/- 3 days)	Day 160-168 (+/- 14 days)	Day 169 (≤ 30 days of RP)	Day 169 (+/- 14 days)	Post Surgery Follow Up[c]	Follow-Up Visits[d]
Informed Consent	X							
History and Physical[e]	X	X	X	X			X	X
Digital Rectal Examination[f]	X							
ECOG Performance Status	X	X	X	X			X	X
Vital Signs[g]	X	X	X	X			X	X
Hematology[h]	X	X	X	X			X	X
Serum Chemistry[i]	X	X	X	X			X	X
Fasting Lipid Panel[j]	X			X				X
Coagulation Factors[k]	X			X				
EKG	X			X				
ECHO	X							
Testosterone	X	X		X				X
Serum Hormones[l]		X		X				
Serum ACTH		X		X				
Circulating Tumor DNA		X		X				X [w]
Research Sample[m]		X						
PSA	X	X	X	X			X	X
Bone Scan	X							
CT or MRI abdomen/pelvis[n]	X							
Dispense Drug[o]		X	X					
Administer Leuprolide[p]		X						
Compliance Assessment		X	X	X				
Prior and Concomitant Medications	X	X	X	X				
Adverse Events[q]	X	X	X	X		X	X	

Prostatectomy[r]						X		
Bone marrow aspirate[s]	X				X			
Request Diagnostic Biopsy[t]	X							
Intra-Operative/Post-Operative Complications[u]							X	X
Quality of Life Questionnaire[v]	X				X		X	X

a: Baseline evaluations are to be conducted within 30 days prior to registration with the exception of scans and DREs. Scans and DREs may be done within 60 days prior to registration. All baseline screening should be done prior to registration.
b: A cycle will be defined as 28 days.
c: The post surgery follow-up visit will be conducted approximately 30 days (+/- 5 days) after the last dose of oral treatment or prior to the investigator initiating a new systemic antineoplastic therapy or investigational agent, whichever comes first. Participant will be asked about post-operative complications (see Appendix F).
d: Follow up visits will take place every 3 months (+/- 1 month) following RP for 2 years in research clinic. After the first 2 years, follow up will take place every 6 months (+/- 1 month) for up to 5 years during which time assessments may be done locally and information may be collected via medical record review.
e: Physical examination should include general description of participant, head, eyes, ears, nose, and throat, chest, abdominal, extremities, neurologic, skin, and lymph node examination. Any other evaluation is up to the discretion of the practitioner. It will not be considered a violation if the exam is not described as outlined here. Information regarding cardiovascular events to include the following list will be documented pretreatment, prior to RP, every 3 months (+/- 1 month) for 2 years, and then every 6 months (+/- 1 month) after 2 years for up to 5 years. This includes: CAD (angina, NSTEMI, STEMI and need for intervention such as stent, CABG), cardiomyopathy/heart failure, valvular heart disease, arrhythmia (defined as need for intervention (cardioversion) or need for new medication), hypertension (defined as need for new medication, peripheral artery disease, cerebrovascular disease (defined by new TIA, CVA)).
f: Digital rectal examination must be performed after PSA blood test has been drawn.
g: Vital signs include upright blood pressure, heart rate, respiratory rate, body temperature and weight. BMI (weight in Kg/height in m^2) will be collected pretreatment, prior to RP, and at 3, 6, 12, 18, and 24 months post RP. The follow-up collections can occur locally.
h: Hematology testing to include WBC, ANC, hemoglobin, and platelet count.
i: Serum chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, magnesium, AST, ALT, alkaline phosphatase, total bilirubin and direct bilirubin.
j: Fasting lipid panel to be collected pretreatment, prior to RP, and at 3, 6, 12, 18, and 24 months post RP. Fasting can be defined as no food or liquids except for water for 8 hours.
k: Coagulation factors to include PT, PTT, and INR.
l: Serum hormones to include DHEA, androstenedione, testosterone, DHT, DHEA-S, DHEA-G, androsterone-S, androsterone-G, pregnenolone, progesterone, deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxypregnenolone, 17α-hydroxyprogesterone, 11-deoxycortisol, cortisol.
m: Blood for germline DNA/RNA analysis. See the Lab Manual for processing instructions. The lab manual is maintained as a separate document
n: Participants eligible given T3 disease must have a prostate MRI documenting the presence of T3 disease prior to start of therapy.
o: Participants will be randomized to treatment with AA + prednisone + enzalutamide + leuprolide vs. enzalutamide + leuprolide.
p: Participants who have started leuprolide within one month of cycle 1/day 1 are eligible to enroll. Participants will receive at minimum 6 months of leuprolide and at maximum 7 months of leuprolide. Participants may receive monthly leuprolide.
q: Adverse events should be collected from the date informed consent is signed and until the 30-day and 90-day post-RP follow-up visits..
r: RP should occur on day 169. A window of +/- 14 days is permitted however oral dosing should continue until 1 day before surgery. Day 160-168 assessments should occur within ≤ 15 total days prior to RP. Study drug accountability should be performed within 24 hours of RP. Preoperative and postoperative evaluation and treatment will be administered as per the instruction of the surgeon. Information will be collected regarding perioperative complications, including intraoperative blood loss, operative time, and surgical assessment of dissection difficulty and surgical complications.
s: Bone marrow aspirates at baseline (+/- 30 days of starting treatment) are highly encouraged but will be optional. Bone marrow aspirates prior to RP are mandatory (+/- 30 days of day 169).
t: Tissue from the diagnostic biopsy will be requested (tissue blocks wherever possible; if not possible, 10 unstained slides from each positive core sample for a total of 30 to be sent to the central analytical laboratory. See the Lab Manual for processing instructions. Pathology report (including the assessment of the local pathologist regarding Gleason score) from diagnostic biopsy must accompany registration materials.
u: Intra-operative and peri-operative (hospital course) complications are to be collected via questionnaire (see Appendix E). Post-operative complications are to be captured by the treating investigator via the Clavien classification (Appendix F). The post-operative complications will be collected at 30 (+/- 5) and 90 (+/- 5) days post-operatively.
v: The EPIC-26 with 2 additional questions will be used to evaluate quality of life parameters (see Appendix G). This will be completed by the patient pretreatment, prior to RP, and at 1, 3, 6, 12, and 24 months post-RP.
w: cfDNA will be collected at a minimum every 6 months post-RP whenever follow-up assessments are conducted at participating study sites.

10. MEASUREMENT OF EFFECT

10.1 Primary Variable

pCR and MRD: The primary efficacy variables are the pCR and MRD. pCR is defined as the absence of morphologically identifiable carcinoma in the RP specimen. MRD will be defined as residual tumor in the RP specimen measuring ≤ 5 mm. If the tumor is multifocal, the size of the largest focus will be used to determine the size of the residual tumor. RP specimens will initially be evaluated by the site pathologist using standard methods and will be evaluated by central pathology review at completion of the study.

10.2 Secondary Variables

Pathologic Outcomes: RCB will be calculated as tumor volume x percent cellularity. Tumor volume and percent cellularity will be evaluated by central pathology review at completion of the study. Cribriform or intraductal spread will be evaluated by central pathology review at the completion of the study. At the time of RP, pathologic specimens will be assessed for positive surgical margins, extracapsular extension, positive seminal vesicles, and positive lymph nodes, which will be determined by each site pathologist.

PSA: PSA will be assessed at baseline and at every cycle while the participant is on neoadjuvant therapy. Following RP, PSA will be assessed every 3 months to assess 2-year freedom from biochemical recurrence and then every 6 months thereafter for up to 5 years post RP. Biochemical recurrence will be defined as a serum PSA ≥0.2 ng/mL, which is confirmed by a second determination with a PSA ≥0.2 ng/mL.

Serum Hormone Levels: DHEA, androstenedione, testosterone, DHT, DHEA-S, DHEA-G, androsterone-S, androsterone-G, pregnenolone, progesterone, deoxycorticosterone, corticosterone, aldosterone, 17α-hydroxypregnenolone, 17α-hydroxyprogesterone, 11-deoxycortisol, cortisol will be assessed at baseline, during treatment (day 1 +/- 3 days of cycle 4), and prior to RP. Hormones will be assayed by mass spectroscopy. Additionally, testosterone levels will be checked by routine laboratory at baseline, every 3 months for 2 years, and then every 6 months for up to 5 years following RP until recovery. Recovery will be defined as a testosterone level > 250 ng/dL.

Prostate Androgen Levels: DHEA, androstenedione, testosterone, DHT, DHEA-S, DHEA-G, androsterone-S, androsterone-G will be assayed from RP specimens by mass spectroscopy.

IHC/expression analysis of AR and proteins involved in androgen synthesis, apoptosis, WNT signaling, and PTEN-PI3K-AKT pathways: Proteins will be assayed by IHC and expression analysis.

Circulating tumor DNA: Circulating tumor DNA will be assayed by high-throughput ddPCR for specific mutations at based line, during treatment, and pre-RP.

Whole Exome and Transcriptome Sequencing: Whole exome and transcriptome sequencing will be performed at the Broad Institute Sequencing platform, which has vast experience in cancer sequencing. Following sequencing, exome data will be analyzed for somatic mutations, insertions and deletions, and copy number alterations using established pipelines at the Broad Institute.

Transcriptome data will be analyzed for overexpressed genes, chimeric transcripts (possibly indicative of structural genomic rearrangements), and alternatively spliced variants. Sequencing information will be analyzed using novel computations algorithms, which have been developed at the Broad Institute.

Analysis of disseminated tumor cells in bone marrow aspirates: We will test the hypothesis that prostate cancer cells surviving high intensity AR suppression represent a dormant cell phenotype localized to the perivascular niche in bone. Optional bone marrow aspirates obtained at baseline and mandatory bone marrow aspirates obtained at the time of RP (from those treated with 6 months of intense AR suppressive therapy) will be fixed, sectioned, and stained for PSA, PSMA, CD31 (endothelium) and Ki67, or microdissected for qRT-PCR assays of these markers after their location in the bone marrow niche is established.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 AE

An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 SAE

A SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

AEs can be 'Expected' or 'Unexpected.'

- Expected adverse event

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

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

- Unexpected adverse event

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

11.2 Procedures for AE and SAE Recording and Reporting

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

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

11.3 Expected Toxicities

Please see section 6.1 for a listing of AEs associated with each of the study agents used in this study.

11.4 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the study agent(s) should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

- **Attribution of the AE:**

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

11.5 Expedited Adverse Event Reporting

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

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For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 hours of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

Participating investigators must report each SAE to the DF/HCC Overall PI and Astellas within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the SAE immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE. Report SAEs by telephone, email or facsimile to:

Mary-Ellen Taplin, MD
Phone: 617-582-7221
Email: Mary_Taplin@DFCI.harvard.edu
Fax: 617-632-6220

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

If the significant other of a study participant becomes pregnant while the study subject is in the trial, the pregnancy must be reported within the SAE reporting timelines (1 business day)

Reporting to Astellas:
The Site Investigator will submit a copy of the MedWatch 3500A form to Astellas by either e-mail or fax, within 24 hours. If submission of this SAE to FDA or Astellas or is not possible within 24 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The SAE documentation, including the Medwatch 3500A Form and available source records should be emailed or faxed to:

Astellas Pharma Global Development – United States
Email: Safety-us@astellas.com
Fax number: (847) 317-1241
The following minimum information is required:
Subject number, sex and age.
The date of report.
A description of the SAE (event, seriousness of the event).
Causal relationship to the study drug.
Follow-up information for the event should be sent within promptly (within 7 days) as necessary.

11.6 Expedited Reporting to the Food and Drug Administration (FDA)

If this study is NOT IND Exempt, the Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

11.7 Expedited Reporting to Hospital Risk Management

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

11.8 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study

12.1.2 Data Submission

The schedule for completion and submission of CRF (paper or electronic) to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT.
On Study Form	Within 14 days of registration.
Baseline Assessment Form	Within 14 days of registration.
Treatment Form	Within 10 days of the last day of the cycle.
Adverse Event Report Form	Within 10 days of the last day of the cycle. If AEs are ongoing at the end of the last cycle, continue to submit adverse event reports until resolution or 30 days post-treatment.
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation.
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason.

Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call.

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

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

Please see section 5.0 of the DSMP found in Appendix D for additional information regarding study monitoring.

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

12.4 Department of Defense Research Monitor Responsibilities

The Research Monitor, Shalender Bhasin, MD, is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol. The Research Monitor may discuss the research protocol with the investigators; shall review the DSMB and monitoring repots. Any safety or compliance issues will be discussed with the principal investigator.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

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

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall PI will disseminate protocol amendment information to all participating investigators.

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

13.2 Informed Consent

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

13.3 Ethics and Research Practices

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

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – IRBs www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – IND Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

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

13.4 Study Documentation

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

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

13.5 Records Retention

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

13.6 Multi-Center Guidelines

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

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

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

- Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design and Sample Size:

This is a multicenter, prospective, randomized phase II trial designed to assess the pCR and MRD rate between neoadjuvant therapy with ARM 1 (enzalutamide + abiraterone + prednisone + leuprolide) compared to ARM 2 (enzalutamide + leuprolide) in men with intermediate-high risk prostate cancer who are candidates for RP.

The primary endpoint is proportion of participants with pCR and MRD (defined as residual tumor in RP specimen measuring ≤ 5 mm) at RP following therapy with ARM 1 and ARM 2. We hypothesize that treatment with ARM 2 will have a pCR plus MRD of 10% based on our prior experience. We hypothesize that treatment with ARM 1 will have a pCR plus MRD rate of 35%. 75 men with localized, intermediate-high risk prostate cancer will be enrolled and randomized in 2:1 ratio to Arm 1 (N=50) or Arm 2 (N=25). This sample size will have 84% power to distinguish a pCR/MRD rate of 35% in Arm 1 (N=50) from a rate of 10% in Arm 2 (N=25), using Fisher's exact test with one-sided type I error of 0.1.

14.2 Primary Endpoint and Methods of Analysis:

Number and percent of participants achieving pCR/MRD will be summarized with two-sided 80% exact binomial confidence interval (CI) by treatment arm. The primary comparison between arms will be conducted using Fisher's exact test, with one sided *P* value of ≤ 0.10 considered significant. The Cochran-Mantel-Haenszel test may also be used for comparison, adjusting for the stratification factor at randomization.

The primary efficacy endpoint will be analyzed in all participants who are randomized and have received at least one cycle of protocol therapy. Participants who do not undergo prostatectomy or have pathological outcome unevaluated will be treated as non-responders. Reasons off study prior to prostatectomy will be recorded.

14.3 Secondary Endpoint(s) and Methods of Analysis:

Pathological endpoints:

Other pathological endpoints include (1) proportion of participants with pCR at RP, (2) proportion of participants with favorable RCB (defined as the 33rd percentile of the RCB index calculated as the volume x cellularity) at RP, (3) proportion of participants with cribriform or intraductal spread at RP, and (4) proportion of participants with positive surgical margins, extracapsular extension, positive seminal vesicles, and positive lymph nodes at time of RP following therapy with ARM 1 and ARM 2. Number and percent of participants with pCR, favorable RCB or presenting each of these pathological features as described above will be summarized by arms with a two-sided 95% confidence interval; comparison between arms will be conducted using Fisher's exact test.

PSA kinetics prior to RP:

PSA kinetics prior to RP include median nadir value, the proportion of participants achieving PSA < 0.2 ng/mL, the proportion of participants achieving 50% and 90% decrease in PSA from baseline, and median time to PSA nadir for each treatment arm. PSA kinetics will be summarized with descriptive statistics (e.g. median, range, and proportions) and presented by arm. Comparison between arms will

be conducted using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Biochemical recurrence post RP:
Time to biochemical recurrence (defined as serum PSA ≥0.2 ng/mL, which is confirmed by a second determination with a PSA ≥0.2 ng/mL*)* will be estimated by the Kaplan Meier method and comparison between arms will be conducted by the log-rank test. The 2-year estimates of freedom from biochemical recurrence for those achieving a pCR/MRD and not achieving a pCR/MRD for each study arm will be also estimated from these results. Multivariable analysis using Cox's proportional hazards model will be used to determine whether treatment, achieving pCR/MRD or an interaction is predictive of freedom from biochemical failure.

Safety endpoints:
Safety analysis will be conducted using the Safety Population defined as any participant receiving one dose of study treatment. For toxicity reporting, all adverse events and treated adverse events will be graded and analyzed using CTCAE version 4. Type of adverse events, intensity, and attribution will be provided in a listing. Adverse events will be summarized by grade and by treatment arm. The worst grade will be used if any toxicity event is reported multiple times on the same participant. All adverse events resulting in discontinuation, dose modification, and/or dosing interruption, and/or treatment delay of drug will also be summarized. All laboratory test results will be classified according to the CTCAE version 4.

Quality of Life (QOL) endpoints
The QOL will be measured using the Expanded Prostate Cancer Index Composite 26 (EPIC-26). The questionnaires will be administered at baseline, prior to and post prostatectomy and during follow up. Resulting domain scores for EPIC-26 (urinary incontinence, urinary obstruction, sexual, bowel, hormonal/vitality) is on a 0–100 scale, with higher values representing a more favorable health-related QOL. For each treatment group, calculated scores on each domain and changes from baseline will be summarized by timepoints; comparison between treatment groups at selected timepoints will be conducted using a two-sided t-test. ANOVA or linear regression models will be conducted to include the stratification factor and the important baseline characteristics in the model as appropriate. The effect of treatment may also be evaluated using a repeated measures model to incorporate assessments across time into a single analysis.

14.4 Correlative Endpoint(s) and Methods of Analysis:

Time to testosterone recovery:
The Kaplan-Meier product limit method will be used to estimate the distribution of the time from RP until testosterone recovery (defined as testosterone level > 250 ng/dL) for each study arm. Comparison between treatment arms will be assessed using the log rank test.

Serum/Tissue androgen concentrations:
Serum and prostate tissue androgen concentrations (DHEA, androstenedione, testosterone, DHT, DHEA-S, DHEA-G, androsterone-S, androsterone-G) will be assayed by mass spectroscopy. Tissue androgens will only be assayed in RP specimens. Mean change in serum androgen concentrations from baseline to during treatment and to prior to RP will be summarized; comparisons between arms will be

conducted using the ANOVA methods (with log transformation as appropriate) or the non-parametric Wilcoxon rank-sum test. Linear mixed model may be analyzed for comparing the overall pattern of serum androgen levels over time between arms.

IHC staining:
The expression of the AR and proteins involved in the androgen synthesis, apoptosis, WNT signaling, and PTEN-PI3K-AKT pathways from the RP specimens will be assessed by the IHC staining, scored as percentage of cells staining for the specific protein (i.e. categorized as 0, <5, 5-25, 25-50, >50%) and/or the intensity of the staining. These semi-quantitative measurements at each timepoint will be compared between treatment arms using the Cochran–Armitage test for trend or other appropriate methods.

Whole Exome and Transcriptome Sequencing:
Changes in whole exome and whole transcriptome between pretreatment prostate biopsy and RP specimens between treatment arms will be analyzed using novel computational algorithms developed at the Broad Institute. It is anticipated that whole genome sequencing of prostate cancer will be undertaken in at least 80% of participants (N=60) (pre and post neoadjuvant hormonal therapy**)** to study de novo or acquired resistance to neoadjuvant therapy in terms of genomic alterations such as base mutations, small insertions/deletions (indels), copy number changes, and structural rearrangements.

Gene mutation frequencies and mean ± SD of quantitative gene expression profile will be summarized pre and post therapy. For detection of rare gene mutations, with 60 participants, there are 0.95, 0.84 and 0.45 probabilities to observe ≥1 mutation if the true underlying mutation rate is 5%, 3% and 1% respectively. For more prevalent mutations, the 90% exact binominal CI width is 0.14 and 0.21 with the observed mutation rate of 0.1 and 0.3 respectively. To compare pre-post therapy changes in gene expression, there is 80% power to detect a 0.37 SD mean change between time points with n=60 using a paired t-test (two-sided α=0.05).

14.5 Sample Size/Accrual Rate

For a sample size of 75 participants, we expect a total of 12-15 months to complete the accrual at a rate 5-6 participants/month.

15. PUBLICATION PLAN

The data will be collected by Dr. Taplin and study team and analyzed by Dr. Taplin and Dr. Montgomery, and the statistical team at DFCI. It is anticipated that the results will be made public within 12 months of the end of data collection. A report is planned to be published in a peer-reviewed journal, however initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors.

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17. APPENDICES

17.1 APPENDIX A: Performance Status Criteria

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APPENDIX A: Performance Status Criteria

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

APPENDIX B: PARTICIPANT'S PILL DIARY

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

ARM 1: Enzalutamide + Abiraterone Acetate + Prednisone + Leuprolide
ARM 2: Enzalutamide + Leuprolide

INSTRUCTIONS TO THE PARTICIPANT:

Study Drug A: Enzalutamide Dose: _____
Study Drug B: Abiraterone Acetate Dose: _____ (enter N/A if not on ARM 1)
Study Drug C: Prednisone Dose: _____ (enter N/A if not on ARM 1)

1. You should take enzalutamide at the same time each day with or without food. Vomited doses will not be made up. If you miss your dose, you may take your dose later in the day, but no later than 12 hours after your scheduled dose was due.
2. For ARM 1 participants only: You should take abiraterone acetate at the same time each day. Abiraterone acetate should be taken on an empty stomach; no food or other medications should be consumed for at least two hours before the dose is taken and for at least one hour after the dose is taken. Do not take your abiraterone acetate at the same time you take your enzalutamide capsules. Vomited doses will not be made up. If you miss your dose, you may take your dose later in the day, but no later than 12 hours after your scheduled dose was due.
3. For ARM 1 participants only: You should take prednisone at the same time daily. Prednisone should be taken with food. You may take prednisone at the same time you take enzalutamide.
4. If a dose is skipped, missed or vomited, it should not be taken (or retaken if vomited) on the day of the missed dose but dosing should be resumed the following day. Doses should be taken no later than 12 hours after the scheduled time for dosing.
5. Record the date, time and the number of tablets you took.
6. Please bring your pill bottle and this form to your physician when you go to your next appointment.
7. Study drugs should not be crushed, chewed, or dissolved in water.
8. Do not consume grapefruit or grapefruit juice products with study drugs.

APPENDIX B: PARTICIPANT'S PILL DIARY

Today's Date: _____

Participant Name: _____

Participant Study ID: _____

ARM 1: Enzalutamide + Abiraterone Acetate + Prednisone + Leuprolide

ARM 2: Enzalutamide + Leuprolide

Date	Day	Number of Tablets or Capsules and Time of Day					
		Abiraterone (take alone on an empty stomach)	Time AM/PM	Enzalutamide	Time AM/PM	Prednisone	Time AM/PM
	1						
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						
	11						
	12						
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APPENDIX C: Representative Medications that May Predispose to Seizure

Classification	Generic Name	Trade Name
Antiasthmatic drugs	Aminophylline	Neophyllin, Albina, Kyophyllin, etc
	Theophylline	Theodur, Uniphyl, etc.
Atypical antipsychotics	Clozapine	Clozaril, etc.
	Olanzapine	Zyprexa, etc.
	Risperidone	Risperdal, etc.
	Quetiapine	Seroquel, etc.
	Perospirone	Lullan, etc.
	Aripiprazole	Abilify, etc.
	Blonanserin	Lonasen, etc.
Insulin	Insulin aspart	Novorapid, etc.
	Insulin lispro	Humalog, etc.
	Insulin glulisine	Apidra, etc.
	Human insulin	Humulin, Novolin, etc.
	Insulin glargine	Lantus, etc.
	Insulin detemir	Levemir, etc.
Lithium	Lithium carbonate	Limas, etc.
Pethidines	Pethidine hydrochloride	Pethidine hydrochloride, Opystan, Pethilorfan, etc.
Phenothiazine antipsychotics	Chlorpromazine	Wintermin, Contomin, Vegetamin, etc.
	Trifluoperazine	Trifluoperazine powder, etc.
	Levomepromazine	Hirnamin, Levotomin, etc.
	Fluphenazine	Flumezin, Fludecasin, etc.
	Prochlorperazine	Novamin, Compazine, etc.
	Propericiazine	Apamin, Neuleptil, etc.
	Perphenazine	PZC, Trilafon, etc.
Certain antidepressants	Bupropion	Wellbutrin, Xyban, etc.
	Amitriptyline	Tryptanol, etc.
	Imipramine	Imidol, Tofranil, etc.
	Maprotiline	Ludiomil, etc.
	Mirtazapine	Reflex, Remeron, etc.
	Amoxapine	Amoxan, etc.
	Dosulepin hydrochloride	Prothiaden, etc.
	Nortriptyline hydrochloride	Noritren, etc.
	Lofepramine hydrochloride	Amplit, etc.
	Mianserin hydrochloride	Tetramide, etc.
	Setiptiline maleate	Tecipul, etc.
	Trimipramine maleate	Surmontil, etc.
	Clomipramine hydrochloride	Anafranil, etc.

APPENDIX D
Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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INTRODUCTION

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

Purpose

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

Multi-Center Data and Safety Monitoring Plan Definitions

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

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

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

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

Coordinating Center: The entity (i.e. Lead Institution) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol

document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

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

DF/HCC Sponsor

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

Coordinating Center

The Coordinating Center will assume the following general responsibilities:
Assist in protocol development
Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all Participating Institutions.
Maintain FDA correspondence, as applicable.
Maintain updated roster of participants.
Verify eligibility.
Verify response.
Oversee the data collection process from Participating Institutions.
Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
Carry out plan to monitor Participating Institutions either by on-site or remote monitoring
Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation of all relevant communications.

Participating Institution

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

The general responsibilities for each Participating Institution are as follows:
Document the delegation of research specific activities to study personnel.
Commit to the accrual of participants to the protocol.
Submit protocol and/or amendments to their local IRB.
Maintain a regulatory binder in accordance with DF/HCC requirements.
Provide the Coordinating Center with regulatory documents as requested.
Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
Update Coordinating Center with research staff changes on a timely basis.
Register participants through the Coordinating Center.
Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.

Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
Have office space, office equipment, and internet access that meet HIPAA standards.
Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

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

Protocol Distribution

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

Protocol Revisions and Closures

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

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

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

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

Informed Consent Requirements

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

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

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

IRB Documentation

The following must be on file with the Coordinating Center:
Initial approval letter of the Participating Institution's IRB.
Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
Participating Institution's IRB approval for all amendments.
Annual approval letters by the Participating Institution's IRB.

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

IRB Re-Approval

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

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

Participant Confidentiality and Authorization Statement

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

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB will provide a consent template, which covered entities (Participating Institutions) must use.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

DF/HCC Multi-Center Protocol Confidentiality

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

DF/HCC Multi-Center Registration

Participant Registration and Randomization
To register a participant, the following documents should be completed by the Participating Institution and faxed to the Coordinating Center at Dana-Farber Cancer Institute at (617) 632-6220 or e-mailed to the DFCI Clinical Research Coordinator and Research Nurse team. Please notify the DFCI team in advance that a registration packet is to be expected with the following items:
Current IRB approved informed consent document signed by participant and investigator
HIPAA authorization form (if separate from the informed consent document)
Signed and dated DFCI eligibility checklist
The following source documentation is typically required. Please note additional documentation may be required by the lead institution:
Labs for PSA values used to determine eligibility (lab values used to determine eligibility, including screening PSA)
Reports documenting disease status: Chest CT, CT or MRI Abdomen and Pelvis, Bone Scan
Pathology Report
Concomitant medication list
Progress note or equivalent documentation of consenting visit
Progress note documenting medical history and oncologic history
All screening labs
Screening visit note, with BP, vital signs, ECOG Performance status
Screening ECG

MUGA Scan or ECHO

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:
Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
Upon receiving confirmation of registration by the QACT, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and if applicable the dose treatment level.

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

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

Initiation of Therapy

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

Eligibility Exceptions

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

Verification of Registration, Dose Levels, and Arm Designation

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one business day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

DF/HCC Protocol Case Number

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

Protocol Deviations, Exceptions and Violations

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

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

Definitions

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

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

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

Reporting Procedures

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

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

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

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

Safety Assessments and Toxicity Monitoring

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

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

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

Guidelines for Reporting Serious Adverse Events

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

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

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

Guidelines for Processing IND Safety Reports

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

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

Data Forms Review

When data forms arrive at the DF/HCC QACT, they are reviewed for completeness, protocol treatment compliance, adverse events (toxicities) and response. Data submissions are monitored

for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

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

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

Requisitioning Investigational Drug

The ordering of investigational agent is specified in the protocol sections 7.1.8, and 7.2.7.

Participating Institutions should order their own agent regardless of the supplier (pharmaceutical company, commercial supply, etc.)

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

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

MONITORING: QUALITY CONTROL

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

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

The DF/HCC Lead Institution will implement monitoring activities ongoing to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management.
Site visits will generally occur once a year for sites that are actively enrolling participants and have participants in treatment. Additional monitoring activities may occur if incidences of non-compliance are discovered or at the request of the DF/HCC Sponsor. Virtual monitoring (source documents are sent to DFCI for review) may be performed in lieu of a site visit if the study staff and PI determine that virtual monitoring is appropriate for the site. The decision to perform virtual monitoring in lieu of a site visit will be based upon the site's enrollment, study compliance history, history collaborating with DFCI on other multi-center studies, and number of participants in active treatment.

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

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

Evaluation of Participating Institution Performance

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

Monitoring Reports

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

AUDITING: QUALITY ASSURANCE

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

DF/HCC Sponsored Trials

This study may be audited by the QACT if the Sponsor-Investigator determines that an audit of the participating site is necessary.

Participating Institution

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

DF/HCC Sponsor and Coordinating Center

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

Sub-Standard Performance

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

Corrective Actions

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

APPENDIX E: Intra-operative and post-operative RP complications questionnaires

Intraoperative Surgical Questionnaire
(to be completed day of surgery)

Date ___/___/___

I. Patient Data

A. Patient's First Name _____ B. Patient's Last Name _____

C. ID# _____

II. Operative Information

A. Age at Surgery: _____ yrs

B. Date of Surgery: ___/___/___

C. Surgical Approach: Retropubic____, Perineal____, Laparoscopic____, Robotic_____

D. Neurovascular Bundle Preserved: Two_____, One_____, None_____

E. Ease of Neurovascular Bundle Preservation: Easy____, Moderate____, Difficult_____

F. Lymph Node Dissection: Yes____, No____

G. Technical Modifications: _____

H. Estimated Blood Loss (cc) _____

I. Blood Transfusion Required: Yes____, No____; if yes,

Intraoperative Autologous Units_____, Postoperative Autologous Units_____

Intraoperative Nonautologous Units_____, Postoperative Nonautologous Units_____

J. Hemodiluted: Yes____, No_____

K. Intraoperative Complication: Yes____, No_____; if yes, type of intraoperative

complication:_____

In Hospital Complications Surgical Questionnaire
(to be completed after surgery)

Date ___/___/___

I. Patient Data
A. Patient's First Name _____ B. Patient's Last Name _____

C. ID# _____

II. Hospital Course
A. Post-operative days admitted_____

B. In Hospital Complication: Yes ____, No _____. If yes, circle all appropriate.
General:
1. Fever
2. Paralytic ileus
3. Deep vein thrombosis
4. Pulmonary embolism
5. Myocardial infarction
6. Cerebrovascular stroke

Specific:
1. Prolonged tube drainage
2. Foley Catheter Fell Out
3. Wound infection
4. Wound dehiscence
5. Hematuria with clots
6. Obstructed catheter

Other (not listed above): _____

C. Transfusion Yes ____, No _____. If yes, # of units: _____

APPENDIX F: Robotic Assisted Radical Prostatectomy Complications

Cardiac
Arrhythmia (Y____N____)
Myocardial Infarction (Y____N____)
Not otherwise specified (Y____N____)
Lymphovascular
Lymphocele (Y____N____)
Infected lymphocele (Y____N____)
Lymphedema (Y____N____)
Postop bleeding (Y____N____)
Gastrointestinal
Diarrhea (Y____N____)
Ileus (Y____N____)
Enterotomy (Y____N____)
Rectal laceration (Y____N____)
Rectal Bleeding (Y____N____)
SBO (Y____N____)
Not otherwise specified (Y____N____)
Infectious
C. Difficile (Y____N____)
Pneumonia (Y____N____)
UTI (Y____N____)
Abscess (Y____N____)
Epididymitis/orchitis (Y____N____)
Neurologic
Neuropraxia (Y____N____)
Transient Ischemic Attack – Stroke (Y____N____)
Syncope (Y____N____)
Psychiatric event (Y____N____)
Pain not otherwise specified (Y____N____)
Pulmonary
Respiratory distress/failure (Y____N____)
Pulmonary Embolus (Y____N____)
Deep Vein Thrombosis (Y____N____)
Renal
Acute renal failure (Y____N____)

Urologic
Ureteral trauma (Y____N____)
Intractable bladder spasms (Y____N____)
Clot retention (Y____N____)
Disrupted anastomosis (Y____N____)
Gross hematuria (Y____N____)
Retention (Y____N____)
Foley malfunction (Y____N____)
Urine leak / urinoma (Y____N____)
Wound
Dehiscence (Y____N____)
Infection (Y____N____)
Hernia (Y____N____)
Ophtalmologic
Xerophthalmia (Y____N____)
Other
Dehydration (Y____N____)
Allergic reaction (Y____N____)
Unplanned Admission (Y____N____)
Unplanned Emergency Room Visit (Y____N____)

Note: For any question answered "Yes", please complete the Adverse Event page as necessary.

APPENDIX G: The Expanded Prostate Cancer Index Composite (EPIC-26)

This questionnaire is designed to measure Quality of Life issues in patients with Prostate Cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely. Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Name: _____
ID: _____
Today's Date: ___/____/____

1. Over the **past 4 weeks**, how often have you leaked urine? (Circle one number)

More than once a day.....	1
About once a day.....	2
More than once a week.....	3
About once a week.....	4
Rarely or never.....	5

2. Which of the following best describes your urinary control **during the last 4 weeks**? (Circle one number)

No urinary control whatsoever.....	1
Frequent dribbling.....	2
Occasional dribbling.....	3
Total control.....	4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**? (Circle one number)

None.....	0
1 pad per day.....	2
2 pads per day.....	3
3 or more pads per day.....	4

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**? (Circle one number on each line)

	No Problem	**Very Small Problem**	**Small Problem**	**Moderate Problem**	**Big Problem**
a. Dripping or leaking urine.....	0	1	2	3	4
b. Pain or burning on urination.....	0	1	2	3	4
c. Bleeding urination.....	0	1	2	3	4
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4
e. Need to urinate frequently during the day.....	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**? (Circle one number)

No problem.....	1
Very small problem.....	2
Small problem.....	3
Moderate problem.....	4
Big problem.....	5

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	**Very Small Problem**	**Small Problem**	**Moderate Problem**	**Big Problem**
a. Urgency to have a bowl movement.....	0	1	2	3	4
b. Increased frequency of bowel movements.....	0	1	2	3	4

c. Losing control of your stools.....	0	1	2	3	4
d. Bloody stools.....	0	1	2	3	4
e. Abdominal/Pelvic/Rectal Pain.....	0	1	2	3	4

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**? (Circle one number)

No problem.....	1
Very small problem.....	2
Small problem.....	3
Moderate problem.....	4
Big problem.....	5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	**Poor**	**Fair**	**Good**	**Very Good**
a. Your ability to have an erection?..	1	2	3	4	5
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**? (Circle one number)

None at all.....	1
Not firm enough for sexual activity.....	2
Firm enough for masturbation and foreplay only.....	3
Firm enough for intercourse.....	4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**? (Circle one number)

I NEVER had an erection when I wanted one.....	1

I had an erection LESS THAN HALF the time I wanted one...	2
I had an erection ABOUT HALF the time I wanted one.....	3
I had an erection MORE THAN HALF the time I wanted one.	4
I had an erection WHENEVER I wanted one.....	5

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**? (Circle one number)

Very poor.....	1
Poor.....	2
Fair.....	3
Good.....	4
Very good.....	5

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**? (Circle one number)

No problem.....	1
Very small problem.....	2
Small problem.....	3
Moderate problem.....	4
Big problem.....	5

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	**Very Small Problem**	**Small Problem**	**Moderate Problem**	**Big Problem**
a. Hot Flashes.....	0	1	2	3	4
b. Breast tenderness/enlargement..	0	1	2	3	4
c. Feeling depressed.....	0	1	2	3	4
d. Lack of energy.....	0	1	2	3	4
e. Change in body weight..	0	1	2	3	4

Supplemental Questions

1. Are you currently using any of the following medications, treatment, or devices for urinary incontinence? Check all that apply:
   ___A. Oral Medications (Ditropan, Detrol, Sancture, etc.)
   ___B. Surgical Sling

___C. Artificial Sphincter
___D. None of the above

2. Are you currently using any of the following medications, treatment, or devices for erectile dysfunction? Check all that apply:
___A. Oral Medications (Viagra, Levitra, Cialis)
___B. MUSE (intra-urethral alprostadil suppository)
___C. Vacuum erection device (such as Erect-Aid)
___D. Penile prosthesis
___E. No treatment (none of the above)