STATUS PAGE
PROTOCOL **16-223**

Closed To New Accrual

Closure Effective Date: 11/05/2018
Reason: Study Accrual Goal Met

No new subjects may be enrolled in the study- as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Protocol Version Date: January 3, 2019

DF/HCC Protocol #: 16-223

Title: Phase II randomized study of neoadjuvant and adjuvant abiraterone acetate + apalutamide for intermediate-high risk prostate cancer undergoing prostatectomy.

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IND #: 130502
IND Sponsor: Mary-Ellen Taplin, MD

Study Agents:
Abiraterone acetate supplied by Janssen Scientific Affairs, LLC
Apalutamide supplied by Janssen Scientific Affairs, LLC
Leuprolide (Commercial Supply)
Prednisone (Commercial Supply)

ABBREVIATIONS

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
Apparent diffusion coefficient – ADC
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
Center for Molecular Oncologic Pathologies – CMOP
Circulating Tumor Cells – CTCs
Code of Federal Regulations – CFR
Common Terminology Criteria for Adverse Events – CTCAE
Computed tomography – CT
Dana Farber Cancer Institute – DFCI
Dana-Farber/Harvard Cancer Center – DF/HCC
Dana-Farber/Partners Cancer Care – DF/PCC
Data Safety and Monitoring Committee – DSMC
Dynamic contrast-enhanced – DCE
Dehydroepiandrosterone – DHEA
Dehydroepiandrosterone-sulfate – DHEA-S
Dihydrotestosterone – DHT
Disease-free survival – DFS
Eastern Cooperative Oncology Group – ECOG
Echocardiogram – ECHO
Electrocardiogram – EKG
Food and Drug Administration – FDA
Good Clinical Practice – GCP
Hazard ratio – HR
Health Insurance Portability and Accountability Act – HIPAA
Immunohistochemistry – IHC
IND – Investigation new drug
Institutional Review Board – IRB
International Normalized Ratio – INR
Liquid Chromatography Mass Spectrometery/Mass Spectrometery – LCMS/MS
Liver function test – LFT
Luteinizing hormone-releasing hormone – LHRH
Magnetic Resonance Imaging – MRI

Multiparametric Magnetic Resonance Imaging – mpMRI
Maximum plasma concentration – C_{max}
Minimal Residual Disease – MRD
National Cancer Institute – NCI
National Surgical Adjuvant Breast and Bowel Project – NSABP
New York Heart Association – NYHA
Office for Data Quality – ODQ
Office for Human Research Studies – OHRS
Overall survival – OS
Pathologic complete response – pCR
Principal Investigator – PI
Progression free survival – PFS
Prostate specific antigen – PSA
Partial Prothrombin Time – PTT
Radical Prostatectomy – RP
Residual cancer burden – RCB
Response Evaluation Criteria In Solid Tumors – RECIST
Serious adverse event – SAE
Skeletal related event – SRE
Sponsor Investigator – SI
Time to PSA Progression – TTPP
Upper limit of normal – ULN
WBC – White blood cell count

Schema:

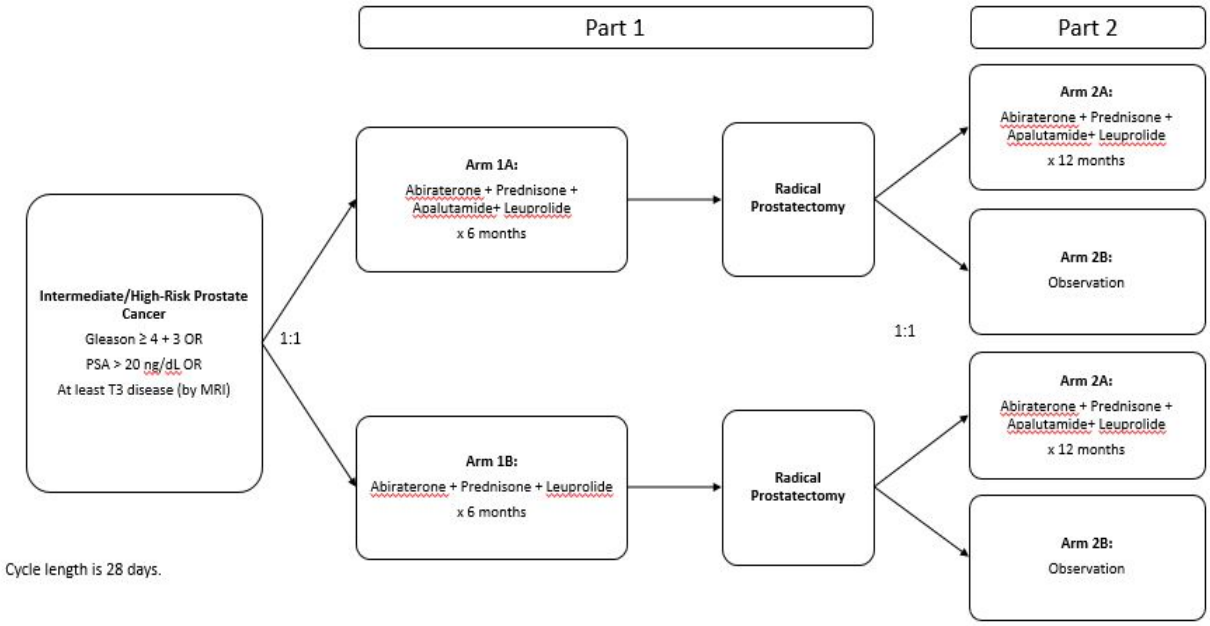
Part 1
Part 2
Intermediate/High-Risk Prostate Cancer
Gleason ≥ 4 + 3 OR
PSA > 20 ng/dL OR
At least T3 disease (by MRI)
1:1
Arm 1A:
Abiraterone + Prednisone + Apalutamide+ Leuprolide
x 6 months
Arm 1B:
Abiraterone + Prednisone + Leuprolide
x 6 months
Radical Prostatectomy
Radical Prostatectomy
1:1
Arm 2A:
Abiraterone + Prednisone + Apalutamide+ Leuprolide
x 12 months
Arm 2B:
Observation
Arm 2A:
Abiraterone + Prednisone + Apalutamide+ Leuprolide
x 12 months
Arm 2B:
Observation
Cycle length is 28 days.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a multicenter, phase II, prospective, randomized trial designed to investigate the efficacy of neoadjuvant and adjuvant abiraterone acetate + apalutamide for men with intermediate-high risk prostate cancer who are candidates for RP. The study includes two parts. In part 1, patients will be randomized in 1:1 ratio to receive 6 months of abiraterone acetate, apalutamide, leuprolide and prednisone (Arm 1A) versus 6 months of abiraterone acetate, leuprolide and prednisone (Arm 1B) followed by RP, stratified by risk factor (intermediate versus high-risk). High-risk factors will be defined as a Gleason score ≥ 8, PSA > 20 ng/dL, or T3 disease on MRI. In part 2 (post-RP), patients will be randomized in 1:1 ratio to receive an additional 12 months of abiraterone acetate, apalutamide, leuprolide and prednisone (Arm 2A) or observation (Arm 2B) stratified by type of neoadjuvant therapy and pathological T-stage (< pT3 versus ≥ pT3) after RP but before cycle 7 day 1 following neoadjuvant therapy. There will be an early stopping rule for Part 2 should a high rate of patients refuse to participate or drop out early while receiving adjuvant therapy (<6 months).

1.2 Primary Objectives

Part 1:

- To determine whether combination of abiraterone acetate + apalutamide improves frequency of achieving a pCR or MRD (defined as residual tumor in RP specimen measuring ≤ 5 mm) at RP as compared with abiraterone acetate alone, in men treated with neoadjuvant leuprolide and prednisone prior to RP.

Part 2:

- To determine whether the use of adjuvant abiraterone acetate + apalutamide + prednisone following RP improves biochemical progression free survival (bPFS) at 3 years post-RP as compared with no adjuvant treatment.

1.3 Secondary Objectives

Part 1:

- To evaluate the frequency of achieving a pCR at RP following therapy with Arm 1A compared to Arm 1B.

- 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 1A compared to Arm 1B.

- To evaluate the frequency of presenting cribriform or intraductal carcinoma at RP following therapy with Arm 1A compared to Arm 1B.

- 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 1A compared to Arm 1B.

- 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 1A compared to Arm 1B.

- To assess intra-operative and post-operative complications following RP between treatment arms (1A and 1B).

Part 2:

- To determine the effect of treatment on freedom from biochemical failure at 2-, 3-, and 5-years post-RP between Arms 2A and 2B among patients who achieve testosterone recovery (defined as a testosterone > 200 ng/dL).

- To determine the effect of treatment on (or freedom from) further prostate cancer therapy (to include adjuvant or salvage radiation therapy, ADT, or other therapies) at 2-, 3-, and 5-years post-RP between Arms 2A and 2B.

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

- To assess quality of life parameters over time between treatment arm 2A and observation arm 2B.

1.4 Correlative Objectives

- To assess time to testosterone recovery, body-mass index, lipids, and cardiovascular events for treatment Arms 2A and 2B.

- To assess changes in serum hormone levels (DHEA, androstenedione, testosterone, DHT, androsterone, progesterone, pregnenolone, deoxycorticosterone, cortisol, DHEA-S) by mass spectroscopy from pretreatment to during treatment to prior to RP and to post-RP between treatment Arms 1A and 1B and Arms 2A and 2B.

- To correlate serum hormone levels from pretreatment to during treatment and to prior to RP with pathologic response at RP.

- To compare serum abiraterone acetate and apalutamide levels to tissue abiraterone and apalutamide levels and serum and hormone levels with pCR + minimum residual disease.

- To compare prostate androgen levels by mass spectroscopy in the RP specimens between treatment Arms 1A and 1B.

- 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 treatment Arms 1A and 1B and between patients with MRD compared to those without MRD.

- To assess changes in circulating tumor DNA from pretreatment to during treatment to prior to RP and to post-RP between Arms 2A and 2B.
- To assess changes in the whole exome and whole transcriptome by high throughput parallel sequencing technologies in evaluable samples from RP between treatment Arms 1A and 1B.
- To assess proportion of patients with downstaging on second multi-parametric prostate MRI compared to baseline MRI between Arms 1A and 1B.
- To correlate imaging T stage at second multi-parametric prostate MRI with pathologic T stage in all patients and by treatment arm.
- To determine if multi-parametric prostate MRI can be used to predict pathologic response (defined as pCR, MRD, and RCB) following neoadjuvant hormone therapy.
- To assess the prevalence of germline mutations in homologous recombination genes in all enrolled patients.
- To correlate homologous recombination gene germline mutation status with pathologic response (defined as pCR, MRD, and RCB).
- To evaluate family history of cancers in the study population and correlate family cancer history with germline mutation status.

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.[4] 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.[5-7] Following RP upwards of 50% of patients with high-risk disease will experience a biochemical recurrence at 5 years.[7] 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 from their disease.[8] 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 and adjuvant therapy 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.[9] A meta-analysis of nine randomized studies, including a total of 3,946 women, demonstrated that neoadjuvant cytotoxic therapy was equivalent to adjuvant cytotoxic therapy in terms of survival and overall disease progression.[10] Few studies have evaluated pCR rates to hormonal therapy and theses are on the order of approximately 10% in breast cancer. The metrics for neoadjuvant hormonal therapy studies focus on ORR, breast conservation, PFS and OS as endpoints. Additionally, neoadjuvant cytotoxic therapy is routinely utilized in the treatment of bladder[11,12], esophageal[8,13,14], and rectal cancer[11].

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.[15] 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.[16] Favorable RCB was defined as the 40th percentile of the RCB index values which was used as the cutoff point to separate favorable RCB (including pCR and minimal residual disease) from moderate or extensive residual disease. 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.[16] They determined that RBC was independently prognostic in a multivariate model.

Historically, the development of new drugs in the early disease setting has been predicated on a demonstration of improved overall survival. In 2014, the FDA drafted a

guidance act, which uses pCR to the neoadjuvant treatment of high-risk early breast cancer as an endpoint to support accelerated approval of new drugs. Pertuzumab was the first drug which was granted the FDA's accelerated approval in the neoadjuvant setting. The approval was based primarily on results from the NEOSPHERE study, a phase II neoadjuvant study using pertuzumab in HER2-positive early stage breast cancer.[1]

ADT is the mainstay of first-line systemic therapy for patients with metastatic prostate cancer. However, clinical trials of ADT in the neoadjuvant stetting prior to RP have been disappointing. Table 1 provides a review of clinical trials of neoadjuvant ADT prior to RP.[17-28]

Table 1. Trials of neoadjuvant ADT.

Trial	Patients	Clinical Stage	Regimen	Outcomes (Neoadjuvant ADT + RP vs. RP alone)				Median Follow Up (Years)
				Positive Surgical Margin Rate	pCR Rate	PFS	OS	
Dalkin *et al* (1996) [17]	56	T1c-T2b	G x 3 mo	18% vs. 14%	NR	NR	NR	
Labrie *et al* (1997) [18]	161	T2-T3	L + F x 3 mo	7.8% vs. 33.8%[a]	6.7% vs. 0%	NR	NR	
Fair *et al* (1999) [19]	140	T1-T3	L + F x 3 mo	19% vs. 37%[a]	NR	No difference	NR	2.9
Van Der Kwast *et al* (1999) [20]	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) [21]	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) [22]	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) [25]	303	T2b	L + F x 3 mo	18% vs. 48%[a]	NR	64.8% vs. 67.6%	NR	5
Selli *et al* (2002) [24]	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) [23]	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) [26]	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) [27]	167	T1a-T2b	L + C x 3 mo	39% vs. 60%[a]	NR	NR	NR	
Yee *et al* (2009) [28]	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[18] 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.[20,22,24] The Canadian Urologic Oncology Group (CUOG) conducted the largest randomized trial evaluating neoadjuvant ADT prior to RP.[22] 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.[29] 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.[18,20,22,26] 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.[21] 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.[21,23,26]

The discordance between the improvement in immediate pathologic endpoints and the lack of benefit in DFS or OS is likely multi-factorial in nature. This is likely multifactorial given that these trials included heterogeneous patients populations (including patients who did not have high-risk disease), various treatment regimens (including an LHRH agonist, an antiandrogen, or combination of both), various durations of therapy (with most durations lasting three months), and limited sample size

to detect realistic differences between treatment arms. Additionally, this could be related to minimal efficacy standard ADT and more maximal suppression of the androgen axis is necessary to observe a therapeutic effect.

Additionally, in prostate cancer, neoadjuvant therapy changes the morphology of the residual, rendering the Gleason score of the post-therapy specimen inadequate. A study of 115 patients with high-risk prostate cancer who had preoperative therapy with androgen ablation alone or in combination with chemotherapy evaluated morphologic patterns in the RP specimens that may be helpful in assessing prognosis.[30] Based on hierarchical clustering analysis, three morphologically distinct groups were identified. On multivariate analysis, the presence of cribriform or intraductal spread morphology were strong predictors of biochemical relapse.

With regard to adjuvant therapy, there are only limited data about the role of adjuvant hormone therapy without radiation therapy after RP. ECOG (ECOG3886) evaluated immediate versus deferred ADT in men with node-positive prostate cancer.[31] Between 1988 and 1993, 98 men who underwent a radical prostatectomy and pelvic lymphadenectomy and found to have microscopic lymph node metastases were randomized to receive immediate lifelong ADT or to be observed and receive ADT on symptomatic recurrence or detection of distant metastatic disease. At a median follow-up of 11.9 years, the men assigned to the immediate ADT arm had a significant improvement OS (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.01–3.35, P 5 .04), prostate cancer–specific survival (HR 4.09, CI 1.76–9.49, P 5 .0004), and progression-free survival (HR 3.42, CI 1.96–5.98, P<.0001). In this study, patients in the observation arm were initiated on ADT only after the development of symptomatic recurrence or detectable metastatic disease and not at the time of biochemical recurrence, which can occur at a median of 8 years before the onset of radiologic evidence of metastatic disease.[32]

A separate retrospective observational study using Surveillance, Epidemiology, and End Results (SEER)–Medicare data was done to evaluate the impact of adjuvant ADT for patients who have node-positive prostate cancer in the contemporary era of postoperative PSA surveillance to detect biochemical recurrence.[33] Wong and colleagues used the SEER-Medicare database to construct a cohort of men with lymph node– positive disease who had undergone RP between 1991 and 1999 and classified them as receiving adjuvant ADT (within 120 days of RP) or not receiving adjuvant ADT (subsequent ADT initiated >120 days from surgery or no ADT). Among the 731 men identified, 209 had received ADT within 120 days of RP. After adjusting for potential confounders of receiving adjuvant ADT (ie, tumor characteristics, extent of nodal disease, demographics, receipt of radiotherapy), there was no statistically significant difference in the OS between the adjuvant ADT and non-ADT group (HR 0.97, 95% CI 0.71–1.27). Additionally, there was no statistically significant survival difference when various definitions of adjuvant ADT (90, 150, 180, and 365 days) were tested. One important limitation of this study is that the indication for ADT (adjuvant versus salvage) was not available through the database.

In the SWOG (Southwest Oncology Group) S9921 trial, 983 men with high-risk prostate cancer (extraprostatic extension, positive nodes, positive margin Gleason 7 or Gleason grade >7) received adjuvant therapy with ADT (goserelin and bicalutamide for 2 years) alone or in combination with 6 cycles of mitoxantrone chemotherapy after a prostatectomy.[34] For the 481 men who received ADT only, the estimated 5-year biochemical failure-free survival was 92.5% (95% CI 90–95) and the 5-year OS was 95.9% (95% CI 93.9–97.9). This trial was closed to accrual in January 2007 after 3 cases of acute myelogenous leukemia were reported in the mitoxantrone treatment arm. The final analysis of the primary end point of OS comparing the 2 arms for this trial has not been reported; however, the results seen in the ADT-only arm make a compelling argument to counsel patients with high-risk prostate cancer about adjuvant ADT after a RP. This study represents the largest prospective cohort of patients with high-risk prostate cancer receiving adjuvant ADT and showed favorable results.

Though prior clinical trials of ADT in the neoadjuvant and adjuvant setting have not proved effective, promising results of a number of rationally-designed next generation hormone therapies in patients with metastatic disease are providing rational for use in early disease stages in an attempt to improve survival in high-risk patients with localized prostate cancer.

We evaluated abiraterone acetate in a phase II neoadjuvant trial in patients with intermediate and high-risk prostate cancer.[3] Fifty-eight patients were randomized to treatment with AA (1000 mg PO daily) + leuprolide + prednisone (5 mg PO daily) or leuprolide alone for 12 weeks. After 12 weeks, patients underwent prostate biopsy. Subsequently all patients received an additional 12 weeks of combination AA (1000 mg PO daily) + leuprolide + prednisone (5 mg PO daily). After 24 weeks, patients underwent RP. This study demonstrated that the pathologic pCR and near pCR rate (defined as tumor measuring < 5 mm) was 14% in the overall cohort and was 24% in patients treated with abiraterone acetate for 24 weeks and 4% in those treated with leuprolide alone followed by 12 weeks of combination therapy (p=0.089). PSA measurements did not reflect pathologic outcomes in patients in both arms of the trial. Though 86% of all patients 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.

We completed accrual and are analyzing a randomized phase II trial evaluating neoadjuvant enzalutamide alone versus enzalutamide, dutasteride, and leuprolide in men with localized intermediate and high-risk prostate cancer.[35] 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. Apalutamide is a novel second-generation anti-androgen, with a similar mechanism of action to enzalutamide that binds directly to the ligand-binding domain of the AR, impairing nuclear translocation and DNA binding. It has not been investigated in the neoadjuvant setting.

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 acetate 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 acetate with a potent antiandrogen.

We propose to evaluate the efficacy of neoadjuvant abiraterone acetate + apalutamide + prednisone + leuprolide compared to abiraterone acetate + prednisone + leuprolide followed by RP and subsequent adjuvant therapy abiraterone acetate + apalutamide + prednisone + leuprolide compared to no further adjuvant treatment in patient with intermediate to high-risk prostate cancer. The primary objective will be analysis of pCR + minimal residual disease (MRD, defined as residual tumor in RP specimen measuring ≤ 5 mm) in RP specimens following neoadjuvant therapy as well as of freedom from biochemical recurrence post-RP.

2.3 Study Agent(s)

2.3.1 Abiraterone acetate

2.3.2 Abiraterone acetate (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.[36,37] 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).[38] Abiraterone acetate is a potent inhibitor with an apparent inhibition constant of 0.5 nM.[37]

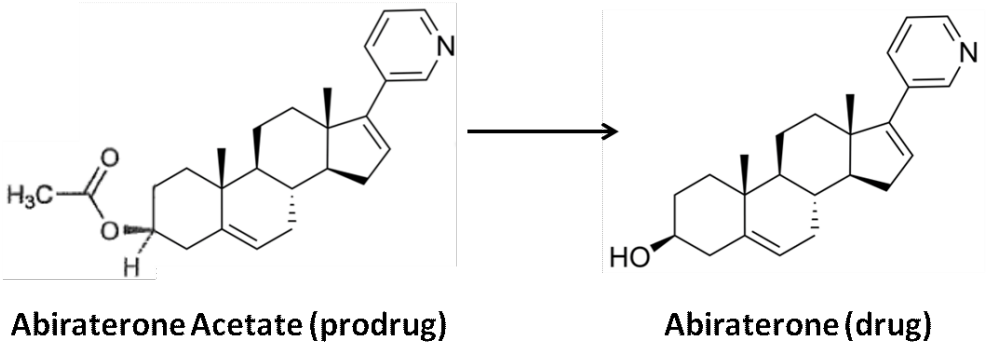

Figure 1. The pro-drug abiraterone acetate is converted to abiraterone after absorption.

Abiraterone acetate is the 3-acetylated analog and pro-drug of abiraterone (given poor bioavailability) suitable for oral administration (Figure 2). Abiraterone acetate is rapidly deacetylated and converted to the active form abiraterone. Abiraterone is metabolized by CYP3A4 and is an inhibitor of CYP2D6.[39]

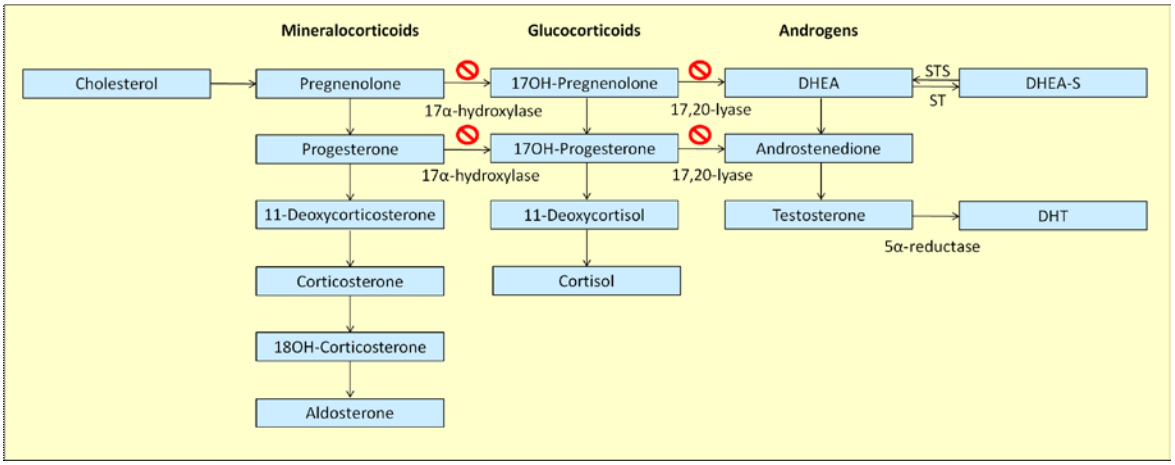

Figure 2. The steroid biosynthesis pathway. Abiraterone inhibits 17α-hydroxylase (crossed in red) which results in reduction of serum cortisol and consequent increase in adrenocorticotropic hormone (ACTH) that drives the steroid biosynthesis pathway. Abiraterone also inhibits 17,20-lyase (crossed in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

Rationale for Using Abiraterone Acetate in Prostate Cancer

Ketoconazole, a weak and nonspecific CYP17 inhibitor, is commonly used in clinical practice. Ketoconazole, an imidazole antifungal agent, inhibits several enzymes in the steroid biosynthesis pathway including desmolase and 11β-hydroxylase, in addition to CYP17.[40] When administered at a dose of 400 mg three times daily, ketoconazole reduced testosterone, androstenedione and DHEA.[41]

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.[42] 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.[43]

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 more potent and selective inhibition of CYP17, once daily administration, limited drug-drug interactions, that lacks a requirement for concomitant corticosteroids would represent a significant advancement in the management of CRPC and desirable alterative to therapy with ketoconazole.

Clinical Data with Abiraterone Acetate

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 Abiraterone Acetate.

Study	Patient	Drug	Efficacy	Toxicity
Phase 1 Attard et al (2008)[44]	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)[45]	33 Chemo-naive Keto-naive (14) (non-metastatic and metastatic)	AA 250-1000 mg daily, fed and fasting cohorts, 4 dose escalations	Decreased testosterone, downstream, androgenic steroids; PSA decline ≥50% at week 12 in 55% (47% vs. 64% prior keto vs. no keto); Median TTPP 234 days (283 vs. 230 days prior keto vs. no keto)	Hypertension (36%), hypokalemia (24%), peripheral edema (24%), fatigue (67%), headache (33%), nausea (33%), diarrhea (30%); Grade 3 hypertension (12%), grade 3/4 hypokalemia (9%)

Phase II Attard et al (2009)[46]	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)[47]	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)[48]	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)[49]	1195 Chemo-treated (metastatic only)	AA 1000 mg daily versus placebo (fasting) + prednisone 5 mg twice daily	AA-prednisone vs. placebo-prednisone median OS 14.8 vs. 10.9 months (p<0.001), TTPP 10.2 vs. 6.6 months (p<0.001), PFS 5.6 vs. 3.6 months (p<0.001), PSA	AA-prednisone vs. placebo-prednisone hypertension 10% vs. 8%, hypokalemia 17% vs. 8%, fluid retention 31% vs. 22%

			response rate 29% vs. 6% (p<0.001)	
Phase III Ryan et al (2012)[50]	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.[51] 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.[44,46] The phase I study (n=21) evaluated once, daily, continuous abiraterone acetate, which escalated through five doses (250-2,000 mg) in three-patient cohorts. In this study, abiraterone acetate 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. Abiraterone acetate 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.[46] 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 circulating tumor cell (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 abiraterone acetate, 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.[47,48] 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 abiraterone acetate was demonstrated in a phase III trial in which 1,195 men previously treated with docetaxel were randomly assigned to abiraterone acetate plus prednisone or placebo plus prednisone.[49] The primary end point was OS. After a median follow-up of 12.8 months, abiraterone acetate 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 abiraterone acetate and prednisone on OS was consistent across all subgroups.

The most common adverse event was fatigue which occurred at a similar frequency in the two treatment groups. Other common AEs including back pain (30% in the abiraterone acetate 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 abiraterone acetate 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 liver function test (LFT) abnormalities were more common in the abiraterone acetate group than in the placebo group (55% vs. 43%, p<0.001). The incidence of fluid retention and edema was higher in the abiraterone acetate group (31% vs. 22% in the placebo group). Hypokalemia occurred in a higher proportion of patients in the abiraterone acetate 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 abiraterone acetate 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 abiraterone acetate and placebo groups. A lower proportion of patients in the abiraterone acetate group than in the placebo group had an AE that resulted in death (12% vs. 15%). Based on this trial, abiraterone acetate was approved by the FDA in April 2011 for the treatment of patients with metastatic CRPC following docetaxel.[49]

A randomized, phase III study evaluated abiraterone acetate in chemotherapy-naive patients with metastatic CRPC. In this double-blind study, 1,088 patients were randomly assigned to treatment with abiraterone acetate 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 abiraterone acetate 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, Hazard Ratio (HR) 0.75, 95% CI 0.61-0.93, p=0.01) over placebo plus prednisone. Abiraterone acetate decreased the risk of decline in 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 abiraterone acetate 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 abiraterone acetate group and 3% in the placebo group. AEs classified as cardiac disorders were reported in 19% of patient in the abiraterone acetate 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.[44,45] 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 area under the curve (AUC) and maximum plasma concentration (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.[45] Less than proportional increased in both C_{max} and AUC were observed across dose levels in fed and fasted patients.

Table 3. Abiraterone Acetate Pharmacokinetics Parameters.

Parameter	Abiraterone Acetate
Absorption	Systemic absorption (C_{max} and AUC) increases with increasing fat content of meals. The AUC was approximately 5-fold higher when administered with a low-fat meal, and approximately 10-fold higher when administered with a high-fat meal. Exposure (area under the curve) of abiraterone acetate increases up to 10 fold when abiraterone acetate is taken with meals. Abiraterone Cmax and AUC0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. Abiraterone AUC0–∞ was approximately 7-fold or 1.6-fold higher, respectively, when a single dose of abiraterone acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 491 calories) compared to overnight fasting. Systemic exposures of abiraterone in patients with metastatic CRPC, after repeated dosing of abiraterone acetate were similar when abiraterone acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days. 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, abiraterone acetate 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 abiraterone acetate, 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 5.4.

2.3.3 Apalutamide (JNJ-56021927)

2.3.4 Apalutamide is synthetic biaryl thiohydantoin compound. It is a novel second-generation antiandrogen that binds directly to the ligand-binding domain of the AR, impairing nuclear translocation and DNA binding. Apalutamide is approved by the FDA for the treatment of non-metastatic castration resistant prostate cancer, however in this study apalutamide is still considered investigational in this trial setting. It is currently under investigation as a single agent in a Phase I/II study of patients with metastatic CRPC.[52]

Rationale for Using Apalutamide in Prostate Cancer

First generation antiandrogens, including bicalutamide, nilutamide, and flutamide, are reversible inhibitors of the AR and have a **se**veral-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.[30,53,54] 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.[55]

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.[43] 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.[52] Thus, more potent antagonists lacking agonist activity are necessary.

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.[56] It has been tested in two placebo-controlled, randomized phase III studies (AFFIRM and PREVAIL) to evaluate the efficacy and safety of in patients with advanced prostate cancer. The AFFIRM study evaluated the safety and efficacy of enzalutamide in 1,199 patients with CRPC after chemotherapy with docetaxel.[57] Patients 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 (HR 0.63, 95% 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 event (SRE) (16.7 vs. 13.3 months, $p<0.001$). The PREVAIL trial is a double-blinded, randomized, placebo-controlled trial is investigating the effectiveness of enzalutamide in patients with metastatic CRPC who have not yet received chemotherapy. The primary endpoints are OS and PFS. The study was stopped after a planned interim analysis showed a benefit of the active treatment. The rate of radiographic PFS at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% confidence interval [CI], 0.15 to 0.23; $P<0.001$). Based on this data, enzalutamide was approved for treatment of metastatic CRPC prior to chemotherapy.

Clinical Data of Apalutamide

Apalutamide is currently under investigation as a single agent in a Phase I/II study of patients with metastatic CRPC. In the phase I trial, which was presented at the 2010 Genitourinary Cancers Symposium, patients with metastatic CRPC received apalutamide orally on a continuous daily dosing schedule. In the phase 1, 7 doses (30-300 mg) were tested in a standard 3 x 3 dose escalation design. Twenty-four patients were treated. The most common grade 1-2 treatment related AEs were fatigue (38%), nausea (29%), and pain (24%). There was only one treatment-related grade 3 AE (abdominal pain) at 300 mg, likely related to higher pill burden. The pharmacokinetics were linear and dose-dependent. Twelve patients (55%) had ≥ 50% PSA declines. Based on preclinical assessment of maximum efficacious dose, pharmacokinetics, and promising activity across all doses, 240 mg was selected as the recommended phase II dose.

Results of the Phase II portion of this multicenter trial were presented at the 2013 Genitourinary Cancers Symposium. Activity of apalutamide was tested in three populations (high-risk non-metastatic CRPC, treatment naive

metastatic CRPC, metastatic CRPC progressive after treatment with abiraterone acetate). All patients received treatment with apalutamide 240 mg/day. The primary endpoint was PSA response rate at 12 weeks according to the PCWG2 criteria. Twenty-five patients were enrolled on the treatment naive arm and 21 patients were enrolled in the post abiraterone acetate cohort. Of patients with metastatic disease, to date, 15 patients had discontinued the study. The most common treatment related AEs were fatigue (30%), abdominal pain (24%), nausea (22%), and diarrhea (17%). There was only one treatment-related grade 3 AE of abdominal pain. At 12 weeks, the PSA response was 88% (treatment naive) and 29% (post abiraterone acetate). Forty-seven patients were enrolled with non-metastatic CRPC. At a median treatment duration of 20 weeks, three patients discontinued the study. The most common treatment-related AEs were fatigue (30%), diarrhea (28%), nausea (17%), rash (13%), and abdominal pain (11%), the incidence of grade 3 AE was 6.4% and no seizures have been observed. The 12-week PSA response was 91% at the time to PSA progression has not been reached.

A phase III clinical trial evaluating apalutamide against placebo in a high-risk, non-metastatic castration-resistant prostate cancer population is currently ongoing (SPARTAN). The primary outcome measure is metastasis-free survival. Secondary outcome measures include overall survival, time to symptomatic progression, time to initiation of cytotoxic chemotherapy, progression free survival, time to metastasis, change in quality of life questionnaire scores, AEs, and plasma concentrations of apalutamide and metabolites ARN000308 and ARN 000066. Of the participants treated to date on the experimental abiraterone acetate treatment arm, the most common grade 3-4 laboratory abnormalities were low phosphorous (7.2%), low potassium (5.3), and high AST (2.1%). The most common laboratory AEs of any grade were high triglycerides (62.5%), high AST (30.6%), low potassium (28.3%), and low phosphorous (23.8%). Any grade of laboratory AEs in the 394 participants on the placebo arm were high triglycerides (53%), high AST (36.3%), low potassium (19.8%), and low phosphorous (15.7%). The most common non-laboratory grade 3-4 AEs in the experimental, abiraterone acetate plus prednisone arm were joint swelling/discomfort (4.2%) and muscle discomfort (3.0%). Grade 3-4 urinary tract infection was in 2.1% of participants treated with abiraterone acetate and prednisone.

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 treating investigator should consult with the sponsor investigator before enrolling the subject in the study.

3.1 Eligibility Criteria

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

3.1.1 Male ≥ 18 years of age.

3.1.2 Histologically confirmed adenocarcinoma of the prostate without histological variants comprising >50% of the sample as determined by academic center central review (including neuroendocrine differentiation, small cell, sarcomatoid, ductal adenocarcinoma, squamous or transitional cell carcinoma).

3.1.3 Must have 3 core biopsies involved with cancer. Prostate biopsy must be within seven months from screening. Less than 3 core biopsies is allowed if the patient has >1cm or T3 disease on MRI.

3.1.4 Patients must have the following features:

- Gleason ≥ 4+3=7 OR
- Gleason 3+4=7 AND at least one of the following: PSA > 20 ng/mL, or T3 disease (as determined by MRI).

3.1.5 No evidence of metastatic disease as determined by radionuclide bone scans and CT/MRI. Lymph nodes must be less than 20 mm in the short (transverse) axis.

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

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

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

- Hemoglobin ≥ 9.0 g/dL
- ANC ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL, independent of transfusions/growth factors within 3 months of treatment start
- Serum potassium ≥ 3.5 mmol/L
- Serum total bilirubin ≤ 1.5 x ULN (except in subjects with Gilbert's syndrome who have a total bilirubin > 1.5 x ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤ 2 x ULN, subject may be eligible)
- AST, ALT ≤ 2.5 x ULN
- Serum albumin ≥ 3.0 g/dL
- Serum creatinine < 2.0 x ULN

- INR ≤ 1.5 ULN unless on warfarin therapy (investigator would need to determine if safe for participant to stop warfarin prior to surgery and warfarin therapy
- PTT ≤ 60

3.1.9 Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

3.1.10 Medications known to lower the seizure threshold must be discontinued or substituted prior to study treatment.

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

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

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

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

3.2 Exclusion Criteria

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

3.2.1 Prior hormone therapy for prostate cancer including orchiectomy, antiandrogens (including first-generation antiandrogens, enzalutamide, apalutamide and others), CYP17 inhibitors (including abiraterone, TAK-700, galeterone, ketoconazole, and others), estrogens, Luteinizing Hormone Releasing Hormone (LHRH) agonist/antagonists. Prior therapy with 5α-reductase inhibitors is allowed. LHRH therapy allowed if begun within 5 weeks of day 1. Up to 30 days of bicalutamide is allowed if it is stopped two weeks prior to day 1.

3.2.2 Prior chemotherapy, radiation therapy for the treatment of prostate cancer, or immunotherapy for prostate cancer.

3.2.3 Prior systemic treatment with an azole drug within two weeks of start of treatment. Please refer to section 5.4.

3.2.4 Hypogonadism or severe androgen deficiency as defined by screening serum testosterone < 200 ng/dL. Patients who have a low screening testosterone due to prior ADT (per 3.2.1) will still be allowed to enroll on study if they do not have a known history of hypogonadism or severe androgen deficiency.

3.2.5 Clinically significant cardiovascular disease within 6 months of study treatment including:

- Severe or unstable angina;
- Myocardial infarction;
- Symptomatic congestive heart failure;
- New York Heart Association (NYHA class II-IV heart failure)
- Arterial or venous thromboembolic events (such as pulmonary embolism cerebrovascular accident including transient ischemic attacks);
- 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;
- Uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg). Participants with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive therapy.

3.2.6 History of seizure or any condition or concurrent medication that may predispose to seizure (including but not limited to prior stroke, transient ischemic attack, loss of consciousness within one year prior to randomization, brain arteriovenous malformation; or intracranial masses such as schwannomas and meningiomas that are causing edema or mass effect).

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to apalutamide, abiraterone acetate, or other study drugs.

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

3.2.9 Active infection (such as human immunodeficiency virus (HIV) or viral hepatitis) or other medical condition that would make corticosteroid use contraindicated.

3.2.10 History of pituitary or adrenal dysfunction.

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

3.2.12 Pre-existing condition that warrants long-term corticosteroid use greater than the equivalent of 10 mg prednisone daily. Physiologic replacement is permitted. Topical, intra-articular steroids or inhaled corticosteroids are permitted.

3.2.13 Concomitant use of medications that may alter pharmacokinetics of abiraterone or apalutamide

3.2.14 Individuals with a history of another malignancy are not eligible if the cancer is under active treatment or the cancer can be seen on radiology scans or if they are off cancer treatment but in the opinion of their oncologist have a high risk of relapse within 5 years.

3.2.15 Major surgery or radiation therapy within 4 weeks from start of treatment.

3.2.16 Any condition that in the opinion of the investigator would preclude participation in this study.

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 Institutions

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

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Sponsor-Investigator, Dr. Mary-Ellen Taplin. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

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

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute (DFCI) by the Study Coordinator. All sites must call the Study Coordinator to verify treatment availability. The required forms will be provided to all participating institutions by the DFCI Study Coordinator.

Following registration, participants should begin protocol treatment within 7 days or as soon as possible. Issues that would cause treatment delays should be discussed with the PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must 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 Appendix I should be completed by the research nurse or data manager and faxed (617-632-6220) or e-mailed to the DFCI Clinical Research Manager and Clinical Research Coordinator.

The research nurse or data manager at the participating site will then call the Clinical Research Manager or email the DFCI Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedures for Human Subject Research titled Subject Protocol Registration

(SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number and treatment arm to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration.

Note: Registration and randomization with ODQ 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

5.1 Treatment Summary and Randomization

5.1.1 In Part 1, eligible patients will be randomized in 1:1 ratio to receive 6 cycles of neoadjuvant treatment with either:

- abiraterone acetate, apalutamide, leuprolide and prednisone (Arm 1A), OR
- abiraterone acetate, leuprolide and prednisone (Arm 1B).

Randomization will be stratified by risk factor: Intermediate (Gleason 4+3) vs. high risk (Gleason>7, or PSA>20, or T3 disease). During Part 1, a cycle will be defined as 28 days (+/- 2 days). Following neoadjuvant treatment as designated in each of the above arms, patients will undergo RP.

5.1.2 In Part 2 (post-RP), patients will be re-randomized in 1:1 ratio to receive either:

- an additional 12 months of abiraterone acetate, apalutamide, leuprolide and prednisone (Arm 2A), OR
- observation (Arm 2B).
- Patients who do not get randomized to part 2 will follow the 2B arm.

Randomization will be stratified by type of neoadjuvant therapy and pathological T-stage (< pT3 versus ≥ pT3) after RP but before cycle 7 day 1 following neoadjuvant therapy. Patients will be randomized regardless of post-operative PSA. Adjuvant or salvage radiation therapy will be allowed at the discretion of the treating investigator. Patients do not need to re-meet eligibility criteria at re-randomization to Part 2 of the study. There will be an early stopping rule for Part 2 should a high rate of patients refuse to participate or drop out early while receiving adjuvant therapy (<6 months).

Participants may enter the study with no more than one month of an LHRH agonist treatment prior to cycle 1/day 1.

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 4. Treatment Plan.

Treatment Description					
Agent[1]	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Abiraterone acetate	No food should be consumed for at least two hours before the dose and for at least one hour after the dose	1000 mg (four 250 mg tablets)	Orally	Once daily	28 days (+/-2 days) during Part 1; 28 days (+/- 14 days during Part 2)
Apalutamide	Can be taken with or without food	240 mg (four 60 mg tablets)	Orally	Once daily	
Prednisone	For patients receiving abiraterone alone; take with food	5 mg	Orally	Once daily	
	For patients receiving both abiraterone and apalutamide; take with food	5 mg	Orally	Twice daily	
Leuprolide	None	22.5 mg every three months	Intramuscular	Every three months	

1. Abiraterone acetate should not be dosed with apalutamide. Apalutamide and prednisone can be taken together with food. Abiraterone acetate, apalutamide and prednisone will be prescribed by prescription in an unblinded fashion and taken by the participant on an outpatient basis. Leuprolide will be administered intramuscularly by a health care professional.

5.2 Pre-treatment Criteria

5.2.1 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 (patients on exogenous potassium supplementation will require weekly monitoring of potassium levels for one month)
- AST/ALT ≤ 2.5 x ULN
- Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except in subjects with Gilbert's syndrome who have a total bilirubin > 1.5 x ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤ 2 x ULN, subject may be eligible)

- Systolic blood pressure ≤ 160 mmHg or diastolic blood pressure ≤ 90 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.

5.3 Agent Administration

5.3.1 Abiraterone acetate

- Administration: Patients will be treated with 1,000 mg orally once daily of abiraterone acetate prior to RP. Treatment can continue for 6 cycles (+/- 2 days). Following RP, patients randomized to further adjuvant therapy will continue abiraterone acetate with apalutamide for another 12 cycles. However, therapy will be held on the day of RP and will resume on the cycle 7/day 1 visit.

- Patients who are not randomized to further adjuvant therapy will administer their last dose of abiraterone acetate on the day prior to RP.

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

- Oral Doses: Abiraterone acetate must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken. 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. Doses should not be crushed, chewed or dissolved. They should be taken whole. Participants will be asked to record actual dosing in a drug diary (Appendix C). There is no specified order of administration of the study drugs prescribed in this protocol.

5.3.2 Apalutamide

- Administration: Patients will be treated with 240 mg orally once daily of apalutamide. Treatment can continue for 6 cycles (+/- 2 days). Following RP, patients randomized to further adjuvant therapy will continue apalutamide with abiraterone acetate for another 12 cycles. However, therapy will be held on the day of RP and will resume on the cycle 7/day 1 visit.

- Patients who are not randomized to further adjuvant therapy will administer their last dose of apalutamide on the day prior to RP.

- Dosing: 240 mg orally taken once daily as four 60 mg tablets. Possible dose modifications are outlined in Section 6.

- Oral Doses: Apalutamide 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. Doses should not be crushed, chewed or dissolved. They should be taken whole. Participants will be asked to record actual dosing in a drug diary (Appendix C). There is no specified order of administration of the study drugs prescribed in this protocol.

5.3.3 Prednisone

5.3.3.1 Patients taking Abiraterone Only

- Administration: Patients will be treated with prednisone 5 mg orally once daily. Following RP, patients randomized to further adjuvant therapy with abiraterone acetate and apalutamide will take prednisone 5 mg twice daily, starting at cycle 7/day 1 visit (for a total of 12 cycles). Prednisone in Part 1 of the study may be stopped the day prior to RP, (same day abiraterone is stopped), or may be tapered at the discretion of the treating investigator. The treating physician or surgeon may administer a higher dose of corticosteroids if there are signs or symptoms of adrenal insufficiency, or concerns for adrenal insufficiency.

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

- Oral Doses: Prednisone should be taken once daily with food. If a dose is missed for greater than 12 hours, that dose should not be taken, and if the dose is missed for less than 12 hours, it should be taken prior to the next scheduled dose if possible. Vomited doses should not be re-taken. Doses should not be crushed, chewed or dissolved. Tablets should be taken whole. Patients will be asked to record actual dosing in a drug diary (Appendix C). There is no specified order of administration of the study drugs prescribed in this protocol.

5.3.3.2 Patients taking apalutamide in combination with Abiraterone on Arm 1A and Arm 2A

- Administration: Patients will be treated with prednisone 5 mg orally twice daily. Following RP, patients randomized to further adjuvant therapy with abiraterone acetate and apalutamide will take prednisone 5 mg twice daily, starting at cycle 7/day 1 visit (for a total of 12 cycles). Prednisone in Part 1 of the study may be stopped the day prior to RP (same day abiraterone and apalutamide stopped), or may be tapered at the discretion of the treating investigator. The treating physician or surgeon may administer a higher dose of corticosteroids if there are signs or symptoms of adrenal insufficiency, or concerns for adrenal insufficiency.

- In Part 1A and 2A, if apalutamide is permanently discontinued due to toxicity, patients taking abiraterone alone should take prednisone once daily.

- In Part 1A and 2A, if abiraterone is permanently discontinued due to toxicity, patients may take apalutamide without prednisone.

- Dosing: Prednisone 5 mg orally twice daily. It is recommended that prednisone be taken with food. Dose reduction is not allowed.

- Oral Doses: Prednisone should be taken with food twice per day at approximately 10-12 hour intervals. If a dose is missed for greater than 12 hours, that dose should not be taken, and if the dose is missed for less than 12 hours, it should be taken prior to the next scheduled dose if possible. Vomited doses should not be re-taken. Doses should not be crushed, chewed or dissolved. Tablets should be taken whole. Participants will be asked to record actual dosing in a drug diary (Appendix C). There is no specified order of administration of the study drugs prescribed in this protocol.

- If patients are 80% compliant with their prednisone dosing, missed doses do no need to be reported to the IRB as violations.

5.3.4 Leuprolide

- Administration: Participants may enter the study with no more than one month of LHRH agonist/antagonist treatment with or without an anti-androgen prior to cycle 1/day 1. Treatment will be administered intramuscularly by a health care professional. Leuprolide will be administered as two 3-month injections or four 3-month injections during Part 2A. Treatment with degarelix or goserelin as a substitute to leuprolide is permissible.

- Dosing: 22.5 mg intramuscularly every three months.

5.4 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 two weeks of start of treatment (unless otherwise indicated below) and throughout the time on study:

- Androgens (testosterone, DHT), estrogens, or progestational agents
- 5α-reductase inhibitors
- Azole medications
- Spironolactone
- Diethylstilbestrol, saw palmetto or other preparations thought to have endocrine effects on the prostate

Potential Drug Interactions with Abiraterone
Abiraterone 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 1000 mg daily and prednisone 5 mg twice daily.[58] The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold. Avoid co-administration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (i.e. thioridazine).

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

Based on *in vitro* data, abiraterone is a substrate if CYP3A4. The effects of strong CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, rifapentine, and phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated *in vivo*. *In vitro,* studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and CYP2C8 and a moderate inhibitor of CYP2C9, CYP2C19, and CYP3A4/5.

In a clinical study to determine the effects of abiraterone 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.

In vitro, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter OATP1B1. There are no clinical data available to confirm transporter based interaction.

Concomitant use of medications that may alter pharmacokinetics of abiraterone acetate or apalutamide will not be allowed on this study. Specifically, strong CYP3A4 inducers (see Table 5) that decrease the exposure of abiraterone will not be allowed.

Table 5. Strong CYP3A4 Inducers and Inhibitors.

Strong CYP3A4 Inducers	**Strong CYP3A4 Inhibitors**
Aminoglutethimide	Itraconazole
Bexarotene	Clarithromycin
Bosentan	Erythromycin
Carbamazepine	Diltiazem
Dexamethasone	Verapamil
Efavirenz	Delavirdine
Fosphenytoin	Atazanavir
Griseofulvin	Indinavir
Modafinil	Nefazodone
Nafcillin	Nelfinavir
Nevirapine	Ritonavir
Oxcarbazepine	Saquinavir
Phenobarbital	Telithromycin
Phenytoin	Voriconazole
Primidone	Grapefruit juice (or grapefruits)
Rifabutin	
Rifampin	
Rifapentine	
St. John's wort	

Potential Drug Interactions with Apalutamide

Prohibited Medications:

As a class effect, androgen receptor antagonists have been associated with seizures due to an off-target mechanism of action ($GABA_A$ inhibition). To date, one patient receiving apalutamide has experienced seizures, however, in preclinical experiments, at very high doses, dogs treated with apalutamide had tremors and generalized seizures. Patients will be closely monitored for seizures, but as a precautionary measure, the following drugs known to decrease the seizure threshold and/or cause seizure will be prohibited while on study:

- Aminophylline, theophylline
- Atypical anti-psychotic drugs: clozapine, olanzapine, ziprasidone
- Bupropion
- Lithium
- Meperidine (Demerol) and pethidine

- Phenothiazine anti-psychotic drugs: chlorpromazine, mesoridazine, thioridazine
- Tricyclic and tetracyclic anti-depressants: amitriptyline, desipramine, doxepine, imipramine, maprotiline, mirtazapine (Remeron)

See Appendix D for a more comprehensive representative list of medications that may predispose to seizures.

The potential for drug-drug interactions with apalutamide and warfarin (Coumadin) is unknown at present. If a subject is taking warfarin, reassess INR as clinically indicated and adjuvant the dose of warfarin accordingly.

Restricted Medications:
Apalutamide is metabolized primarily by human CYP3A4, thus co-administration with strong inhibitors or inducers of CYP3A4 must be avoided. Apalutamide may also induce CYP3A4; therefore, apalutamide should not be taken in conjunction with CYP3A4 substrates that have a narrow therapeutic index. The CYP3A4 inhibitors and inducers listed in Table 5 should be avoided.

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).

5.5 Duration of Therapy

Treatment on study will be for 6 cycles (28 days +/- 2 days) of neoadjuvant therapy followed by 12 months of adjuvant therapy. 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.

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, if the treating physician feels it is in the participant's best interest.

5.6 Duration of Follow-Up

Participants randomized to adjuvant therapy as designated by Arm 2A will be followed every 3 months (+/- 28 days) following completion of the 12 cycles of adjuvant therapy for years 2-3. After year 3 post-RP, follow-up will take place every 6 months (+/- 28 days) for up to 5 years post-RP. Long-term follow-up assessments in years 4-5 may be done locally and information may be collected via medical record review. Whenever long-term follow-up PSA blood draws are done at the research clinic conducting the study, the research team should collect ctDNA samples.

Participants randomized to no adjuvant therapy as designated by Arm 2B will be followed every 3 months (+/- 28 days) during years 1-3 post-RP. After 3 years post-RP, follow-up will take place every 6 months (+/- 28 days) for up to 5 years post-RP. Long-term follow-up assessments in years 4-5 may be done locally and information may be collected via medical record review. Whenever long-term follow-up PSA blood draws are done at the research clinic conducting the study, the research team should collect ctDNA samples.

Participants who do not get randomized to part 2 will follow the 2B arm.

Participants removed from study for unacceptable AEs will be followed until resolution or stabilization of the AEs.

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria are met:

- 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;
- Participants Lost to Follow-up;
- Death.

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).

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) between abiraterone acetate, apalutamide, prednisone, and leuprolide.

Anticipated toxicities ere detailed below. Toxicity assessments will be done using the Cancer Therapy Evaluation Program (CTEP) Active Version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (version 4) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

6.1 Anticipated Toxicities

A list of the AEs and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

6.1.1 AEs for Apalutamide

Apalutamide has been associated with grade 1-2 AEs up to a dose of 240 mg by mouth when administrated as a single agent in a phase I/II study. Anticipated AEs from preliminary results of this study include fatigue, nausea, skin rash, changes in thyroid function, taste alterations, decreased appetite, itching, vomiting, dizziness, falls, insomnia, increase in blood cholesterol, increase in blood triglycerides, fractures, constipation, diarrhea, hot flashes and rarely, seizures. Reported grade 3 toxicity was abdominal pain, likely related to pill burden.

6.1.2 AEs for Abiraterone

Hypertension, Hypokalemia, Fatigue and Fluid Retention
Abiraterone may cause hypertension, hypokalemia, fatigue and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. In a phase III randomized clinical trial, grade 3 to 4 hypertension occurred in 1.3% of patients, grade 3 to 4 hypokalemia in 5.3% of patients,

grade 3 or 4 fatigue in 2.2% of patients and grade 3 to 4 edema in 1.9% of patients treated with abiraterone.

Co-administration of a corticosteroid suppresses ACTH drive, resulting in a reduction in the incidence and severity of these adverse reactions. In this trial 5 mg daily of steroids will be used. The safety of abiraterone in patients with left ventricular ejection fraction < 50% or NYHA Class III or IV heart failure (in the COU-AA-301 study) or NYHA Class II to IV heart failure (in the COU-AA-302 study) 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 and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving abiraterone 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 abiraterone.

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 abiraterone, typically during the first three 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. No deaths clearly related to abiraterone were reported due to hepatotoxicity events.

For guidance on management of side symptoms of mineralocorticoid excess, symptoms related to androgen deprivation, 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 (http://www.zytiga.com/).

6.1.3 AEs for Prednisone

A daily dose of 5-10 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.

6.1.4 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.

6.1.5 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

Management of abiraterone and apalutamide related toxicities are detailed below. Patients who have abiraterone treatment related toxicities many continue on apalutamide and leuprolide. Patients who have apalutamide toxicities may continue on abiraterone, prednisone, and leuprolide. If both study drugs are held, a patient will remain on schedule for all study assessments. If a patient requires a dose reduction in Part 1 of the study, the dose reduction should also be followed in Part 2, if the patient is randomized to part 2A.

6.2.1 Management of Apalutamide Related Toxicity

Apalutamide is generally well-tolerated based on phase I/II data. The starting dose of apalutamide will be 240 mg daily. In the presence of any apalutamide related toxicities > grade 2 (NCI CTCAE version 4) during treatment with apalutamide at the starting dose level, treatment will be held. Once toxicity improves to ≤ grade 1, the dose of apalutamide will be decreased to 180 mg daily. Two levels of dose de-escalation are planned for the study. If > grade 2 toxicity occurs at dose level -2, apalutamide will be discontinued. Therapy with apalutamide will be discontinued at first occurrence of seizure of any grade or grade 4 neurotoxicity.

Dose Level	Apalutamide
Starting dose level	240 mg orally once daily
-1	180 mg orally once daily
-2	120 mg orally once daily

6.2.2 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 apalutamide. When toxicity resolves to ≤ grade 1, resume at first dose modification level. 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 apalutamide at second dose modification level. If grade 3 toxicity recurs, the patient will be discontinued from the study.

6.2.3 Management of Abiraterone Related Toxicity

The starting dose of abiraterone will be 1000 mg daily. For grade 1-2 toxicities, unless otherwise described below, management per investigator. In the presence of any abiraterone related toxicities > grade 2 (NCI CTCAE version 4) during treatment with abiraterone at the starting dose level, treatment with abiraterone will be held. When toxicity improves to ≤ grade 1, the dose of abiraterone will be decreased to 750 mg daily in the subsequent dose level. Two levels of dose de-escalation are planned for the study. If > grade 2 toxicity occurs at dose level -2, participants will be removed from the protocol. Management of other toxicities is detailed below.

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

6.2.4 Management of Hypertension

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

- Grade 3-4 Hypertension:
  - Hold abiraterone. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor antagonist, eplerenone. When toxicity resolves to ≤ grade 1, resume abiraterone at full dose.
  - If grade 3 toxicity recurs x 1, hold abiraterone, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤ grade 1, resume abiraterone at first dose level reduction (750 mg).
  - If grade 3 toxicity recurs x 2, hold abiraterone, and adjust or add medications to mitigate the toxicity. When toxicity resolves to ≤ grade 1, resume abiraterone at second dose level reduction (500 mg daily).
  - If grade 3 toxicity recurs x 3 despite optimal medical management and two dose level reductions, discontinue abiraterone.

6.2.5 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 oral potassium supplementation and/or consider the specific mineralocorticoid receptor antagonist, eplerenone. Once toxicity presents potassium will be monitored weekly until 2 consecutive values are documented in the normal range.
- Grade 3-4 Hypokalemia:
  - Hold abiraterone. Adjust or add medications to mitigate the toxicity and/or consider the specific mineralocorticoid receptor

antagonist, eplerenone. Once toxicity presents potassium will be monitored at least weekly until 2 consecutive values are documented in the normal range. Once toxicity resolves (potassium ≥ 3.5 mmol/L), resume abiraterone at first dose level reduction (750 mg) after discussion with PI. Once abiraterone 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 toxicity recurs, hold abiraterone, and adjust or add medications to mitigate the toxicity. Once toxicity presents, potassium will be monitored at least weekly until 2 consecutive values are documented in the normal range. When toxicity resolves to ≤ grade 1, resume abiraterone at second dose level reduction (500 mg daily) after discussion with PI. Once abiraterone is reinitiated, potassium should be monitored at least weekly for the first two weeks and then every two weeks for four weeks, and then monthly.
- If grade 3 toxicity recurs despite optimal medical management and two dose level reductions, discontinue abiraterone.

6.2.6 Management of LFT abnormalities

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

  - If grade 3 increases in AST, ALT, or bilirubin recur after the first dose reduction hold abiraterone and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at minimum weekly) until the LFTs return to baseline value or grade 1. If abiraterone resumption is considered for participants who have experienced grade 3 increases in AST, ALT, or bilirubin with the first dose reduction, and the PI agrees, resume abiraterone with the second dose level reduction (500 mg) when AST, ALT, or bilirubin returns to baseline value or grade 1. For participants who resume abiraterone, monitor LFTs at a minimum of every 2 weeks for 3 months and monthly thereafter.
- Grade 4 LFT Abnormalities (increase in AST or ALT to > 20 x ULN; increase in total bilirubin to > 10 x ULN):
  - Participants must discontinue abiraterone immediately and will not be re-challenged. They should be followed until resolution of LFT abnormalities to ≤ grade 1 or baseline.
- Concurrent elevation of AST/ALT > 3x ULN with bilirubin >2x ULN (unless the concurrent elevation is related to biliary obstruction or other causes unrelated to study treatment)
  - Discontinue abiraterone acetate. No change or consider tapering prednisone if abiraterone acetate discontinued.

6.2.7 Rash Management

- Dose modifications for rash are allowed only for apalutamide and are summarized in below table.
- If the skin rash has any component of desquamation, mucosal involvement, or pustules, stop dosing with apalutamide, refer to dermatologist for evaluation, and a skin biopsy is recommended (in addition to the interventions listed in below Table)
- If the skin rash is Grade 3 or higher, asking the subject to consent to documentation by a photograph and further evaluation by a dermatologist should also be considered.

Severity	Intervention

Grade 1	• Continue apalutamide at current dose
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines
	• Monitor for change in severity[a]

Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide for up to 28 days
	• Initiate dermatological treatment[a]
	  o Topical steroid cream AND
	  o Oral Antihistamines
	• Monitor for change in severity[a]

	○ If rash or related symptoms improve, reinitiate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction.
Grade ≥3[d]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] ○ Topical steroid cream AND ○ Oral Antihistamines AND ○ Consider short course of oral steroids • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist ○ Reinitiate apalutamide at a 1 dose level reduction[c] when rash is Grade≤1. ○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact Janssen to discuss further management and possible discontinuation of study drug.

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 4.03 for specific grading criteria for other types of rash.

a Obtain bacterial/viral cultures if infection is suspected
b Subject presents with other rash related symptoms such as pruritus, stinging, or burning
c If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact Janssen.
d If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact Janssen

6.3 Dose Modifications/Delays

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

There are no dose modifications for leuprolide and prednisone.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Apalutamide

7.1.1 Description

Name: Apalutamide
Chemical Classification: Non-steroidal anti-androgen
Chemical Name: (4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide)
Molecular Formula: $C_{21}H_{15}F_4N_5O_2S$
Molecular Weight: 477.44
Appearance: White to off-white powder

7.1.2 Form

The tablet formulation of apalutamide is an immediate release oral tablet containing 60-mg of drug substance, with a non-functional green film coat. Each 60-mg tablet contains the following inactive ingredients: hydroxypropyl methylcellulose acetate succinate (HPMC-AS), colloidal anhydrous silica, croscarmellose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, and magnesium stearate. Commercially available Opadry® coating powder is used for the film coating, which is comprised of polyvinyl alcohol (partially hydrolyzed), titanium dioxide, polyethylene glycol, talc, and colorants iron oxide yellow and iron oxide black (E172).

7.1.3 Storage and Stability

Apalutamide tablets (60-mg) are packaged in 120-count, 160 cc high-density polyethylene (HDPE) bottles with child-resistant closure (CRC) and include desiccant. For clinical formulation-specific and batch-specific storage instructions, see the packaging labels. At the clinical site and at the patient's home, the study drug should be stored at room temperature and protected from heat and should not be frozen. Participants should be advised to keep all medications out of the reach and out of sight of children.

7.1.4 Compatibility

We do not anticipate any excess toxicity combining apalutamide with abiraterone as 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).

7.1.5 Handling

There are no specific instructions for handling apalutamide. 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.

7.1.6 Availability

Apalutamide tablets will be provided to each site. Participants will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 2 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.

7.1.7 Ordering

Apalutamide is to be ordered directly from Janssen Scientific Affairs, LLC.

7.1.8 Accountability

Accountability for study treatment is the responsibility of the investigator. The study site must maintain accurate records demonstrating dates and amount of apalutamide 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. The following information will be confirmed: lot numbers, quantities shipped/delivered, and date of receipt.

7.1.9 Destruction and Return

Drug should be destroyed at the site per each research pharmacy's drug destruction policy. Destruction will be documented in the Drug Accountability Record Form.

7.2 Abiraterone acetate

Refer to the package insert for abiraterone acetate information.

7.2.1 Description

The chemical nomenclature of abiraterone acetate (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate Its empirical formula is C26H33NO2 and it has a molecular weight of 391.55. Once absorbed after oral administration, abiraterone acetate is rapidly deacetylated and converted to the active form abiraterone.

7.2.2 Form

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

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.

7.2.6 Pregnancy

Abiraterone may cause fetal harm when administered to a pregnant woman. Abiraterone is contraindicated in women who are or may become pregnant. Women who are pregnant or who may be pregnant should wear gloves if they need to touch abiraterone acetate tablets. This medicine may cause harm to the unborn child if taken by women who are pregnant. It should not be taken by women who are breast-feeding. If abiraterone is used during pregnancy, or if the participant becomes pregnant while taking this drug, the participant should be apprised of the potential hazard to the fetus. Study staff and caregivers should be notified of this information, to ensure the appropriate precautions are taken.

7.2.7 Availability

Abiraterone acetate tablets will be provided to each site. Participants will be provided with a 30-day supply to allow for visits to occur every 28 days with a ± 2-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 is supplied and will be provided free-of-charge.

7.2.8 Ordering

Abiraterone acetate is to be ordered directly from Janssen Scientific Affairs, LLC.

7.2.9 Accountability

Accountability for study treatment is the responsibility of the investigator.

The study site must maintain accurate records demonstrating dates and amount of 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.

7.2.10 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.

7.3 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 apalutamide, abiraterone acetate, 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 site specific pharmacy.

7.4.4 Compatibility

We do not anticipate any excess toxicity combining apalutamide, abiraterone acetate, 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 is commercially available and will be ordered by the institution's pharmacy.

8. CORRELATIVE STUDIES

8.1 Correlative Studies Background

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.[53] We hypothesize the PTEN loss may be a mechanism of intrinsic resistance to androgen ablation.

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.[59] 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 fresh-frozen tissue at pretreatment biopsy and RP) and their matched normal counterparts (from whole blood obtained from the same patient). For control purposes, blood will be assessed for germline DNA. This will be accomplished by paired-end, massively parallel sequencing of tumor and normal DNA using the Illumina platform.

AR Signaling Axis and Serum Hormones and Hormone Levels

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.

ctDNA

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.[60,61] 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.

Multiparametric Prostate MRI

We previously conducted a pilot study to investigate multiparametric MRI as a biomarker for predicting response to neoadjuvant hormone therapy with enzalutamide +/- leuprolide + dutasteride for high-risk localized prostate cancer undergoing prostatectomy. From this small pilot study of 8 patients, we demonstrated that at baseline, there was a significant difference in mpMRI parameters in areas of tumor versus normal tissue. Following neoadjuvant therapy, there was no significant change in diffusion parameters in response to therapy, but a significant change in parameters derived from dynamic contrast imaging (DCE), which may indicate a decrease in neovascularity and perfusion, but no significant change in cellular density. Using Spearman's rank correlation, there was a significant correlation between tumor volume on post-treatment MRI (Apparent diffusion coefficient (ADC), T2, and Dynamic contrast-enhanced (DCE)) and pathology volume, indicating that multiparametric MRI post-therapy may be useful to predict tumor volume at prostatectomy. Using Wilcoxon means for difference in volumes, there was no significant difference between

pathology volumes and multiparametric MRI volumes. There was a significant moderate-large correlation between quantitative DCE parameters of the post-treatment MRI and RCB: mean AUC (Spearman correlation of 0.79, p=0.028) and mean Ktrans (Spearman correlation of 0.76, p=0.037). There was also a strong negative correlation between minimal ADC 500 value in the post-treatment MR and RCB (r=-0.91, p=0.0046). Again, this may indicate that multiparemteric MRI indices may be useful for predicting the RCB at prostatectomy.

Sequencing of Germline DNA for assessment of Aberrations in Homologous Recombination Genes

Pritchard and colleagues reported on the germline DNA analysis of 692 men with documented metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis. Germline DNA was isolated and multiplex sequencing assays were used to assess mutations in 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes. These genes included: *ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, cHek2, FAM17A, GEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, XRCC2*. A total of 84 germline DNA-repair gene mutations that were presumed to be deleterious were identified in 82 men (11.8%); mutations were found in 16 genes, including BRCA2 (37 men [5.3%]), ATM (11 [1.6%]), CHEK2 (10 [1.9% of 534 men with data]), BRCA1 (6 [0.9%]), RAD51D (3 [0.4%]), and PALB2 (3 [0.4%]). Mutation frequencies did not differ according to whether a family history of prostate cancer was present or according to age at diagnosis. Overall, the frequency of germline mutations in DNA-repair genes among men with metastatic prostate cancer significantly exceeded the prevalence of 4.6% among 499 men with localized prostate cancer (P<0.001), including men with high-risk disease.

For this work, next-generation targeted sequencing of germline DNA will be performed using the Illumina TruSight Cancer Sequencing Panel (http://www.illumina.com/products/trusight_cancer.html). The panel includes 94 genes, 35 of which have been identified as being involved in human DNA repair. Libraries will be created using 50ng germline DNA and sequenced by Illumina MiSeq platform using PE150 chemistry, according to the manufacturer's instructions. To identify genomic variants we will use two independent commonly used standard variant calling pipelines (GATK and samtools/bcftools). Bowtie2 aligner will be applied. Alterations will be visualized by IGV tool and validated by Sanger Sequencing.

8.2 Correlative Studies Methodologies

Detailed methodologies regarding sample collection, processing, storing, shipment and analytical methodologies are detailed in the study laboratory manual. Please refer to this document for specific details regarding the specifics of the correlative laboratory procedures.

PTEN and the PI3K Pathway
During this study, we will use IHC analysis to assess PTEN expression in pretreatment prostate biopsies and RP specimens to determine whether PTEN status (loss or no loss) is associated with pathological response.

IHC will be performed for the following targets on archival prostate biopsies and FFPE RP specimens at Center for Molecular Oncologic Pathologies (CMOP)/DFCI: AR, apoptosis markers, WNT signaling, PTEN-PI3K-AKT pathway, PSA, ERG, and Ki67. Scoring systems will be specific to each target scored, and will follow the accepted quantitative and qualitative system for each target.

Whole Exome and Transcriptome Sequencing
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 fresh-frozen tissue at pretreatment biopsy and RP) and their matched normal counterparts (from whole blood obtained from the same patient). For control purposes, blood will be assessed for germline DNA. This will be accomplished by paired-end, massively parallel sequencing of tumor and normal DNA using the Illumina platform. This will be performed at the Broad Institute.

Upon completion of 24 weeks of neoadjuvant therapy, participants will undergo RP according to each institution's policy. The on-treatment samples will be collected on the day of operation with the last dose of oral medications for Part 1 taken the day prior to the operation. Coordination efforts with the interventional radiology and pathology teams will vary depending on the institution.

Whole Blood for Germline DNA
Collection
1. Five (5) mL of blood will be drawn into purple top vacutainers with EDTA. Gently invert tubes 8-10 times. **DO NOT** use heparin as anticoagulant, since the polymer will tightly bind downstream PCR enzyme during sequencing.
2. Immediately transfer the blood into 5 cryovails (1 mL per cryovial) and store in -80^{0}C.

Storage
Store at -80ºC until shipment in batches together with matching tissue specimens. The whole blood should be shipped to CMOP following the RP and preferably with RP tissue.

Shipment
Whole blood and matching tissue specimen should be shipped together to CMOP. This specimen will be shipped on dry ice by express overnight courier. Shipping reservations must be made to allow delivery, prior to 2:00 PM next day, delivery on Tuesday through Friday. Call the receiving laboratory the day prior to shipping to confirm plan for receipt. Do not ship on Friday as there is no weekend coverage in the laboratory and the frozen samples should not sit in transit over a weekend.

CMOP will receive the "Blood for Germline DNA/RNA" and store it at labeled conditions (i.e -80 ^{0}C) 'as is' (package intact and unopened), and will ship this package together with RP tissue specimens to the Broad.

Please see the Study Laboratory Manual for specific instructions.

AR Signaling Axis and Serum Hormones and Hormone Levels
We hypothesize that following treatment with either treatment arm, we will observe changes in the AR signaling axis in RP specimens compared to pretreatment biopsy specimens. We will assess the AR axis by assaying serum androgens prior to treatment, during treatment, and prior to RP. Additionally, we will assay tumor androgens from pretreatment biopsy and RP specimens. Additionally, we will perform IHC analysis to include, but not limited to, assessment of the following: AR signaling pathway, steroidogenesis and hormone receptors, DNA repair pathway, PI3K pathways and other AR and AR-regulated genes (PSA, ERG).

Subject samples (including blood and tissue samples) at the time of collection will be handled and procured by a dedicated technician or physician at each study site. Samples processing will be performed by trained technicians or physician at each study site place by dedicated technicians and physicians. Samples will be processed for correlative studies and remaining samples will be stored for future use to include assessment of biological and molecular predictive and prognostic biomarkers. Hormone levels assessed will include DHEA, androstenedione, testosterone, DHT, androsterone, progesterone, pregnenolone, deoxycorticosterone, cortisol, and DHEA-S.

Samples will be stored and protected atCMOP. Multi-center sites will ship samples to DFCI on a quarterly or other specified basis as described in the laboratory manual. Participants will be de-identified by assigning each participant a unique subject ID.

Instructions on sample collection and processing are contained in the Laboratory Manual

ctDNA
cfDNA plasma will be drawn into (2) 10mL Streck BCT tubes according to institutional phlebotomy guidelines. Blood collected at DF/HCC sites will be processed in the Balk lab. Blood collected at outside sites will be processed in local laboratories and then sent to the Balk lab. Samples will be stored in a -80°C freezer. Plasma for cfDNA will be collected at C1D1, C4D1, Day 170-179 (+/- 4 days) and q3 andq6 months following RP.

See Study Lab Manual for further instructions regarding specimen and tissue processing.

Multiparametric Prostate MRI

On this study, we will be performing baseline and post-treatment multiparametric MRI and correlating MRI with pathologic outcomes to determine if this could be a predictor of pathologic response to treatment.

Any further future analyses not specified in this protocol or above will be agreed upon by prior approval from Janssen Scientific Affairs, LLC.

9. STUDY CALENDAR

PART 1

	Pre-Study[a]	Day 1 of Cycle 1 and Cycle 4 (+/- 2 days)[b]	Every Two Weeks for the first 3 Cycles	Day 1 of Each Cycle (+/- 2 days)	Pre-Operative Day 170-179 (+/- 14 days)	Day 180 (+/- 14 days)
Informed Consent	X					
History and Physical[c]	X	X		X	X	
Digital Rectal Examination	X					
ECOG Performance Status	X	X		X	X	
Vital Signs[d]	X	X		X	X	
Hematology[e]	X	X		X	X	
Serum Chemistry[f]	X	X		X	X	
TSH[g]	X	X				
Liver Function Tests[h]	X	X	X	X	X	
Fasting Lipid Panel		X				
Coagulation Factors[i]	X				X	
EKG	X				X	
ECHO or MUGA	X					
Testosterone	X	X			X	
Serum Hormones[j]		X			X	
Research Sample[k]		X				
ctDNA Plasma Sample		X			X	
PSA	X	X		X	X	
Bone Scan	X					
CT or MRI abdomen	X					
Prostate MRI including pelvis[l]	X				X	
Dispense Drug[m]		X		X		
Administer Leuprolide[n]		X				

AA and Apalutamide Compliance Assessment		X		X	X	
Prior and Concomitant Medications	X	X		X	X	
Adverse Events[o]	X	X		X	X	
Prostatectomy[p]						X
Request Diagnostic Biopsy[q]	X					
Quality of Life and Family Questionnaires[r]		X			X	
Randomization for Part 2[s]					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. Note: the treating physician must refer participants to genetic counseling within the first year (preferably before RP) of being on study. This must be documented in the clinic note and case report forms.
b: A cycle will be defined as 28 days (+/- 2 days). Criteria outlined in Section 5.2 must be met prior to treatment on C1D1.
c: 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 and prior to RP during Part 1. 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)).
d: Vital signs include upright blood pressure, heart rate, respiratory rate, body temperature, height (baseline only), and weight.
e: Hematology testing to include WBC, ANC, hemoglobin, and platelet count.
f: Serum or plasma chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, and magnesium
g:TSH will be done at screening, day 1 of cycles 1 and 4.. T3 and T4 will be done only if TSH is abnormal at baseline.
h: Liver function tests to include: albumin, globulin, AST, ALT, alkaline, phosphatase, total bilirubin, and direct bilirubin. LFTs will be collected every two weeks for the first three cycles of treatment and every cycle thereafter. LFTs on day 15 of cycles 1-3 can be completed locally. Direct bilirubin and globulin do not need to be collected if labs are done locally or if a participating institution does not collect it.
i: Coagulation factors to include PTT, PT and INR.
j: Serum hormones to include DHEA, androstenedione, testosterone, DHT, androsterone, progesterone, pregnenolone, deoxycorticosterone, cortisol, and DHEA-S.
k: Blood for germline DNA. See the Lab Manual for processing instructions. The lab manual is maintained as a separate document.
l: The baseline MRI will be standard of care; however, the pre-RP MRI will be conducted as research. The pre-RP MRI is only required for DFCI patients and optional for participating site patients.
m: For Part 1 of the study, participants will be randomized to treatment with AA + prednisone + apalutamide + leuprolide or AA + prednisone + leuprolide.
n: Participants who have started leuprolide within four weeks of cycle 1/day 1 are eligible to enroll. Participants may receive monthly leuprolide.
o: Adverse events should be collected from the date informed consent is signed until 30 days after discontinuation from the study. SAEs will reported starting from the first dose of study drugs.
p: RP should occur on day 180 (+/- 14 days). Dosing should continue until 1 day before surgery. Treatment will resume on Cycle 7 Day 1 for Part 2A participants.. Preoperative and postoperative evaluation and treatment will be administered as per the instruction of the surgeon.
q: Tissue from the diagnostic biopsy will be requested (tissue blocks wherever possible; if not possible, 15 unstained slides from each positive core sample for a total of 45 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.
r: The EPIC-26 with 2 additional questions will be used to evaluate quality of life parameters (see Appendix G). The Family Questionnaire only needs to be completed at C1D1 (see appendix H).
s: The study team will randomize participants to their Part 2 assignments after RP but before cycle 7 day 1. Participants will not need to re-meet eligibility criteria prior to Part 2 randomization. Part 2 will commence within 28 days post-RP (Cycle 7 Day 1). Participants who do not get randomized to part 2 will follow the 2B arm.

PART 2A

	Year 1 (Adjuvant Treatment) (Cycle length 28 days) (+/- 2 days)				Years 2-3 (Follow-up)		Years 4-5 (Follow-up)
	Day 1 of Cycles 7-18[a]	Cycle 7, 10, 13, and 16	Cycle 13	End of Treatment (1 year post-RP)	Every 3 Months (+/-1 month)	2 years post-RP (+/-1 month)	Every 6 Months (+/-1 month)[b]
History and Physical[c]	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Vital Signs[d]	X	X	X	X	X	X	
Hematology[e]	X	X	X	X			
Serum Chemistry[f]	X	X	X	X			
Liver Function Tests[g]	X	X	X	X			
TSH[h]		X		X			
Fasting Lipid Panel[i]		X	X	X	X	X	
Testosterone[j]					X	X	X
Serum Hormones[k]			X	X		X	
ctDNA[l] Plasma Sample		X	X	X	X	X	X
PSA[m]	X	X	X	X	X	X	X
Dispense Drug[n]	X	X	X				
Administer Leuprolide		X	X				
AA and Apalutamide Compliance Assessment	X	X	X	X			
Prior and Concomitant Medications	X	X	X	X			
Adverse Events[o]	X	X	X	X			
Intra-Operative/Post-Operative Complication[p]	X[p] (Cycles 7 and 10 Day 1 only)	X[p] (Cycles 7 and 10 Day 1 only)					
Quality of Life Questionnaires[q]			X	X		X	

a: A cycle will be defined as 28 days (+/- 2 days). During Part 2 of the study, patients randomized to further adjuvant therapy will be seen once every cycle for 12 cycles until end of treatment. Cycle 7 Day 1 will take place 28 days (+/- 5 days) post-RP. All following visits will depend upon when the first visit post-RP occurred. Note: the treating physician must refer participants to genetic counseling within the first year (preferably before RP) of being on study. This must be documented in the clinic note and case report forms.
b: After completion of adjuvant therapy on Part 2A of the study, all patients will be followed every 3 months (+/- 1 month) for years 2-3. Follow up will take place every 6 months (+/- 1 month) during years 4-5 post-RP. During years 4-5 post-RP, assessments may be done locally, and information may be collected via medical record review. It is recommended that testosterone continue to be checked (q3 cycles) until normalized according to institutional range.
c: 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 during Part 2 every 3 months (+/- 1 month) for 3 years post-RP, and then every 6 months (+/- 1 month) for up to 5 years post-RP. 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).
d: Vital signs include upright blood pressure, heart rate, respiratory rate, body temperature, height (C7D1 only), and weight. During the follow up period, BMI (weight in Kg/height in m^2) will collected every 3 months (+/- 1 month) 2-3 post-RP and then every 6 months (+/- 1 month) during years 4-5 post-RP.
e: Hematology testing to include WBC, ANC, hemoglobin, and platelet count.
f: Serum or plasma chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, and magnesium.
g: Liver function tests to include albumin, AST, ALT, alkaline phosphatase, total bilirubin, and direct bilirubin. Direct bilirubin and globulin do not need to be collected if labs are done locally or if a participating institution does not collect it.
h: TSH will be done at Cycle 7 Day 1, Cycle 13 Day 1 and End of Treatment. T3 and T4 will be done only if TSH is abnormal at baseline.
i: A fasting lipid will be collected every 3 cycles (+/- 2 days) for year 1 and every 6 months (+/- 1 month) for years 2-3. Fasting is defined as no food or liquids except for water for 8 hours.
j: Testosterone will be checked in follow-up every 3 months (+/- 1 month) for the years 2-3 post-RP and then every 6 months (+/- 1 month) for years 4-5 post-RP until recovery to the institutional normal range.
k: Serum hormones to include DHEA, androstenedione, testosterone, DHT, androsterone, progesterone, pregnenolone, deoxycorticosterone, cortisol, and DHEA.-S
l: ctDNA will be collected at all time points that PSA is collected during years 1-3 post-RP. It is recommended that study teams collect ctDNA plasma samples from participants whenever long-term follow-up assessments are conducted at the research site during years 4-5, if possible.
m: PSA will be collected every cycles (+/- 2 days) for year 1 and every 3 months (+/- 1 month) for years 2-3 and then every 6 months (+/- 1 month) for up to 5 years post-RP.
n: For Part 2 of the study, participants will be randomized to AA + prednisone + apalutamide + leuprolide versus no further treatment.
o: Adverse events should be collected from the date informed consent is signed until 30 days after discontinuation from treatment.
p: Intra-operative and peri-operative (hospital course) complications will be collected via questionnaire (see Appendix E) at Cycle 7 Day 1. Post-operative complications will be captured via the Clavien classification (Appendix F). The post-operative complications will be collected at Cycle 7 Day 1 and Cycle 10 Day 1 post-operatively.
q: The EPIC-26 with 2 additional questions will be used to evaluate quality of life parameters (see Appendix G).

PART 2B

	Year 1 (NO Adjuvant Treatment) (Cycle length 28 days) (every 3 cycles +/- 2 weeks)			Years 2-3 (Follow-up) Every 3 months (+/- 1 month)		Years 4-5 (Follow-up)
	Day 1 of cycle 7, 10,13, 16 Post-RP [a]	Cycle 13	End of Treatment (1 year post-RP)	Every 3 Months (+/- 1 month)	2 years post-RP (+/- 1 month)	Every 6 Months (+/- 1 month)[b]
History and Physical[c]	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	
Vital Signs[d]	X	X	X	X	X	
Hematology[e]	X	X	X			
Serum Chemistry[f]	X	X	X			
Liver Function Tests[g]	X	X	X			
Fasting Lipid Panel[h]	X	X	X	X	X	X
Testosterone[i]	X	X	X	X	X	X
Serum Hormones[j]		X	X		X	
ctDNA Plasma Sample[k]	X	X	X	X	X	X
PSA[l]	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X			
Adverse Events[m]	X	X	X			
Intra-Operative/Post-Operative Complication[n]	X (Cycle 7 Day 1 and Cycle 10 Day 1 only)					
Quality of Life Questionnaires[o]		X	X		X	

a: A cycle will be defined as 28 days (+/- 14 days). Patients randomized to no further adjuvant treatment will be seen once every 3 months beginning at cycle 7. Cycle 7 Day 1 will take place within 28 days (+/- 5 days) post-RP. All following visits will depend upon when the first visit was post-RP. Note: the treating physician must refer participants to genetic counseling within the first year (preferably before RP) of being on study. This must be documented in the clinic note and case report forms.
b: Participants in Part 2B will be followed every 3 cycles (+/- 2 weeks) for the first 1 year, every 3 months (+/- 1 month) for ears 2-3 and then every 6 months (+/- 1 month for up to 5 years post-RP during which time assessment may be done locally and information may be collected via medical record review. It is recommended that testosterone continue to be checked until normalized according to institutional range. It is also recommended that study teams collect ctDNA plasma samples from participants whenever PSA blood tests occur and whenever long-term follow-up assessments are conducted at the research site, if possible.
c: 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 during Part 2 every 3 cycles (+/- 2 weeks) for year 1, every 3 months (+/- 1 month) for years 2-3 and then every 6 months (+/- 1 month) for up to 5 years post-RP. 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).
d: Vital signs include upright blood pressure, heart rate, respiratory rate, body temperature, height (C7D1 only), and weight. During the follow up period, BMI (weight in Kg/height in m^2) will collected every 3 cycles (+/- 2 weeks) for year 1, every 3 months (+/- 1 month) for years 2-3 and then every 6 months (+/- 1 month) for up to 5 years post-RP.
e: Hematology testing to include WBC, ANC, hemoglobin, and platelet count.
f: Serum or plasma chemistry to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, and magnesium.
g: Liver function tests to include albumin, AST, ALT, alkaline phosphatase, total bilirubin, and direct bilirubin. Direct bilirubin and globulin do not need to be collected if labs are done locally or if a participating institution does not collect it.
h: During Part 2B, fasting lipid will be collected every 3 months (+/- 2 weeks) for year 1 and every 6 months (+/- 1 month) for years 2-3. Fasting is defined as no food or liquids except for water for 8 hours.
i: Testosterone will be checked in follow-up every 3 cycles (+/- 2 weeks) for year 1, every 3 months (+/- 1 month) for years 2-3 and then every 6 months (+/- 1 month) for up to 5 years post-RP until recovery to the institutional normal range.
j: Serum hormones to include DHEA, androstenedione, testosterone, DHT, androsterone, progesterone, pregnenolone, deoxycorticosterone, cortisol, and DHEA-S.
k: ctDNA will be collected whenever PSA blood draws are being collected during years 1-3 post-RP. During years 4-5 post-RP, when follow-up assessments may be done locally, ctDNA is recommended only if follow-up assessments are being conducted at the research clinic conducting the study.
l: PSA will be collected every 3 cycles (+/- 2 weeks) for year 1, every 3 months (+/- 1 month) for years 2-3 and then every 6 months (+/- 1 month) for up to 5 years post-RP.
m: Adverse events should be collected from the date informed consent is signed until 30 days after RP.
n: Intra-operative and peri-operative (hospital course) complications will be collected via questionnaire (see Appendix E) at Cycle 7 Day 1. Post-operative complications will be captured via the Clavien classification (Appendix F). The post-operative complications will be collected at Cycle 7 Day 1 and Cycle 10 Day 1 post-operatively.
o: The EPIC-26 with 2 additional questions will be used to evaluate quality of life parameters (see Appendix G).

10. MEASUREMENT OF EFFECT

10.1 Primary Variable

Pathological Response (Part 1): The primary efficacy measure is pathological response, defined as achieving either pCR or MRD at RP. 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. Prostate biopsy specimens will be evaluated by central pathology review at completion of the study.

Biochemical Progression Free Survival (bPFS) (Part 2): The primary efficacy measure is the rate of 3-year biochemical progression-free survival (bPFS). bPFS will be defined as the time from the date of randomization to the date of first evidence of disease progression (defined below) or death from all causes, censored at the date of last disease follow-up

- Biochemical failure (defined as a serum PSA ≥0.2 ng/mL, which is confirmed by a second determination with a PSA ≥0.2 ng/Ml, according to the 2007 American Urological Association Prostate Guidelines). It is expected that the majority of patients will relapse biochemically with a rising PSA.
- Any new evidence of metastatic disease based on bone or CT/MRI scan.
- Local recurrence in prostate bed as demonstrated onCT/MRI scan.
- Treatment with post-operative radiotherapy for a rising PSA or adjuvant radiation initiated more than 6 months following surgery.

10.2 Secondary Variables

Pathologic Outcomes: RCB will be calculated as tumor volume x percent cellularity. A favorable RCB is defined as the 33rd percentile of the RCB index. 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 Kinetics prior to RP: PSA kinetics prior to RP include nadir value, achieving nadir PSA < 0.2 ng/mL, achieving 50% or achieving 90% decrease in PSA from baseline, and time to PSA nadir.

Safety and Tolerability: CTCAE version 4 will be used to characterize toxicity during treatment.

Peri-Operative and Post-Operative Complications: Peri-operative and post-operative complications will be determined via questionnaires that will be completed at time of surgery, at discharge and in the post-operative period. The Clavian

Classification will be used to determine post-operative complications and will be collected at 30 and 90 days post-operatively.

Quality of Life: The Expanded Prostate Cancer Index Composite (EPIC-26) with 2 additional questions will be used to evaluate quality of life parameters. This will be completed by the patient pretreatment, prior to RP, and every 3 months for 2 years post-RP.

Body-Mass Index, Lipids, and Cardiovascular Events: Weight, height, fasting lipid panel, and cardiovascular events will be collected.

Serum Hormone Levels: Pregnenolone, progesterone, deoxycorticosterone, cortisol, DHEA, DHEA-S, androstenedione, testosterone, DHT, androsterone will be assessed at baseline, during treatment, prior to RP and post-RP. Hormones will be assayed by mass spectroscopy. Additionally, testosterone levels will be checked by routine laboratory at baseline and every 3 months until recovery. Recovery will be defined as a testosterone level > 200 ng/dL.

Prostate Hormone Levels: DHEA, DHEA-S, androstenedione, testosterone, DHT will be assayed from pretreatment prostate biopsy and RP specimens by mass spectroscopy.

Ki-67 Expression: Ki-67 expression will be assessed by IHC staining. This will be scored on the percentage of cells that display nuclear staining for Ki67.

AR and AR-Regulated Gene Expression: AR and AR-regulated gene (PSA, ERG) expression will be assessed by IHC staining. This will be scored based on the percentage of cells staining for the specific protein and the intensity of the staining.

PTEN Status: PTEN status (loss versus presence) will be assessed by IHC staining via a dichotomous scoring system. Staining will be classified as negative if the intensity was markedly decreased or entirely negative across tumor cells (either all cells or if >5% cells are negative/markedly reduced) compared with the surrounding benign glands and/or stroma.

ctDNA: Blood will be collected for ctDNA and will be processed in the Balk Laboratory. Plasma will be used to extract ctDNA. DNA will be analyzed using PCR and will be compared to genome analysis of residual primary tumor. The PCR will be will be based on patient specific mutations identified from sequencing the primary tumors. Emergence of specific ctDNA alterations will be correlated with disease progression.

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.

Quantitative MRI: From T2, ADC and DCE MR sequences, quantitative parameters will be extracted from all loci within a lesion. The attributed PI-RADS score from each MR sequence and the final overall PI-RADS score (1-5 scale: 1-normal, 5-definite cancer) will be recorded for each lesion per ESUR 2012 guideline

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Overview

As the sponsor of the Study, DFCI and Mary-Ellen Taplin, MD shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. Safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The DFCI and Mary-Ellen Taplin, MD will provide safety information to Janssen on adverse events, special situations including pregnancies and product quality complaints.

11.2 Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is:

Apalutamide (56021927, Apalutamide)
Abiraterone acetate

11.3 Definitions

11.3.1 Adverse Events (AEs)

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated

with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Adverse Events of Special Interest (AESIs)
There are no adverse events of special interest identified for apalutamide or abiraterone acetate.

11.3.2 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- An identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- An identifiable reporter (investigational site)
- A Janssen medicinal product
- An adverse event, outcome, or certain special situations

The minimum information required is:

- Suspected Janssen medicinal product (doses, indication)
- Date of therapy (start and end date, if available)
- Batch or lot number, if available
- Subject details (subject ID and country)
- Gender
- Age at AE onset
- Reporter ID
- Adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

11.3.3 Product Quality Complaint (PQC)

A PQC is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe

- Suspected Contamination
- Suspected Counterfeit

11.3.4 Serious Adverse Event (SAE)

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

Life-Threatening Conditions

The cause of death of a subject in a study within 30-days of the last dose of apalutamide or abiraterone acetate drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

11.4 Expectedness

11.4.1 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.

- 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.

11.4.2 Attribution

Attribution is the relationship between an adverse event or SAE and the study treatment. Attribution will be assigned as follows:

- 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 Unlisted (Unexpected) AE/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

For abiraterone acetate, the link to the package insert is

https://www.zytiga.com/shared/product/zytiga/zytiga-prescribing-information.pdf

For apalutamide, the expectedness of an adverse event will be determined by whether or not it is listed in the Informed Consent Form, which includes the latest risk information listed in the Investigator's Brochure.

11.6 Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- For abiraterone acetate only, failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- For abiraterone acetate only, unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from the standpoint of Janssen, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen within 24 hours of becoming aware of the event.

11.7 Pregnancy

Because the Janssen medicinal product may have an effect on sperm, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PI within 24hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11.8 Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. DFCI and the PI shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may

be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen's request.

11.9 Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen

All adverse events and special situations, whether serious or non-serious, related or not related, **following exposure to a Janssen medicinal product** are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

11.9.1 SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Participating investigators must report each SAE to the Sponsor Investigator (Dr. Mary-Ellen Taplin) within 24 hours of learning of the occurrence. In the event a participating investigator is not made 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. Non DF/HCC sites participating in this research are expected to submit each SAE to its local ethics committee according to FDA and local IRB guidelines.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PI, **within 24 hours becoming aware,** to Janssen using Janssen's Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE or special situation is required.

- DFCI and/or PI is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not

considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to the COMPANY within **24 hours of such report or correspondence being sent to applicable health authorities**.

11.9.2 Non-Serious AEs

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

11.9.3 PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen, and are mandated by regulatory agencies worldwide. Janssen has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen by the PI **within 24hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PI must report the PQC to Janssen according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen.

11.10 Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PI should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

11.11 Transmission Methods

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

- Electronically via Janssen SECURE Email service (preferred) to the Janssen IIS-BIO/VIRO-GCO central mailbox <RA-OMPUS-COBS_Cen_E@its.jnj.com>
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax – 866.451-0371), receipt of which is evidenced in a successful fax transmission report

Please use the contact information and process information provided by Janssen.

11.12 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen will provide to the INSTITUTION and/or SPONSOR INVESTIGATOR, a listing of all SAEs reported to Janssen. SPONSOR INVESTIGATOR will review this listing and provide any discrepancies to the Janssen.

Upon request, INSTITUTION and SPONSOR INVESTIGATOR shall provide Janssen with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

11.13 Final Study Report

The INSTITUTION/SPONSOR INVESTIGATOR will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the executed Research Funding Agreement with Janssen.

11.14 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.

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

11.15 Reporting Requirements

The DF/HCC will serve as the Sponsor of this multi-site trial. Each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with Food and Drug Administration (FDA) regulations, local safety reporting requirements, and reporting requirements of the Sponsor. Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report SAEs to the study sponsor and/or others as described below.

11.16 Reporting to the Study Sponsor-Investigator

11.16.1 SAE Reporting

All SAEs that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall PI on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

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

Participating investigators must report each SAE to the DF/HCC Overall PI 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: 617-632-2165

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 (24 business hours).

11.16.2 Non-SAE Reporting

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

11.17 Reporting to the IRB

Investigative sites within DF/HCC will report all SAEs directly to the DFCI Office of Human Research Studies (OHRS).

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

Mary-Ellen Taplin, MD
Phone: 617-582-7221
Email: Mary_Taplin@DFCI.harvard.edu
Fax: 617-632-2165

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

11.18 Reporting to the FDA

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.

11.19 Reporting to Hospital Risk Management

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

11.20 Monitoring of AEs and Period of Observation

All AEs, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

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

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

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and monitor data for this study.

12.1.2 Data Submission

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

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with ODQ.
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 Safety and Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety, and other data from this trial. 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 with the PI, a statistician and study team members. Should any major concern arise, the DSMB will offer recommendations regarding whether or not to suspend the trial.

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, AEs and SAEs reported by category, summary of any deaths on study, audit results, and summary provided by the study team. Other information (i.e. 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, Good Clinical Practice (GCP), and any applicable regulatory requirements.

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

To ensure proper oversight of local and external study conduct, on-site and virtual monitoring will take place at the beginning of the study and periodically for the duration of the clinical trial. The lead site will host monthly teleconferences with external sites to discuss amendments, SAEs, data, sample processing, and more.

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 GCP

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

- E6 GCP: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- 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 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - 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 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

  - Title 21 Part 312 – Investigational New Drug 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 H).

- 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, phase II, prospective, randomized trial designed to investigate the efficacy of neoadjuvant and adjuvant abiraterone acetate + apalutamide for men with intermediate-high risk prostate cancer who are candidates for RP. The study includes two parts. In part 1, patients will be randomized in 1:1 ratio to receive 6 months of neoadjuvant abiraterone acetate, apalutamide, leuprolide and prednisone (Arm 1A) versus 6 months of abiraterone acetate, leuprolide and prednisone (Arm 1B) followed by RP. Randomization will be stratified by disease risk factor (intermediate versus high risk). In part 2 (post-RP adjuvant), patients will be randomized in 1:1 ratio to receive additional 12 months of adjuvant abiraterone acetate, apalutamide, leuprolide and prednisone (Arm 2A) or observation (Arm 2B) stratified by type of neoadjuvant therapy and pathological T-stage (< pT3 versus ≥ pT3).

For part I, the primary analysis will compare the proportion of patients with pCR or MRD (pCR plus MRD, see section 10.1) at RP following therapy with Arm 1A and Arm 1B. We hypothesize that treatment with abiraterone acetate, leuprolide and prednisone (Arm 1B) will have a pCR plus MRD rate of 15% based on our prior experience.[3] We hypothesize that with the addition of apalutamide (Arm 1A), the rate of pCR plus MRD will increase to 35%. 120 patients will be enrolled and randomized in part 1. This sample size provides 81% power to distinguish a pCR plus MRD rate of 35% in Arm 1A (N=60) from a rate of 15% in Arm 1B (N=60), using a chi-square test for binomial proportion (one sided a=0.05).

For part 2, the primary analysis will compare the rate of bPFS (see section 10.1) at 3 years after RP between the two arms with and without adjuvant therapy. There is limited data with regard to long term outcomes of use of novel hormonal agents. Based on the institutional experience of patients treated with neoadjuvant abiraterone acetate, 3-year bPFS rate is expected to be approximately 70%. Assuming that 90% of the population is able to complete RP and agrees to participate the adjuvant part of the study, there is 83% power to distinguish a 3-year bPFS rate of 90% in Arm 2A (adjuvant arm: N=54) from a rate of 70% in Arm 2B (observation arm: N=54), using a chi-square test for binomial proportion (one sided a=0.05).

14.2 Primary Endpoint and Methods of Analysis:

Part 1: The number and percent of patients achieving pCR plus MRD will be summarized with two-sided 90% exact binomial CI by treatment arm. All patients who are randomized in part 1 will be included. The primary comparison between Arm1A and Arm1B will be conducted using the chi-square test for binomial proportion, with one-sided P value of ≤ 0.05 considered statistically significant. The Cochran-Mantel-Haenszel test accounting for the stratification factor at randomization will be performed as a sensitivity analysis.

Part 2: At time of final analysis, the 3-year bPFS rate (SE and two-sided 90% CI) will be estimated using the Kaplan-Meier method according to treatment arm. bPFS is defined in section 10.1. All patients who are randomized in part 2 will be included in the analysis. If the lower limit of 90% CI (two sided) for the difference in 3-year bPFS (estimated from the Kaplan Meier method, as adjuvant treatment arm 2A minus observation arm 2B) is greater than 0, we will consider there is a statistically significant difference between the two treatment arms.

This approach to hypothesis testing is used instead of using the observed rate at 3-years post-surgery, or instead of comparing the bPFSdistribution using logrank test for multiple reasons. It is the 3year timepoint that is of clinical interest. There may be censored data prior to 3 years that can be included using a time-to-event endpoint. In addition there may be different hazards during the first year (i.e. when one group receives active treatment and the other is observed) than in the next 2-year period and may not meet a proportionality assumption. The analysis will include plotting hazard functions over time to assess whether there are different hazards in the first and subsequent year periods. Proportional hazard assumption will also be assessed in order to estimate hazard ratio from Cox proportional hazards model.

It is anticipated that the primary analysis of bPFS will be conducted when the last subject enrolled in part 2 has been followed up to 3 years post RP, or has experienced biochemical progression (as defined in section 10.1), or has been removal from study, whichever occurs first.

14.3 Secondary Endpoint(s) and Methods of Analysis:

Pathological endpoints (part 1)
Other pathological analyses include (1) proportion of participants with pCR at RP, (2) proportion of participants with favorable RCB (see section 10.2) 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 1A and Arm 1B. 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 90% confidence interval; comparison between arms will be conducted using chi-square test or Fisher's exact test as appropriate.

PSA kinetics prior to RP (part 1)
PSA kinetics prior to RP include nadir value, achieving nadir PSA < 0.2 ng/mL, achieving 50% or achieving 90% decrease in PSA from baseline, and time to PSA nadir. PSA kinetics will be summarized with descriptive statistics (e.g. median, range, and proportions) and presented by arm (Arm 1A and 1B). Comparison between arms will be conducted using chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Safety endpoints (part 1 and 2)

Safety analysis will be conducted using the Safety Population defined as any participant receiving one dose of study treatment. All safety endpoints will be summarized according to treatment arm, separately for part 1 (neoadjuvant part) and part 2 (adjuvant part).

For toxicity reporting, all adverse events will be graded and analyzed using CTCAE version 4. Type of adverse events, intensity (grading), and attribution will be provided in a listing. 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 (part 1 and 2)
The QOL will be measured using the Expanded Prostate Cancer Index Composite 26 (EPIC-26). The questionnaires will be administered at baseline, prior to RP and every 3 months for 2 years post RP. Analysis will be conducted separately for part 1 (neoadjuvant part) and part 2 (adjuvant part).

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 time points. The effect of treatment will be evaluated using a repeated measures model to incorporate assessments across time into a single analysis, using model contrasts to compare treatment groups at selected time points, prior to RP and 2 years post-RP.

Quantitative MRI
Prostate gland volumes and quantitative indices (T2, ADC DCE metrics) will be compared pre- and post neoadjuvant therapy (by lesion or by patient) using Wilcoxon signed-rank test. Their changes from baseline will be correlated, using Spearman's rank correlation, with (1) pathological RCB index (2) changes in PSA values (3) changes in serum/tissue androgen levels. Comparison of quantitative changes between pathological response groups will be conducted using Wilcoxon rank-sum test or t-test. Logistical regression will be conducted to predict pathological response using different mpMRI parameters or their combination. Model performance will be evaluated by the AUC index.

14.4 Correlative Endpoint(s) and Methods of Analysis:

Time to testosterone recovery (part 2)
The Kaplan-Meier product limit method will be used to estimate the distribution of the time from RP until testosterone recovery, or censored at date of last test of testosterone level, for Arm 2A and 2B. Comparison between treatment arms will be assessed using the log rank test.

Serum/Tissue androgen concentrations (part 1 and part 2)
Serum androgen concentrations will be measured at multiple timepoints (see section 10.2) by mass spectroscopy. Tissue androgens will only be assayed in RP specimens. Mean change in serum androgen concentrations from baseline to during neoadjuvant treatment and to prior to RP will be summarized for Arm 1A and 1B (part 1). Mean change during follow-up post RP will be summarized for Arm 2A and 2B (Part 2). Comparisons between arms will be conducted using the ANOVA methods (with log transformation as appropriate) or the non-parametric Wilcoxon rank-sum test.

IHC staining (part 1)
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 will be compared between treatment arms (Arm 1A versus 1B) using the Cochran–Armitage test for trend or other appropriate methods.

Whole Exome and Transcriptome Sequencing (part 1)
Changes in whole exome and whole transcriptome between pretreatment prostate biopsy and RP specimens between treatment arms (Arm1A and 1B) 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 about 60% of participants (N=72) using fresh-frozen tissue at pretreatment biopsy and RP 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 neoadjuvant therapy. For detection of rare gene mutations, with 72 participants, there are 0.98, 0.89 and 0.52 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 0.13 and 0.19 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 0.34 SD mean change between time points with n=72 using a paired t-test (two-sided α=0.05). To compare gene expression between groups (e.g. treatment arms, pathology response), we will use student t-test for continuous values or Fisher's exact test if the data are summarized as % of patients with up- or down-regulated expression.

Germline mutations (Part 1)
The prevalence of germline mutations in homologous recombination genes will be assessed in all enrolled patients. With N=120, the 90% exact binominal CI width is 0.10~ 0.15 with the observed mutation rate of 0.1~ 0.3 respectively. Fisher's exact test will be used to compare pathologic response (such as pCR, MRD, and RCB) with homologous recombination gene germline mutation status as an exploratory analysis.

14.5 Sample Size and Accrual Rate

For a sample size of 120 participants, we expect a total of 15 months to complete the accrual at a rate 8 participants/month.

14.6 Study monitoring

The DF/HCC DSMB on a semi-annual basis will review the study for safety, progress toward completion and the status of case report forms. Interim analysis of efficacy endpoints is not planned. However, the following events will be monitored to ensure that the study has sufficient statistical power for the analysis of the primary efficacy endpoint in part 2.

Rate of participation in part 2
We assume that 90% of the population agrees to participate in the adjuvant part of the study (part 2) after completion of RP. The statistical power reduces to 61% if only 50% of subjects are randomized into part 2. Therefore, among the first 40 patients who complete RP, if 21 or more subjects refuse to be randomized into part 2, "part 2(adjuvant therapy post RP)" of the study will be terminated early due to insufficient participation rate.

The following table gives the statistical power if various numbers of patients are enrolled in the part 2 under the same design parameters.

% enrolled in part 2	90%	80%	70%	60%	50%
N per arm	54	48	42	36	30
Power	83%	79%	74%	68%	61%

Treatment compliance in Arm 2A
We will also monitor the rate of early discontinuation of adjuvant hormone therapy (defined as receiving <6 months of adjuvant therapy in Arm 2A). Among the first 20 (out of 54, 37%) subjects on the Arm 2A, if 8 or more patients withdraw therapy within 6 months, "part 2" of the study may be terminated early due to low treatment compliance in part 2. Using this rule, the probability that the study may be terminated early is 0.03 if the true early discontinuation rate is 20% and 87% if the rate is 50%.

	True but unknown rate of early discontinuation					
	10%	20%	30%	40%	50%	60%
Probability of observing 8 or more receiving<6month adjuvant therapy in the first 20 patients in Arm 2A	<0.1	0.03	0.23	0.58	0.87	0.98

15. PUBLICATION PLAN

The data will be collected by Dr. Taplin and study team and analyzed by Dr. Taplin 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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17.3 APPENDIX C: Patient's Pill Diary

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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:

Please notify the lead clinical research coordinator at the time a participant is identified or consented to the study. The DFCI coordinator will register the participant once the below documentation is finalized using the DFCI OnCore registration system. Non-DF/HCC participating sites will send the documents to the DFCI research coordinator to complete registration. Please allow a one-week turn-a-round time for the DFCI research team to determine participant eligibility. The following documentation is required prior to participant registration:

- Current IRB approved consent form signed by participant and Investigator (MD only)
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated DFCI eligibility checklist (signed by MD and RN)
- The following source documentation is typically required:
- Please note: Additional documentation may be required by the lead institution.
    - Labs for PSA values used to determine eligibility (lab values used to determine eligibility, including screening PSA)
    - Documentation of prior treatments/procedures performed to treat prostate cancer (e.g. Chemotherapy, Cryotherapy, Hormone Therapy, Radiation therapy with start and stop dates and dosing information if applicable)
    - Reports documenting disease status
        - CT abdomen
        - MRI prostate including 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

APPENDIX C: PATIENT'S PILL DIARY

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

PART 1:
ARM 1A: Apalutamide + Abiraterone Acetate + Prednisone + Leuprolide
ARM 1B: Abiraterone Acetate + Prednisone + Leuprolide

PART 2:
ARM 2A: Apalutamide + Abiraterone Acetate + Prednisone + Leuprolide

INSTRUCTIONS TO THE PATIENT:

1. Study Drug A: Apalutamide Dose: _____ (enter N/A if not in Arm 1A)
   Study Drug B: Abiraterone Acetate Dose: _____
   Study Drug C: Prednisone Dose: _____
2. You should take your full dose of abiraterone acetate at the same time once daily. For abiraterone acetate administration, no food should be consumed for at least two hours before the dose is taken and for at least one hour after the dose is taken. 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. Abiraterone acetate should not be taken at the same time as apalutamide or prednisone.
3. You should take prednisone at the same time daily. Prednisone should be taken with food.
4. For ARM 1A or 2A participants: You should take your full dose of apalutamide at the same time once daily with or without food. Apalutamide may be taken with prednisone (and 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.
5. Your study medications should not be crushed, chewed, or dissolved in water.
6. You may not consume grapefruit or grapefruit-containing products while taking the study medications.
7. Record the date, time and the number of tablets you took.
8. If you have any comments or notice any side effects, please record them in the comments column.
9. Please bring your pill bottle and this form to your physician when you go to your next appointment.

APPENDIX C: PATIENT'S PILL DIARY (Part 1)

Today's Date: _____ Cycle Number: _____

Patient Name: _____ Patient Study ID: _____

Date	Day	Number of Tablets or Capsules/Time of Day				Comments
		Abiraterone Acetate	Apalutamide	Prednisone (AM)	Prednisone (PM)	
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					

Patient's Signature: _____ Date: _____

APPENDIX C: PATIENT'S PILL DIARY (Part 2A)

Today's Date: _____ Cycle Number: _____

Patient Name: _____ Patient Study ID: _____

Date	Day	Number of Tablets or Capsules/Time of Day				Comments
		Abiraterone Acetate	Apalutamide	Prednisone (AM)	Prednisone (PM)	
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					
	29					
	30					

Patient's Signature: _____ Date: _____

APPENDIX D: Representative Medications that May Predispose to Seizure

Generic Name	Brand Name*
aminophylline	Aminocont; Aminomal; Diaphyllin; Filotempo; Neophyllin; Norphyl; Phyllocontin; Syntophyllin; Tefamin; Truphylline; Xing You Shan;
aminophylline in combination	Asmeton; Cha Xin Na Min; Emergent-Ez; Fufang Dan An Pian; Ke Zhi
amitriptyline	Amirol; Amitrip; Amixide; Deprelio; Diapatol; Elatrol; cElatrolet; Elavil; Endep; Enovil; Emitrip; Klotriptyl; Laroxyl; Levate; Limbitrol; Limbitryl; Mutabase; Mutabon; Nobritol; Novo-Triptyn; Pertriptyl; Redomex; Saroten; Sarotex; Sedans; Syneudon; Teperin; Triptizol; Triptyl; Tryptizol
amitriptyline in combination	PMS-Levazine
bupropion	Aplenzin; Buproban; Contrave; Elontril; Forfivo; Fortivo XL; Le Fu Ting; Prexaton; Quomem; Voxra; Wellbutrin; Wellbutrin XL; Wellbutrin SR; Yue Ting; Zyban
chlorpromazine	Aminazin; Chlorazin; Hibernal; Klorproman; Largactil; Megaphen; Ormazine; Plegomazin; Solidon; Taroctyl;Thorazine; Vegetamin; Wintermin; Zuledin Note: in Ireland also called "Clonazine" – very easy to confuse with clozapine.
clozapine	Azaleptin; Clopine; Closastene; Clozaril; CloZAPine; Denzapine; Elcrit; Fazacio ODT; Klozapol; Lanolept; Leponex; Lozapine; Nemea; Ozapim; Synthon, Versacloz; Zaponex
desipramine	Deprexan; Norpramin; Nortimil; Pertofrane
doxepin	Adapin; Anten; Aponal; Deptran; Gilex; Li Ke Ning; Quitaxon; Silenor; Sinepin; Sinequan; Zonalon
imipramine	Impril; Melipramin; Mipralin; Norfranil,; Novo-Pramine; Persamine; Pertofram; Pryleugan; Talendep; Tofranil; Tolerade
lithium	Arthriselect; Camcolit; Carbolith; Carbolithium; Eskolith; Hypnorex; Li-Liquid; Licarbium; Limas; Liskonum; Litarex; Lithane; Lithicarb; Lithioderm; Lithionit; Lithobid; Liticarb; Litiomal; Lito; Maniprex; Neurolepsin; Plenur; Priadel; Quilonorm; Quilonum; Saniquiet; Sedalit; Teralithe
lithium in combination	Boripharm No 23; Emser Salz; Girheulit HOM; Helidonium-Plus; Heweurat N; rheuma-loges; Rhus Toxicodendron Compose; Rhus-Plus; Ricinus Compose
maprotiline	Cronmolin; Deprilept; Ludiomil; Mapromil; Melodil; Neuomil; Psymion
meperidine/pethidine	Alodan ; Atropine and Demerol; Centralgine ; Demerol ; Dolantin ; Dolantina,; Dolantine ; Dolargan,; Dolcontral,; Dolestine ; Dolosal ; Dolsin; Fada; Hospira; Liba; Mepergan ; Meprozine,; Mialgin,; Opystan; Pethidine ; Petigan Miro ; Psyquil compositum
meperidine/pethidine in combination	Pamergan P100
mesoridazine	Serentil, Mesorin
mirtazapine	Arintapin; Avanza; Axit; Combar; Esprital; Mi Er Ning; Miro; Mirta TAD; Mirtabene; Mirtachem; Mirtadepi; Mirtagamma; Mirtalan; MirtaLich; Mirtamylan; Mirtaron; Mirtaz; Mirtazelon; Mirtazon; Mirtazonal; Mirtel;

	Mirtin; Mirtor; Mirzaten; Norset; Noxibel; Paidisheng; Psidep; Remergil; Remergon; Remeron; Remirta; Rexer; Yarocen; Zispin
olanzapine	Anzorin, Arenbil; Arkolamyl; Atyzyo; Bloonis; Clingozan; Egolanza; Lansyn; Lanzek; Lazapix; Nolian; Nykob; Olafid; Olanzaran; Olanzep; Olanzin; Olanzine; Olapin; Olasyn; Olazax; Olpinat; Olzapin; Olzin; Ou Lan Ning; Ozilormar; Parnassan; Ranofren; Sanza; Stygapon; Synza; Ximin; Zalasta; Zamil; Zappa; Zapris; Zerpi; Zolafren; Zolaxa; Zonapir; Zopridoxin; Zylap; Zypadhera; Zypine; Zyprexa; Zyprexa Relprew; Zydis
olanzapine in combination	Symbyax
risperidone	Aleptan; Apo-Risperid; Arketin; Calmapride; Diaforin; Doresol; Hunperdal; Jing Ping; Ke Tong; Leptinorm; Lergitec; Orizon; Ozidal; Perdox; Ranperidon; Resdone; Ridal; Ridonex; Rileptid; Ripedon; Risepro; Rispa; Rispaksole; Rispefar; Rispemylan; Rispen; Rispera; Risperanne; Risperdal; Risperdalconsta; Risperdaloro; Risperigamma; Risperon; Rispolept; Rispolux; Rispond; Rispons; Risset; Rixadone; Rorendo; Ryspolit; Si Li Shu; Sizodon; Speridan; Suo Le; Torendo; Zhuo Fei; Zhuo Fu; Ziperid; Zoridal
theophylline	Aerolate; Afonilum; Aminomal; An Fei Lin; Apnecut; Apo-Theo; Asmalix; Asmalon; Bi Chuan; Bronchoparat; Bronchoretard; Cylmin; Diffumal; Elixifilin; Elixophyllin; Etipramid; Euphyllin; Euphyllina; Euphylline; Euphylong; Frivent; Gan Fei Lin; Nuelin; Protheo; Pulmophylline; Quelesu; ratio-Theo-Bronc; Respicur; Retafyllin; Shi Er Ping; Slo-Bid; Slo-Phyllin; Telbans; Teotard; Terdan; Teromol; Theo-24; Theo-Dur; Theo; Theochron; Theodur; Theofol; Theolair; Theoplus; Theospirex; Theostat ; Theotard; Theotrim; Theovent; Tromphyllin; Unicon; Unicontin; Unifyl; Uniphyl; Uniphyllin Continus; Uniphyllin; UniXan; Xanthium; Xi Fu Li; Yan Er
theophylline in combination	Antong; Baladex; Bi Chuan; Binfolipase; Broncho-Euphyllin; Broncomar; Do-Do ChestEze; Elixophyllin-GG; Elixophyllin-KI; Insanovin; Marax ; Neoasma; Theofol Comp; Theophedrinum-N; Xu Hong; Yi Xi Qing
thioridazine	Detril; Elperil; Melleril; Ridazin; Ridazine; Thiodazine; Thioril; Sonapa
ziprasidone	Geodon; Li Fu Jun An; Pramaxima; Si Bei Ge; Ypsila; Zeldox; Zipwell; Zypsila; Zypsilan

**** Note: this document is intended as an aid in identifying prohibited meds, but due to the global scope of the apalutamide studies may not be all inclusive.**

APPENDIX E: Intra-operative and Post-operative RP Complications Questionnaires

Intraoperative Surgical Questionnaire

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. Patient Data

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: Post-Operative Complications (Clavian Classification)

Note: For any question answered "Yes", please grade and attribute in the patient note.

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____)

Ophthalmologic

- Xerophthalmia (Y____N____)

Other

- Dehydration (Y____N____)
- Allergic reaction (Y____N____)
- Unplanned Admission (Y____N____)
- Unplanned Emergency Room Visit (Y____N____)

Provider Signature: _____ Date: _____

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: _____
Cycle: _____
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 bowel 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)

APPENDIX H: Family History Questionnaire

Name:_____ Date of Birth_____
Please complete this form by listing all family members (**blood relatives**) known to you with a cancer diagnosis.
Please identify your relatives using their first name, and first letter of their last name only.

Relative	Cancer(s) – What Type(s)?	Approximate Age at Diagnosis
Mother		
Father		
Children		
Grandchildren		
Mother's Mother (grandmother)		
Mother's Father (grandfather)		
Father's mother (grandmother)		
Father's father (grandfather)		
Brothers **Example:** John C.	Prostate Cancer	58
Sisters		
Nieces (children of brothers/sisters)		
Nephews (children of brothers/sisters)		

Other Relatives on Mother's side **Describe how related:** **Example:** Mary S. Maternal aunt	Ovarian Cancer	67
Other Relatives on Father's side **Describe how related:**		

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

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1.0 INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

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

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

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Sponsor 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.

2.0 GENERAL ROLES AND RESPONSIBILITIES

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

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, 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.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (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.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The Coordinating Center will assume the following general responsibilities:

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

2.3 DF/HCC Office for Data Quality (ODQ)

In addition to the Coordinating Center, the DF/HCC ODQ provides the following support services to assist the DF/HCC Sponsor:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide a central participant registration, which includes review of consent and eligibility.
- Provide auditing services (funding and ODQ approval required).

2.4 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.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

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

3.1 Protocol Distribution

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

3.2 Protocol Revisions and Closures

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

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

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

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

3.3 Informed Consent Requirements

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

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

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

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- 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.

3.5 IRB Re-Approval

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

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

3.6 Participant Confidentiality and Authorization Statement

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

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

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

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

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 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 Manager and Clinical Research Coordinator.

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. Participant name and MRN must be redacted. Please ensure the participant's initials are written on each page of the informed consent document.
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated DFCI eligibility checklist
- The following source documentation is typically required. Please note additional documentation may be required by the lead institution:
  - Labs for PSA values used to determine eligibility (lab values used to determine eligibility, including screening PSA)

- Reports documenting disease status: 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 ODQ
- Upon receiving confirmation of registration by the ODQ, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and if applicable the dose treatment level.

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

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

3.7.2 Initiation of Therapy

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

3.7.3 Eligibility Exceptions

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

3.7.4 Verification of Registration, Dose Levels, and Arm Designation

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

3.8 DF/HCC Protocol Case Number

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

3.9 Protocol Deviations, Exceptions and Violations

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

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

3.9.1 Definitions

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

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

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

3.9.2 Reporting Procedures

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

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

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

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

3.10 Safety Assessments and Toxicity Monitoring

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

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

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

3.10.1 Guidelines for Reporting Serious Adverse Events

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

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

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

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol.These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

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.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4.0 REQUISITIONING INVESTIGATONAL 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.

5.0 MONITORING: QUALITY CONTROL

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

5.1 Ongoing Monitoring of Protocol Compliance

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

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

treatment, regulatory records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management.

Site visits will generally occur 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.

5.2 Evaluation of Participating Institution Performance

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

5.2.1 Monitoring Reports

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

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and

accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Sponsored Trials

This study may be audited by the DF/HCC Office of Data Quality (ODQ) if the Sponsor-Investigator determines that an audit of the participating site is necessary.

6.2 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 Audit Notification

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

6.4 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4.1 Corrective Actions

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

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may 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. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**16-223**
Protocol Name:	**Phase II randomized study of neoadjuvant and adjuvant abiraterone acetate + ARN-509 for intermediate-high risk prostate cancer undergoing prostatectomy**
DFCI Site PI:	Mary-Ellen Taplin MD
DFCI Research Nurse:	Judy Prisby, Meghara Walsh, Amanda Pace , Ralph Eugene

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	• Study Drugs: Section 2.3. – Abiraterone CYP17 inhibitor, second generation antiandrogen (Section 2.3.2) • ARN-509 (Aptilutamide)- novel second generation antiandrogen that binds directly to the ligand binding domain of the androgen receptor impairing nuclear translocation and DNA binding (Section 2.3.4) • Leuprolide – GNRH agonist – lowers testosterone (Lexicomp) • Study Design – Section 1.1 • Study Rationale – Section 2.2 • A cycle is defined as 28 days – Section 5, Table 4, Study Calendar, Section 9

Dose Calc.	• All drugs are in fixed doses, dosing Section 5
	• Leuprolide Section 5.3.4
	• Pre-Prostatectomy
	  ○ Arm 1A – Abiraterone +Prednisone + ARN-509 + Leuprolide X 6 cycles (Section 1.1; Study schema)
	  ○ Arm 1B – Abiraterone + Prednisone + Leuprolide X 6 cycles (Section 1.1; Study schema)
	• Post prostatectomy
	  ○ Arm 2A – Abiraterone + Prednisone + ARN-509 + Leuprolide X 12 cycles (Section 1.1; Study schema)
	  ○ Arm 2B - Observation (Section 1.1; Study schema)

Study Drug Administration	Agent *Administration* Guidelines are found in Section 5 • Abiraterone is taken orally, daily, on an empty stomach (nothing to eat 2 hours pre and 1 hour post) – Section 5.3.1 • Prednisone is taken orally, daily, with food – Section 5.3.3, Table 4 • ARN-509 is taken orally, daily, with or without food, may be taken with prednisone – Section 5.3.2, Table 4 • Leuprolide – given IM for 6 cycles pre prostatectomy (both arms) and 12 cycles post prostatectomy (if in Arm 2A) – Section 5.3.4 • Criteria to treat – Section 5.2 and Section 6 • Oral Agents cannot be crushed, chewed, or dissolved, must be taken whole. – Section 5.3 • Missed doses should be taken no later than 12 hours after the scheduled time for dosing. – Section 5.3 • Vomited doses should not be made up. – Section 5.3
Dose Mods & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 6 • This protocol uses NCI CTCAE criteria, version 4.0
Con Meds	*Concomitant Therapy* Guidelines are in Section 5.4 and Appendix D
Required Data	*Study Calendar and Assessment Required data* are outlined in Section 9 • The study calendar is in Section 9 • **Vital signs:** Study Calendar • **ECGs**: Study Calendar & Section 3 –Fridericia correction formula • **Correlative studies**: Section 8, 8.2, Study Calendar and Lab Manual

Charting Tips	**All study drugs require documentation of exact administration time.** Abiraterone, Prednisone, and ARN-509 are under Oncology Research Plan, Leuprolide under Oncology Supplemental Plan in EPIC. Please be sure to also DOCUMENT routes of administration, injection sites, and exact time of any correlative sample collection